Nutritional Status and dietary intake in patients with Non-Cystic Fibrosis Bronchiectasis (NCFB)

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The candidate confirms that the work submitted is his/her own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others

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Abstract

Bronchiectasis is a heterogeneous complex disease, characterised by persistent cough, purulent sputum and abnormal thickening and dilation of the bronchial wall. Inflammation, both lung and systemic, and phenotypic presentation continues to compound research challenges. Worsening symptoms and lung function lead to increased severity of disease. Within this thesis, in study 1, the narrative review revealed Body Mass Index (BMI) is associated with morbidity and mortality in bronchiectasis. There is a lack of data on body composition and its influence, but an emerging role of vitamin D.

Characterisation of a bronchiectasis population (study 2) revealed a novel measure [Hand grip Strength (HGS)] was impaired within 70% of the regional population and in 96% of a younger cohort with primary ciliary dyskinesia (PCD). BMI was a significant predictor of lung function in bronchiectasis, with HGS and weight a statistically significant predictor of lung function in PCD.

Energy intakes are suboptimal, with 71-81% of estimated average requirement (EAR). Dietary intakes have identified important micronutrients, vitamin E, zinc and vitamin D with consumption consistently <35% of the Reference Nutrient Intake (RNI). Those with PCD have lower overall intakes compared with other aetiological groups.

HGS impairment (study 3) was reported retrospectively, over one year, and was associated with lung function ($r = (84)\ 0.234$, $p=0.04$). Feasibility (study 4) implies consumption of a leucine oral supplement gel is manageable, with 60% consumption despite poorer reported palatability and does not impact dietary intakes. Energy and protein intakes are impaired compared with calculated requirements and failed to reach calculated requirements even with supplementation. Supplementation showed improvements in HGS and serum vitamin D levels over 3 months. Key outcomes and future study have been identified including HGS, micronutrients, dietary intakes, quality of life and exacerbations.

Table of Contents

Table of Contents

List of Figures

List of Tables

Abbreviations

ADP	Air Displacement Plethysmography
ACT	Airway Clearence Techniques
AMP	Anti-Microbial Peptides
ARTI	Acute Respiratory Tract Infections
BC	Body Composition
BIA	Bioelectrical Impedance Analysis
BMD	Bone Mineral Density
BMI	Body Mass Index
BSI	Bronchiectasis Severity Index
CEOH	Committee on Environmental and Occupational Health
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CONSORT	Consolidated Standards Of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease
CRP	C-Reactive Protein
CT	Computerised Tomography
DXA	Dual-energy X-ray Absorptiometry
EAR	Estimated Average Requirement
EE	Energy Expenditure
E-FACED	Exacerbation -FEV_1, Age, Colonisation, Extension, Dyspnoea
EI	Energy Intake
EMBARC	European Multicentre Bronchiectasis Audit and Research Collaboration
EPR	Electronic Patient Record
ESPEN	European Society of Parenteral and Enteral Nutrition
EU	European Union
EWGSOP	European Woking Group on Sarcopenia in Older People
FACED	FEV_1, Age, Colonisation, Extension, Dyspnoea

FEV_1	Forced Expiratory Volume in 1 second
FEV_1%	FEV1/ FVC1
FFM	Fat Free Mass
FFMI	Fat Free Mass Index
FFP3	Filtering Face Piece
FM	Fat Mass
FVC	Forced Vital Capacity
GLIM	Global Leadership Initiative on Malnutrition
HADS	Hospital Anxiety and Depression Scale
HAES	Habitual Activity Estimation Scale
HCPC	Health and Care Professions Council
HGS	Hand Grip Strength
HMB	Hydroxymethylbutyrate
HRA	Health Research Authority
IBM	International Businesses Machine corporation
ICD-10	International Classification of Diseases
IL6	Interleukin-6
IL8	Interleukin-8
IMD	Indices Multiple Deprivation
IQR	Inter Quartile Range
IRAS	Integrated Research Application System
ISAK	International Society for the Advancement of Kinanthropometry
LCQ	Leicester Cough Questionnaire
LSOA	Lower layer Super Output Areas
LTM	Lean Tissue Mass
MAC	Mid Arm Circumference
MAMC	Mid Arm Muscle Circumference
MD	Mediterranean Diet
MUST	Malnutrition Universal Screening Tool
MRC	Medical Research Council

MRI	Magnetic Resonance Imaging
MPR	Multiple Pass Recall
NCFB	Non-Cystic Fibrosis Bronchiectasis
NDNS	National Diet Nutrition Survey
NHS	National Health Service
NIHR	National Institute Health and care Research
OH(D)	Hydroxyvitamin D
OPEP	Oscillating Positive Expiratory Pressure
PAL	Physical Activity Level
PCD	Primary Ciliary Dyskinesia
PhD	Doctor of Philosophy
PHQ-9	Patient Health Questionnaire
PIS	Participant Information Sheet
PPE	Personal Protective Equipment
PPI	Patient and Public Involvement
PREDIMED	PREvención con DIeta MEDiterránea (Prevention with Mediterranean Diet)
PROTAGE	Protein Age international study group
QoL	Quality of Life
QoL-B	Quality of Life - Bronchiectasis
QoL-PCD	Quality of Life – Primary Ciliary Dyskinesia
RDA	Recommended Dietary Allowance
RNI	Reference Nutrient intake
SACN	Scientific Advisory Committee on Nutrition
SF-36	Short Form - 36
SGRQ	St Georges Respiratory Questionnaire
SOP	Standard Operating Procedure
SP	Study Participants
SPSS	Statistical Package for Social Scientists

STROBE	Strengthening The Reporting of Observational Studies in Epidemiology
TEM	Technical Error of Measurement
TNFα	Tumour Necrosing Factor alpha
TSF	Triceps Skinfold Thickness
UK	United Kingdom
VAS	Visual Analogue Scale
VDBP	Vitamin D Binding Protein
WHO	World Health Organisation
6MWT	6-Minute Walk Test

Publications

Peer reviewed journal article

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Abstract submission

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Conference poster

King, L., Peckham, D., White, H., Ispoglou, H., 2016. Nutritional status and intake in patients with non-cystic fibrosis bronchiectasis (NCFB), Conference poster, SARCA (Appendix Q)

Chapter 1
Introduction

1.1 Lung Disease and associated burden

People with lung disease often present with acute self-limiting exacerbations, within a milieu of chronic underlying symptoms and disease progression. Estimates from the Global Burden of Disease Study (Soriano et al., 2020) suggest that 550 million people had chronic respiratory disease in 2017, marking a 40% increase since 1990. This significant health burden consistently ranks as one of the most common causes of mortality in developed countries (Naghavi et al., 2017). Worldwide, chronic respiratory diseases account for 7% of all deaths (Li et al., 2020a), with variations in outcomes between countries. The UK stands out as an outlier when compared to other EU countries with higher rates of respiratory related morbidity and mortality (Salciccioli et al., 2018).

Approximately 9.6 million people in the UK, have been diagnosed with lung disease, resulting in a direct healthcare spend of £11 billion per year, which is attributable to direct NHS costs and lost productivity (British Lung Foundation, 2016). While 1 in 7 deaths are related to respiratory disease (Office for National Statistics, 2017), large geographical variations in prevalence and health service provision persist (Public Health England, 2019). Together disease prevalence and health disparities have contributed to the prioritisation of respiratory disease in the 2020-2030 NHS Long Term Plan (NHS, 2019). The most common respiratory conditions include Asthma (82%) and chronic obstructive pulmonary disease (COPD) (12%). Bronchiectasis makes up 2.1% of all cases, although prevalence is increasing (Snell et al., 2019), as is its causal association for death in UK adults (0.2 % in 2008 to 0.3% in 2012) (British Lung Foundation, 2016).

Bronchiectasis[1], a complex clinical syndrome characterised by abnormal thickening and dilation of the bronchi is characteristically associated with persistent and often suppurative, cough (King, 2009; Hill et al., 2017). In the UK the estimated number of cases of bronchiectasis ranges between 210,000 to 300,000 (Quint et al., 2016) with a similar prevalence being reported in Germany (Ringshausen et al., 2015), Spain (Monteguedo et al., 2016), America (Henkle et al., 2018) Singapore (Phua et al., 2021) and China (Lin et al., 2016). However, the overall prevalence is increasing globally, as will the long-term

[1] Bronchiectasis will be used to mean non-cystic fibrosis bronchiectasis (NFCB) throughout this thesis, to differentiate from cystic fibrosis related bronchiectasis.

impact on morbidity and mortality (Khoo et al., 2016). Population characteristics indicate female predominance (Snell et al., 2019), with most diagnoses occurring in those over 70 years of age. As with many lung disorders, its impact on individuals ranges from relative clinical stability, acute self-limiting exacerbations, to chronic and often progressive disease. This diversity of presentation and in underlying aetiology contributes to its complex nature, and the potential for underdiagnosis and poor understanding of the various phenotypic presentations of this complex disease. There is also a lack of evidence base for often routinely used clinical intervention as well as a dearth of clinical trials to determine appropriate therapies (Chotirmall and Chalmers, 2018a).

Bronchiectasis can be acquired or congenital with no cause identified (idiopathic) in 40-50% of cases (NICE, 2022; Pasteur et al., 2000; Lonni et al., 2015; O'Donnell, 2022). Its heterogeneity lies within the diversity of its associated conditions (King et al., 2006a). Precipitating underlying diseases include childhood infections such as, measles, whooping cough, pneumonia, tuberculosis, rheumatoid arthritis, aspiration from gastro-oesophageal reflux disease (GORD), environmental exposure, primary ciliary dyskinesia (PCD), immunodeficiency and Cystic Fibrosis (Scullion and Holmes, 2013). In an early study of 150 adults with bronchiectasis, the ability to establish an underlying aetiology enabled changes toward more effective treatment and management in 5-37% of cases (Pasteur et al., 2000). These findings support the importance of identifying aetiologies such as COPD and Asthma, principles reflected in the NICE clinical knowledge summaries for diagnoses and management of bronchiectasis (NICE, 2022).

Effective management amidst persistent airway infections and recurrent inflammation (Chotirmall and Chalmers, 2018b) should include an initial characterising of the aetiology. This enables the identification of treatable traits such as immune deficiency, the ability to implement appropriate treatment including antibiotic therapy and the assessment of respiratory as well as nutritional and functional status (Ozalp et al., 2012; Qi et al, 2015).

1.1.1 Airway inflammation (Airway response and inflammation in bronchiectasis)

Bronchiectasis can develop as a result of many diverse conditions, including childhood infections such as measles and whooping cough, severe respiratory infections such as pneumonia, immunodeficiencies and autoimmune disorders (Chalmers and Hill, 2013a). The disease is dictated by a triad of factors including bacterial colonisation, airway inflammation and structural lung

damage, which together have a progressive impact on health (Calder et al., 2009; Dente et al., 2015; Eid et al., 2001; Moldoveanu et al., 2009). Although the notion of a cyclical theory of bronchiectasis was first proposed in 1986 (Cole,1986), a more nuanced perspective, has since been proposed where a 'vicious vortex' occurs, reflecting the combined and variable effects of airway inflammation, infection, and structural damage (Flume et al., 2018). This view is reinforced by evidence that pathogens such as *Pseudomonas aeruginosa* exert diverse effects including ciliary downregulation, structural lung damage and neutrophilic inflammation, and suggests an interdependent progression rather than a stepped cyclical model (Keir and Chalmers, 2021).

Identifying the underlying respiratory pathogens and inflammation remain a mainstay for guiding treatment. Chronic lung infections and subsequent progression of disease are often associated with *Aspergillus*, *Haemophilus*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* with the latter predominant in bronchiectasis (Martinez -Garcia et al., 2007). These bacterial populations can be present both acutely or during clinical stability (colonised) (Schäfer et al., 2018) with various treatment options available, including an acute antibiotics course or maintenance therapies such as nebulised antibiotics. Local, national, and international guidelines have been developed to support appropriate and a more standardised approach to timely antibiotic treatment (NICE NG117, 2018). While antimicrobial therapies remain at the forefront of treatment, they are only one of many therapeutic and non-therapeutic interventions which can significantly influence outcome.

The complex and diverse inflammatory response remains poorly understood (Giam et al., 2021). In healthy individuals, the body's reaction to airborne particles and pathogens involves both an adaptive (antigen specific) and innate (inflammatory) response (Brill et al., 2015). In bronchiectasis, there is elevation in pro-inflammatory cytokines (Chalmers and Hill, 2013a) and evidence of impairing neutrophils' phagocytic responses to lung pathogens. It remains unclear if this impairment relates to the pro-inflammatory environment, intrinsic neutrophil defects or a combination of both factors (King et al., 2006b; Pasteur et al., 2000; Ruchaud-Sparagano et al., 2013). Repeated cyclical exacerbations (Rogers et al., 2014), worsening symptoms and lung function, compounded by an ageing population (King, 2009) leads to increased disease severity (Chalmers et al., 2014; Dimakou et al., 2016; Martinez-Garcia et al., 2014). Concomitantly, neutrophil infiltration and pro inflammatory mediators trigger amplified responses locally and systemically (Tsang and Bilton, 2009; Zheng et al., 2001), which generate reactive oxygen species (ROS). Collectively they contribute to significant tissue damage (Schäfer et al., 2018), exacerbating

changes in metabolic pathways (Rogers et al., 2014), leading to worsening lung function and severity of disease (Chalmers et al., 2014; Dimakou et al., 2016; Martinez-Garcia et al., 2014) and evidence of continued over activation of the immune system even in non-exacerbated periods (Olveira et al., 2013). Continuous and unchecked infections result in poorer outcomes and quality of life (Derbyshire and Calder, 2021).

Emerging theories highlight the importance of neutrophilic inflammation and immune-metabolic reprogramming where the inflammatory response changes the cells behaviour (Giam et al., 2021). “Deprogramming” neutrophil behaviour and identifying intricate metabolic responses may provide potential avenues for drug development to reduce disease progression (Chotirmall and Chalmers, 2018a). Drug trials are needed to explore novel therapies in this population, including those that address systemic inflammation (Saleh et al., 2017) and improved lung physiology.

1.1.2 Physiology of the lung and mucociliary clearance in Bronchiectasis

Bronchiectasis, inflammation and repeated infections, result in impairment of mucociliary clearance with the accumulation of tenacious airway secretions. The abnormal structural environment and retained abnormal secretions disrupt normal host defences, increasing susceptibility to infections (Kuek and Lee, 2020). Cilia, hairlike protrusions on lung lining cells, form a vital component of this clearance process (Ho et al., 2001). Cilia beat in a synchronised fashion (12-15mHz), and provide an essential mechanism for removing particles, pathogens, and secretions from the lungs (Figure 1). This ensures mucous movement towards the pharynx for daily clearance through expectorate or swallowing (Tilley et al., 2015). Cilia beat frequency naturally reduces with age and due to external factors, such as smoke and exercise (Ho et al., 2001). In bronchiectasis, mucociliary clearance deterioration amplifies age related changes especially in a population where the condition’s peak age is >70 years for women and >80 years for men (King, 2009). Primary Ciliary Dyskinesia (PCD) is a genetic disorder associated with primary ciliary dysfunction. It results in abnormal mucociliary clearance and a predisposition to respiratory infections and bronchiectasis (Ramsey et al., 2019). Precise diagnosis of the underlying cause of bronchiectasis is therefore crucial for tailored management, distinguishing distinct sub-groups, needing varied treatment strategies.

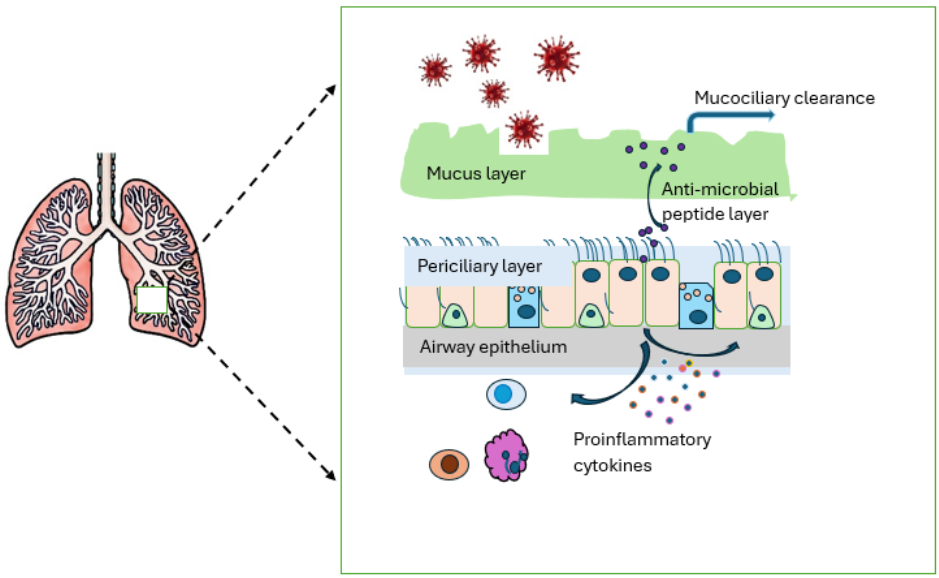


Figure 1 Barrier function, mucociliary clearance, and host defences in the normal airway epithelium

1.1.3 Management and treatment of Bronchiectasis

There are increasing number of local, national and international guidelines and standards of care documents with an emerging emphasis on personalised treatment approaches in managing bronchiectasis. Guidelines for disease management were published by The British Thoracic Society (BTS) over a decade ago (Hill et al., 2011). Subsequently, Hill et al., (2019) published guidelines for the management of adults with bronchiectasis followed by European Respiratory Society guidelines for the clinical care of children and adolescents (Chang et al., 2021b). These publications provide an international roadmap for clinical and research priorities for patients with bronchiectasis (Chang et al., 2021a) as well as standards of care (Chang et al., 2022). Uniformly, all published guidelines have recognised the limited high-quality evidence in support of specific clinical treatments and pathways. However, they have established a standardised structure for care supported with UK quality standards (Hill et al., 2022). In furtherance of future research, the European Multicentre Bronchiectasis and Audit Research Collaboration (EMBARC) Registry (2012) established a prospective longitudinal observational study database, to examine the prognosis and survival of patients with bronchiectasis (Chalmers et al., 2016; De Soyza et al., 2013) and to characterise prevalence with greater accuracy and address five-year mortality rates (Goeminne et al., 2014) Future medical focus is linked to developing a repository of biological materials (sputum, DNA, blood), reviewing airway and systemic inflammation, and the pathophysiology of genomics (Chalmers et al., 2017) and endotypes

(Chalmers and Chortimall, 2018a). Contributions to these data and pathways of care predominantly derive from the UK (Aliberti et al., 2016).

The importance of more personalised approaches to disease management has also been recognised (Aliberti et al., 2022) as has the importance of improving existing knowledge and research gaps (Chalmers et al., 2014). Nutrition has emerged as one such focus, supported by the inclusion of nutritional status (measured by BMI) as one of six monitoring criteria within the current standards of care (Hill et al., 2019) and as a component of a validated disease severity score, the Bronchiectasis Severity Index (BSI) (Chalmers et al., 2014); an index routinely used within clinical practice. Together their inclusion suggests that nutritional status plays a role within disease management, albeit an understudied area of research.

1.1.4 Nutritional status and bronchiectasis

In COPD and Cystic Fibrosis, nutritional status is known to predict mortality (Landbo et al.,1999; Oudijk et al., 2003; Sharma et al., 2001; Schols et al., 1998,) and is established within routine clinical assessment (Keogh and Williams, 2021). This contrasts with bronchiectasis where there is limited research on the impact of nutritional status on disease outcome. To date, BMI alone has been used in monitoring criteria for bronchiectasis but has provided inconsistent associations with outcomes (Chalmers et al., 2014; Despotes et al., 2020). This is despite the association between bronchiectasis, muscle atrophy (Wang et al., 2022), and chronic inflammation (Saleh et al., 2017; Wilson et al., 1998) which together provide clinical mechanisms that are likely to impact on nutritional status beyond BMI (Olveira et al., 2012). Hand Grip Strength (HGS) could offer valuable insights into nutritional status and assessments for improved care. HGS has been proposed as an effective measure by the revised European consensus on definition and diagnosis of sarcopenia (Cruz- Jentoft et al., 2019), it is already acknowledged as a useful tool in COPD (Lee and Wang., 2021) and CF (Bellini et al., 2021; Contreras-Bolívar et al., 2021) but is not yet routinely used in bronchiectasis settings, where it might have similar utility in identifying malnutrition and sarcopenia.

1.1.4.1 Sarcopenia and bronchiectasis

Outside of bronchiectasis, sarcopenia has been considered an outcome of ageing in healthy free-living individuals (Bauer et al., 2013; Deutz et al., 2014; Rosenburg, 1989) and as a disease in its own right, (Anker et al., 2016; Vellas et al., 2018). It has been further differentiated into 'primary sarcopenia', associated with the ageing process and 'secondary sarcopenia' aligned to factors including genetic, hormonal, reduced activity, and malnutrition (Cao et al., 2016). It is accepted that there are multiple causal factors. Moreover, factors that compound inactivity, including chronic illness serve to accelerate sarcopenia (Nunes et al., 2022). This has relevance in bronchiectasis where the presence of a chronic disease, especially in an older population coexists alongside higher energy costs of breathing, reduced activity, and frequent comorbidity (Bellelli et al., 2016; King et al., 2006a). To date there are no studies in bronchiectasis that have quantified sarcopenia, although systematic review evidence provides potential analogies with other respiratory disease. Prevalence of sarcopenia has been reported as 28% across general respiratory disease, (Pacifico et al., 2020) and 15-37% in the more explicit diagnosis of severe COPD (Benz et al., 2019; Sepûlveda-Loyola et al., 2020). These figures exceed reports of prevalence of 10% sarcopenia in healthy community living individuals (Shafiee et al., 2017) and instead align with more diverse populations (Petermann-Rocha et al., 2022) and frailer cohort prevalence (Papadopolou et al., 2020). The frequent 'overlap' of bronchiectasis with other respiratory conditions, (including COPD) has been reported within cohort and systematic review evidence (Du et al., 2016; Marsland et al., 2023; McDonnell et al., 2016). The impact this might have on both population diversity and increased risk of frailty would suggest that sarcopenia requires consideration in bronchiectasis.

In recent years sarcopenia has received greater attention following the publication of the revised European consensus statement, (Cruz- Jentoft et al., 2019). This has resulted in greater standardisation of treatment and has recognised the use of multiple diagnostic criteria across studies, which has previously hindered correct evaluation and comparison between studies (Haase et al., 2022). Within the consensus, sarcopenia was defined as: -

"A progressive and generalized skeletal muscle disorder that is associated with an increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality''.

For the first time, the guidelines moved away from the previous reliance on muscle mass alone, to a tripartite approach, acknowledging that muscle strength was the main predictor of adverse outcome (Cruz- Jentoft et al., 2019; Xu et al., 2022). The criteria were amended to be based primarily on muscle strength, confirmed by a measure of muscle mass and then a measure of physical performance (Figure 2).

Despite this attempt to clarify and standardise the diagnostic criteria, an absence of clear validation studies to establish diagnostic cut-offs and an inability to best define muscle quality, have continued to provide challenges to researchers (Haase et al., 2022). An understanding of the molecular basis of sarcopenia and its application in bronchiectasis has therefore been required.

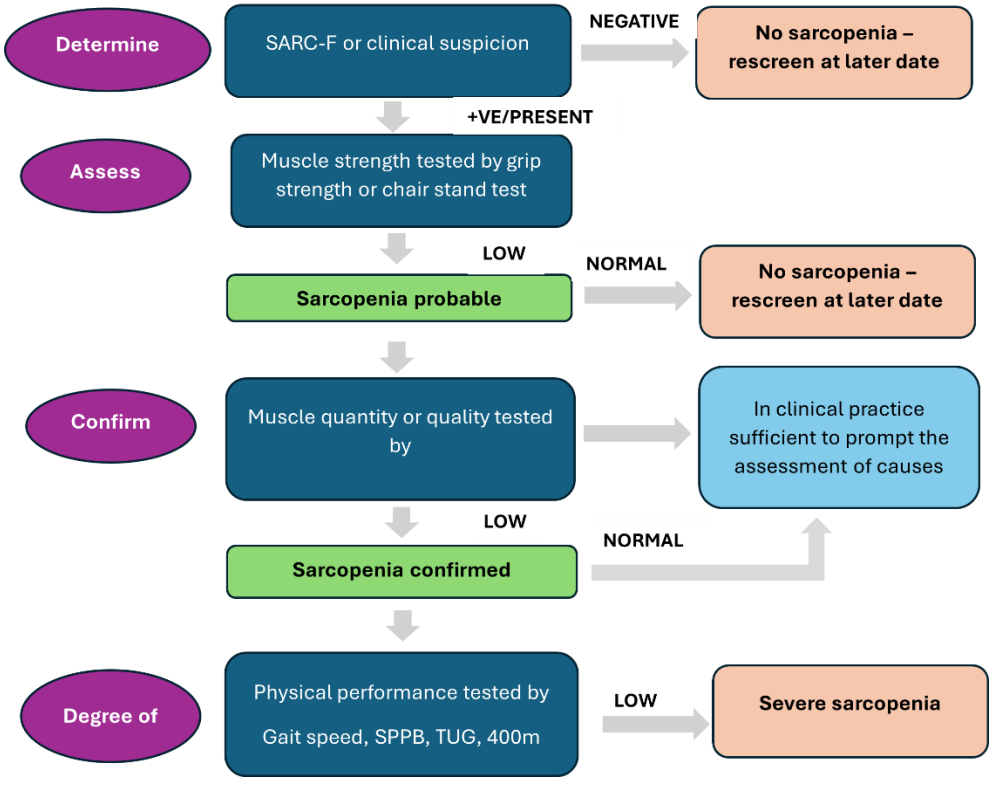


Figure 2 Sarcopenia: algorithm for diagnosing and quantifying severity in practice. (Adapted from Cruz-Jentoft et al, 2019)

Sarcopenia is characterised by disruptions in molecular pathways governing protein turnover in skeletal muscle (Wiedmer et al., 2021), leading to reduced protein synthesis, increased degradation, and subsequent functional decline (Ispoglou et al., 2016; Pascual-Fernandez et al., 2020; Wiedmer et al., 2021). Chronic respiratory conditions like bronchiectasis can exacerbate this process due to enhanced inflammation and muscle deterioration (de Camargo et al., 2018; Jose et al., 2018; Miranda et al., 2022; Ozalp et al., 2012; Wang et al., 2022).

The causal and mechanistic factors for sarcopenia remain poorly understood, but it is proposed that inflammation, nutritional status and age, all influence progression. Notably, whilst systematic review and meta-analysis evidence has established an association between inflammation (measured by raised serum CRP levels) and sarcopenia in general populations (Bano et al., 2017), the relationship and mechanistic pathway between sarcopenia and inflammatory cytokine markers or oxidative stress in respiratory disease remains less clear (Sepulveda-Loyola et al., 2020).

Additionally, the impact of nutritional status, particularly BMI, as a contributory factor to sarcopenia is understudied, and the interpretation of studies is complicated by the complex relationship between BMI and measured outcomes (De Carmago et al., 2017). Assessment beyond BMI to determine body composition and its influence and association with patient outcomes is of interest to enable effective determination of the clinical pathways.

1.1.4.2 Body Composition and bronchiectasis

Body composition measures in bronchiectasis rely on BMI, despite acceptance that it is an imprecise predictive measure, open to confounders such as smoking, exercise capacity, hypercapnia, and muscle mass (Galesanu et al., 2014; Hill et al., 2019). Whilst BMI is a good indicator of adiposity, its inability to differentiate fat from fat free mass and to account for body composition changes has limitations (Thibault et al., 2012). Several reviews have evaluated the utility of a range of measures in health and disease states (Bandera et al., 2016; McCarthy et al., 2021; Thibault et al., 2012) surmising that early characterisation of body composition, may contribute to better quality of life, reduction of healthcare costs and morbidity. Accurate measures of body composition, supplementary to BMI, provide greater ability to assess and monitor comorbidities and consequences of chronic disease (Thibault et al., 2012) such as in COPD (Kyle et al., 2006; Slinde et al., 2005; Thibault et al., 2010). Minimally assessed in bronchiectasis, body composition assessment, beyond BMI, utilising methodology such as BIA, mid arm muscle circumference and handgrip strength (Contreras-Bolivar et al., 2019; King et al., 2021; Olveira et al., 2012; Olveira et al., 2016; Sami et al., 2021) is evolving. Methodological inconsistencies exist, however established and validated use is seen in other lung diseases, (Calella et al., 2018; Charatsi et al., 2016) but lacks evidence to link monitoring strategies to clinical outcomes (Hill et al., 2019). Including validated measures of body composition, would promote the role of fat mass, lean tissue mass and muscle functionality on health outcomes in lung disease, fostering exploration of new interventions and treatments e.g. nutrition,

exercise, and pharmacology (Bone et al., 2017; Peterson et al., 2020; Wang et al., 2022).

Emerging alternative measures of body composition such as Hand Grip Strength (HGS), which can be used in clinical settings could offer valuable insights into nutritional status and assessments for improved care. Proposed as an effective measure by the revised European consensus on definition and diagnosis of sarcopenia (Cruz- Jentoft et al., 2019), HGS has already been acknowledged as a useful tool in COPD (Lee and Wang., 2021) and CF (Bellini et al., 2021; Contreras-Bolívar et al., 2021) but is not yet routinely undertaken in bronchiectasis settings, where it might have similar utility in identifying malnutrition and sarcopenia.

1.1.4.3 Role of nutrition in Bronchiectasis

Unlike CF and COPD where nutritional intervention is key in stabilising disease process (Collins et al., 2012; Stallings et al., 2008) data and specific guidance in bronchiectasis only exists for Spanish populations (Martinez-Garcia et al., 2018) Specific macro and micronutrient contribution in health and disease is essential in tailoring care (WHO, 2019). These remain absent in bronchiectasis; incumbered by a lack of evidence. Nutrition research has therefore been highlighted as a priority (De Soyza et al., 2013; Welsh et al., 2015) and establishing macronutrient distribution, intakes, and sufficiency and the role of nutrition in stabilising disease in bronchiectasis, like COPD and CF, is warranted. Such research is underpinned by a dual rationale; firstly, that specific micronutrients (A, C, D, E, B12, B6, B2, folate, magnesium, zinc, copper, iron, and selenium) (Figure 3) are needed to sustain immunocompetence (Alpert, 2017; Gasmi et al., 2020; Maggini et al., 2018) and if deficient, increase susceptibility to viral infections.

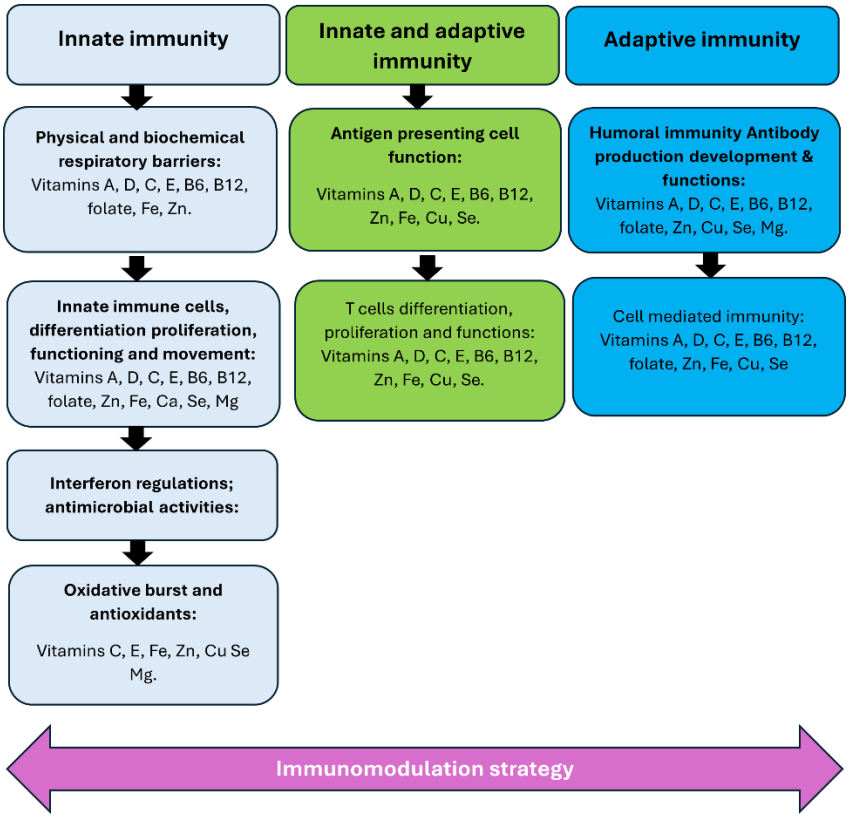


Figure 3. The immunomodulatory strategy and nutrient roles within these processes

Secondly, oxidative stress and inflammation are common occurrence within respiratory diseases such as CF, COPD and bronchiectasis (Causer et al., 2020; de Camargo et al., 2021; Dente et al., 2015; Galli et al., 2012; Galiniak et al., 2022; Ntimbane et al., 2009) and it is feasible that nutritional deficiencies might escalate susceptibility to viral infections and impacting morbidity and mortality. The role of specific micronutrients like vitamin D, along with vitamin D binding protein (VDBP) in modulating inflammation in lung disease/infection is well established (Chishimba et al., 2010; Liu et al., 2021; Maes et al., 2020; Pfeffer and Hawrylowicz, 2012).

Vitamin D deficiency/insufficiency is present in bronchiectasis populations (Ali et al., 2022; Chalmers et al., 2013), impacting pulmonary and physical function (Sami et al., 2021) and associative increases in colonisation of bacteria (Bartley et al., 2013, 2018). With increasing prevalence of vitamin D deficiency worldwide (Moustaki et al., 2017) and continued evidence of vitamin D insufficiency in lung conditions (Minter et al., 2023), optimal dose and delivery requires further scrutiny to support and optimise lung health. Further research is needed to establish optimal doses, treatment strategies, and the overall impact of nutritional interventions on immune function, inflammation, and lung health in bronchiectasis.

1.2 Conclusion

The combined effect of infections and inflammation in bronchiectasis result in significant morbidity and mortality. The complex heterogeneous nature of this disease has made it difficult to harmonise treatments across different patient cohorts and has limited the effectiveness of clinical trials. Whilst medical management such as daily physiotherapy and antibiotics are established treatments (Hill et al., 2019) there is limited data on nutritional status and body composition in bronchiectasis compared to conditions such as COPD and CF. There is a need to understand the role of nutritional intakes, targets, interventions, and body composition beyond BMI in the management of bronchiectasis. Such a multidisciplinary approach may help improve clinical outcome and wellbeing.

1.3 Aim and outline of the thesis.

All participants in this thesis, were receiving care from the Leeds regional bronchiectasis clinic. Formal evaluation of height, weight, lung function, physiotherapy, as well as clinical assessment were routinely undertaken. Despite the likely importance of nutritional status and body composition influencing clinical and disease progression, there is little evidence to support this within the bronchiectasis population.

Chapter 1 provides an overview of bronchiectasis associated clinical challenges, and justification for further research in the areas of nutritional status and body composition.

Chapter 2 conducts and in-depth exploration of nutritional status, intake, and body composition in this group through a systematic review process presented as a narrative review.

Chapter 3 provides an overview of methodologies employed throughout the thesis.

Chapter 4 Given the scarcity of evidence on nutrition and bronchiectasis, this chapter delves into the characteristics of the studied population examining nutritional intake, body composition, functionality, and associated clinical outcomes.

Chapter 5 further investigates dietary data collected in **Chapter 4**, with a specific focus on micronutrients, their role and examining comparison to national diet and nutrition survey (NDNS) data and body composition parameters.

Chapter 6 a retrospective study that assesses muscle functionality using hand grip strength. It explores associations with lung function, breathlessness, BMI, and infective episodes.

In **Chapter 7**, a feasibility study explores the acceptability and palatability of specific amino acid supplementation (40% leucine with additional vitamin D) within a subgroup of Primary Ciliary Dyskinesia patients.

Chapter 8 concludes with an overview of the content of this thesis and explores future research avenues which are likely to benefit the care and outcome for people with bronchiectasis.

It is worth noting the significant impact of COVID -19 pandemic on this research journey. This influence affected research timing and accessibility. Specifically, the original interventional trial in **Chapter 7** was adapted to a feasibility study and data collected for **Chapter 6** was delayed by 1 ½ years, compounded by the part time nature of the study mode.

Chapter 2

Dietary interventions, nutritional status, and body composition in patients with non-cystic fibrosis bronchiectasis: a systematic narrative review

2.1 Introduction

In the previous chapter, bronchiectasis was confirmed to be a heterogeneous disease, with recognised comorbidity and overlap with other respiratory diseases such as COPD (Dou et al., 2018; Sobala and De Soyza, 2022) and Asthma (Crimi et al., 2020; Zhang et al., 2021). This has posed considerable challenge in characterising aspects of the disease, including the impact of nutritional status, body composition, and nutritional intake on outcomes.

Systematic review evidence in COPD has shown the impact of nutritional status on clinical outcome; establishing a relationship between undernutrition and poorer quality of life, pulmonary exacerbations, and mortality (Collins et al., 2013; Gattermann Pereira et al., 2022; van Iersel et al., 2022). Similarly, wasting has been shown to be an independent predictor of survival in CF (Sharma et al., 2001). This is not currently reflected in bronchiectasis, where poorer understanding of phenotypes and emerging endotypes (Josè and Loebinger, 2021) has impacted on nutritional trials. Defined optimal outcomes and endpoints are subsequently lacking and the role of nutritional status in bronchiectasis is less clear. Significantly, in the last umbrella Cochrane review assessing efficacy and safety of medical interventions in those with bronchiectasis (Welsh et al., 2015), there were none that evaluated nutritional status.

Despite analogies with other respiratory conditions, studies examining the role of nutritional status and outcome in bronchiectasis are limited. BMI remains the most used measure of nutritional status within bronchiectasis, included both within the Bronchiectasis disease severity index (BSI) (Chalmers et al., 2014) and as a monitoring component within the current Quality Standards for Care (Hill et al., 2022). The validation study that informed the BSI suggested a non-linear relationship of BMI with outcomes (Chalmers et al., 2014); aligning with the ‘obesity paradox’ reported in COPD, whereby survival is lowest at the extremes of weight and BMI (Brigham et al., 2021; Landbo et al., 1999; Spelta et al., 2018). In contrast, a recent registry study where patients were stratified by BMI category, low BMI was associated with lower lung function but was unrelated to other disease severity markers (Despotes et al., 2020). Overall,

however, research is sparse in bronchiectasis and in the main studies have often failed to include BMI as a potential prognostic indicator of mortality within their modelling (Goeminne et al., 2014; Loebinger et al., 2009). Together it presents a timely opportunity to synthesise the available evidence to date and clarify current findings on the role of BMI in disease outcome.

The inability of BMI to distinguish between fat and fat free mass (Chalmers et al., 2014) has also provided greater focus on adjunct body composition measures, that may have value in defining nutritional status and can better predict important clinical outcomes. Characterising body composition within bronchiectasis can specifically provide insight into the presence of sarcopenia and associated 'sarcopenic obesity' (Petermann-Rocha et al., 2020; Stenholm et al., 2008). Although preliminary case control studies demonstrate significant reductions in muscle strength for individuals with bronchiectasis compared to healthy controls (de Camargo et al., 2018; Miranda et al., 2022), a synthesis of studies that characterise or relate body composition to outcomes are absent. More specifically, studies that use HGS as a measure of muscle strength. Positive associations of HGS with morbidity, mortality and QoL have been noted in COPD (Holden et al., 2021) where systematic review evidence indicates that sarcopenia incidence has ranged in variation by up to 53% (Benz et al., 2019; Sepulveda-Loyola et al., 2020). Already in use as tool to monitor changes in muscle function in COPD (Lee and Wang, 2021) and CF (Bellini et al., 2021; Contreras-Bolívar et al., 2021), the presence of considerable disease overlap (Chalmers et al., 2018b) would suggest that HGS may also have value in bronchiectasis. This supports a need to synthesise the evidence for the impact of body composition (using HGS) on clinical outcomes in this disease.

Determining nutritional intake within populations with bronchiectasis, provides a further link to understanding nutritional status and body composition. Significant dietary deficiencies have been reported across respiratory diseases, including deficiencies in energy and antioxidant intake in COPD (Collins et al., 2019; Mekal et al., 2021; Van de Bool et al., 2013). Systematic review evidence has also reported deficiencies in micronutrient intakes in CF (Greaney et al., 2023) and more recently, research has provided early evidence of changes in dietary intake as a response to new therapies (Caley et al., 2023). Review findings have also identified subsets of populations who will gain greater benefit from targeted and personalised nutritional intervention (Ferreira et al., 2012; McDonald et al., 2021b; Woestenenk et al., 2013). Subsequently these have informed disease related nutritional guidelines in both COPD and CF (McDonald et al, 2021a; Schols et al., 2014; Turck et al., 2016). In contrast,

guidelines in bronchiectasis are only just emerging and are not within UK cohorts (Martinez-Garcia et al., 2018).

The characterisation of dietary intake therefore has potential to inform disease related guidance. Nutritional therapies that decrease oxidative stress and inflammation may improve lung function and patient survival in CF and COPD (Barnes, 2020; Marín-Hinojosa et al., 2021; Wood et al., 2003) where antioxidants can attenuate mucus hypersecretions, inflammation, matrix remodelling and corticosteroid resistance in COPD (Rodrigues et al., 2021) and other chronic inflammatory lung diseases (de Boer et al., 2017). Provision of nutraceuticals to provide antioxidant and anti-inflammatory properties, along with balanced dietary intakes in COPD exert a positive effect on lung function decline and improved pulmonary function, (Scoditti et al., 2019) with consumption of fruits and vegetables providing a positive influence on incidence (Kaluza et al., 2017). Micronutrient supplementation in COVID-19 (Beran et al., 2022) also sheds light on possible future recommendations in lung conditions. The role of vitamin D and zinc in association with immunity and muscle strength are emerging in bronchiectasis (Derbyshire and Calder, 2021; Ferri et al., 2019) along with impact of saturated fat on upregulation of inflammatory response in lung disease (Chen et al., 2022; Franssen et al., 2008; Wood et al., 2010), essential fatty acids influence on downregulation of inflammation (de Boer et al., 2016; Scoditti et al., 2019; Varraso et al., 2015) and protein on muscle synthesis (Engelen et al., 2014; van Bakel et al., 2021) and begin to advocate for the role of nutrition and greater understanding of dietary intakes in bronchiectasis.

2.2 Rationale

As a result, whilst emerging research in many medical therapies for bronchiectasis are recommended, a lack of studies in the fields of nutritional intervention and body composition has led to the extrapolation from COPD and CF management. Whilst this may be appropriate in some instances the diverse nature of the condition and associated aetiologies warrants its own research investigation (Hill et al., 2019).

A scoping search of databases including Cochrane Database of Systematic Reviews, PUBMED, and MEDLINE, revealed that to date, no systematic reviews exploring nutritional intake, nutritional status, or body composition in those with bronchiectasis have been published. The scoping search also revealed published primary research studies that would warrant a review in bronchiectasis, adding to the evidence base in what has been termed an ‘orphan disease’ (Keistinen et al, 1997).

Systematic review and meta-analysis have been used extensively within respiratory disease (COPD, CF), in the field of nutrition interventions (Birch et al., 2018; Collins et al., 2013; Furulund et al., 2021; Mielus et al., 2022; Woestenenk et al., 2013), nutritional status, and body composition (Calella et al., 2018; Nagy et al., 2022; Nicholson et al., 2022). These comprehensive analyses have informed policy and guidance for lung disease and considered an effective methodology to explore these specific areas within bronchiectasis.

Completion of a PROSPERO application was made in April 2019 (Appendix A). An updated end date was added on 3rd February 2023 to enable a two-phase approach due to the duration of the part time, period of study and limited initial evidence. Meta-analysis was not conducted due to the varied nature of the interventions, outcomes, and research focus. Systematic review methodology, in health research, offers excellence in effectiveness, feasibility and appropriateness and provides reviewers, confidence and trust in its recommendations (Evans, 2003).

Whilst the principles of the systematic review process were followed, a lack of research precluded a specific and focused research question. Instead, a wider systematic search and review approach was conducted that aimed to address broader questions, acknowledging that this was underpinned by a comprehensive process (Ferrari, 2015), and contributes significantly to understanding within a specified area. (Grant and Booth, 2009).

This systemic narrative review is therefore the first to draw together and establish outcomes associated with nutrition, nutritional status, and body composition in bronchiectasis populations.

2.3 Aim

The aim of this review of evidence was to: -

1. Establish the impact of nutritional intake, nutritional status and body composition in patients with bronchiectasis on clinical outcomes measured within usual care pathways e.g. lung function, exacerbations, dyspnoea, predominant infection and inflammation.
2. To expand on current knowledge and enable future development of research and clinical practice.

2.4 Objectives

Primary objective

Explore the evidence likely to be effective in optimising nutritional intake, nutritional status, and body composition of patients with bronchiectasis.

Secondary objectives

- Establish whether nutritional status, measured by BMI is associated with lung function, exacerbations (type of infection and dyspnoea), inflammation and quality of life.
- Establish whether body composition, measured by Handgrip Strength (HGS), Fat Mass (FM), Fat Free Mass (FFM), Triceps Skinfold Thickness (TSF), Fat Free Mass Index (FFMI) and Mid-Arm Muscle Circumference (MAMC) is associated with lung function, exacerbations (type of infection, and dyspnoea), inflammation and quality of life.
- Determine whether nutritional intake is associated with lung function, exacerbations (type of infection, and dyspnoea), inflammation and quality of life.

2.5 Methodology

The search and reporting were conducted primarily with one researcher in a part time capacity. The subsequent sections explore and report the evidence from two phases; firstly, the evidence reviewed and collected in the original search (2000-2018) and secondly a search from 2019 to date.

Whilst unorthodox, this approach was required due to the duration of the thesis (7 years). The original search results were limited by a low number of studies, which informed research undertaken as part of this thesis and is discussed in chapter 4. A subsequent search enabled inclusion of further research, that emerged later in the overall timeline of study.

An initial systematic search of the literature was conducted in May 2017, repeated in July 2018 with a subsequent in September 2022.

Databases searched included MEDLINE, EMBASE, CINAHL, PUBMED, PSYCHINFO and WEB OF SCIENCE.

Titles and abstracts were reviewed for eligibility before inclusion/exclusion criteria applied. Reference lists of key papers were screened, and any additional studies were included.

Search terms were also inputted into the Cochrane Database of Systematic reviews both in 2019 and 2022 to ensure that no previous reviews had been undertaken in this area.

2.5.1 Search Strategy

The PICOS system was applied to determine the research question (Table 1) to explore all available research pertaining to the areas outlined above.

Table 1. PICOS table.

Patient/Population	Adults or children with non-cystic fibrosis bronchiectasis
Control	Healthy Control
Intervention and comparator	Nutritional intake, nutritional status, body composition
Outcome	Lung function (FEV_1, FVC and FEV_1/FVC), inflammation (CRP, TNF, Interleukins), Exacerbations as measured by type of infection, dyspnoea (MRC), and Quality of Life.
Study Design	Original research articles describing clinical trials: RCTs; non-randomized controlled trials; single-arm studies; observational studies: cohort studies; case control studies; cross-sectional studies; registry/database studies

Search terms were then created from this to include the following "Non cyst*" OR "fibros*" OR "Bronchiectasis" AND "Nutri*" OR "Diet*" OR "food" OR "intake" OR "supp*" AND "body mass" OR "body composition” OR "lean*" OR "fat*" OR muscle*. All search terms were entered into each database (Appendix B).

2.5.2 Eligibility

Search limiters for the first and second phases were the same with only data parameters differing, 2000-2018 for phase one and 2019-2022 for phase two. Studies included were required to be published, primary research studies and quantitative in design, to answer the nature of the aims and objectives set and written in English. All research methodologies were included except for review articles, editorials, expert opinion, case series and case report due to their

research nature, and categorisation as ‘poor’ when considering the measures of health care interventions research (effectiveness, appropriateness, and feasibility) (Evans, 2003).

2.5.3 Inclusion/Exclusion criteria

Research retrieved from databases were screened against titles and abstracts for appropriateness. Those deemed unrelated were excluded and if this could not be established, full papers were retrieved with any duplicates removed.

Inclusion criteria was framed from the PICOS table (Table 1) and the breakdown from each database can be found in Appendix B. A screening, inclusion/exclusion table was created to be applied to each retrieved study to determine final papers to be included (Table 2).

Table 2. Screening tool, inclusion/exclusion criteria.

Author name	Date
Study ID	Year
Include	Exclude
Patient population is	Patient population is
Human participants Diagnosed with Bronchiectasis Can Non-CF Bronchiectasis be differentiated?	Animal Study No confirmed diagnoses of bronchiectasis Analyses not differentiated by CF and Non-CF Bronchiectasis
Interventions or exposures	Interventions or exposures
Includes nutritional assessment. Includes nutritional intervention. Includes assessment of nutritional status (e.g. BMI) or body composition	Does not include assessment of nutrition or nutritional status (e.g. BMI), body composition
Comparisons or control	Comparisons or control
Compares aspect of body composition parameters (FM, FFM, LTM, HGS) Compares to healthy population. Explores associations within population	Does not consider any body composition parameters (FM, FFM, LTM, HGS) Does not compare to healthy population or associations within population
Outcomes of interest	Outcomes of interest
Lung Function Body composition changes Exacerbations (Dyspnoea, infection) Inflammatory markers (CRP, IL’s, TNF)	Does not review any of the inclusion outcomes.
Study Designs	Study Designs
Published 2000 – 2018/2019-2022. Language is English RCTs; non-randomized controlled trials; single-arm studies; observational studies: cohort studies; case control studies; cross-sectional studies; registry/database studies	Publication prior to 2000 Language is not English Review articles, editorials, expert opinion, case series and case report
Outcome	Include / Exclude
Notes	

2.6 Quality assessment

Quality assessment of the retrieved research was conducted using Critical Appraisal Skills Programme, checklists for randomised controlled trials (CASP, 2020a), cohort (CASP, 2020b), and case control (CASP, 2020c) studies for each of the studies according to their design. Due to the low numbers of studies in this area, even with a wider trawl, all studies were included.

2.7 Data extraction

Data was extracted in accordance with aims and objectives stated from each retained article and are reported in Table 3 and 4.

2.8 Results

Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) criteria and recommendations were followed (Page et al., 2021). This has been reflected in the flow diagrams in Figure 4 (2000-2018) and Figure 5 (2019-2022) and tabulated in Appendix B. The CASP checklists and traffic light table are reported in Appendix C.

In the first phase (2000-2018) a total of 2,826 studies were identified with 29 duplicates removed, 2,797 screened via titles and abstracts eliminating 2,747. Of the remaining 50 studies, 40 did not meet the inclusion criteria, 4 were abstracts only and 1 was a letter. Only 5 studies were included following the inclusion/exclusion comprising of a prospective, single centre randomised control trial (Olveira et al., 2016) two cross sectional studies (Olveira et al., 2014, Olveira et al., 2012) an observational study (Qi et al., 2015) and a case control study (Chalmers et al., 2013b).

In the second phase a total of 761 additional studies were identified with 20 duplicates removed. This left 741 screened via titles and abstracts eliminating 728. Of the remaining 13 studies, 3 were not retrieved/did not meet the inclusion criteria, (1 was secondary data analysis and 2 did not differentiate between CF related bronchiectasis and non-cystic fibrosis bronchiectasis). This resulted in 10 studies for phase 2 of this review and included the published paper discussed in chapter 4.

All 10 were subsequently included and underwent data extraction which can be found in Table 4. The studies included a longitudinal cohort study (Yang et al., 2021) two cross sectional/case control (Ali et al., 2022; Wang et al., 2022) five cross sectional studies (Contreras-Bolivar et al., 2019; Li et al., 2020b; King et al., 2021; Sami et al., 2021; Wang et al., 2021), and a retrospective and a

prospective observational study (Despotes et al., 2020; Lee et al., 2021) respectively.

2.8.1 Main outcomes

Of the initial five studies from 2000-2018, retrieved from the first phase, two explored anthropometry or body composition (Olveira et al., 2012; Qi et al., 2015). The remaining three studies had a nutritional focus, one examining vitamin D status (Chalmers et al., 2013b), one the Mediterranean diet in relation to anxiety and depression in bronchiectasis (Olveira et al., 2014) and the last an intervention with a specific branch chain amino acid supplement with pulmonary rehabilitation (Olveira et al., 2016)

In the subsequent ten studies retrieved from the second phase, one study explored nutritional intake, nutritional status and body composition (King et al., 2021), six of the studies focused on nutritional status and/or body composition within bronchiectasis (Despotes et al., 2020; Lee et al., 2021; Li et al., 2020b; Wang et al., 2021; Wang et al., 2022; Yang et al., 2021) two explored vitamin D status (Ali et al., 2022; Sami et al., 2021) and one explored osteopenia, osteoporosis and body composition (Contreras-Bolivar et al., 2019).

2.8.2 Study Characteristics

Of the five studies (2000-2018), two were conducted by the same primary researcher (Olveira et al., 2012; Olveira et al., 2016), with a third study (Olveira et al., 2014) conducted by the same research group in a Spanish population. The remaining two studies were undertaken in a Chinese population (Qi et al., 2015) and UK population (Chalmers et al., 2013b). Of the ten studies retrieved in the second phase (2019-2022), three were conducted in Spanish populations (Contreras-Bolivar et al., 2019; Wang et al., 2021; Wang et al., 2022), two in Korean (Lee et al., 2021; Yang et al., 2021), one in UK (King et al., 2021), Egyptian (Ali et al., 2022) Chinese (Li et al., 2020b), Iranian (Sami et al., 2021) and US populations (Despotes et al., 2020).

2.8.2.1 Participant numbers, sex, and ages

Participant numbers across all 15 studies totalled 6,338,909. In the first phase, participant numbers totalled 1,069 (30-402) with 438 men (41%). In the second, numbers totalled 6,337,840 (60-6,329,838) with 3,757,196 men (59%). The percentage representation of sexes was similar throughout the initial five studies, ranging from 37%- 44% males, reflecting a predominantly female population, which is reflected in national data (Quint et al., 2016). The percentage representation of sexes in the subsequent ten studies, ranged from

17% - 60% males. Twelve of the fifteen studies had predominantly female populations (Chalmers et al., 2013b; Contreras-Bolivar et al., 2019; Despotes et al., 2020; King et al., 2021; Li et al., 2020b; Olveira et al., 2012, 2016; Olveira et al., 2014; Qi et al., 2015; Sami et al., 2021; Wang et al., 2021; Wang et al., 2022), and the remaining three with equal proportions of both sex (Ali et al., 2022; Lee et al., 2021; Yang et al., 2021).

Mean ages reported in all 15 studies ranged from 9.55 yrs. (± 4.05) (Ali et al., 2022) to 69.9 yrs. (± 15.3) (Wang et al., 2021). The only study in a paediatric cohort (Ali et al., 2022) reported an age range 1-17 years. The remaining fourteen studies reported varied age ranges. Five studies had a reported mean age of participants lying between 60-70 years (Chalmers et al., 2013b; Despotes et al., 2020; King et al., 2021; Wang et al., 2021; Wang et al., 2022), five reported a mean age lying between 50-60 years. (Lee et al., 2021; Li et al., 2020b; Olveira et al., 2014; Olveira et al., 2016; Qi et al., 2015). Of the remaining four studies, two reported mean age lying between 40-50 years (Contreras-Boliver et al., 2019; Sami et al., 2021) and two lying between 30-40 years (Olveira et al., 2012; Yang et al., 2021).

Figure 4 . PRISMA flow diagram 2000-2018

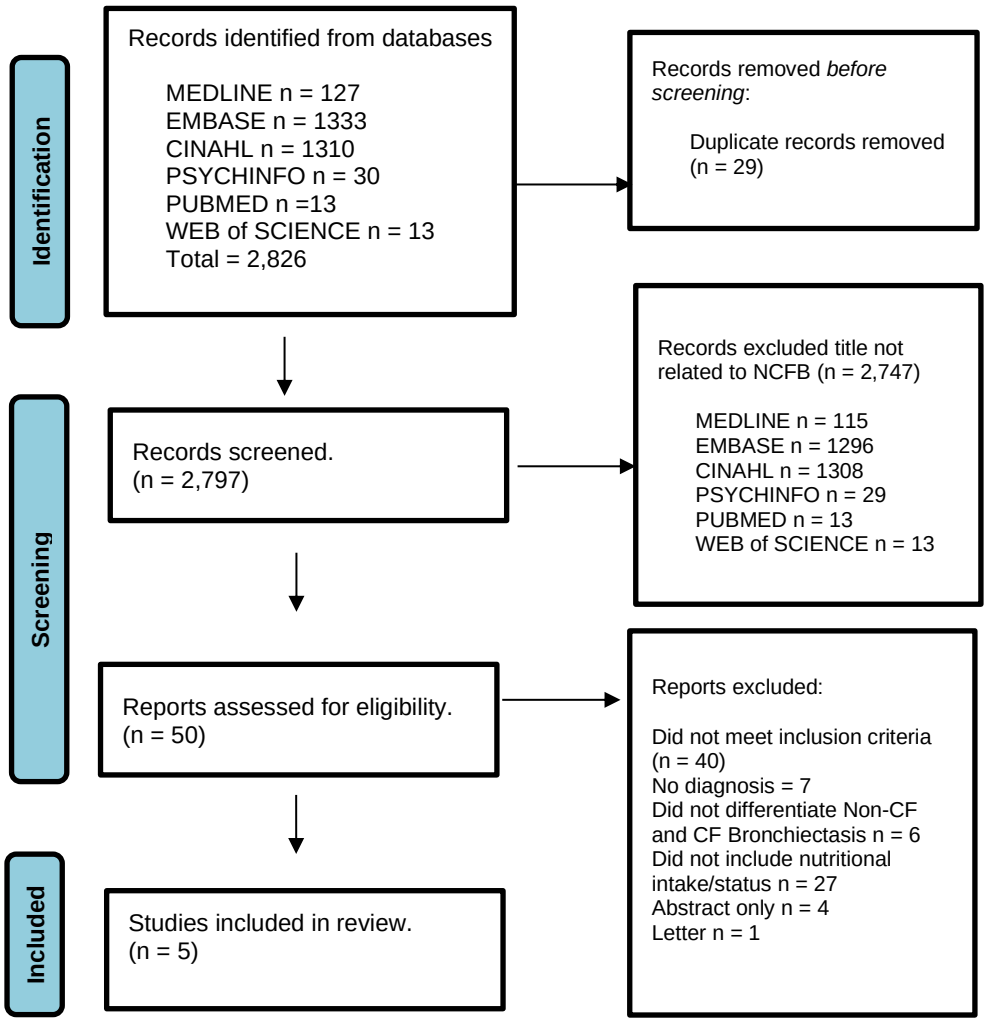
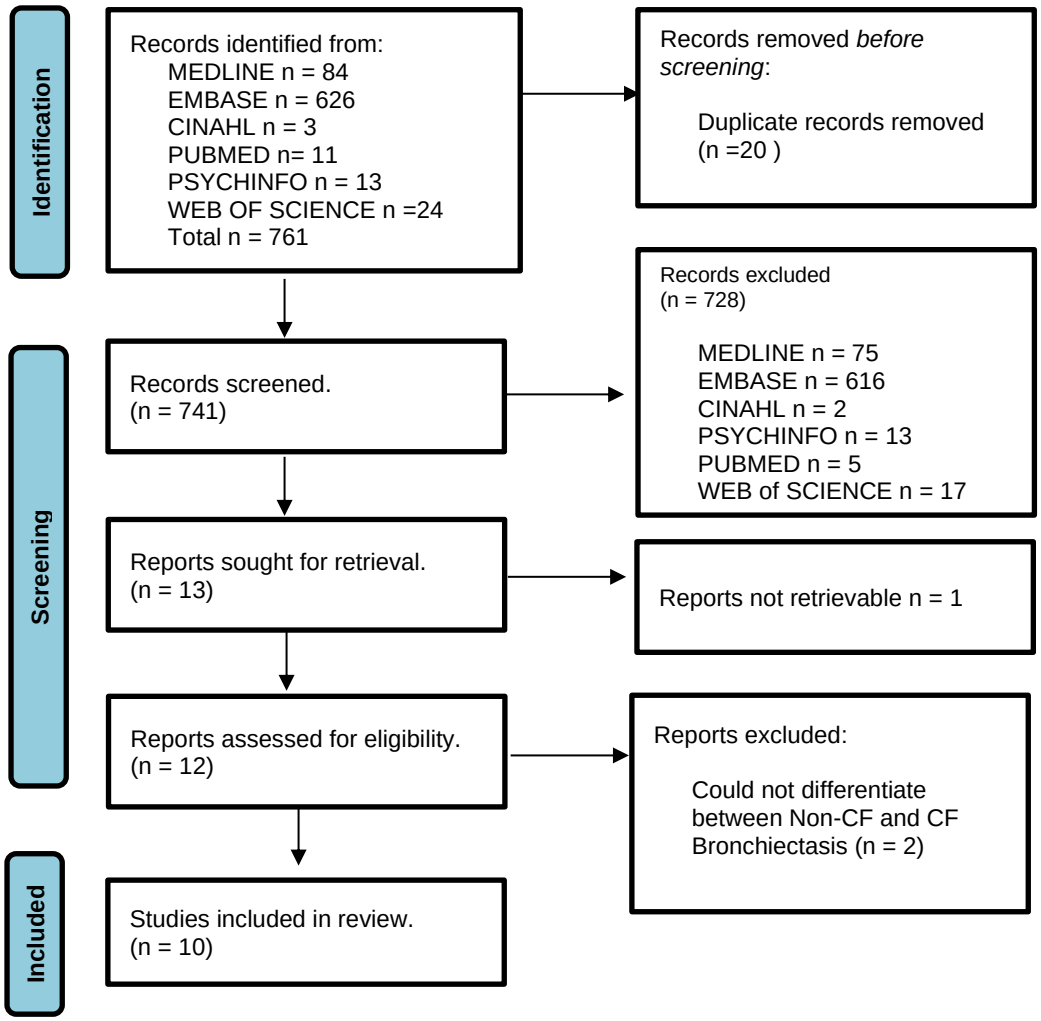


Figure 5. PRISMA flow diagram 2019-2022



2.8.3 Recruitment and design

Of the fifteen studies retrieved in total across both searches, 11 recruited exclusively bronchiectasis patients (Chalmers et al., 2013b; Contreras-Bolivar et al., 2019; Despotes et al., 2020; King et al., 2021; Li et al., 2020b; Olveira et al., 2014; Olveira et al., 2016; Qi et al., 2015; Sami et al., 2021; Wang et al., 2021; Wang et al., 2022). Within the 11 studies, recruitment numbers ranged from 30 to 2121 participants. Six studies recruited less than 200 participants, Olveira et al., (2016), (30), Sami et al., (2021) (62), Contreras-Bolivar et al., (2019), (123), Li et al., (2020b) and King et al., (2021), both recruiting 128, and Wang et al., (2022), recruiting 150. Of the remaining five all recruited more than 200 participants, Olveira et al., (2014), (205), Qi et al., (2015) (339), Chalmers et al., (2013b), (402), Despotes et al., (2020), (496) and Wang et al., (2021) (2121). The remaining four studies, who did not exclusively recruit bronchiectasis

participants, two reviewed whole populations observationally to determine bronchiectasis incidence (Lee et al., 2021; Yang et al., 2021) with 2769 and 6,329,838 participants respectively. Ali et al., (2022) recruited 40 participants 20, CF with bronchiectasis and 20, non-cystic fibrosis bronchiectasis. Olveira et al., (2012) recruited ninety-three, all with bronchiectasis but, termed into 3 specific subgroups, cystic fibrosis (n=41), non-cystic fibrosis bronchiectasis (NCFB) (n=31) and cystic fibrosis transmembrane conductance regulator-related bronchiectasis (CFTR) (n=19).

2.8.3.1 Sampling

Ten of the studies used convenience sampling by utilising clinic populations, with nine using observational study design. Of these ten studies, six utilised cross-sectional design (Contreras-Bolivar et al., 2019; King et al., 2021; Li et al., 2020b; Olveira et al., 2014; Sami et al 2021; Wang et al., 2021), two were cohort studies (Ali et al., 2022; Olveira et al., 2012) and two were of case control design (Chalmers et al., 2013b; Wang et al., 2022). These designs enabled scrutiny of the population at a single time point or over a period of time, prospectively or retrospectively, with case control enabling comparisons to healthy populations. Three studies accessed databases of whole populations, employing an observational longitudinal methodology, with follow up periods of 7.4, 9 and 5 years respectively which enabled emerging trends to be reported (Despotes et al., 2020; Lee et al., 2021; Yang et al., 2022). Qi et al., (2015) conducted a multicentre study in 4 hospitals recruiting consecutively over a period of 3 years. Only, Olveira et al., (2016) employed a single centre randomised trial design, recruiting 30 participants who were randomised into parallel treatment groups.

2.8.4 Outcome indicators

2.8.4.1 Body Composition

Twelve studies reported body mass index (BMI) defined as a measure of nutritional status. Three studies used BMI as a method for grouping the population for analysis (Qi et al., 2015; Sami et al., 2022; Yang et al., 2021). Of those reporting mean values, these ranged from 21.5 kg/m^2 (± 3.63) (Li et al., 2020b), to 27 kg/m^2 (± 4.0), (Wang et al., 2021). Ali et al., (2022) who recruited a paediatric population has not been included in this range as a direct comparison cannot be made to adult populations and data reported was without centiles for correct interpretation.

Body composition assessment included FM, FFM, TSF, MAC, Mid-Arm Muscle Circumference (MAMC), quadricep force and hand grip strength (HGS). These measures were reported in differing combinations in five of the studies (Contreras-Bolivar et al., 2019; King et al., 2021; Olveira et al., 2012; Sami et al., 2021; Wang et al., 2022). Measures were assessed using clinically suitable anthropometrical techniques with protocols reported. Bone mineral density was measured by Dual X-ray Absorptiometry (DXA) by Contreras-Bolivar et al., (2019).

2.8.4.2 Lung function

Pulmonary function was collected across all fifteen studies (FEV_1, FVC, FEV_1 %, FVC%). These parameters were used as a standard comparator to observe changes in lung function throughout disease progression. Lung function measures were also a component of disease severity indices used to determine deterioration during episodes of exacerbation and assist in identifying where treatment may be required.

2.8.4.3 Exacerbation (dyspnoea and infection status)

Bacterial colonisation, at time of study was reported in eleven of the studies with the most common reported colonisation being *Pseudomonas aeruginosa* (Ali et al., 2022; Contreras-Bolivar et al., 2019; Li et al., 2020b; Olveira et al., 2014; Olveira et al., 2016; Qi et al., 2015; Wang et al., 2021; Wang et al., 2022). Predominant colonisation of *Haemophilus influenzae* was reported in studies by Chalmers et al., (2013b) and King et al., (2021) and Nontuberculous Mycobacteria (NTM) infection was predominant in the study reported by Despotes et al., (2020).

Dyspnoea, a measure of breathlessness also termed MRC score, was reported independently in five studies (King et al., 2021; Olveira et al., 2014; Qi et al., 2015; Sami et al., 2021; Wang et al., 2021;) and in combination with sputum volume, purulent sputum (infected) and cough as a collective measure of overall exacerbation (Hill et al., 2017) in three studies (Ali et al., 2022; Li et al., 2020b; Despotes et al., 2020).

2.8.4.4 Inflammation

Markers of disease inflammation such as C-Reactive protein (CRP), interleukin 6 (IL6), interleukin 8 (IL8), and tumour necrosing factor alpha (TNFα) were reported in five studies (Chalmers et al., 2013b; Contreras-Bolivar et al., 2019; Olveira et al., 2012; Qi et al., 2015; Sami et al., 2021) as measures to determine

inflammation and infection and their impact on disease, nutritional intake, nutritional status and body composition.

2.8.4.5 Quality of Life

Quality of life parameters were reported in four studies (Chalmers et al., 2013b; Li et al., 2020b; Olveira et al., 2014; Olveira et al., 2016;) using validated tools for respiratory disease. The Leicester cough questionnaire (LCQ) (Chalmers et al., 2013b; Li et al., 2020b), St Georges respiratory questionnaire (SGRQ) (Chalmers et al., 2013b; Olveira et al., 2014), Quality of Life – bronchiectasis (QoL-B) (Li et al., 2020b; Olveira et al., 2016;) and a generic tool Patient health questionanaire-9 (PHQ-9) (Li et al., 2020b) were used to determine impact of disease on quality of life.

2.8.4.6 Additional outcomes

Due to the diverse nature of the research several other parameters were also collected. Disease specific screening tools such as, the Bronchiectasis Severity Index (BSI) and FACED assessments were used as independent outcomes for exploring associations in two studies (Li et al., 2020b; Wang et al., 2021) and contribute to an overall picture of disease severity within the study timeframe. BSI is reported as having greater sensitivity and FACED greater specificity in predicting mortality (McDonnell et al., 2016). Both include measures already outlined, such as FEV_1, age, dyspnoea score (MRC) and pseudomonas colonisation with BMI also incorporated within the BSI tool.

2.8.5 Nutritional Status (BMI) and lung function, exacerbation, inflammation, and quality of life.

2.8.5.1 Body Mass index

Three studies used an observational approach in determining incidence of bronchiectasis in American and Asian study populations. They reported on BMI associated with lung function, exacerbation, inflammation, and disease incidence within these cohorts. Despotes et al., (2020) reported a retrospective observational study of 496 patients with bronchiectasis retrieved from a registry database (15, US medical centres) exploring markers of disease severity, (number of exacerbations, hospitalisations over a 2-year period, history of haemoptysis, lung resection). Within this study BMI was stratified using World Health organisation (WHO n.d.) definitions, and changes in BMI were observed over a 5-year period. The population had a mean age of 64.6 years (± 13) and

were predominantly female (83.3%) reflecting the largest proportion of females compared with all other studies in this review. The study found no significant associations within the BMI categories for all parameters of disease severity but did show significantly lower lung function in those classified as underweight group (FEV_1% 64.5% ± 22.18%, p = <0.02).

Findings also indicated in 406 of those patients, the majority had a stable BMI (347, (85.5%)) throughout the 5-year study period with 5.4% increasing BMI by ≥ 2kg/m^2 and 9.1% decreasing by ≥ 2kg/m^2. Adjusted regression modelling, showed female patients were 3.19 times more likely to have a low BMI (95% CI 1.87-5.45) compared with male.

Conversely, Yang et al., (2021) explored data in Korea via a national health insurance database, examining individuals aged 20-40 years. Incidence of bronchiectasis recorded under the ICD-10 diagnoses code J47, without concomitant diagnoses of cystic fibrosis (E84) were included. Over a period of 9 yrs. (2009-2018) a cohort of 6,329,838 subjects were categorised by BMI, using Korean specific criteria determined from clinical practice guidelines (underweight < 18.5 kg/m^2, normal weight 18.5-22.9 kg/m^2, overweight 23 – 24.9 kg/m^2 obese 25.0 – 29.9 kg/m^2 and severely obese > 30kg/m^2). Cox proportional hazards regression analysis was performed on occurrence of bronchiectasis within stratified BMI groups.

During the 7.4 year follow up 23,804 subjects developed bronchiectasis with incidence increasing as BMI decreased (p <0.01), a finding that was maintained even when confounders were adjusted for (HR 1.36 95% CI 1.30-1.42). Greater statistical significance was observed in those who were male and in the older age groups (30-39 years) p<0.01. Subgroup analysis, confounding for diseases associated with low BMI (518,955 excluded), strengthen these results, and did not affect statistical significance (HR 1.35, 95% CI 1.29-1.42) p<0.01.

Lee et al., (2021) explored further, the role of BMI as a predictor of mortality in patients with bronchiectasis from a large Korean population. They identified 2769 individuals from the national health insurance health screening cohort also reported on by Yang et al., (2021). Those with existing diagnoses of bronchiectasis, (coded as J47 via ICD-10) with a follow up period of 9 years. The relationship between BMI and mortality was explored using two subgroups of mortality; individuals with all-cause mortality or those with respiratory related mortality (defined as death from tuberculosis, pneumonia, chronic lower respiratory disease, or lung cancer). The population mean age was 59.2 years (± 9.7) and mean BMI 23.4 kg/m^2 (± 3.1) which is comparable to other studies in this review (Despotes et al., 2020; King et al., 2021; Li et al., 2020b; Olveira et

al., 2014; Olveira et al., 2016; Qi et al., 2015 Wang et al., 2022). All explored variables were statistically significantly associated with all cause and respiratory disease related mortality. As BMI increased from underweight to obese, mortality risk decreased, HR 3.04 (95%CI 1.90-4.85, p<0.001). An association still existed when comparing the lower weight categories in both groups (underweight to normal weight in both respiratory disease related mortality and all-cause mortality) HR 2.60 (95%CI 1.92-3.54, p<0.001).

Prior to these observational studies to determine characteristics and incidence, Qi et al., (2015) in their observational, multicentre study investigated the relationship between BMI and disease severity in 339 patients with bronchiectasis. Following categorisation by BMI: (underweight (BMI<18.5 kg/m^2), normal weight (BMI 18.5 - <25.0 kg/m^2), overweight (BMI 25.0- <30.0 kg/m^2), and obese (BMI≥30.0 kg/m^2)) 29% of patients were classified as underweight with a reported mean BMI of 21.9kg/m^2 (± 4.05). Statistically significant differences were found between BMI groups and acute exacerbations, inflammation, extent of bronchiectasis and colonisation by *Pseudomonas aeruginosa* (p <0.001). A positive correlation with lung function (as measured by FEV_1% (0.93 (CI 0.91-0.95), <0.001) and FVC % (0.93 CI 0.92-0.95) p<0.001)) and BMI was established. BMI was also an independent predictor of hospitalisation (-0.26 p<0.001) and mortality increased as BMI decreased (χ^2 = 35.16, p<0.001). There was a statistically significant difference in cumulative survival rates among BMI groups (χ^2 = 31.67, p<0.001) which was lowest in the lower BMI categories.

Lee et al., (2021) reported cumulative survival rates (1,5 and 10 yrs.) as 98.9%, 93.8%, 86.5% respectively, with the lowest survival reported in the underweight group (5-year survival rate of 76.4%). These findings echo those reported by Qi et al., (2015). Despite differences in the proportion classed as underweight in each study (5.1% (Lee et al., 2021) versus 28.6% (Qi et al., 2015)), higher rates of hospitalisation were reported in those with low BMI. These differences are likely due to the differing classification of BMI in the Asian (Chinese and Korean) populations. Recognising cultural expectations of ideal body habitus and body weight in Asian societies (Wardle et al., 2006) could have been discussed in the context of these findings, to strengthen the study. Collection of measures outside BMI such as body composition is needed to determine the role of FM and FFM in these results and is supported by Wang et al., (2022) and Sami et al., (2021).

Lee et al., (2021) reported that being underweight was a considerable contribution to death and death associated with respiratory disease in bronchiectasis, but conversely living with obesity was associated with a

decrease in all-cause mortality. Wang et al., (2022) found BMI was significantly reduced in patients compared with healthy subjects (p<0.001) and particularly in females, also seen in Yang et al., (2021). King et al., (2021) found in their population of 128 participants with bronchiectasis, that BMI was a predictor of lung function (*r* = 0.41, p= 0.042), which did not differ between aetiological groupings. Interestingly, this study reported a lower proportion of study participants (3.9%) classified as underweight (BMI<18.5kg/m^2), similar to that reported in Lee et al., (2021).

2.8.5.2 Disease Severity

Assessment of possible effective markers to establish disease severity was explored in Li et al., (2020b) who retrospectively studied 128 patients in a Chinese population with bronchiectasis. This study utilised BMI and considered albumin and prealbumin in a subset of the population (reporting them as markers of nutritional status). They examined their association with severity of disease by validated disease severity scores BSI (mild, moderate, and severe) and FACED.

All 3 parameters (Albumin, prealbumin, BMI) were reported as statistically significantly associated with BSI severity (r -0.433 p <0.001, r -0.381, p<0.001, r -0.282 p=0.001) respectively. Albumin was noted to be a better reflection of disease severity (BSI) (β -0.404, 95% CI -0.557—0.251, p =0.010) and Pre albumin a better reflection of lung function decline measured as FEV_1% (r 0.379 p = 0.001). Albumin and Pre albumin are affected by the acute phase response, which is inherent within the consistent repeated inflammation and infection within bronchiectasis. These are therefore not reliable markers of nutritional status.

2.8.5.3 Quality of life

Li et al., (2020b) also showed that BSI was significantly associated with all quality-of-life measures, including the Quality of Life Questionnaire – Bronchiectasis (QoL-B), Leicester Cough Questionnaire (LCQ) for clinical symptoms, the COPD assessment test (CAT) which is validated for use in this population (Quittner et al., 2014) and mental health assessment using patient health questionnaire 9 (PHQ -9).

2.8.5.4 Body composition and lung function, exacerbation, inflammation, and quality of life.

Several of the studies explored further measures of body composition additional to BMI, to understand its role and influence on lung function, exacerbation, and inflammation. Olveira et al., (2012) investigated body composition as measured by fat mass and fat free mass using skinfold anthropometry in relation to bronchiectasis. They recruited 93 clinically stable patients with bronchiectasis with aetiology defined as CF, NCFB (10 postinfectious, 11 primary ciliary dyskinesia, one asthma, one yellow nail syndrome, one congenital structural lung malformation, and seven idiopathic) and CF transmembrane conductance regulator (CFTR) associated bronchiectasis. Using mean skinfold thickness measurements, approximately one third of patients with bronchiectasis, independent of the cause, had significant FFM depletion (CF 37%, CFTR 26% NCFB 26%). Within the NCFB group men had greater FFMI compared with women (19.8± 1.3, 15.9 ± 3.4). Fat mass and FFM did not however correlate with inflammation. Those with NCFB had greater incidence of exacerbations compared with other groups (3.8± 3.0 $p<0.001$). Inflammatory markers (CRP, IL_6) were significantly greater in patients with bronchiectasis compared to healthy controls ($p <0.001$, $p <0.05$ respectively).

2.8.5.5 Body composition and inflammation

Like the study by Despotes et al., (2021) in an American population, Wang et al., (2021) undertook to recruit participants from a bronchiectasis registry between 2015-2019, excluding those with CF and who were less than 18 years of age. This observational cross-sectional study with 2,021 participants prospectively included adults diagnosed with Bronchiectasis via HRCT and sought to determine if there were fundamental differences between sex within inflammatory and immunological responses Within this study men were older and had statistically significantly greater disease severity when compared with women ($p<0.001$) as measured by validated tools, BSI, FACED and EFACED. Men had more exacerbations, greater mean BMI (27 kg/m^2) compared to women (25 kg/m^2) $p<0.001$ and significantly higher neutrophils and leukocytes, but no statistically significant associations between any inflammatory markers or nutritional status (BMI). Interestingly, being female was negatively associated with leukocytes and neutrophils (systemic inflammatory markers) (β = - 0.55, 95% CI -0.85 – 0.25, $p = 0.000$ and β = -0.35 95% CI -0.60 - 0.10, $p = 0.007$) when compared with men.

2.8.5.6 Hand grip strength

HGS as a measure of muscle functionality was observed in five studies (Contreras-Bolivar et al., 2019; King et al., 2021; Olveira et al., 2012; Olveira et al., 2016; Wang et al., 2022), with Wang et al., (2022) and King et al., (2021) reporting its association with nutritional status. Wang et al., (2022) explored gender differences further in bronchiectasis looking specifically at respiratory and peripheral muscle strength, and nutritional status. One hundred and fifty patients with NCFB were consecutively recruited at a Spanish clinic, (female (76%)) and compared with 37, age matched, healthy controls (21 females (57%)). They observed worse severity of disease in men compared with women, using the BSI and EFACED assessments (4.97 (SD 2.80) v 5.98 (SD 3.57), $p<0.05$). This study also showed compromised fat free mass when comparing sex, both in the control group and within NCFB groups. They reported males overall having less FM and a greater FFMI. Of note is the overall handgrip strength reductions in patients compared with healthy subjects as well as predicted handgrip strength parameters, also shown in King et al., (2021). Handgrip strength (HGS) was an independent predictor of severity, irrespective of FFM levels and FFMI. Lower FFM found in women was reflected in worse inspiratory muscle assessment, weaker quadricep force and poorer 6-minute walk tests (6MWT).

King et al., (2021) explored both the nutritional intake and functional parameters such as HGS as well as body composition of 128 patients with NCFB. The population reflected similar age and sex to others in this review and was grouped by aetiology (Idiopathic (38.5%,) Primary Ciliary Dyskinesia (19.5%), Bronchiectasis and asthma (18.6%), Other (immunoglobulin, autoimmune, post infective (23.4%)). They found similar findings to Wang et al., (2022), with a median value of 66.5%, of normative values for age and sex, showing impaired HGS (Bohannon et al., 2006). Participants in a younger population (23 years (IQR 19.0-27.0)) with primary ciliary dyskinesia, had handgrip strength found to be associated with lung function (r = 0.18, p 0.03). When stratified by BMI statistically significant differences were seen in all body composition (BC) parameters with the lowest values reported in the underweight group (BMI $<18.5 kgm^2$).

2.8.5.7 Vitamin D Status

Sami et al., (2021) assessed serum 25-hydroxyvitamin D status along with CRP and body composition (TSF, MAMC and MAC), in a cross-sectional study of 62 patients with NCFB in Iran. Exploring the role of vitamin D and any association with lung function, bronchiectasis severity (measured by extent of disease), dyspnoea and 6 MWT, they reported a population with a mean age of 44.14 years (± 15.79). This was the lowest mean age value for the adult studies considered in this review with 73% found to be vitamin D insufficient (<30µg/ml). Vitamin D status and skeletal muscle mass, measured by MAMC, was positively correlated with lung function FEV_1 (r = 0.30, p = 0.035, r = 0.26, p= 0.04). Pulmonary dysfunction (FEV_1/FVC) and FVC were also negatively correlated with body fat (TSF) (r -0.43 p<0.001, r -0.350 p<0.005).

Chalmers et al., (2013b) examined serum vitamin D levels in 402 clinically stable patients with bronchiectasis over 3 years. Serum vitamin D was collected between October and March to reduce seasonal effects of vitamin D production and compared with a control group matched for sex and age. Participants were classified as vitamin D deficient (serum 25-hydroxyvitamin (OH) D <25nmol/l), insufficient (25nmol/l-74nmol/l) or sufficient (>75nmol/l). Exploration of exacerbation frequency, airway inflammation (IL-8, TNF-α, and IL- 1β), lung function (FEV_1%) and sputum bacteria colonisation was reported. Quality of life was also explored using the St George's Respiratory Questionnaire (SGRQ) and the Leicester Cough Questionnaire (LCQ). Mean BMI was 25.7kg/m^2 (22.1-29.5) and there was no statistically significant difference between the subgroups. Deficient levels of vitamin D were associated with a statistically significant higher percentage of chronic bacteria colonisation and bacterial sputum load compared with the insufficient group (p <0.0001). Adjusting for lung function, severity of bronchiectasis, sex and corticosteroid use, vitamin D deficiency was independently associated with chronic colonisation (OR 1.67, CI 1.10-2.56, p+0.01). There was a more rapid decline in lung function (FEV_1 %) in vitamin D deficient groups compared with other groups (p<0.01) with airway inflammatory markers (TNF-α, IL-8, IL1-β) showing significant associations with the vitamin D status (p< 0.05). Vitamin D deficient participants were more likely to suffer greater number of exacerbations requiring hospitalisation (27.4%) and a significant relationship was seen in quality of life through reporting on LCQ and SGRQ (p<0.05). Contreras-Bolivar et al., (2019), reported on the prevalence of osteopenia and osteoporosis in a population with NCFB, through measurement of Bone Mineral Density (BMD) and associations with lung function, body composition, inflammatory markers, calcium and vitamin D intake. They found 64.2% had normal bone mineral density, 23.6% had

osteopenia and 12.2% had osteoporosis. Bone Mineral Density (BMD) was positively associated with handgrip strength ($r = 0.463$ $p < 0.001$) and Vitamin D levels were also significantly associated with fat free mass (FFM) ($r = 0.334$, $p < 0.001$). Those with normal BMD compared with osteopenia and then osteoporosis showed statistically significant differences in lung function (FEV_1%) (74.5 (± 22.6) - 69.9 (± 22.5), $p = 0.026$) (74.5 (± 22.6) - 62.1 (± 12.8), $p = 0.017$).

2.8.6 Nutritional intake and lung function, exacerbation, inflammation, and quality of life.

Only five studies reviewed nutritional intake in variable ways (Ali et al., 2022; King et al., 2021; Olveira et al., 2014; Olveira et al., 2012, 2016). No associations were found in exacerbation or inflammation in any of the studies, but consideration of lung function and quality of life emerged.

Olveira et al., (2014), investigated the relationship between a Mediterranean diet (MD) and levels of depression and anxiety in a cohort of 205 patients with bronchiectasis. The hospital anxiety and depression scale (HADS) as well as the MD questionnaire (PREDIMED), both validated tools, were used in this cross-sectional multicentre study. Those with greater adherence to MD (scores 0-14) had lower likelihood of symptoms of depression and anxiety. Higher anxiety symptoms were associated with both lower MD and MRC score ($p < 0.04$). There were no statistically significant associations found with symptoms of depression and anxiety and sex, lung function, pseudomonas infection or BMI.

Subsequently, Olveira et al., (2016), the only intervention study in this review, explored the use of nutritional supplements with additional leucine in the form of HMB (β-hydroxy -β methylbutyrate) in 30 patients with bronchiectasis. Treatment was associated with improvements in clinical outcomes and health related quality of life as measured by QoL- B a validated tool for use in this population. Mean BMI for recruited participants (30) was reported as 26.6kg/m^2 and participants were randomly assigned to 12 weeks of pulmonary rehabilitation (PR) with or without supplements containing 1.5mg HMB. Outcome measures included body composition (FM, FFM, FFMI, MAMC) Bone Mineral Density (BMD), HGS, QoL, and seven-day dietary intake. Improvements in the supplemented group were seen across all measures from baseline, 12 and 24 weeks. FFM and FFM index at 12 weeks with HGS reaching statistical significance (12 weeks 30.3 ± 11.4 $p < 0.01$, 24 weeks 30.8 ±

11.2 p<0.01). Respiratory training and exercise programmes, along with supplementation of HMB in normally nourished bronchiectasis patients appear to improve muscle strength and BMD from baseline to 3 and 6 months (28.2 ± 11.2, 30.3 ± 11.4 p < 0.01, 30.8 ± 11.2 and 1.141 ± 0.138, 1.154 ± 0.136 p< 0.001, 1.150 ± 0.137 p < 0.01 respectively). Dietary intake measured by macronutrient and total energy intake did not show any statistically significant changes in either group across the time span.

2.8.6.1 Vitamin D intake

The role and interest of Vitamin D status of the population was also explored in a paediatric population with Ali et al., (2022). The vitamin D status of CF and Non-CF bronchiectasis matched for age and sex to a control group was explored. This showed that vitamin D levels were lower in both bronchiectasis groups compared to controls p<0.001. The insufficient group defined by serum 25-(OH) D <20µg was made up of predominantly CF and Non-CF Bronchiectasis (95% and 85%) respectively this could be reflected in the low dietary intakes of Vitamin D (61% RDA) in all groups. This was also reflected in the study by King et al., (2021), which reported vitamin D intakes of less than 20%. In this study multiple pass recall methods (3 x 24-hour recalls) were used to explore intakes in an adult population. Despite the impairment in HGS reported, dietary intakes of protein met or exceeded Reference Nutrient intakes (RNI) and mid arm muscle circumferences (MAMC) (somatic measure of protein reserve) were adequate. When adjusted for increased requirement, as recommended by the PROTAGE study (1g/kg/day), two sub-groups those with PCD and Bronchiectasis with asthma did not meet this target.

Those in the Primary Ciliary Dyskinesia (PCD) and ‘Other’ group failed to meet RNI for iron but with no statistically significant difference between groups all participants consumed less than 20% of the RNI for Vitamin D. Whilst serum levels were not measured this captures the possible factors contributing to overall deficiency identified in this population. Despite meeting reference nutrient intakes for macronutrients such as protein and having adequate reserve, as measured by MAMC, populations are still showing poor muscle functionality through measurement of hand grip strength (King et al., 2021; Conteras-Bolivar et al., 2019) that are associated with lung function decline.

Table 3 Summary of data extracted from studies as part of review (2000-2018)

Author/Yr./Title/origin	Study design	Sample size	Male (n)	Age	BMI (kg/m^2)	Primary Outcomes	Secondary outcomes	Main findings
Olveira et al 2012 "Fat Free Mass depletion and inflammation in patients with bronchiectasis" Spain	Cross sectional cohort study of bronchiectasis population categorised by CF, CF associated disorders and NCFB.	93 clinically stable 43 CF, 31 NCFB, 19 CFTM 100 healthy population	Total 41 males (44.1 %) 20 (47.4%) CF 9 (46.5%) CFTR 12 (38.5%) NCFB	Total 32.2 ± 14.3 CF = 25.1 ± 8.4 CFTR = 37.8 ± 15.1 NCFB = 38.5 ± 16.2	Total 23.8 ± 5.4 CF 21.3 ± 3.6 CFTR 25.9 ± 5.3 NCFB 25.6 ± 6.2	Albumin, CRP, IL6 TNFα, adiponectin, leptin FMI, FFMI, FM, FFM, HGS,	Dietary intake (4 day) FEV1 %, FVC% exacerbations	NCFB had greater number of exacerbations compared to other groups (3.8± p<0.001) NCFB mean intake 2,180Kcal ± 520. Significance found between groups and within groups and control in inflammatory markers but not associated with FM and FFM.
Chalmers et al 2013b "Vitamin D Deficiency is associated with chronic bacterial colonisation and disease severity in bronchiectasis". UK	Case control study observational NCFB patients in 1 regional clinic, categorised by deficient(<25nmol/l), insufficient (25-74nmol/l) and sufficient (>75nmol/l)	Total 402 patients	166 (41%)	67 (58-73)	25.7 (22.1-29.5)	Serum Vit D 25 OHD, VDBP	Bacterial colonisation, FEV_1%, inflammatory markers (IL8, TNFα, IL1β, neutrophil elastase, myeloperoxidase) QoL (LCQ, SGRQ),	Strong association between Vitamin D deficiency group and chronic colonisation (most frequent Haemophilus influenzae) 69.2% chronic colonisation p<0.0001 insufficient group compared to others. Deficient group had poorer QoL scores compared to other 2 groups p <0.05. VDBP elevated in all but statistically significantly in deficiency compared to insufficiency (p<0.0001) Serum 25 OHD 24.7 in NCFB population IQR (16.7-45.4) and 45.3 in control subjects IQR (30.9-68.9) p<0.001 50% of NCFB population were deficient.

Olveira et al, 2014 "Mediterranean diet is associated on symptoms of depression and anxiety with bronchiectasis". Spain	Cross sectional study Mediterranean diet and anxiety and depression. Recruited over 8 months. Recruited following clinical examination to ensure no exacerbations.	205 participants (218 approached, 13 excluded 3 couldn't understand, 10 declined participation)	77 males (37.2%)	57.2 years ± 18.1 (range 17-86)	25.0 ± 4.4	Depression, and anxiety scores and PREDIMED (Mediterranean diet assessment).	QoL, (SGRQ) FEV1%, FVC% chronic Pseudomonas aeruginosa, exacerbations in previous yr., sputum production, MRC, Charlson morbidity index.	NCFB, have higher symptoms of depression and anxiety compared with previous research published in general population. QoL associated with anxiety and depression scores (p = 0.000, p =0.000) Exacerbation frequency associated with elevated anxiety score (p = 0.011), MRC and Charlson morbidity index associated with elevated depression scores (p= 0.008, p=0.03). Those with higher depression and anxiety scores also had lower PREDIMED scores (p =0.005, p=0.049) Logistic regression adjusting for age, educational level, work status, and Charlson comorbidity index. Anxiety, MRC and PREDIMED (p = 0.021 and p = 0.044) Depression, MRC and PREDIMED (p = 0.049 and p = 0.001) When adding in total SGRQ score (p =0.000) this disappeared for anxiety, MRC, and PREDIMED and Depression and MRC.
Qi et al 2015 "Association of body mass index with severity and prognosis in patients with NCFB" China	Observational multicentre study 4 general hospitals consecutively recruited 1st Jan 2010-31 Dec 2013 NCFB included inpatient and outpatient	Total 339 patients NCFB	142 (41.89%)	56 ± 13.52	21.9 ± 4.05	Exacerbations, HRCT extent, CRP ESR and inspiratory capacity, BMI FEV 1 %	FEV, FVC FVC % PaCO2 MRC score, bacterial colonisation	Grouped according to BMI (underweight <18.5kg/m2, (28.61%) normal 18.5 – <25.0kg/m2 (51.03%), overweight 25.0 - <30.0 kg/m2 (16.23%), obese >30.0 kg/m2 (4.13%)) Pseudomonas Aeruginosa (77% of 179), CRP, exacerbations, ESR significantly higher in underweight group (p <0.05). Lung function significantly lower in underweight compared with normal and overweight group (p <0.005). BMI negatively associated with hospitalisation (r -0.26 p<0.001) and mortality risks.
Olveira et al, 2016 "Oral supplementation enriched in HMB combined with pulmonary rehabilitation (PR) improves body composition and health related quality of life in patients with bronchiectasis". Spain	Single centre randomised control trial Parallel treatment design Pulmonary Rehabilitation only and Pulmonary Rehabilitation nutritional supplement	30 patients (59 were screened, 9 excluded prior to randomisation as did not meet inclusion criteria, 20 declined to participate	Total 12 (40%) 4 (26.7%) of the Pulmonary rehabilitation group 8 (53.3%) pulmonary rehab and ONS	Mean age 56.1 ± 13 yrs. PR group 53.7 ±13.1 PRONS 58.4 ± 12.9	26.6 ± 4.7 PR 27.3 ± 5.8 PRONS 25.9 ± 3.4	FM, FFM, FFMI, MAMC, HGS, HRQoL, prealbumin, myostatin and somatomedin c plasma levels	Cholesterol, Insulin, BMD Dietary intake	PR with ONS improved FFM, FFM index, BMD, MAMC, maximum HGS QoL, in normally nourished NCFB Associations found in mean weight changes over 0-3 months, 3-6 months. Statistically significant differences seen between 3 and 6 months in the PRONS group. (3 months Weight, MAMC, QoL-B, FFM (arms) p <0.05, FFM, FFMI, BMD, MAMC, HGS (mean and maximal) p <0.01,) (6 months FFM (arms), QoL-B, p<0.05, BMD, HGS (mean and maximal), p<0.001)

Table 4 Summary of data extracted from studies as part of review 2019-2022.

Author/Yr.	Study design	Sample size	Male (n)	Age	BMI (kg/m^2)	Primary outcomes	Secondary outcomes	Main findings
Contreras- Bolivar et al., 2019 "Osteopenia and Osteoporosis in patients with Bronchiectasis: association with respiratory parameters, body composition, muscle strength and bone remodelling biomarkers" Spain	Cross sectional observational study in clinically stable NCFB	151 recruited with 28 excluded (with reasons stated) 123 patients studied – lost 2 to incomplete data sets. Recruited via clinic assessment done on data normally collected and retrieved of a system.	43 (35%)	49.6 ± 18.8	24.8 ± 4.7 kg/m2	DXA (FFM, FM, BMQ (bone mineral quantity) BMD (bone mineral density), bone metabolism markers, osteocalcin	FEV1, FVC, FEv1/FVC, 4-day dietary to quantify calcium and vitamin D intakes) HGS, TNFα, IL6, exacerbations, colonisation	62.8% and 62.5% (men/women respectively had normal BMD, 30.2% and 22.2% had osteopenia and 7% and 15% osteoporosis Pseudomonas (56.9%) Those with decreased bone mass had significantly lower HGS, Max expiratory volume and Vit D level HGS (normal vs perosis) p =0.049 FEV_1% (normal vs osteopenia) p =0.026, (Normal vs osteoporosis) p= 0.017 D3 (osteopenia vs osteoporosis) p= 0.049
Despotes et al., 2020 "Nutrition and markers of disease severity in patients with bronchiectasis" United states	Retrospective observational longitudinal study using 5 year follow up data. Utilised a database (BRR) 15 academic medical centres across the US	2461 enrolled with clear exclusion/inclusion criteria, 496 recruited.	83 (16.7 %)	64.6 yrs. ± 13.3	22.84 ± 4.37	BMI changes over time	FEV_1 %, FVC % FEV/FVC, bacterial colonisation, aetiology, pulmonary exacerbations (last 2 years) hospitalisation last 2 years, co-morbidities	Explored as BMI groups using WHO cut offs. 12% underweight, 63.7% normal weight, 17% overweight, 6.45% obese. Underweight patients had lower lung function (FEV_1 %) compared to the other groups (p = 0.02) no other significant differences between groups for other markers assessed (exacerbations, frequency, or hospitalisation). Majority of patients displayed stable BMI over 5 years.

Li et al., 2020b "The association between serum albumin/prealbumin level and disease severity in NCFB" China	Retrospective cross-sectional study Inclusion 18-80 yrs. diagnosed NCFB through HRCT	182 NCFB recruited at hospital March 2017-November 2018 (54 excluded to lack of clinical assessment) 128 participants (75 with prealbumin and 79 with albumin).	44 (34%)	57.13 ± 15.61	21.52 ± 3.63	BSI and FACED scores,BMI exacerbations, albumin, prealbumin. Modified Reiff score (radiological appearance)	QoL-B, LCQ, CAT (COPD assessment test) PHQ-9 (patient health questionnaire FEV1%, FVC%, FEV1, FVC) bacterial colonisation, aetiology	Albumin, Prealbumin and BMI were all negatively associated with BSI (*r*-.433 p<0.001, *r*-.381 p<0.001 *r*-.282 p<0.01). Albumin, Prealbumin positively correlated to FACED (*r*.379 p<0.001, *r*.343 p<0.03) and QoL-B, LCQ (*r*.333 p<0.001, *r*.377 p<0.001, *r* .352 p<0.01, *r* .383 p<0.001). Albumin better reflects disease severity. Multivariable linear regression albumin correlated to BSI (β -0.404, 95% CI -0.557 -to -0.251, P = 0.01)
Yang et al., 2021 "Being underweight increases the risk of NCFB in the young population". Korea	Longitudinal cohort study Observational study of generic population. Retrieved from Korean database. Mean follow up of 7.4 years	6,329,838 aged 20-40 years	3,754,667 (59.3%)	30.9 yrs. ± 5.0	BMI was the grouped measure for establishing baseline characteristics, so no mean BMI reported	BMI Incidence of bronchiectasis	Age, gender,	Being male with BMI <18.5 kg/m2 and over 30 years of age all showed higher likelihood of development (HR 1.63 (CI 1.50-1.77, p<0.01, HR 1.51 (CI 1.42 -1.60, p<0.01) than being female and younger. Risk of developing bronchiectasis was (fully adjusted model removing comorbidities associated with low BMI) significantly higher in underweight category (HR 1.36 (CI 1.30-1.42, p<0.01) compared with the normal BMI category. Incidence (23,804 (0.4%).
King et al., 2021 "Nutritional status and intake in NCFB a cross-sectional study" UK	Cross sectional study Clinically stable NCFB patients recruited consecutively at clinic July 2017-2018	128 NCFB (only 125 completed nutritional recordings)	44 (34.4%)	65.5 (IQR 37.5-73)	23.8 (IQR 21.4-28.1)	HGS, MAMC, TSF, MUAC, 24-hour dietary recalls, multiple pass 3 time points FEV1%, FVC, FEV1%, FVC%	bacterial colonisation infection incidence.	HGS impaired in >70% of the NCFB population, significantly so in younger PCD population. Stratified by lung function, no significance difference between groups (Wt., BMI, HGS, MUAC, TSF, MAMC) stratified by BMI categories all anthropometry statistically significant between groups. Predominate infection Haemophilus (42%) Univariate associations observed between weight and FEV_1%, BMI and FEV_1% total population. HGS and FEV_1% with PCD only

Lee et al., 2021 "BMI as a predictor of mortality in bronchiectasis: a nationwide population-based study" Korea	Prospective population based observational study. Data retrieved from database, international classification of disease (ICD-10) with principal diagnoses coded as J47 (bronchiectasis)	2769 (2004-2006) Follow up 2004-2013	1419 (51.3%)	59.2 ± 9.7 Yrs.	23.4 ± 3.1	BMI on prognosis of Bronchiectasis	Age, sex, income, smoking status	409 patients died during study mean follow up period 9.8 ± 2.3 yrs. As BMI increased from underweight to obese, mortality decreased both all cause and respiratory related. Underweight association for all-cause mortality and respiratory-related mortality (2.60 95% CI, 1.92-3.54, p<0.0001 and 3.04 95% CI, 1.90-4.85, p<0.0001). Being female associated with all-cause mortality and respiratory related mortality compared with men (0.45 CI 0.35-0.58 p<0.0001, 0.37 CI 0.23-0.59, p<0.0001) Kaplan-Meier survival curves 1-, 5- and 10-years survival rates in bronchiectasis was 98.9%, 93.8% and 86.5% respectively. Lowest in the underweight group 5 yr. survival 76.4%
Sami et al., 2021 "25-hydroxy vitamin D and body composition are associated with pulmonary function in NCFB. : a cross-sectional study" Iran	Cross sectional study 62 Stable NCFB patients referred from pulmonology clinic	62 participants (2013-2015) with HRCT. Excluded if had CF, COPD, asthma tuberculosis and malignant tumours and those taking Vit D supplements.	24 (38.7%)	44.14 ± 15.79	<18.5 11 - 17.7%) 18.5-25 18 (29.0%) 25-30 18 (29.0%) >30 13 21% No mean BMI provided	Circulating 25-OH vitamin D and all clinical outcomes	FEV_1, FVC, FEV1%, FVC%, FEV_1/FVC, MRC, 6MWT, TSF, MAMC, MAC, and CRP	Vitamin D insufficiency 73% BMI negative assoc. with 6-minute walk test Pulmonary dysfunction (FEV1/FVC) and FVC negatively correlated with body fat (TSF) (*r* -0.43 p<0.001, *r* -0.350 p<0.005) and positively but less so with skeletal muscle (MAMC) (*r* 0.26 p = 0.04)
Wang et al., 2021 "Differences in nutritional status and inflammatory biomarkers between female and male patients with bronchiectasis: A large cohort study Spain	Observational, cross sectional prospective multicentre study 2121 patients recruited from 43 centres based on their characteristics for inclusion.	43 centres participated Feb 2015-Oct 2019 Exclude CF and younger than 18 total 2121 included	753 (35.5%)	Male 69.9 (15.3) Female 68.5 (14.4)	Male 27 (SD 4) Female 25 (SD 5)	Sex, FEV1%, FVC%, FEV_1/FVC	BSI, FACED, EFACED, MRC exacerbations, hospitalisations, bacterial colonisation albumin, creatinine, total proteins, Hb, CRP, ESR, neutrophils leukocytes,	Comparison between male and female and excluding those with COPD. BMI significantly higher in males than females in this population (p<0.001) and for BMI>25 (45% to 63%) p<0.001 Systemic inflammatory markers were greater in males than females (as well as disease severity (Charlson index, P<0.001, EFACED score p<0.01, and FACED score p <0.01)

							lymphocytes, eosinophils	
Wang et al., 2022 "Respiratory and peripheral muscle weakness and body composition abnormalities in Non-Cystic Fibrosis bronchiectasis patients: gender differences" Spain	Prospective cross sectional, case control study with patients recruited over 2 years Stable NCFB recruited consecutively from MDT unit	Total 150 consecutively recruited. Matched to 37 healthy controls	36 (24%)	64.6 ± 13.2 NCFB 62.4 ± 9.8 Controls	Mean BMI not reported in characteristics.	Sex difference in MEP, MIP, SNIP, FFMI, FFM, FM, HGS, quadricep maximum voluntary contraction (QMVC),	FEV_1%, FVC%,6MWT.	Significant differences in BMI between NCFB and Healthy ($p < 0.01$) also seen specifically in women ($p<0.05$) Women with NCFB have less quadricep force ($p<0.001$) than men and lower BMI than healthy group, FFM and FFMI than men ($p < 0.05$, $p<0.001$) Females had impaired HGS compared with men ($p<0.05$) and NCFB lower HGS % predicted than healthy controls. MIP greater in males but decreased overall in NCFB.
Ali et al., 2022 "Impact of vitamin D status on CF and non-CF bronchiectasis" Egypt	Cross sectional case control cohort study. Recruited outpatient and chest clinics patients. Data split by CF and NCFB compared with controls.	60 under 18-year-olds 20 CF Bronchiectasis and 20 NCFB 20 age and sex matched healthy controls without respiratory disease. 1st March 2019 to 1st September 2019	10 (50%)	NCFB 9.55 yrs. ± 4.05 Range 1-17 years	16.56 ± 2.91	Dietary intake of vitamin D, and as % of RDA, serum 25 OHD,	Exacerbations, and bacterial colonisation	Serum Vit D levels significantly different from control in NCFB ($p<0.01$) Vit D deficiency not uncommon in CF and NCFB Deficient group in NCFB significantly different than controls ($P < 0.05$). No significance found between NCFB FEV_1% and Vit D groups but became significant when comparing deficient and insufficient to sufficient group ($p<0.05$). Note some P values not reported

2.9 Discussion

This systematic narrative review was the first to establish outcomes associated with nutrition, nutritional status, and body composition in populations with bronchiectasis.

Across all 15 studies in total, there was a consistent finding that BMI continues to be a strong predictor of mortality and associated disease exacerbation in bronchiectasis. Differentiation of body composition adds further detail to associations with exacerbation and disease severity but not inflammatory markers yet. The simple measure of HGS as an emerging tool for identifying vulnerable groups needs further exploration. Nutritional intake overall, with the limited evidence here, does not seem to play any significant role, yet, but specific review of protein in consideration of muscle depletion, fat, and its effect on lung function and the role of micronutrients, specifically vitamin D as emerging themes is warranted.

It is apparent that there remains a lack of evidence to support any clear guidelines in support of assessment of body composition or focused nutritional intervention. Whilst studies of dietary intake in bronchiectasis are few, they suggest intakes are sub optimal (King et al., 2021), may influence reported anxiety and depression (Olveira et al., 2014) and could augment muscle synthesis and function (Olveira et al., 2012), but characterisation of dietary intake is lacking and should be established to determine its impact on lung function, exacerbation, and inflammation.

2.9.1 Study quality.

The studies methodologies were suitable for the populations being investigated. Observational studies, cross sectional, cohort, and case control pose less ethical challenges compared with intervention studies and enable pooling and collection of baseline characteristics of diverse, heterogeneous, clinical populations that RCT’s may not capture (Yang et al., 2010). Future studies exploring cause and effect should look to reflect a similar parallel design undertaken in Olveira et al., (2016) or a crossover treatment design. This allocation into either intervention arm reduces the risk of researcher bias (Phillips et al., 2022a). Research in bronchiectasis is predominantly cross sectional and observational in nature and could be argued of poorer quality to draw conclusions, however Concato et al., (2000) report well-constructed observational studies do not systematically overestimate the effects of treatment compared with RCT’s in the same area.

2.9.2 Sampling

All studies used convenience sampling, recruiting populations from respiratory or bronchiectasis clinics, enabling easy access to populations of interest and enhancing recruited numbers. This is strengthened further when utilising cohort methodology (Chalmers et al., 2013b; Olveira et al., 2012), which provides greater understanding of impact on outcomes. An observational approach, as seen in Qi et al., (2015), which includes all participants with the diagnoses, is a useful way to establish characteristics of the population with longitudinal observance to establish incidence. This reduces bias but is unable to offer inference or causation.

2.9.3 Origin

Within this review, populations were derived from the US, Europe, and Asia. It has enabled comparisons to be made for generalisability but has highlighted differences in BMI and dietary intake in Asian populations especially, which must be heeded. Asian populations have 40% lower prevalence of individuals lying within an overweight BMI category and have 3% higher underweight BMI compared with European populations (WHO, n.d.). All studies were comparable in relation to sex distribution with the majority predominantly female, which is reflected in the national statistics (Snell et al., 2019). Predominance of females in those with bronchiectasis may be influenced by anatomical size of the lung or hormone types and patterns, but there is a lack of focused research to confirm these (Vidaillic et al., 2018). Other lung diseases report predominantly male cohorts (Ntritsos et al., 2018; Somayaji and Chalmers., 2022;). Populations living with COPD and CF have reflected poorer outcomes and more severe disease in women (Sørheim et al., 2010; Vidaillac et al., 2018) but greater incidence in men (Somayaji and Chalmers, 2022). In contrast, the only study in this review comparing sex (Wang et al., 2021), showed more severe exacerbation in males and an inverse relationship with inflammation in females. Raghavan and Jain, (2016), identified many factors that contribute to sex differences in lung disease including genetics, anatomy, airway microbiology and hormones, which have been hypothesised to influence outcomes in women (Brooke-Hollidge et al., 2021), all of which need to be considered in future research.

2.9.4 Age

Apart from a paediatric population reported by Ali et al., (2022), and Yang et al., 2021, who studied an entire population to determine incidence of bronchiectasis and so not directly comparable here, age distribution was similar and reflected

national statistics. Only the study by Olveria et al., (2012), reported a lower mean age for their population with bronchiectasis (38.5 years ±16.2). Most studies reported on age groups lying within 50-60 years. This is considered to lie within middle aged population boundaries of 45-65 years; a period of life that precedes the onset of old age. Ageing is considered an independent risk factor for severity of disease (Chalmers et al., 2014; Martínez-García et al., 2014). This affords comparison, as individuals are typically concurrent in their life cycle and therefore influences in ageing can be considered in context. Deterioration of muscle mass and ageing of cells, that may influence metabolic processes, inflammatory responses, and preferred dietary intake (Drenth-van Maanen et al., 2020) can be safely assumed. The impact established in bronchiectasis, suggests that earlier intervention, from childhood, may help with improved outcomes and is supported by the emerging evidence in paediatric bronchiectasis populations (Ullman et al., 2021).

2.9.5 Nutritional Status

This review has confirmed that low BMI is associated with incidence of bronchiectasis, with females 3.19 times more likely to have a low BMI compared with males. BMI is negatively associated with hospital admissions, mortality risk (Qi et al., 2015) and severity of disease (Li et al., 2020b) and may be considered a predictor of lung function in specific subgroups (King et al., 2021). Exacerbations are more frequent in bronchiectasis populations compared with controls and more so in men than women (Chalmers et al., 2018b; Olveira et al., 2012; Wang et al., 2021).

There is a lack of understanding of the impact of greater BMI values in bronchiectasis, and whether there is alignment with the obesity paradox which has been shown in COPD (Yao et al., 2023). In COPD, an increase in BMI, beyond normal range, is associated with a reduction in the relative risk of death (Guo et al., 2016). The lowest risk was reflected in those with a BMI of 30 kg/m^2. No significant difference was seen in mortality when BMI was greater than 32 kg/m^2, compared with a BMI <21 kg/m^2 (Guo et al., 2016). Whilst nutritional status in patients with bronchiectasis has predominantly been defined through BMI (Pasteur et al., 2010) the measure itself fails to differentiate between fat mass (FM), fat free mass (FFM) and lean tissue mass (LTM). Neither does it determine the role or presence of confounding diagnoses such as sarcopenia observed in other respiratory diseases such as COPD (de Blasio et al., 2018; de Blasio et al., 2016a; Raad et al., 2019).

Detailed body composition measures can offer insight into FM and FFM where BMI alone may mask impairment. It would also provide greater understanding of the potential metabolic influence, providing further insight into the impact of lower BMI on poorer outcomes, mortality risk and development of bronchiectasis (Yang et al., 2021). This is supported by King et al., (2010) who reported depletion in FFM in 14% of their patients with CF. Of those with FFM depletion, 58% were 'missed' through BMI assessment alone. Alvarez et al., (2016), reported an inverse relationship between excess fat mass and lung function and suggested value in additional body composition measures. Detailed body composition could contribute to determining if ratios of FM and FFM and distribution of FM may be further influencing mechanisms associated with metabolic pathways and lung function (Dixon and Peters, 2018; Wehrmeister et al., 2012). The inclusion of body composition assessment also enables differentiation in fat mass within populations e.g. populations from Asia when compared with European populations (Consultation, 2004).

Kwack and colleagues, (2019) found that deposition of fat, viscerally and subcutaneously, was shown to be inversely associated with lung function in men. Subcutaneous fat alone, was inversely associated with lung function in women. This relationship is useful in contextualising the potential role of fat on lung function in respiratory disease and has been considered key in growing children (Engelen et al., 2012). Hormonal and genetic influences of sex on outcomes for those with bronchiectasis, with typically lower muscle mass and higher fat mass in females compared with males, further strengthens the need to consider measuring body composition as a disease characteristic in establishing endotypes (Raghavan and Jain, 2016). This is supported by a reported inverse association with percentage body fat measured by TSF and FEV_1 (r -0.43 $p<0.001$) including lower skeletal muscle mass overall in bronchiectasis (Sami et al., 2021).

These specific measures may contribute to disease severity as seen in other respiratory conditions (Perrot et al., 2020). Lack of specific and consistent measures of body composition may lead to misunderstanding of disease severity. This is a key measure which has been shown to be useful in determining association with lung function and quality of life in other respiratory diseases (Alvarez et al., 2016; Calella et al., 2018).

Further research to assess body composition without reliance solely on BMI contributes to assessments within COPD and CF (King et al., 2010; Mead et al., 2015) and could expand on previous work by Martínez-García et al., (2007) indicating bacterial colonisation, inflammation and exacerbations which are associated with disease progression in bronchiectasis. Further studies and

development of risk stratification is key to determining, mortality, exacerbation, and hospitalisation risk (Chalmers et al., 2014). In turn this can influence the development of a clinical pathway which commences with screening and enables better understanding for early intervention and treatment (José and Loebinger, 2021; Yang et al., 2021). Of note, length of diagnosis was not considered in relation to BMI within the research. Disease progression is an obvious consequence of length of diagnosis; associated with increased exacerbations, treatment, and reducing lung function, all of which can impact on BMI. Length of diagnosis should therefore be considered a potential confounder of BMI and included as a factor in further studies.

2.9.6 Disease severity

Recognition of the diverse aetiologies in bronchiectasis that reflect contradictory molecular pathways but the same disease phenotypically, require greater understanding. Development of specific subgroups, irrespective of aetiology, to improve quality of life and clinical outcomes is recommended (José and Loebinger, 2021). The establishment of endotype subgroups for tailored treatment is purported in asthma were the PRACTALL (PRACtical ALLergy) report which has produced disease characteristics that have led to examples of endotypes for treatment (Lötvall et al., 2011). This work allows for more focused clinical study designs and novel therapies for future care in asthma and has influenced initial considerations in bronchiectasis (José and Loebinger, 2021). Establishing disease severity, utilising severity tools, and its associations with nutritional and body composition measures is warranted

2.9.7 Hand Grip Strength

A reduction in handgrip strength in research populations with bronchiectasis compared with healthy subjects is of note (King et al., 2021; Olveira et al., 2016). Handgrip strength appears to be an independent predictor of severity, irrespective of FFM levels and FFMI. This is also reflected in CF where low levels of HGS are significantly associated with exacerbations and reduced lung function (Contreras-Bolívar et al., 2021) and in COPD where reduced HGS is associated with poorer lung function (Holden et al., 2021; Strandkvist et al., 2016). HGS provides a practical assessment, easily completed within clinical settings and minimally invasive, with development in digital methods enhancing its use (Varadarajan et al., 2024) and is emerging as an important tool in assessment within lung disease (Mgbemena et al., 2022). It is also part of the EWGSOP pathway to identify possible sarcopenia (Bahat et al., 2016). This is

key, as systematic review in lung disease have identified that prevalence of sarcopenia is as high as 63% in nursing home populations with COPD (Benz et al., 2019) and exists within CF populations (Calella et al., 2018).

2.9.8 Nutritional Intake

Whilst only one study examined leucine supplementation in bronchiectasis it provides early insight into potential interventions, that may optimise muscle functionality and mass to improve clinical outcomes. This intervention showed statistically significant change and improvement in FFM and FFMI (Olveria et al., 2016). Elevated proportions of leucine consumption are shown to stimulate protein synthesis (Katsanos et al., 2006) and its use is recognised in COPD to optimise muscle strength and improve anthropometry (Bernardes et al., 2023). Jonker et al., (2014, 2017) explored the role of essential amino acid mixtures, (casein and whey protein meals) in patients with COPD with and without additional leucine. Improvement in both groups was seen in the latter, suggesting leucine stimulates whole body protein anabolism more than protein alone in those with COPD (Jonker et al., 2017). Positive outcomes in muscle attainment following leucine supplementation have been shown in free living older adults (Ispoglou et al., 2016) and supports attainment of nutritional targets for protein (Bauer et al., 2013).

The initial work by Olveira et al., (2016) and evidence in COPD (Bernardes et al., 2023; Jonker et al., 2017), coupled with the observed impaired handgrip strength and BMI that may mask sarcopenia (King et al., 2021; Olveira et al., 2012) advocates for a larger multicentre research trial to explore feasibility of consumption of leucine as a supplement in those with bronchiectasis to determine impact on body composition and clinical outcomes.This review has also shown that research exploring dietary intakes are sparse in bronchiectasis. Only five studies collected dietary intake data and of those only one fully reviewed overall intakes and compared with National Diet and Nutrition Survey (NDNS) data (King et al., 2021). This contrasts with research in CF (Armaghanian et al., 2020; McDonald et al., 2021b) and COPD (Beijers et al., 2023) where nutritional intake, requirements, and specific dietary interventions play a key role in treatment. An established understanding of intakes and changes within and during episodes of infection, exacerbations and impacts on clinical outcomes, in other lung conditions such as Cystic Fibrosis and COPD (Collins et al., 2013; Dodge and Turck, 2006; McDonald et al., 2021b; Schönenberger et al., 2019) is lacking in bronchiectasis. Gathering data on

dietary intake and its potential role in treatment and impact should also be considered in future research trials.

2.9.8.1 Vitamin D

There is growing evidence for the importance of vitamin D in lung diseases such as COPD and Asthma (Bartley et al., 2013). This review demonstrates the emerging role of vitamin D status (Ali et al., 2022; Chalmers et al., 2013; Contreras-Bolívar et al., 2020; Sami et al., 2021) and its association with inflammatory markers and quality of life in bronchiectasis. Whilst these studies did not explore nutritional intake, consideration of low levels of vitamin D and intakes seen in populations worldwide (Cashman, 2020; SACN, 2016), and in these groups with altered metabolic pathways may indicate an increased requirement. In this review, studies reviewing consumption showed, when compared to NDNS data, vitamin D intake was below reference nutrient intakes (King et al., 2021) and that insufficiency exists in more than 70% of the population (Sami et al., 2021). Consideration of low serum levels and intakes seen in populations worldwide (Cashman, 2020; SACN, 2016), and in all ages in bronchiectasis with altered metabolic pathways, that may require increased requirements, is of note and further study to understand influence of supplementation, its continued role in the lung axis and associations with disease severity and exacerbations is needed.

More recently, developments in the role of vitamin D specifically in the lung and in lung diseases have been influenced by research undertaken during the COVID -19 pandemic. A systematic review of evidence emerged, indicating low vitamin D status may be associated with coronavirus disease risk and called for further supplementation studies to consolidate this (Liu et al., 2021). Deficiency in vitamin D is seen in COPD and CF despite supplementation, with its role of role in pulmonary exacerbations emerging (Daley et al., 2019; Zhu et al., 2016). It is further explored in association with sarcopenia in COPD (Chua and Tee, 2020). However, its role is only emerging in bronchiectasis and likely compounded by an older population, challenged with lung function, and increased bone disease (Kyle et al., 2004). This review has also shown that poorer outcomes associated with handgrip strength and vitamin D status and intake is seen in younger and paediatric populations (Ali et al., 2022; King et al., 2021).

This could also contribute to further exploration of the roles of other micronutrients in respiratory conditions and their contribution. Contreras-Bolívar et al., (2019), further expanded into vitamin K requirements, hypothesising

potential deficiency due to its role as a co-factor in bone mineralisation and the impact of repeated antibiotic treatments for infection. In turn these alter the microbiota resulting in reduced K_2 production in the intestine. The authors speculated that greater use of antibiotics could proliferate subclinical vitamin K deficiency, leading to increase in loss of bone mass, overall warranting exploration of nutritional intake and need.

2.9.8.2 Antioxidants

Antioxidants and their role in defence and suppression of oxidative stress is established in bronchiectasis (Martín Giménez et al., 2021). Peckan et al., (2018) explored antioxidant treatment and oxidative stress in a paediatric population reporting that an increase in oxidative stress was associated with decreased antioxidant capacity. It was postulated that antioxidant treatment may reduce severity and frequency of exacerbations. Extension of research into adult populations could afford better understanding of the influence of antioxidants on oxidative stress and inflammation in cohorts with bronchiectasis. Considering repeated infections and lower muscle mass or muscle wasting that may exist (Norman et al., 2011), understanding the interplay in these mechanisms in bronchiectasis is crucial, with consideration particularly in relation to sex differences and disease progression. Men exhibit more severe disease later in life, greater BMI, and a loss of FFM, whilst women have lower BMI and less FFM overall. These characteristics require further investigation (Vidaillac et al., 2018).

2.10 Limitations

The methodological approach chosen of a systematic narrative review was informed by two factors: the limited evidence available in 2017 and the lack of guidance for alternative approaches to the assimilation of literature at that time. PRISMA guidance regarding the role of a ‘scoping review’ (Tricco et al., 2018) was subsequently published in 2018 (PRISMA ScR) and added an alternative approach to appraisal of the literature. A systematic review follows a highly structured and defined process intended to minimise bias and evaluate specific outcomes that can subsequently underpin clinical guidelines. In contrast, a ‘scoping review’ aims to appraise all available evidence using distinct inclusion criteria in order to identify knowledge gaps in emerging fields. It has been considered a precursor to a systematic review (Munn et al., 2018) and seeks to clarify the current state of evidence. A scoping review therefore provides a framework for including all literature within an emerging topic area; a

methodology which given the disparate evidence available, would have better underpinned the current review

Further factors also contributed to the choice of review methodology. Encompassing 8 years of study, the length of the PhD informed two separate phases to the literature review. In the first review phase (articles published between 2000-2018), knowledge gaps were identified that informed Chapter 4. Undertaking a second review phase (articles published between 2019-2024) ensured the completeness of research data within the thesis. This necessitated a uniform approach between both phases, which was achieved by adhering to the original available methodology of Phase 1. It is acknowledged however, that by utilising this approach it limited the scope of the results and discussion.

2.11 Conclusion

There is insufficient evidence to support, better understanding of the appropriate classification of this population, their characteristics, and therapeutic needs beyond those understood through British Thoracic Society guidelines (Hill et al., 2019). This review has identified that emerging assessments in body composition, such as HGS as a measure of strength and a tool in identifying sarcopenia, are needed to complement the existing generic BMI assessment. The research to better understand any specific nutritional need and or body composition associations with inflammation, disease severity and quality of life in bronchiectasis is still lacking. Whilst similarities in characteristics can be drawn (age, BMI, affected sex), repeated research is needed to establish data that secures solid common themes to inform practice.

Lack of evidence to date has meant that classification of aetiological subgroups of bronchiectasis, remains important, until other considered markers like albumin, CRP and inflammation can be used to establish metabolic endotypes. Specific nutritional intakes and deficiencies such as protein, specifically leucine supplementation, vitamin D, and other micronutrients, their role in disease progression requires continued exploration.

As a result of the first phase of this review, (initial research papers) a study to establish the characteristics of a regional clinic of bronchiectasis patients was undertaken. These incorporated aspects discussed within this chapter as a contribution to the evidence base and was included in the second phase of this review. This published research is reported and discussed in detail in chapter 4.

Chapter 3
Methodologies

The Leeds Bronchiectasis service was established in 1998 with the aim to provide secondary and tertiary care for people with bronchiectasis within the Leeds locality and West Yorkshire region. The cohort studied in chapters 4,5,6 and 7 were recruited through access to participants attending the regional Bronchiectasis and Primary Ciliary Dyskinesia clinics which formed part of this service.

Within the thesis there are shared methodologies that have been employed across investigations. This chapter will outline and critique the contribution that each of these designs has added to the rigour of the thesis. The rationale for data collection techniques, ethical process and research governance has also been defined, including modifications that were required during COVID-19.

Observational study design underpins the early phases of the thesis (Chapters 4-6), whilst the final study (chapter 7) utilises a feasibility study design. The strengthening of reporting of observational studies in epidemiology (STROBE) guidance was followed (Vandenbroucke et al., 2007). Whilst these guidelines do not offer a methodological framework, they do provide 22 clear parameters for reporting of observational studies, and aim to enhance clarity of the planning, data collection and reporting process (Cuschieri, 2019; Da Costa et al., 2011)

3.1 Research methodologies

3.1.1 Prospective Cross-sectional methodology

Within chapter 4 and 5 a prospective cross-sectional design was employed to establish a baseline understanding of a local population with bronchiectasis. Cross sectional study is defined by its observational approach in the absence of an intervention. There are accepted strengths and limitations of the design, but it was utilised in the early phases of the thesis for three reasons: an ability to characterise the cohort as a whole at a single point in time, to examine subsets of the population, and to establish prevalence of comorbidity and nutrient sufficiency or deficiency. Through examining a wide range of characteristics, it provided a holistic overview of participants and their burden of disease. It also enabled multiple testing of a number of potential associations simultaneously.

It is recognised that in using a cross-sectional design there is no ability to determine causality or define sequential links between exposure and outcomes (Mann, 2003; Wang and Cheng, 2020). This can be mitigated to a small extent,

by the ability of cross-sectional study design to follow a descriptive or analytical approach (Kesmodel, 2018; Wang and Cheng, 2020). An analytical design in which regression analysis is used to establish associations between variables, therefore enables inferences (but not causality) to be revealed. This approach was used in chapter 4 and subsequently formed the basis for testing specific hypotheses in a subset of the population with Primary Ciliary Dyskinesia (PCD) in chapter 7.

The principles of good cross-sectional study design rest on the avoidance of bias. Although many causes of bias exist, two of the most crucial are considered to be selection bias and information bias (Tripepi et al., 2010; Wang and Cheng, 2020). Both are judged to affect the internal validity of studies, through the introduction of systematic error. This can be due to selected participants not fully representing their population or when measures collected are inaccurate due to diagnostic, measurement or data misclassification errors. These elements of bias were mitigated in two ways and are discussed later in this chapter; firstly, through maximising participation (65% of the population were recruited) and secondly through prospective collection of data (chapter 4 and 5). The extraction of data from an electronic patient record (EPR) that had been collected in ‘real time’ reduced bias further by ensuring the greatest rigour with actual data collected. Compounded by limited control over missing data when collected retrospectively (chapter 6) repeated measures provide lived outcomes in real time.

3.1.2 Retrospective longitudinal design

The utilisation of EPR data was also employed in Chapter 6, where longitudinal measures of handgrip strength (HGS) was reported on, retrospectively, within a calendar year.

Within chapter 4 it had been established that all aetiological groups observed, failed to achieve normative values (>85%) for handgrip strength, a measure of functionality described further in this chapter, but was significant in those with Primary Ciliary dyskinesia (96%). Following causation inference results, and subsequent publication, the use of HGS measures were then introduced within the Bronchiectasis and PCD regional clinics as a standard measure of care. This enabled effective monitoring of this outcome over time to establish any identified nutritional and physical interventions required.

Two models of study design were incorporated; firstly, a longitudinal design, where HGS was monitored over time for all participants; secondly a service

evaluation, also termed clinical effectiveness study or baseline audit (Bowie et al., 2007), that evaluates the effectiveness or efficiency of an evidenced base practice either existing or newly introduced (Brain et al., 2011) to inform local decision making. Comparison of HGS measures against a standard HGS reference, adjusted for age and sex (Bohannon et al., 2006), enables consideration of changes which can give rise to inference of associations with commonly collected standards of care. This provides evidence to support continuation of this newly introduced practice (Bowie et al., 2012; Twycross and Shorten, 2014). As HGS measures are taken at clinic appointments, which can be annual or more frequent depending on clinical need, values are also able to be observed over time. Each individual, in addition to usual measures undertaken within clinic appointments had a HGS measure, conducted in accordance with standard operating procedures, (SOP) (Appendix D.1) taken and reported.

Retrospective analysis is limited by assumptions that, except for the variable under study, participants are assumed the same, missing data leads to an incomplete picture, and influences of variables not captured are lost from analysis (Talari and Goyal, 2020). The longitudinal design intended to establish frequency of contact and potential changes over time, compared with concurrent clinical measures of disease progression such as lung function. This analysis and exploration of secondary data required a retrospective approach, due to the impact of access to clinic during the COVID–19 pandemic. This resulted in observed measures taken in real time, without the author present. This approach enables reduction in bias over data outcomes that may be influenced by the need to find results.

Complementing this approach, the use of baseline audit was intended to provide a reference HGS measure for participants, against which the impact of future interventions could be assessed. The standard considered here are HGS measures that identify impairment or insufficiency and explore associated impact on observed routine care parameters. This methodology can offer meaningful data that informs improvement or change in a service (Moule et al., 2016) but can be hindered by poor aims with the objectives ascertaining if the measure provided adequate data that informed best practice to improve patient care. Whilst there is still continued debate over its use as a tool for improvement (Antonacci et al., 2023), its ability to be nationalised to substantiate service approaches, validates its usefulness in improvement of quality and care. It is limited by its perceived reputation of not ensuring high quality care (Antonacci et al., 2023), with much of the debate around use of measures outside specific research avenues, poor feedback mechanisms, and variability in effectiveness

(Wright-Hughes et al., 2022). In addition, interpretation of results and diminished ownership or key identification of next steps can all influence its potential to inform future care (Johnston et al., 2000). This can be mitigated by establishing agreed hypothesis to advance audit and feedback intervention research (Colquhoun et al., 2021) and ensuring engagement in outcomes that influence future services in a beneficial way. As HGS was newly introduced in this clinic the use of audit can be beneficial in establishing practice and contributing towards registry data that can inform trends and overall outcomes nationally and internationally. This study was impacted by the COVID -19 pandemic, with no direct access to clinics and measures such as HGS, not being completed this resulted in the retrospective approach as opposed to the originally proposed prospective methodology. A prospective approach would not have been achievable in the time frame outlined for PhD study.

3.1.3 Feasibility studies

Chapter 7 discusses the outcome of a feasibility study exploring acceptability and palatability of a gel supplement containing 40% leucine and 10µg of vitamin D within a subset of the population with PCD who had been identified as nutritionally compromised.

This study was also impacted by the COVID-19 pandemic resulting in the original Randomised Control Trial (RCT) protocol adjusted to a feasibility study. Two factors influenced this decision: firstly, the time lost associated with the pandemic (stopping of clinics) and reduction in numbers of service users returning to face-to-face clinics, rendered the RCT not achievable within the time frame; secondly the supplement used had a specified shelf life that was exceeded due to COVID-19 imposed delays.

Feasibility studies are defined as preliminary investigations that determine feasibility, safety or acceptability of an intervention (Arnold et al., 2009) undertaken to test the threshold for use of a drug or in this case nutritional supplement and are commonly used in cancer therapies. Feasibility studies exist within respiratory disease, (Cheung et al., 2010; Engel et al., 2016; Santana et al., 2013; Vermeeren et al., 2004) but are termed pilot studies. This approach enabled exploration of use of the supplement in terms of palatability and acceptability/adherence and effect on dietary intake. This resulted in utilising a smaller participant group with reduced timeframe, to determine if a larger RCT should be conducted. It also enabled the focus of appropriate outcome measures following results. With the primary outcome as acceptability to inform the gels continued use, this supports the feasibility approach.

Concordant lower recruited numbers mean they are also unpowered and should not test hypothesis but may provide clinically important variables to be considered as part of future trials (Eldridge et al., 2016a). They also offer underpowered estimates of effect, on clinically relevant outcomes (Arnold et al., 2009). It is essential to recognise they are limited by the small numbers of likely, motivated participants, which could lead to misrepresentative results (Arnold et al., 2009; Teresi et al., 2022) but are effective if guidelines are followed (Lancaster and Thabane, 2019) and reporting is in accordance with Consolidated Standards of Reporting Trials (CONSORT) extension (Eldridge et al., 2016a). There is still debate over the terms feasibility and pilot study, and their mutual exclusivity. Statements exist to identify the differences and utilisation of the correct terminology is advocated (Eldridge et al., 2016b). Feasibility studies, like the one conducted in chapter 7, look to develop trial interventions and consider which outcomes are appropriate, with pilot studies replicating on a smaller scale, a full RCT (Abbott, 2014). As the work in chapter 7 was to determine if the gel was acceptable to the PCD cohort a feasibility study was the most appropriate method.

3.2 Respiratory outpatient methods

The following describe the methods undertaken when participants attend respiratory outpatient clinic as part of their usual care and were utilised throughout research reported in chapters, 4, 5, 6 and 7. Routine measures are collected for all individuals unless contraindicated at point of exam.

3.2.1 Pulmonary function tests

Pulmonary function tests measure lung function through standardised test quality definitions (Miller et al., 2005) to ensure consistency in results. Any results of tests are classified against reference population data (Stanojevic et al., 2022) and interpreted in conjunction with therapeutic intervention, diagnosis, and prognosis (Miller et al., 2005). Results are affected by patient effort and are used with other relevant clinical data (as described below).

Lung function is measured at each clinical appointment if the patient is well enough to perform the measure, this is fundamentally a measure of volume against time. Assessed by means of standard spirometry using a Vitalograph Compact II Spirometer (Vitalograph Ltd, UK).

Normal techniques include:

- Sitting upright or standing.
- Instructed to take a big breath in and then breathe out as hard and fast as possible into the spirometer that is connected to a computer.
- Usually repeated until 3 acceptable and repeatable measures have been obtained.
- Input of height, weight, age, gender and ethnicity into spirometer

Measures Forced Expiratory Volume in 1 second (FEV_1) is the maximum amount of air that can be forcefully expelled during one second following maximum inhalation (David and Edwards, 2022), Forced Vital Capacity (FVC) as well as FVC/FEV_1 ratio, also known as FEV_1 percent predicted, are produced using established standards (Hankinson et al., 1999) and interpreted by clinicians allowing determination of obstructive or restrictive defects e.g. COPD, Asthma and interstitial lung diseases respectively. FEV_1 can be used in quantifying severity (Ranu et al., 2011) and contributing to measurable picture of lung capacity. Values can be considered alongside previous measures, and over time, to reflect lung improvement/deterioration (Stanojevic et al., 2022).

3.2.1.1 Additional PPE measures during COVID-19 pandemic

Following the COVID-19 pandemic additional measures were undertaken by physiotherapists who predominantly take the measure within the clinic setting. Full PPE was used (FFP3 mask) with fit testing, gloves and surgical gown, disposed of following completion of assessment following the providers health and safety guidance in COVID-19 pandemic.

3.2.2 Clinical assessment

A clinical assessment is conducted by the consultant at each outpatient appointment with the following parameters measured. Minimal recommendation of contact is annual surveillance (Hill et al., 2019) with increased contact according to clinical need defined by the clinician at assessments.

3.2.2.1 Pulmonary Exacerbations

Pulmonary exacerbations are recorded by the clinical team during their appointment. The definition for bronchiectasis exacerbations is

"a person with bronchiectasis with a deterioration in three or more of the following key symptoms for at least 48 h: cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; haemoptysis AND a clinician determines that a change in bronchiectasis treatment is required" (Hill et al., 2017).

Individuals who attend the regional bronchiectasis clinic are treated using the health pathway, Bronchiectasis- Acute exacerbation clinical guideline (NG117), (NICE, 2018). This pathway provides a consistent evidenced based, and structured approach to antibiotic therapy for individuals with bronchiectasis in order to assuage symptoms and improve outcomes.

3.2.2.2 Breathlessness

MRC (Medical Research Council) score is reported with patients asked to rate their level of breathlessness against a scale attributed to a described activity (Table 5).

Based on epidemiological studies and originally published in 1960, its responsibility lies with The Committee on Environmental and Occupational Health (CEOH) and the most recent version (1986) is what remains in use today.

Table 5. MRC degree of breathlessness scale (used with permission of the Medical Research Council)

Grade	Degree of breathlessness related to activity
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on a level or when walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking 100 yards, or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing/undressing

3.2.2.3 Sputum purulence and volume

Sputum samples are collected to assess volume and change in purulence and enable testing for infective bacteria (culture), in order to offer targeted antibiotic therapy. Individuals are required to take deep breaths and long huffs, followed by a cough, with clearing of the throat to spit into the pot provided. This is usually completed with the physiotherapist or nurse. Antibiotic therapy should not be commenced until culture has been identified.

3.2.2.4 Physiotherapy

The role of physiotherapy in bronchiectasis is a cornerstone of treatment. It comprises Airway Clearance Techniques (ACT) and pulmonary rehabilitation (PR). ACT's have been shown to reduce exacerbations improve sputum volume production and quality of life (Spinou and Chalmers, 2019). British Thoracic society guidelines state oscillating positive expiratory pressure (OPEP) and other airway breathing techniques should be used in support of patients to assist in effective airway clearance (Hill et al., 2017). All techniques are used within the clinic setting and are chosen based on service user need at time of contact.

3.2.2.5 Height, Weight and BMI

The British Thoracic society recommends the recording of BMI (weight/height ratio, (weight/height^2)) to indicate nutritional status (Hill et al., 2019). Commonly, weight (wt.) and height (ht.) are collected and used to calculate Body Mass Index (BMI). BMI is also collected as part of the EMBARC registry (The European Bronchiectasis Registry) (Chalmers et al., 2016) to enable trend analysis. BMI has been utilised extensively in other respiratory diseases. In COPD BMI's of less than 25 kg/m^2 result in poorer outcomes and an increase overall risk in mortality (Collins et al., 2013), echoed in cystic fibrosis with greater BMI reflecting improvement in lung function (Nagy et al., 2022; Stephenson et al., 2013). BMI is also limited by its inability to differentiate body composition.

Standard operating procedures (SOP) are used to reduce assessor bias and maintain consistency and have been utilised in all studies reported in chapter 4, 5, 6 and 7 (Appendix D).

3.3 Additional study methods

Additional study methods employed within each of the research studies undertaken in chapters 4, 5, 6 and 7 are outlined below. These methods are positioned outside of the usual care process, but employed within aspects of research undertaken in chapters 4, 5, and 7. An exception to this is hand grip strength (HGS), which was not a standard of care assessment at the commencement of the research, but was introduced as a standard care measure, following the outcomes discussed in chapter 4 and evaluated in chapter 6 .

3.3.1 Anthropometry

Understanding body composition (BC) in respiratory disease and bronchiectasis specifically, beyond BMI, is becoming progressively explored to ascertain influence of nutritional status on clinical outcomes and quality of life within lung disease (Peterson et al., 2020). Masking of FFM loss with normal BMI is reported in Chronic Obstructive Pulmonary Disease (Wouters, 2021) with associations of body composition parameters significantly affecting pulmonary function in people living with COPD (Martínez-Luna et al., 2022). Vermeeren et al., (2006) found 15% of 389 patients with moderate to severe COPD, having normal BMI but low, Fat Free Mass index (FFMI) (muscle mass relative to height).

The measurement of BC via anthropometry is one of 6 components that provide affective assessment within the Model and Process for Nutrition and Dietetic Practice (Anthropometric, Biochemical, Clinical, Dietary, Environmental, Functional), (British Dietetic Association, 2020).

Its use requires further examination within bronchiectasis, to understand better the role of fat mass and fat free mass within quality and clinical outcomes. It should be used conjunctionally with BMI, to determine if masking exists in this population. Definition of sarcopenia utilising limb lean mass, muscle strength and functionality will aid in understanding the role of body composition better (Trajanoska et al., 2018), reported in a systematic review and meta-analysis exploring sarcopenia and COPD with prevalence of 21.6% across varying population settings (Benz et al., 2019; Martínez-Luna et al., 2022).

3.3.1.1 Hand Grip Strength

Handgrip dynamometry (HGS), a measure of muscle strength and body function (Bohannon, 2019), also proved as an emerging practical and economic measure to use and an indicator of poor health and outcomes in healthy populations in a recent systematic review (Mgbemena et al., 2022). It has been repeatedly shown to be associated with all-cause mortality in some chronic diseases (Leong et al., 2015), is reflective of nutritional status, responding earlier to nutritional deficiency or repletion compared to parameters such as BMI (Norman et al., 2011) and is a simple, standalone method to identify muscle weakness and poor health status (Bohannon, 2019). Explored in COPD (Burtin et al., 2016) reporting 24% of 998 patients had weakness in HGS at baseline, with 41% of those that died during the study period had a weakened handgrip (<10th centile), in contrast to 21% with weakened handgrip of survivors. This suggests HGS is a valuable measure in assessing mortality risk. In a systematic review and meta-analysis of HGS and COPD by Holden et al., (2021), moderate associations were reported with lower HGS and health related quality of life, morbidity and likelihood of death, despite heterogeneous practice in measurement of HGS. This highlights associations with COPD as a predictor of outcomes, with similar findings beginning to emerge in bronchiectasis and other respiratory diseases. The collective evidence from chapter 2 and the published evidence in chapter 4 advocate for its use in bronchiectasis.

Peripheral muscle strength was evaluated by Hand Grip Strength (HGS), in Chapters 4, 5, 6 and 7. A Takei 5401 Handgrip dynamometer (Takei Scientific Instruments Co., Ltd, Tokyo, Japan) was used. Although there are a variety of dynamometers (Jamar, MyoGrip), the digital Takei has been validated and is reliable to assess handgrip strength (Savas et al., 2023; Trajković et al., 2024). Its reliability requires a consistent use of a SOP, and that the dynamometer is calibrated in accordance with manufacturer guidance.

All participants were assessed in standing position, arm by their side with full elbow extension. Measurements were repeated 3 times for the non-dominant side. Values were expressed as a mean of all three measures. Measures were then compared to consolidated grip strength values adjusted for age and sex with values less than 85% of standard mean considered as impaired muscle function (Bohannon et al., 2006).

A SOP was utilised in studies reported in chapters 4, 5, 6 and 7 and can be found in Appendix D in full.

3.3.1.2 Triceps skinfold thickness and Mid upper arm Circumference

Triceps skinfold thickness (TSF) [a measurement of the upper arm and an assumed indicator of fat mass that reflects a component of total fat mass] was measured in studies found in Chapters, 4, 5, and 7 using Harpenden skinfold Callipers (Baty International, Burgess Hill, West Sussex, UK).

For each participant, the midpoint was determined from the acromion to the olecranon process and a skinfold measure was taken at the midpoint, with a mean determined from three repeated measures. Mid Upper Arm Circumference (MUAC) [used to determine the mid arm muscle circumference (MAMC) an assumed indicator of fat free mass FFM] was recorded at this midpoint using a tape measure. Mid arm muscle circumference (MAMC), an established measure of muscle protein mass, was calculated from MAC and TSF using a standard formula: MAMC = MAC - (3.1415 × TSF). The assessment was completed by the same observer with level 1 International Society of the Advancement of Kinanthropometry (ISAK) accreditation which assesses individual's competency of skinfold measures against international standards and reduces intra observer bias.

Skinfold calliper measures, allow estimations of body composition parameters for comparison to standardised norms (Madden and Smith, 2014). As a less invasive approach, offering significant practical benefits in clinical settings, the measure quantifies fat mass and fat free mass to enable identification of component nutritional status and any associated nutritional risk in a minimally invasive way. TSF has been shown to improve the prognostic value of the Global Leadership Initiative on Malnutrition (GLIM) criteria for assessing malnutrition in lung cancer (Yin et al., 2022) offering a further prognostic parameter to contribute to overall detection of increased risk. Employed accurately, they can provide a useful measure to characterise the baseline of a population and changes over time (Frisancho,1981). Results can be affected by limitations such as obesity and overestimation of fat when compared with other methods of determining fat mass in bronchiectasis (Dona et al., 2018,), and other respiratory diseases (King et al., 2005). Increasing dependability can be achieved by consistency of assessor, training and reported Technical Error of Measurement (TEM), which reinforces the reliability of the results. (Ulijaszek and Kerr, 1999). The use of this methodology is justified as an indicator of understanding body composition when considering chronic respiratory diseases, where access to Bio electrical Impedance (BIA) and Dual X-ray Absorptiometry (DXA) may be restricted.

A SOP was utilised in studies from chapter 4 and 7 and can be found in Appendix D.4.

3.3.2 Dietary assessment methods

A 24-hour dietary recall (using a multiple pass technique) was undertaken by a HCPC registered dietitian for each participant within studies undertaken in chapter 4, 5 and 7 (Appendix E). Within chapter 4 and 5 this was completed at 3 time points (baseline recruitment and each subsequent week for 2 weeks, until a total of 3 were retrieved) within chapter 7 the approach was also used but with 4, 24-hour dietary recalls, at specific timepoints (baseline, month one, month two and month three). Dietary recall interviews were undertaken face to face at the clinic appointment and then by telephone interview.

Dietary surveillance is an essential component of assessing nutritional status, which has been defined as

> "The health condition of an individual as influenced by his intake and utilisation of nutrients, determined from the correlation of information obtained from physical, biochemical, clinical and dietary studies." (Anon, 1973)

Many methodologies exist, (food diaries, food frequency questionnaires and 24 hour recalls) in determining nutritional intake in participants and populations (Thompson and Subar, 2013). Food frequency questionnaires allow for identification of specific nutrients and are used successfully in epidemiological study (Bingham et al., 2001). Twenty-four-hour recalls are quick and easy to complete and have been shown to be as effective as weighed food intakes at collecting accurate data on macro and micronutrient intake (Bingham et al.,1994).

The multiple pass 24-hour recall (taken on two or more occasions) aims to refine this technique still further by undertaking structured, multiple rounds of questioning, designed to extract the maximum detail from the recall, including portion size and cooking methods. It has been shown to be effective in dietary assessment (Adamson et al., 2009). In a systematic review (Burrows et al., 2019) it was also reported that 24-hour recalls were associated with a lower degree of misreporting when compared with other dietary assessment techniques. The approach has also been recommended as standard by the international dietary data expansion project (Coates et al., 2018) which has promoted it as an effective way to provide quantitative data on food and nutrient intakes at an individual level. It has also been shown to offer higher degrees of accuracy than food frequency questionnaires (Gibson et al., 2017). In addition, when validated against doubly labelled water, energy intakes were shown to be

accurate at the group level for this measure, when compared to 7- day food records, which underestimated energy intake by 16% (Biltoft-Jensen et al., 2023). Whilst employing a single multiple pass 24-hour recall provides an estimation of mean intake for individuals, the addition of a second daily recall (a feature of Chapter 4, 5 and 7 within the thesis) allows the estimation of 'usual' intake and mitigates against day-to-day variation. However, the technique is not without its limitations.

The advantages of the multiple pass 24-hour record includes the increasing dietary detail obtained from each round of questioning, but also relies on a skilled interviewer in order to minimise measurement error. Such errors can be random errors which reduce precision (including the day-to-day variation already referred to), or systematic in nature. The bias introduced by systematic error reduces accuracy and leads to potential errors in reporting results. In a recent systematic review that examined misestimation of food and drink intake, the misreporting of portion size was noted to be a major contributor to systematic error (Whitton et al., 2022). The potential for participant recall bias, social desirability, defined by a respondent's desire to provide answers they believe are more acceptable, (Thompson et al., 2015; Dao et al., 2019) and reactivity (dietary behavioural change due to an awareness that dietary intake is being measured) are all elements that can enhance bias further. These can ultimately result in under or over-reporting. Use of the Goldberg cut-off formula to identify these respondents has been identified as a means of addressing such bias (Goldberg et al., 1991). This is discussed in detail later in this chapter.

This method can be optimised by using technology to improve accuracy of dietary intake assessment and supported with additional dietary assessment methodology such as food frequency questionnaires. It can offer potential advantages including convenience, accuracy, accessibility and efficient coding (Amoutzopoulos et al., 2018), as well as reducing limitations, among others, of patient burden, recall and social desirability (NIHR, 2020). Whilst trends in data collection to inform large scale research and epidemiological study are employing digital methods, this research did not seek to utilise this approach. The focus of this research was on assessment and intervention in current clinical settings, where digital methods are not employed yet. Lack of funds to support purchase of any tools that utilise technology was also an influencing factor. Dietary measurement toolkits exist (NIHR, 2020). Their strengths lie in accuracy and cost effectiveness, among others but are limited by internet access, non-response bias, cost for use, and reductional modifiability for diverse groups. Due to the nature of the attendance and engagement in the

regional clinic, the methodological approaches of the research, and potential impact on data reporting, this approach was not used.

Inclusion of the dietary assessment methods are essential. Poor nutritional status can result from inadequate or excessive intake of specific nutrients and or energy resulting in or compounding chronic disease (WHO, 2019). To date only five studies have examined dietary intake in contribution to nutritional status in bronchiectasis. Comparatively in other chronic lung disease, contribution from assessment of dietary intake and subsequent nutritional analysis, has led to established nutritional intervention with nutrition support in COPD. Specifically, increase in weight by 2kg, through oral nutritional supplementation, having clear positive impact on outcome measures in COPD (Collins et al., 2012). Assessment of dietary intake in Cystic Fibrosis populations have utilised food diary approaches to assess nutritional intake (Armaghanian et al., 2020; Calvo-Lerma et al., 2017; White et al., 2004; White et al., 2007) providing insight into nutritional status and deficiencies over sequential days and weeks.

3.3.3 Dietary analysis

Food records were analysed by the same dietitian using MyFood 24© (Carter et al., 2015) in the study within chapter 4 and 5 and Nutritics, (Nutritics, 2019) in chapter 7. Both programmes are utilised for assessment and analysis of dietary intake, created by teams of nutritionists, dietitians and software developers. MyFood 24© has been validated against biomarkers, showing equal attenuation with multiple pass recall and improved against food frequency questionnaires (Wark et al., 2018). Nutritics has been used as a dietary analysis tool in studies seeking to validate food frequency questionnaires assessing independent nutrients (Evans et al., 2022; Watkins et al., 2021). Each nutritional analysis programme was used within the chapter specified, due to availability to the researcher at the time of completion.

Limitations of food composition databases include accuracy and completeness of data, with factors such as farming practice, soil quality, geographical location, preparation and cooking methods that may not be fully captured (Hannah et al., 2018). Seasonal and regional variation in the nutrient content of foods, and lack of detail on nutrients like phytochemicals, bioactive compounds and trace elements should also be considered as limitations of dietary analysis tools. Methods for extracting compounds and inputting analytical data may strengthen the data if processes and cost are considered in the analysis (Md Noh et al., 2020). Both databases used here are reported as high functioning in terms of

reliability and comparison against validated biomarkers, but limitations of such systems should be acknowledged (Koch et al., 2021; Cade et al., 2019).

Mean values, recorded from the total number of reported recalls in chapters 4 and 5, were compared to the Estimated Average Requirement (EAR) (energy) and Reference Nutrient Intakes (RNI), (Department of Health, 1991, SACN, 2011). Macronutrient values were also presented as a proportion of total energy intake. Public Health England commissioned the National Diet and Nutrition Survey (NDNS) in 1992. Randomly selected UK households were surveyed using a 4-day food diary of one selected person, with blood and urine sample collected alongside. Trends in food consumption, types and quantities were captured, providing nutritional comparators of intakes of clinical populations to healthy cohorts (Whitton et al., 2011).

Within the respective chapters 4, 5 and 7, nutrients of interest were drawn from analysis and reported where appropriate to reflect where deficiency in intake and patterns may exist.

3.3.3.1 Meal and protein distribution

Meal distribution and protein distribution were also drawn from multiple pass recalls for chapter 4. Application of a dichotomised yes/no for consumption of food at each of the identified meal points as part of the recalls were recorded. This reflects similar approaches to other work that describes timing of meals reflected as meal and snack recurring at 3 episodes throughout the day (Peterson et al., 2023). In this study the use of breakfast, mid-morning, lunch, mid-afternoon, evening meal and supper were used to collect this data. In addition, the distribution of protein in grams was recorded across each of these identified episodes for each individual 24 hr recall (3) to obtain a mean value for each meal episode to compare protein intakes.

3.4 Additional methods

3.4.1 Acceptability and palatability

Palatability assessment was used as a primary outcome in chapter 7 and is one of the key factors in formulation of medicines and in this case supplement tolerability. It is the hedonic reward associated with consumption and there are various scales that can be used. Assessment of palatability research predominantly lies in assessment of medication palatability in paediatric populations and there are no validated tools that are consistently used within research (Squires et al., 2013). Hedonic scales are commonly used, specifically the 9-point scale which partition aspects such as like/dislike enabling

participants to measure the magnitude of the response on the scale (Cardello and Jaeger, 2010). These scales use the unstructured linear scale approach, represented by a line with anchors at the minimum and maximum rating of good and bad. These visual analogue scales provide the participant greater freedom to align their acceptance against a sliding scale, with interpretation consolidated scores to determine over acceptability and palatability of the tested meal or supplement (Flint et al., 2007).

At baseline assessment 168 gels were provided to each participant (2/day for 3 months). Total consumption of gels was measured by counting the used and remaining full sachets against number provided and this was recorded as a percentage. To assess palatability headings in the visual analogue scale (VAS) reflected Visual appeal, Smell, Taste, Aftertaste and Palatability at baseline, month one, month two and month three. The additional use of the hedonic scale A five-point hedonic scale, not nine, was used to reduce time associated with the extended appointment and telephone consultation to improve engagement and to supplement and confirm any findings from the VAS, both methods were used to determine if either were different in how they were reported or completed, these scales can be found in Appendix G.

3.4.2 Dietary requirements

As part of the feasibility study (chapter 7), participants specific energy requirements were calculated using fat free mass measures derived from Bio Impedance Analysis (BIA) assessment at baseline and 3 months (30 x FFM (kg) x PAL) (Todorovic and Marfrici, 2018). This provides an estimated nutritional requirement as a resting metabolic rate. In order to understand the individuals, overall calculated requirements, the level of reported activity, derived from the habitual activity estimation scale (HAES) was used to calculate the Physical Activity Level (PAL) for each participant. Calculating tailored nutritional requirements provides direct comparison to intakes at a point in time and have greater accuracy. They are determined utilising age, sex, weight or body composition, and are personalised if compared with EAR, which are reflective of the whole population. They also allow for the application and calculation of Goldberg cut offs for a population, to determine if energy intake reporting is considered habitual or not. Whist they do provide a specific target, they are subject to poor validity overall (Reeves and Capra, 2003) and should be used in conjunction with clinical judgement. There is no existing evidence to recommend specific protein requirements in this population, therefore protein requirements were calculated using two methods for comparison, the first

utilising FFM values as reflected in the calculation of energy requirements, FFM x 1.5g/d (Dekker et al., 2022), and the second using ESPEN guidelines 1.5g/kg/day (Duetz et al., 2014). Comparison of mean dietary intake of energy and protein at baseline to three months, with and without supplementation was compared to calculated requirements. Utilising these two methods, enabled a range of protein requirement to be determined, with the assumption that the actual requirement lies within these parameters, with one accounting for specific body composition and the other overall weight and with a view to considering clinical need and variation at differing life stages (Volpi et al., 2013; Morris et al., 2020). Within Chapter 4 all participants Basal Metabolic Rate (BMR) was calculated using Schofield equations. This was a requirement to apply Goldberg cut offs (Goldberg and Black., 1998). Whilst there are limitations to this method of estimating metabolic rate such as over and under estimation at the extremes (Mifflin et al., 1990; Daly et al., 1985;) this was a requirement of the formula to consider those that may be reporting non habitual intakes.

3.4.3 Vitamin D assessment

Assessment of vitamin D status in clinical settings is through the measurement of 25-hydroxy vitamin D in the blood, using radioimmunoassay, considered to be the most representative marker presently with recognition of within assay variability (Binkley et al., 2014). Whilst newer markers of vitamin D status exist such as bioavailable 25-OH (D), free circulating 25-OH (D) and vitamin D metabolite ratio, challenges in consistent interpretation and measurement declare their use impractical in clinical settings (Herrmann et al., 2016). There is work to determine and standardise measurement of vitamin D and consider the most appropriate measure, based on bioavailability, considered in research and clinic settings (Binkley et al., 2014; Carter, 2011; Holick, 2009).

The assessment of vitamin D in the primary ciliary dyskinesia clinics include an annual measurement. Frequency is increased if deficiency is identified and intervention needed. As part of the feasibility study discussed in chapter 7, 25-OHD samples were taken from participants at baseline and 3 months (end of study). A 4ml serum (gold capped) vacuette was used and sent to pathology for assessment. Levels were recorded on the participants pathology reports, extracted and entered into an excel spreadsheet as part of data collection.

3.4.4 Bioelectrical Impedance analysis (BIA)

BIA is used to assess body composition. The human body is considered an electrical conductor in an alternating current circuit, and its resistance to the current (impedance) is measured (seca, n.d.). The seca medical Body Compositions analyser 515/514 with a four-point method via a pair of hand electrodes and one pair of foot electrodes was used. BIA uses specific validated equations to measure impedance, providing results across many parameters (Fat Mass (FM), Fat Free Mass (FFM), BMI, and others). This particular machine has been validated for use in populations with specific predictive equations, that reflect accuracy of prediction of body composition parameters when compared with established gold standard methodology (Air Displacement Plethysmography and Dual-Energy X-ray Absorptiometry) (Bosy-Westphal et al., 2013)

It is considered safe, minimally invasive and cost effective, when compared with other assessments which measure body composition, such as computerised tomography (CT), magnetic resonance imaging (MRI), Air Displacement Plethysmography (ADP) and Dual-Energy x-ray absorptiometry (DXA). It can be simple and more cost effective with a comparative standard error of measure of 9% when compared to MRI (Janssen et al., 2000). BIA techniques have been used within respiratory disease research (Pison et al., 2011). In chronic respiratory failure (Dona et al., 2018), in bronchiectasis (King et al., 2005) and in Cystic Fibrosis (Calella et al., 2019). Comparison of assessment methods have recommended the use of DXA as the preferred technique when comparing with skinfold assessment and BIA as these tend to overestimate fat free mass (Dona et al., 2018). The use of DXA was the originally planned methodology for the work undertaken in chapter 7, however, availability of DXA, along with the subsequent impact of COVID-19 pandemic resulted in retracted access to the scanner. As a result, skinfold (as described earlier) calliper anthropometry and BIA were employed to explore feasibility and practicality in a clinical setting, with limitations of their use considered. Comparison of body composition assessment methods have seen consistency with BIA and DXA (Achamrah et al., 2018; Day et al., 2018) and interchangeability at population level with FM and FFM estimations (de Castro et al., 2018) reflected in other explorations of differing BIA devices (Lahav et al., 2021).

BIA was performed at baseline and 3 months. A Pre assessment guide and Standard Operating Procedure (SOP) was created for use in the Primary Ciliary Dyskinesia clinic as part of clinical research undertaken in chapter 7 (Appendix C.5).

3.4.5 6-minute walk test (6MWT)

The 6MWT is used extensively in research and is identified as a tool for determining change following interventions in patients with lung diseases (Enright, 2003). It is recommended as part of routine care by the British Thoracic Society (Hill et al., 2019). It can be used as measure of functional status and a predictor of morbidity and mortality in lung disease (Caminati et al., 2009; Lederer et al., 2006). This simple method has been validated in patients with end stage lung disease, during the COVID-19 pandemic (Just et al., 2021) and has demonstrated its repeatability in bronchiectasis (Rovedder et al., 2020) and use in children with Primary Ciliary Dyskinesia (Firat et al., 2022). In a systematic review, assessing the measurement properties in chronic respiratory disease the 6MWT was reported as a reliable, valid measure for exercise capacity (Singh et al., 2014).

Utilised as part of research undertaken and discussed in chapter 7, a pre-assessment guide and SOP was created for use in the Primary Ciliary Dyskinesia clinic (Appendix C.6).
The BORG scale is a measure of perceived exertion using a tabled scale (Table 6 (Borg, 1998) and is utilised standard in the 6MWT

Table 6. BORG scale

Rating	Perceived Exertion
6	No Exertion
7	Extremely light
8	
9	Very Light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very Hard
18	
19	Extremely Hard
20	Maximal Exertion

3.4.6 Quality of life measure and habitual activity scale

3.4.6.1 Quality of life (QoL) measures

Quality of life tools were utilised in the research undertaken in chapter 7, and are validated measures of quality of life, demonstrating indicators and outcomes associated with respiratory disease. The disease specific St George's respiratory questionnaire (SGRQ) (Jones et al., 1991) is a set of questions pertaining directly to respiratory disease generally. This enables comparisons to other respiratory diseases, as well as assessing changes over the study period. The SF-36 outcomes measure (Ware et al., 1993; Ware, 2000) is generic and can be used to compare PCD to many other clinical diseases based on their comparative quality of life scores. The PCD (QoL- PCD) is a validated tool for use specifically within a PCD population and has been shown to have strong associations with SGRQ (Behan et al., 2017a). This QoL measure, specifically for PCD was not used as outputs from the feasibility study were to be considered for use in future randomised control trials (RCT) that enable comparisons to other respiratory diseases and therefor SGRQ was more appropriate. This was completed at baseline and three months by participants recruited in chapter 7.

3.4.6.2 Habitual activity scales

The Habitual Activity Estimation Scale (HAES) is a questionnaire to determine baseline activity levels and assess perceived changes in activity. This can be used to measure activity throughout the course of a clinical condition or specific treatment or intervention and was developed to establish the activity of paediatric populations with lymphoblastic leukaemia (Hay and Cairney, 2006). HAES has been validated against other measures of activity for use in a Canadian cystic fibrosis population, showing ICC (measure of interrater reliability) comparison from week 1 to week 2 as = 0.72 ($p<0.0001$) for HAES, = 0.76 ($p<0.0001$) for 3 day activity diary and = 0.63 ($p<0.0001$) for accelerometer, showing good reliability and moderate reliability respectively (Wells et al., 2008). Findings are limited by low numbers of participants and have been contradicted in adults with CF, with HAES overestimating the effect of physical activity (Savi et al., 2013). HAES has also been used in children with PCD, assessing skeletal muscle metabolism, to effectively capture activity and quantify completion of physical activity programmes, (Wells et al., 2011). Accelerometers could have been used as part of the feasibility study, but were not for two reasons: firstly due to this being undertaken during reopening in the COVID-19 pandemic, with additional practices undertaken to reduce spread of

infection, it was concluded that tools which could be completed at clinic appointments, would ensure consistency at the point of completion: secondly additional associated costs of accelerometers. The HAES questionnaires were all completed at baseline and three months by the participants. The questionnaire requires the participant to recall all activity for one typical weekday and one typical weekend day considering the percentage of time spent in each of the different activity levels (Figure 6), using meal consumption as section breaks. The full questionnaire can be found in Appendix H.

Figure 6 HAES activity descriptors

ACTIVITY LEVEL DESCRIPTIONS

These descriptions give you examples of activities that are typical of each activity level. You should refer back to these descriptions as often as you need when completing your estimates.

a) inactive – *lying down*, sleeping, resting, napping

b) somewhat inactive – *sitting*, reading, watching television, playing video games, time in front of the computer, playing games or activities which are mostly done sitting down

c) somewhat active – *walking*, shopping, light household chores

d) very active – *running*, jumping, skipping, bicycling, skating, swimming, games that require lots of movement and make you breathe/sweat hard

3.5 Statistical methods

Data was analysed using IBM SPSS statistics version 24 (chapter 4 and 5) version 28 (chapter 7) and version 29 (Chapter 6 and 7) (IBM Corp, Armonk, N.Y. USA) due to the duration of the thesis and the impact of COVID -19. Statistical analysis of all study outputs was recorded as follows.

Data was checked for normality using Shapiro Wilks. Normally distributed data were presented as means and standard deviations, with other reported as median and interquartile ranges (IQR). Were data variables differed in distribution standard median and IQR were used for reporting outcomes. Pearson's (r) and Spearman's (rho) correlations were used to explore associations between variables. Kruskall-Wallis was used to determine differences between the medians of values and Fishers-Freeman-Halton exact for comparison of differences between categorical variables, with the Dunn test applied if determination of differences and groups required identification. Linear

regression was used to understand predictors of lung function in data from chapter 4. Wilcoxon rank was used to determine differences between dependent variables in chapter 7 and repeat measures in chapter 6. Mann-Whitney U was applied for comparison between bronchiectasis and PCD groups in chapter 6 and groups that consumed >50% and ≤ 50% of supplement in chapter 7. Statistical results were deemed significant at <0.05. All data was stored on password protected University of Leeds One drive.

3.6 Ethical Approval

Health Research authority (HRA) and Health and Care Research Wales (HCRW) approval process for research projects in England and Wales was used in chapters 4, 5 and 7, alongside ethics approval of University of Leeds, Medicine and Health, Graduate School, Ethics committee in Chapter 6.

The study undertaken in Chapter 4 and 5 was approved by Health Research authority, South Central Hampshire B (IRAS 216351) via, proportionate review on 19th April 2017 utilising the integrated research application online system (IRAS), (Appendix H.1). Research undertaken and reported in Chapter 7 was approved on 24th December 2020 by South Central and Hampshire A, Health Research Authority (IRAS 222335) following attendance at the Ethics committee on 10th November 2020. These studies also received ethical approval from the NHS host site research and innovation department (Appendix H.2). All eligible studies were registered on Clinicaltrial.gov (NCT06877091 and NCT06028607)

Chapter 6 was approved by the University of Leeds, Medicine and Health, graduate school ethics committee on the 16th of February 2023, following completion of the Health Research Authority, is my study research form, deeming it not considered generalisable, a Caldicott letter was requested from the information governance team and was provided on 27th October 2022 (Appendix H.3).

3.7 Conclusion

All methodologies reported in this chapter were carried out as described and were or will be referred to in preceding and subsequent chapters respectively.

Recruitment consent: All study participants in Chapter 4, 5 and 7 consented to involvement in studies following receipt of participant information sheets (PIS). Consent forms and PIS can be found in Appendix I. PIS for chapter 4 and 5 can be found in Appendix I.1, consent form for chapter 4 and 5 can be found in

Appendix I.2. PIS for chapter 7 can be found in Appendix I.3 and consent form in Appendix I.4.

Due to the nature of the study in chapter 6, consent for involvement was given as part of overall consent for data collected as part of routine care to be used for investigation purposes, therefore no additional recruitment and consent processes were required.

Chapter 4

Nutritional Status and intake in patients with non-cystic fibrosis bronchiectasis (NCFB) – a cross-sectional study

This chapter will discuss the outcome of the initial characterisation research undertaken following the original review of evidence in 2019 (chapter 2). Some of this work was published in 2021 in the Journal of Clinical Nutrition and aspects of that publication have been reported here verbatim.

4.1 Background/Justification for research

As discussed in chapter 2, body composition and nutritional interventions in populations with bronchiectasis is lacking. Following the review of literature up until 2018 the lack of research (5 studies in total) led to this study into characterisation of the population of a regional bronchiectasis clinic. This aimed to address a research gap; establishing body composition and nutritional intakes in a regional adult UK population and testing emerging associations, between nutritional intake and body composition measures.

Emerging evidence suggests that the measurement and understanding of body composition is important to support effective medical and nutritional management of chronic conditions (Wells and Shirley, 2016) through its impact on reduced lean tissue mass (LTM) and fat mass and its proinflammatory impact in chronic lung disease. Whilst initial case control studies in small populations have identified reductions in peripheral muscle endurance (Ozalp et al., 2012) and fat free mass (Balañá et al., 2016) compared to healthy individuals, an understanding of the relationship between nutritional status, dietary intake and body composition is lacking. Within current guidance for the management of bronchiectasis the need for research into nutritional supplementation has been acknowledged (Hill et al., 2019) but requires further underpinning knowledge of current nutritional status in bronchiectasis.

While studies support the concept that nutrition is important in determining outcomes in bronchiectasis (Despotes et al., 2020; Onen et al., 2007; Qi et al., 2015) the evidence base remains weak. Unlike other respiratory diseases such as cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) where nutritional intervention has a distinct role in disease stabilisation or functional status (Collins et al., 2013; Woestenenk et al., 2013) the wide spectrum of clinical phenotype associated with bronchiectasis and lesser understood endotypes (Flume et al., 2018), has created challenge in assessing new therapies and interventions such as nutrition. There is a growing need to

understand both phenotypes and endotypes of bronchiectasis to better determine appropriate and targeted therapies, to achieve and optimise patient and clinical outcomes (José and Loebinger, 2021).

Few studies have explored the role of nutrition in disease management, and little is known about nutritional requirements during periods of either stability or metabolic stress (Brill et al., 2015). Nutritional guidance is lacking and instead treatments have focused on physiotherapy (Spinou and Chalmers, 2019) and antibiotic therapy (Welsh et al., 2015) to enable chest clearance and management of infection.

Of the nutritional studies that have been undertaken most have focused on micronutrient status, in particular Vitamin D. In a study by Ferri et al., (2019) 64% of subjects were found to be deficient in Vitamin D and reduced levels were associated with an increase in bacterial lung colonisation alongside Chalmers et al., (2013b) recording considerable deficiency (n = 201 (50%)) and insufficiency (n = 173 (43%)) in their bronchiectasis population. Vitamin D supplementation may also contribute towards reduced frequency of exacerbations and suppression of the inflammatory response in lung disease (Martineau et al., 2017) with work in asthma (Hall and Agrawal, 2017), COPD (Janssens et al., 2009) and CF (Hall et al., 2010) established.

Less is known about macronutrient intakes, and only one study, to date, has addressed macronutrient intakes in bronchiectasis. In a single cross-sectional study, population (n= 205), Olveira et al., (2014) examined the role of consumption of a traditional Mediterranean diet and its influence on anxiety and depression. To date no further studies have been undertaken to establish intake and possible deficit according to nutritional status and body composition.

4.2 Aim

The aim of the study was to characterise the nutritional status and dietary intakes in a cohort of patients with bronchiectasis and identify potential, clinically relevant associations with body composition and functional capacity.

4.3 Methods

This research took the form of a cross sectional, prospective approach, forming data that enabled a snapshot. Discussion of the methodology employed can be found in Chapter 3. A prospective cross sectional observational study in a regional bronchiectasis clinic from July 2017- July 2018 (n= 188) was undertaken. Participants were consecutively recruited at their routine clinic appointments as part of annual review during a period of clinical stability. All

participants had confirmed bronchiectasis, diagnosed by high-resolution computerised tomography (HRCT) and were ≥ 17 years. Patients who were pregnant, had a cancer diagnosis or were aged less than 17 years. were excluded.

4.3.1 Measures

Baseline data recorded as part of routine care were retrieved for each participant. Characteristics of participants were collected including age, sex and postcode to determine social indices (Jordan et al., 2004). The recording of each parameter was undertaken following a standardised operating procedure outlined at each clinic visit.

4.3.2 Anthropometry

Weight (kg) and height (m) were collected using calibrated seca weighing scales (seca 956 Class III, seca, Birmingham. UK) and Leicester Height measure (MK II, seca, Birmingham, UK). Body mass index (BMI) was calculated for each participant (Weight/Height^2). Participants were classified according to the following BMI ranges; ≤18.5 kg/m^2 (Underweight), 18.6-24.9 kg/m^2 (normal range), 25-29.9 kg/m^2 (overweight), 30-39.9 kg/m^2 (obese), 40-49.9 kg/m^2 (morbidly obese) (WHO, 2000)

4.3.3 Pulmonary function

Pulmonary function was assessed by means of standard spirometry using a Vitalograph Compact II Spirometer (Vitalograph Ltd, UK). FEV1 and FVC were compared with reference values and reported as the percentage of the predicted normal value (Stanojevic et al., 2022).

4.3.4 Peripheral Muscle Strength

Peripheral muscle strength was evaluated by Hand Grip Strength (HGS), using a Takei 5401 Handgrip dynamometer (Takei Scientific Instruments Co., Ltd, Tokyo, Japan). This was performed in accordance with the standard operating procedure reported in chapter 3 (appendix C.3). Values were expressed as a mean of all three measures. Measures were then compared to consolidated grip strength values adjusted for age and sex with values less than 85% of standard mean considered as impaired muscle function (Bohannon et al., 2006).

4.3.5 Triceps skinfold thickness and mid arm muscle circumference

Triceps skinfold thickness (TSF) was measured using Harpenden skinfold callipers (Baty International, Burgess Hill, West Sussex, UK). This was

performed following the standard operating procedure (appendix C.4) and methods reported in chapter 3. Mid arm muscle circumference (MAMC), an established measure of muscle protein mass, was calculated from MAC and TSF using a standard formula: MAMC = MAC - (3.1415 × TSF). The MAMC and TSF results were expressed as a percentage of the expected reference values, adjusted for sex and age (Burr and Phillips, 1984). Values were then dichotomised into those >50th centile and those <50th centile according to reference norms.

4.3.6 Nutritional Intake

A 24-hour dietary recall (using a multiple pass technique) was undertaken for each participant at 3 time points (baseline recruitment and each subsequent week for 2 weeks, until a total of 3 were retrieved) by a registered dietitian. Dietary recall interviews were undertaken face to face at the clinic appointment and then by telephone interview. Each dietary recall was coded, and energy, protein, carbohydrate, fat, vitamin D, iron and calcium intakes were calculated. A mean of all seven nutrients for each individual patient was then recorded. Food records were analysed by the same dietitian using MyFood 24© (Carter et al., 2015) and intakes compared to the EAR (energy) and RNI (protein, calcium, vitamin D) (Department of Health, 1991, SACN, 2011). Macronutrient values were also presented as a proportion of total energy intake. Meal distribution and protein distribution throughout mealtimes was also recorded. Meal distribution was recorded by inputting yes or no when reviewing the corresponding mealtimes on the 24 hour recalls. If food was consumed yes was recorded. Protein intake in grams at each mealtime was recorded and inputted into an excel spreadsheet to determine protein intake at each meal. This enabled analysis of meal and protein distribution across the whole population and disease aetiologies.

Application of the lower end Goldberg cut off (physical activity level (PAL) 1.35) (Goldberg et al. 1991) was applied to compare reported mean energy intake (EI) to calculated energy expenditure (EE) using the Schofield equation to determine non habitual intake. A value of below 1.35 for an EI: BMR denotes intakes that are not habitual. At the upper limit, the Goldberg cut off of 2.82 was used (Goldberg and Black., 1998).

Using this equation, proposed deficits in energy intake (underreporting) were aligned with 5 categories ≤100kcal; 100-250kcal; 251-500kcal; 501-1000kcal; >1000kcal).

4.3.7 Disease Aetiology

All participants were characterised by disease aetiology defined as Primary Ciliary Dyskinesia (PCD), Idiopathic cause, Bronchiectasis in association with Asthma and other (inclusive of Immunoglobulin, Post Infective, Auto–Immune, other Genetic Causes)

4.3.8 Stratification groups

The population were also stratified in groups according to predicted FEV_1 % quartiles (< 52%, 53-67%, 68-80%, > 81%) and Body Mass Index (BMI) (< 18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, >30 kg/m^2), to determine differences in groups were categories of lung function and BMI can be qualified.

4.3.9 Microbiology

All participants were also characterised by their predominant microbiological status throughout the study period, grouped as none isolated, *Haemophilus Influenzae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aspergillus* and other.

4.3.10 Comorbidity

Presence of diabetes was also recorded for all participants to determine influence on outcomes.

4.3.11 Indices of multiple deprivation (IMD)

Participant postcodes were identified to determine measures of deprivation on outcomes. Predominantly measured in health research through Townsend deprivation scores (Jarman et al.,1991). The use of IMD has been assessed against Townsend deprivation scores and has been shown to be comparable (r^2 =0.44 vs 0.53) (Jordan et al., 2004) and is therefore justified in its use here. Postcodes were entered into the IMD government explorer (2015) and their ranking recorded against the nine categories used to determine deprivation (income, employment, education (skills and training), health, crime, housing, living environment, income affecting children, and income affecting older people). The ranking identifies locations throughout England from 1-32,844 (most deprived to least deprived) grouped as a geographical area termed Lower layer super output areas (LSOA) and reports this as a proportion percentage e.g. ranking 26,925 amongst the 20% least deprived or decile ranking of 8. Decile rankings (1-10), for each participant were grouped into 3 categories for

analysis, from most deprived to least deprived, group 1 (1-3 rank), group 2 (4-6 rank) and group 3 (7-10 rank).

4.3.12 Number of infective episodes

The number of infective episodes over the previous year was recorded establishing frequency of exacerbation and any associations with nutrition and body composition parameters.

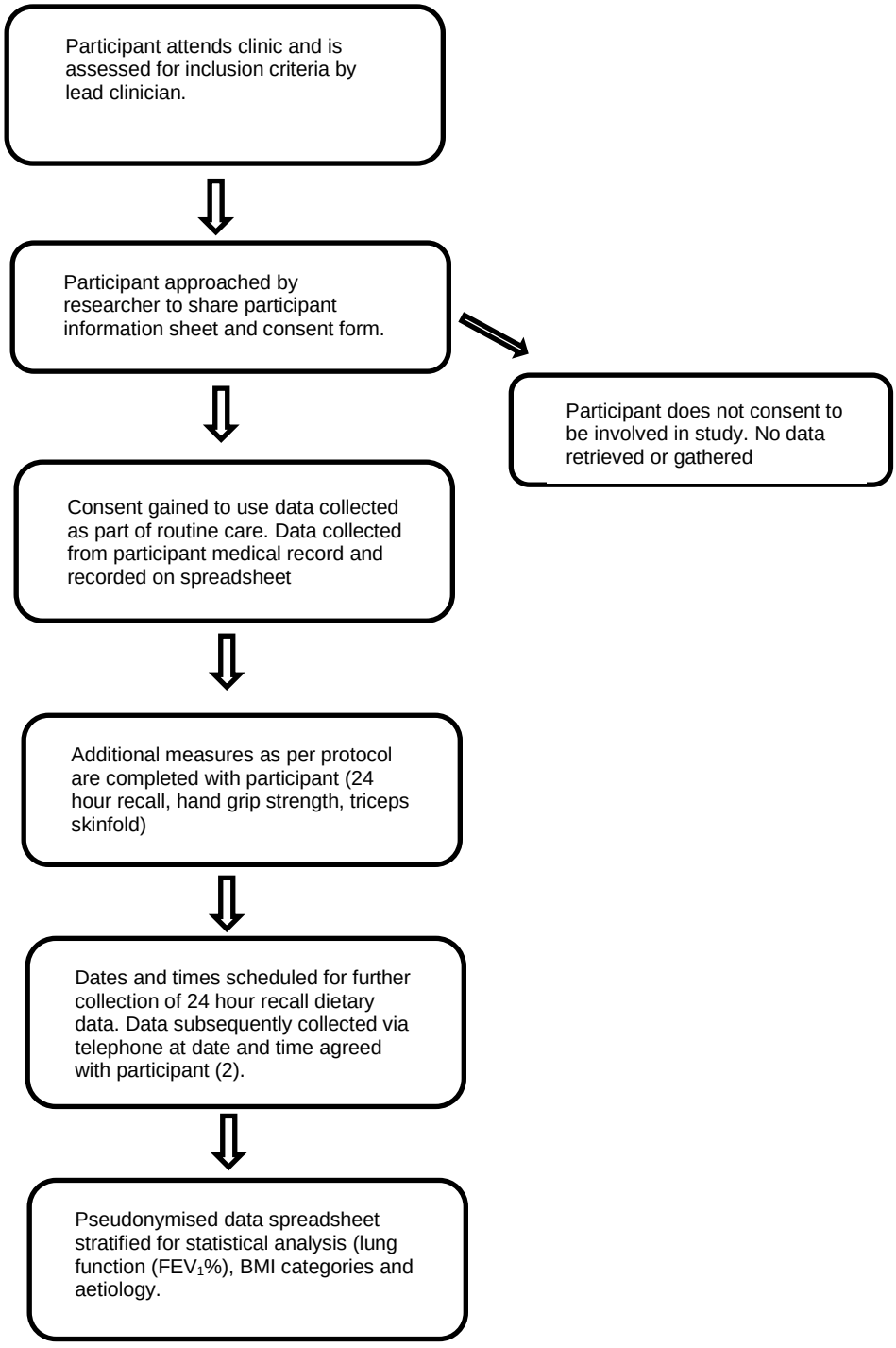
4.3.13 Statistical analysis

Data was analysed using IBM SPSS statistics version 24 (IBM Corp, Armonk, N.Y. USA) by whole population and then grouped by aetiology. Data was checked for normality using the Shapiro Wilk test. Data variables were varied in their distribution. Data was therefore presented in a standard way as median and interquartile range (IQR). Pearson´s (r) or Spearman´s (rho) correlations were used to explore associations of lung function (FEV_1%) with anthropometric measures (MAMC, HGS, TSF, BMI, Weight) and nutrient intake (energy, protein, carbohydrate, fat, vitamin D, iron and calcium). Kruskal- Wallis was used to determine differences between the medians of values within aetiological groups. Linear regression analysis was used to identify predictors of lung function outcome. Statistical significance was set at a p-value less than 0.05 ($p<0.05$).

4.3.14 Ethics

The ethics process is reported in chapter 3. Health Research Authority granted ethical approval, by proportionate review at South Central Hampshire B Research Ethics Committee (IRAS 216351) (Appendix H.1)

Figure 7 Flow diagram of participant recruitment and data collection



4.4 Results

In total, 129 participants were recruited to the study, a flow diagram of recruitment can be seen in Figure 7. Of this number, one was lost to incorrect diagnosis of bronchiectasis (n=128). Three participants were not contactable/did not respond to the subsequent attempts via telephone, resulting in 125 participants completing all 3 nutritional recall interviews. The total population was predominantly female (n=84) (65.6%) (Figure 8) with the majority of participants lying just within the overweight range [mean BMI 25.1(± 5.4) kg/m^2]. Participant characteristics are presented in Table 7.

Analysis by disease aetiology indicated that idiopathic disease was the most predominant (38.5%), (Figure 9). Significant difference was noted in median age between aetiological groups; those with PCD [23.0 years (IQR 19.0-27.0)] more than 4 decades younger than those presenting with idiopathic disease [70.0 years (IQR 59.0-75.0)], bronchiectasis in association with asthma [67.0 years (IQR 59.0-71.0)] or 'other' aetiologies [70.0 years ([IQR 54.0-75.0)], $p<0.001$, (Figure 10).

4.4.1 Anthropometry

Mean handgrip strength in the total sample was only 66.5% (IQR 60.5-89.8) of reference population norms. Significant differences were noted between aetiological sub-groups. Participants with PCD and bronchiectasis with asthma had the lower percentage of normative values than other aetiologies, [58.0% (IQR 43.5-70.0), 56.0% (IQR 37.5-74.5)]. In contrast there were no differences noted in MAMC (an estimate of somatic protein reserve) or triceps skinfold thickness between groups (Table 7). Mean MAMC adjusted for age and gender reflected 46% of the total population having adequate measurements based on calculations of ≤90% of 50th centile being inadequate and ≥90% of 50th centile being adequate compared to normative values with similar results in all other aetiologies. TSF, a measure of predicted fat mass, did reflect higher numbers less than 50th centile cut offs (76%).

When the total population was stratified by lung function (FEV_1 (%) quartile) no differences were observed between participants (Table 8). In contrast, significant differences were observed across all strength parameters in the total population when classified by BMI into categories of underweight, normal weight, overweight and obese. Those classified as underweight had lower handgrip strength, handgrip as a percentage of the norm, mid upper arm circumference, triceps skinfold thickness and mid arm muscle circumference

(Table 8). No differences were observed between aetiological groups and calculated indices of depravation.

Figure 8 Distribution of sex by disease aetiology

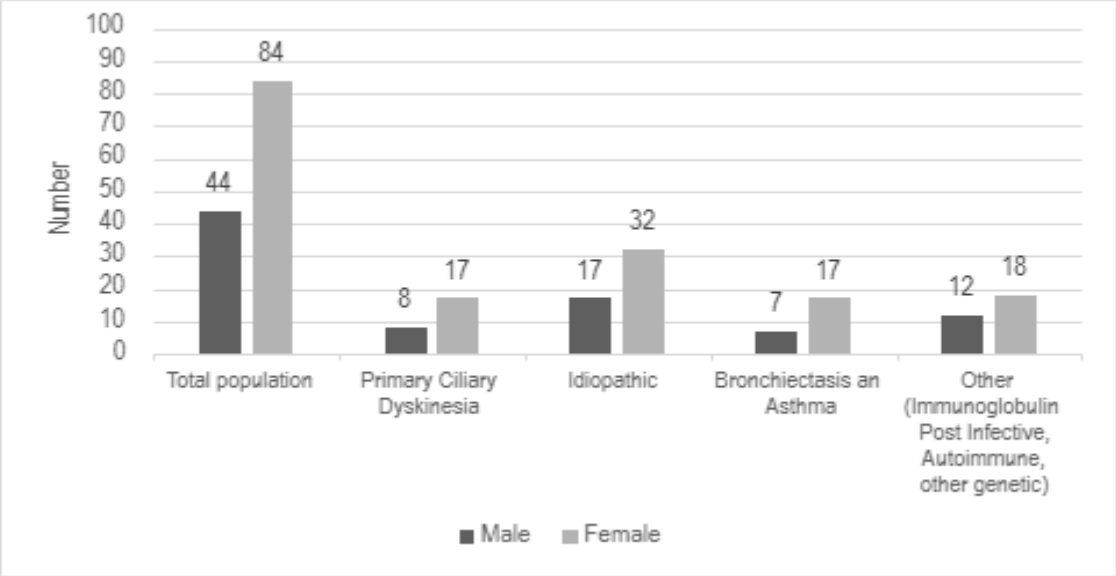


Figure 9 Distribution of participants by disease aetiology.

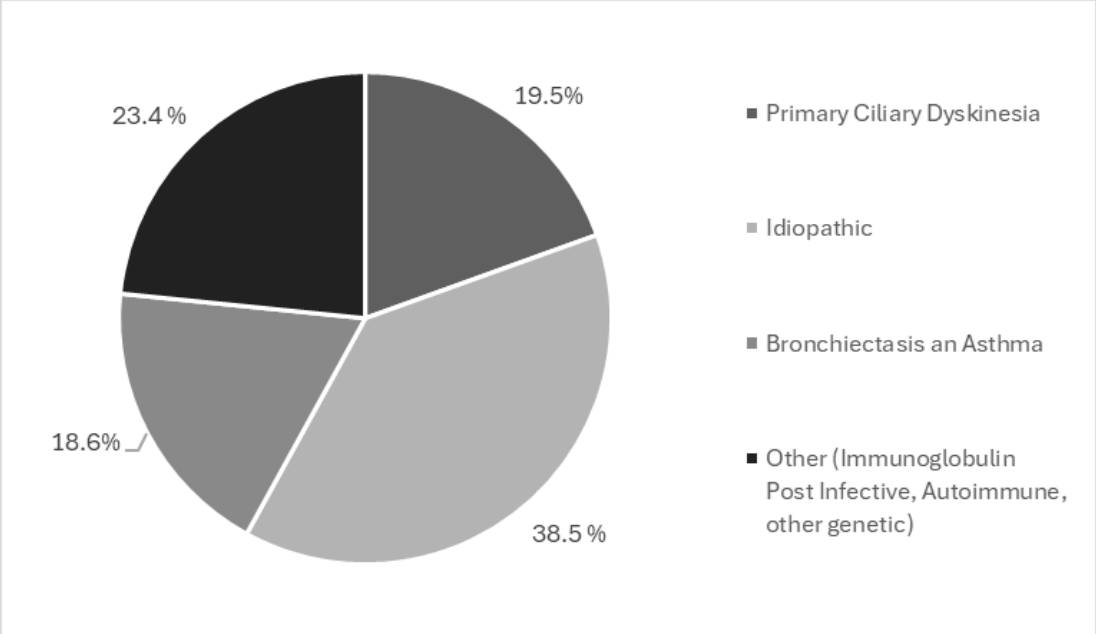


Figure 10 Median age (years) reported by disease aetiology

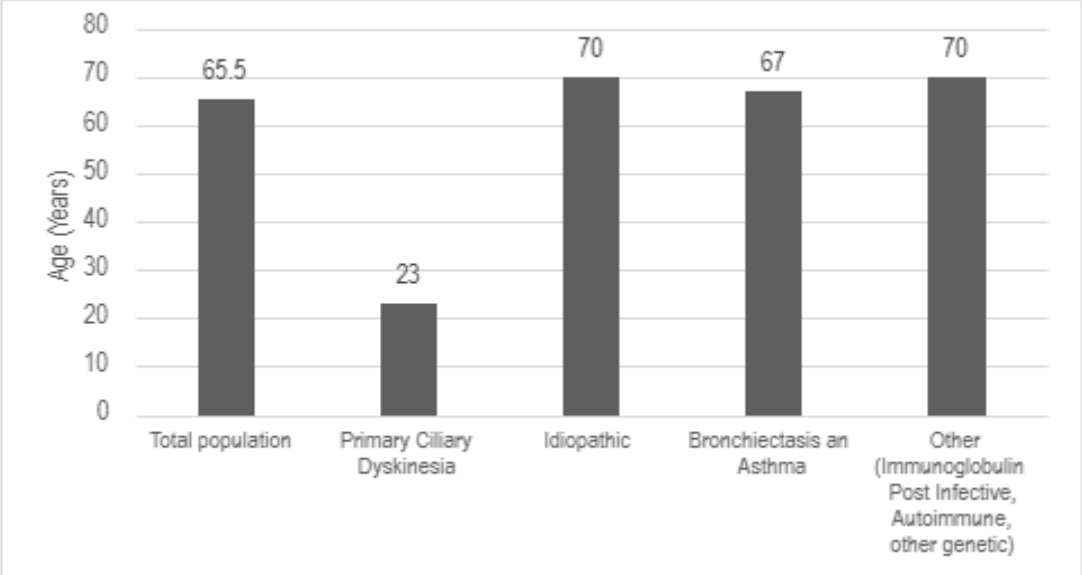


Table 7. Characteristics of participants with bronchiectasis [total and by disease aetiology]

			Aetiology				
	Total participants Proportion (%) or median (Interquartile range)		Primary ciliary dyskinesia (PCD) Proportion (%) or median (Interquartile range)	Idiopathic Proportion (%) or median (Interquartile range)	Bronchiectasis + asthma Proportion (%) or median (Interquartile range)	Other (Immunoglobulin Post Infective, Autoimmune, other genetic) Proportion (%) or median (Interquartile range)	p value
Number (%)	128		25 (19.5%)	49 (38.5%)	24 (18.6%)	30 (23.4%)	
Sex (M/F) %	44/84 (34.4% M).		8/17 (32.0% M)	17/32 (35.0%M)	7/17 (29.0% M)	12/18 (40.0% M)	p=0.85
Age (Years)	65.5 (37.5-73)		23.0 (19.0-27.0)	70.0 (59.0-75.0)	67.0 (59.0-71.0)	70.0 (54.0-75.0)	p<0.001*
Weight (kg)	63.1 (55.0-77.6)		60.9 (51.7-68.3)	66.0 (56.1-83.5)	63.4 (57.9-75.6)	66.9 (51.8-83.8)	p=0.48
BMI (Kg/m^2)	23.8 (21.4-28.1)		22.1 (20.6-25.4)	25.6 (21.6-30.1)	23.5 (22.1-30.1)	23.0 (20.5-26.6)	p=0.15
FEV_1 (L)	1.5 (1.1-1.2)		1.6 (1.4-2.8)	1.6 (1.1-1.2)	1.4 (1.0-1.2)	1.6 (1.1-2.1)	p=0.70
FEV_1 (%)	67.0 (52.3-80.8)		64.0 (50.5-75.5)	70.0 (55.0-83.0)	63.0 (53.0-80.0)	68.0 (50.0-84.0)	p=0.20
FVC (L)	2.4 (1.9-3.1)		2.7 1.9-3.2)	2.5 (1.8-3.2)	2.3 (1.8-3.0)	2.5 (2.0-2.9)	p=0.70
FVC (%)	80.5 (65.0-94.0)		73.0 64.0-86.5)	86.0 (68.0-86.5)	79.0 (71.5-100.5)	75.0 (63.0-100.0)	p=0.10
Handgrip (Kg/f)	15.4 (10.5-22.8)		15.6 (12.7-19.9)	16.8 (10.6-28.1)	13.4 (8.9-17.4)	15.8 (10.5-23.8)	p=0.23
Handgrip (% norm)	66.5 (60.5-89.8)		58.0 (43.5-70.0)	78.0 (56.0-97)	56.0 (37.5-74.5)	77.0 (50.0-95.0)	p=0.02*
MAC	29.3 (26.5-32.3)		29.0 (26.6-31.0)	29.5 (26.5-32.8)	29.5 (26.5-32.9)	29.4 (25.8 -32.0)	p=0.72
TSF (mm)	15.7 (12.2-18.5)		15.7 (12.4-18.1)	16.9 12.1-13.7)	16.1 (13.0-17.7)	14.3 (11.2-17.9)	p=0.52
○ TSF >50th percentile	31/128 (24%)		7/25 (28%)	14/49 (29%)	11/24 (46%)	7/30 (23%)	p=0.47

MAMC (cm)	24.1 (22.1-26.9)		23.6 (21.5-26.2)	25.1 (21.8-26.9)	25.0 (22.6-27.9)	24.1 (21.8-± 4.1)	p=0.66
○ % MAMC >50th percentile	59/128 (46%)		12/25 (48%)	22/49 (44%)	12/24 (50%)	13/30 (43%)	p=0.95
Infections (number previous year)	2.0 (1.0-4.0)		3.0 (0.5-5.5)	2.0 (1.0-3.0)	2.0 (1.0-5.0)	3.0 (1.0-5.0)	p=0.49
Diabetes	4/128 (3.1%)		0/25 (0%)	1/49 (2%)	1/24 (4%)	2/30 (6.7%)	p=0.99
Microbiology n (%) ○ None isolated ○ Haemophilus ○ Pseudomonas ○ Staph Aureus ○ Aspergillus ○ Other	 31 (24.2%) 42 32.8%) 33 (25.8%) 7 (5.5%) 6 (4.7%) 9 (7.0)		 2 (8.0%) 12 (48%) 9 (36%) 2 (8.0%) 0 0	 21 (42.9%) 10 (20.4%) 10 (20.4%) 1 (2.0%) 3 (6.1%) 4 (8.2%)	 4 (16%) 10 (40%) 7 (28%) 0 (0%) 1 (4%) 3 (12%)	 4 (13.8%) 10 (34.5%) 7 (24.1%) 4 (13.8%) 2 (6.9% 2 (6.9%)	p=1.00
Index of multiple deprivation (IMD) • 1-3 high deprivation • 4-6 moderate deprivation • 7-10 low deprivation	 40 (31%) 33 (26%) 55 (43%)		 12 (30%) 6 (18%) 7 (13%)	 14 (35%) 15 (45%) 20 (36%)	 9 (23%) 5 (15%) 10 (18%)	 5 (12%) 7 (22%) 18 (33%)	p=0.18

$FEV_{1,}$ forced expiratory volume in 1 second; FEV_1 (%) forced expiratory volume in 1 second (% predicted value); FVC, forced vital capacity; FVC (%) forced vital capacity (% predicted value); BMI, Body Mass Index, MAC, mid arm circumference; MAMC, midarm muscle circumference; TSF, triceps skinfold thickness.

Table 8 Nutritional and strength parameters [stratified by lung function and BMI category]

	Predicted FEV_1(%) quartiles				
	1st Quartile (<52%) Median (IQR)	2d Quartile (53% -67%) Median (IQR)	3rd Quartile (68%-80%) Median (IQR)	4th Quartile (>81%) Median (IQR)	P-value
Number (n)	32	33	33	30	
Weight (kg)	62.3 (50.9-70.4)	60.0 (52.2-71.5)	72.9 (58.5-83.6)	65.3 (53.4-86.8)	p=0.10
BMI (Kg/m^2)	22.2 (20.6-26.9)	23.5 (21.2-27.5)	25.4 (21.8-30.4)	24.0 (21.5-29.3)	p=0.16
Handgrip (Kgf)	15.7 (10.7-27.1)	14.0 (9.9-18.7)	17.8 (11.5-23.8)	15.4 (11.1-28.5)	p=0.41
Handgrip (% norm)	65.5 (48.0-86.8)	65.0 (50.5-88.5)	68.0 (52.5-91.5)	70.0 (45.8-90.5)	p=0.89
MUAC (cm)	28.8 (25.7-31.4)	28.4 (25.6-31.5)	31.0 (28.3-32.6)	29.7 (27.4-33.3)	p=0.08
TSF (mm)	14.1 (10.8-17.4)	15.6 (13.5-20.5)	16.0 (11.5-18.2)	16.8 (13.2-19.2)	p=0.09
MAMC (cm)	24.3 (21.2-26.5)	23.4 (20.5-26.7)	25.7 (24.0-27.8)	24.1 (22.5-28.3)	p=0.08
	BMI Categories				
	Underweight (BMI<18.5) Median (IQR)	Normal weight (BMI 18.5-24.9) Median (IQR)	Overweight (BMI 25.0-29.9) Median (IQR)	Obese (BMI >30) Median (IQR)	P-value
Number (n)	5	71	28	24	
Handgrip (Kgf)	11.7 (9.1-14.5)	14.1 (9.9-18.2)	22.4 (16.3-29.8)	15.7 (13.2-27.2)	p=0.003*
Handgrip (% norm)	56.0 (33.6-69.0)	61.0 (47.0-79.0)	75.0 (66.0-99.5)	83.0 (54.5-95.5)	p=0.01*
MAC (cm)	21.0 (20.8-22.6)	27.0 (25.7-29.0)	32.0 (31.0-34.0)	33.3 (31.7-38.8)	p<0.001*
TSF (mm)	13.6 (7.4-16.0)	14.9 (11.4-17.5)	16.2 (12.1-18.9)	19.3 (17.2-24.2)	p=0.001*
MAMC (cm)	17.9 (16.8-18.7)	22.9 (20.8-24.5)	26.8 (25.4-28.7)	28.3 (25.5-31.1)	p<0.001*

* statistically significant results

There was a significant association between weight and lung function (FEV_1%) within the total population *r* (126) =0.18, p =0.036 and BMI and lung function (FEV_1%), *r* (126) =0.18, p =0.043.

In those with PCD there was a significant association between handgrip strength and lung function *r* (23) =0.41 p=0.042, which was not seen in other aetiologies.

4.4.2 Nutritional intake

Mean total energy intakes for the whole population (n=125) were below estimated requirements as were energy intakes for each sub-group (Table 12). Protein intakes exceeded the RNI for protein for the whole population and all sub-groups with Vitamin D consistently ≤ 20 % of the RNI (Table 12). Whilst none reached statistical significance between groups, those with PCD had the lowest mean intakes of iron, calcium and vitamin D.

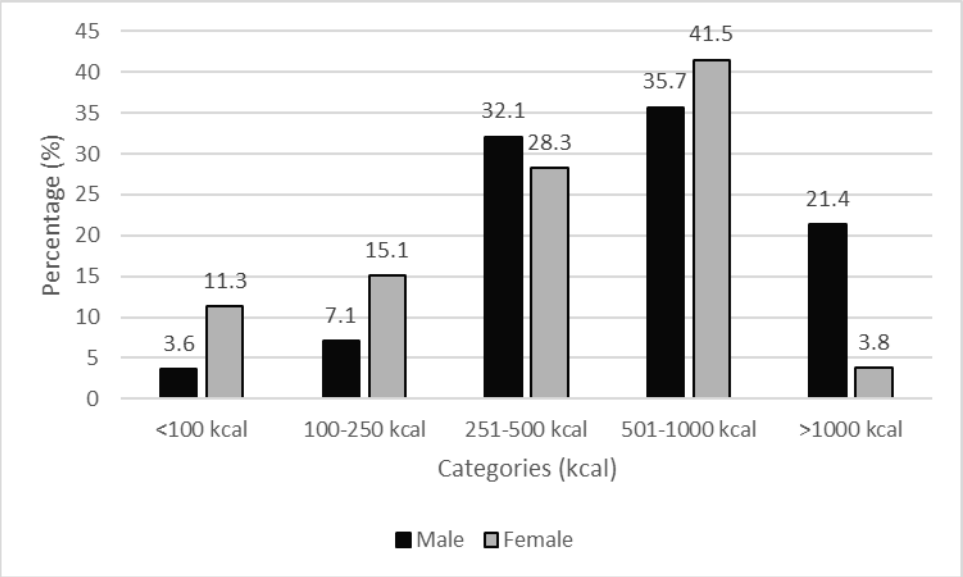
4.4.2.1 Energy adjustment (Goldberg)

Applying the Goldberg cut-off (lower end) of 1.35 Physical Activity Level (PAL), identified 81 participants (64%) whose reported energy intake (EI) could not be considered habitual when compared with calculated energy expenditure (EE), with a mean deficit of -551 kcals. Mean percentage differences between EI and EE for the whole group were -25.9%, and for the 81 participants where habitual intakes were not reflected was - 46.7%. When categorised by kilocalorie (kcal) difference for the 81 reporting non habitual intake with the greatest number resided in the category underreporting by 501-1000 kcals (Table 9). Interestingly, more men underreported the highest number of kcals when compared with women (Figure 11). The calculated ratio of EI:BMR for this population was 1.22. Mean ratios for each of the groups can be found in Table 9.

Table 9 Categorisation of underreporting of energy intakes by participants (n=81)

Kcal Category	Participant number (%)	Mean difference (kcal)	EI: BMR (range)
<100 kcal	7 (8.7%)	- 47	1.31 (1.28 – 1.34)
100 - 250 kcal	10 (12.3 %)	-182	1.21 (1.16 -1.26)
251 - 500 kcal	24 (29.6%)	-375	1.08 (0.93 – 1.18)
501 – 1000 kcal	32 (39.5%)	-728	0.85 (0.55 – 1.03)
>1000 kcal	8 (9.9%)	-1271	0.61 (0.28 -0.76)

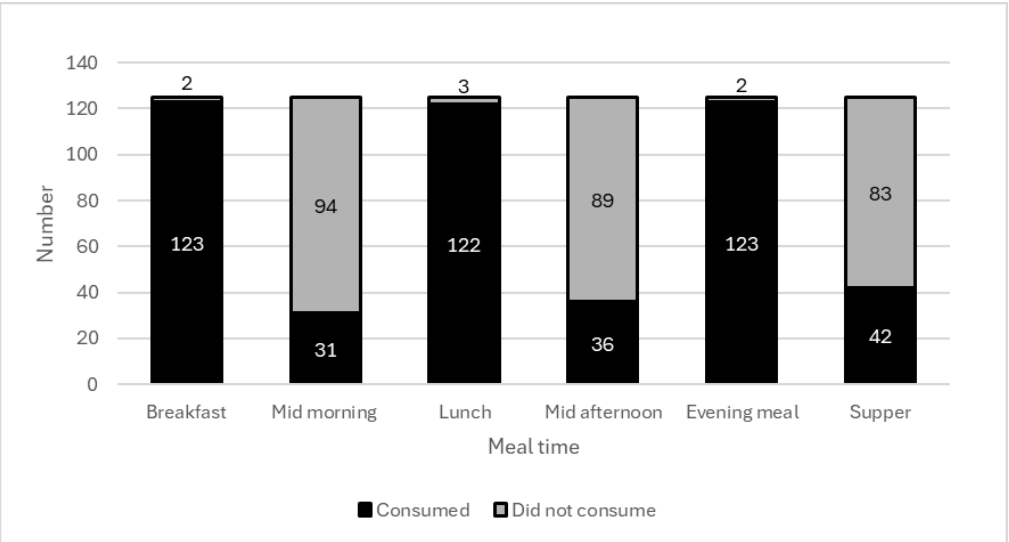
Figure 11 Quantification and distribution of underreporting of energy intake by sex.



4.4.2.2 Overall intake distribution and protein distribution across mealtimes

When reviewing the multiple pass recalls, meal distribution was recorded using standardised forms (Appendix E) with headings including breakfast, mid-morning, lunch, mid-afternoon, evening meal and supper to determine distribution and consumption at these points during the 24-hr recall. Distribution of meal intake can be found in Figure 12. Ninety eight percent of participants consumed a breakfast, lunch and an evening meal with only 25% consuming something mid-morning, 29% consuming food mid-afternoon and 37% consuming something at supper time.

Figure 12 Meal distribution across 24 hour recalls (n=125)



When grouped by aetiology (figure13) the majority that did not consume anything mid-morning (33%) and mid-afternoon (36%) were those with an idiopathic aetiology. This changed to 'Other' (immunoglobulin, post infective, autoimmune, other genetic) for food intake at supper, with the majority (33%) not consuming anything at supper.

Figure 13 Distribution of non-consumption at mid-morning, mid-afternoon and supper times by disease aetiology

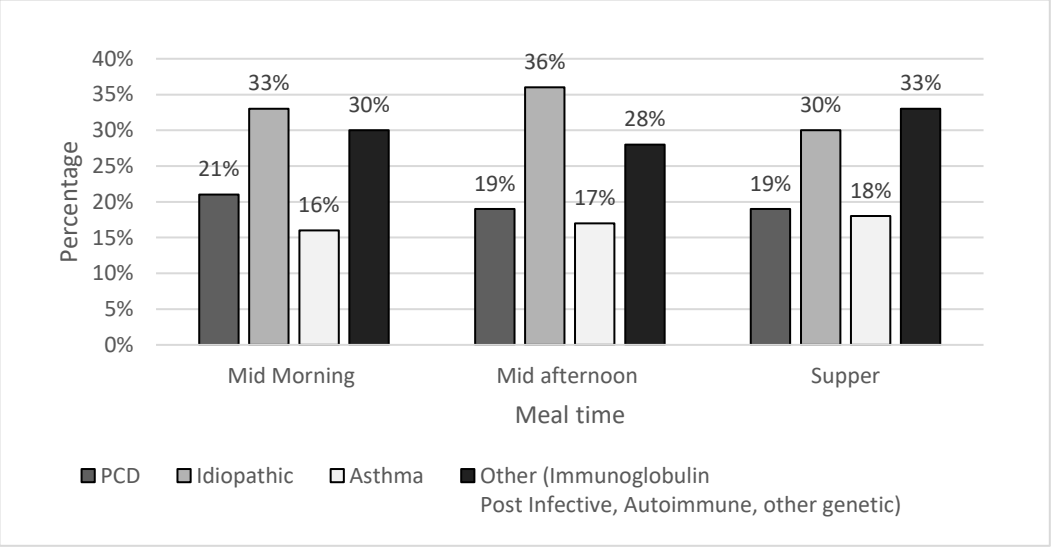


Table 10 shows median intakes of protein by whole population (n=125). Protein intake categorised by disease aetiology across mealtimes can be found in Table 11. There were no statistically significant differences between aetiological groups in their intakes of protein across mealtimes.

Table 10 Distribution of protein across mealtimes for the whole population (n=125)

Mealtime	Protein (g) Median (Interquartile range (IQR))
Breakfast	13.7 (9.0 – 20.0)
Mid-Morning	0.0 (0-0.7)
Lunch	18.0 (12.7 – 25.2)
Mid Afternoon	0.0 (0 – 0.7)
Evening Meal	28.3 (21.5 – 36.5)
Supper	0.0 (0 – 2.7)

Table 11 Distribution of protein (g) intake across mealtimes by disease aetiology

Mealtime	PCD **median (Interquartile range)**	Idiopathic **median (Interquartile range)**	Bronchiectasis (asthma) **median (Interquartile range)**	Other (Immunoglobulin Post Infective, Autoimmune, other genetic) **median (Interquartile range)**	P value
Breakfast	12.7 (8.5 -19.7)	14.8 (10.2 – 20.0)	12.3 (7.0 – 20.3)	12.8 (8.9 – 18.2)	p=0.69
Mid-Morning	0 (0-0.2)	0 (0-0.7)	0 (0-0.7)	0 (0-0.7)	p=0.87
Lunch	17.5 (12.1-30.4)	19.1 (15.1 – 28.7)	14.7 (10.0-22.3)	17.2 (12.7 – 22.3)	p=0.32
Mid Afternoon	0 (0-0.7)	0 (0-0.7)	0 (0-1.0)	0 (0-0.9)	p=0.99
Evening Meal	29.5 (18.1– 43.4)	28.3 (20.1 – 36.8)	28.3 (22.7–39.0)	27.9 (22.0 – 32.4)	p=0.71
Supper	0 (0-1.8)	0 (0 – 3.3)	0 (0-2.7)	0 (0-2.1)	p=0.81

4.4.3 Predictors of lung function

Univariate regression indicated that weight (β = .185, p = 0.036), and BMI (β = .179 p < 0.043) were statistically significant predictors of lung function in the whole population with HGS and weight identified as statistically significant predictors of lung function in PCD (β = .431, p = 0.03, β = .409 p = 0.04) (Table 13) Vitamin D intake was a significant predictor of lung function for 'other' aetiologies, but not for any other category.

Table 12. Comparison of nutritional intake by whole population and according to aetiology

	Whole population (125)	PCD	Idiopathic	Bronchiectasis + asthma	Other (Immunoglobulin, post Infective Auto-immune, other genetic)	p value
Energy intake (kcal)	1645 (1262-2019)	1615 (1161-2352)	1768 (1322- 2003)	1496 (1236.- 2019)	1680 (1340-1843)	0.14
Energy intake (%EAR)	77.0 (62.3-94.8)	79.0 (66.0-95.5)	81.1 (± 28.8)	71.0 (59.0-98.0)	79.0 (65.0-93.0)	0.50
Energy Intake (kcal/kg/body weight)	24.0 (18-33)	27.5 (17.8 – 37.0)	24.0 (17.0 – 32.7)	23.0 (17.5 – 33.7)	26.0 (18.5 – 33.0)	0.93
Protein intake (g)	66.0 (52.0-81.0)	70.0 (52.0-84.0)	70.18 (± 24.7)	62.0 (50.0-78.5)	62.0 (53.5-84.5)	0.34
Protein (% total energy)	16.1 (3.0-18.5)	15.0 (13.0-19.0)	15.5 (13.8-18.0)	15.0 (13.0-17.5)	17.0 (13.3-18.8)	0.27
Protein intake (g/kg/body weight)	1.0 (0.7-1.3)	0.9 (0.7-1.3)	1.1 (0.7 – 1.3)	0.9 (0.7 – 1.2)	1.0 (0.8 – 1.2)	0.89
Protein (% RNI)	131.3 (93.9-168.8)	116.0 (88.2-170.4)	139.2 (98.8-173.2)	120.6 (95.9-169.1)	133.1 (110.9-160.8)	0.54
Protein (% 1 g/kg)	99.9 (73.7-127.8)	90.6 (67.8- 128.1)	104.7 (74.6-130.4))	90.5 (71.9 -126.8)	100.0 (83.4-120.8)	0.65
Carbohydrate intake (g)	181.1 (141.3-216.0)	183.3 (153.3-227.3)	181.1 (134.9-218.8)	191.3 (140.7-240.2)	175.5 (134.5-194.0)	0.81
Carbohydrate (% total energy)	41.0 (36.4-46.7)	44.5 (37.0-49.1)	40.1 (± 7.0)	45.5 (37.8-48.9)	40.4 (36.1-45.9)	0.12
Carbohydrate (g/kg/body weight)	2.7 (2.1-3.5)	3.1 (2.3-3.7)	2.6 (1.7 – 3.4)	2.7 (1.8 – 3.5)	2.6 (2.1 – 3.5)	0.62
Fat (g)	66.3 (48.4-82.9)	61.3 (44.2-82.8)	74.1 (54.6-90.3)	65.3 (48.5-89.3)	64.3 (46.6-75.2)	0.23
Fat (% total energy)	37.2 (31.9-41.0)	34 (30.2-38)	40.3 (35.3-43.1)	37.0 (30.9-39.8)	36.0 (30.4-38.7)	0.004
Fe (mg)	9.2 (7.0-11.9)	8.0 (6.2-9.5)	9.2 (7.3-11.1)	10.0 (8.0-13.5)	9.0 (7.0-11.9)	0.68
Fe (% RNI)	100.7 (68.9-126.4)	80.4 (57.4-113.2)	103.4 (80.4-126.4)	114.9 (78.7-155.1)	86.2 (68.9-136.7)	0.40
Ca (mg)	721 (570.5-954.5)	702.0 (468.5-916.5)	786.0 (593.0-1065.0)	705.0 (532.5-928.0)	713.5 (587.8-995.8)	0.72
Ca (% RNI)	103.0 79.8-134.3)	100.2 (66.9-124.0)	112.3 (82.7-112.1)	100.7 (76.1-132.6)	101.9 (84.0-142.3)	0.72
Vitamin D (µg)	2.0 (1.0-3.0)	1.0 (0.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-2.0)	0.81
Vitamin D (% RNI)	20.0 (10.0-30.0)	10.0 (0.0-30.0)	20.0 (10.0-30.0)	20.0 (10.0-30.0)	20.0 (10.0-20.0)	0.81

Table 9 legend: EAR, Estimated average requirement; RNI, Reference Nutrient intake

Table 13. Univariate predictors of lung function by whole population

	All participants		PCD		Idiopathic		Bronchiectasis + Asthma		Other	
Predictors	P value	Confidence Intervals	P value	Confidence Intervals	P value	Confidence Intervals	P value	Confidence Intervals	P value	Confidence Intervals
Aetiology	0.082	- 4.84 - 0.29								
Sex	0.388	- 4.27, – 10.94	0.11	-26.03 – 2.85	0.25	- 0.46 – 17.61	0.19	- 6.32 – 30.89	0.61	- 15.43 – 25.60
Weight	0.036*	0.02 - 0.44	0.04*	0.02 - 1.15	0.90	- 0.31 – 0.27	0.51	- 0.38 – 0.75	0.05	- 0.09 – 1.07
BMI	0.043*	0.02 - 1.34	0.40	- 1.20 – 2.90	0.78	- 0.82 –1.09	0.49	- 1.10 – 2.21	0.07	- 0.16 – 3.00
HGS	0.983	- 3.93 - 0.38	0.03*	0.12 - 2.32	0.06	- 0.10- 0.02	0.76	- 0.97 - 1.31	0.68	- 0.77 – 116
TSF	0.061	- 0.030 -1.36	0.38	-0.73 – 1.83	0.59	-0.77 – 1.34	0.82	- 1.95 – 2.43	0.09	-0.28 – 3.16
MAMC	0.141	- 0.23 – 1.61	0.88	- 2.08 – 2.42	0.49	-0.92 – 1.90	0.28	- 0.89 – 2.95	0.42	- 1.49 – 3.47
Energy	0.481	- 0.00 – 0.01	0.77	- 0.01 – 0.12	0.46	-0.01– 0.01	0.15	-0.00 – 0.01	0.96	- 0.025 – 0.02
Protein	0.548	- 0.07 – 0.13	0.69	- 0.28 – 0.19	0.32	-0.33 -0.11	0.10	- 0.02 – 0.24	0.78	-0.56 – 0.42
Vitamin D	0.246	- 0.24 – 0.61	0.40	- 2.32 – 5.58	0.26	- 2.78 – 0.77	0.35	- 1.82 – 4.87	0.01*	- 12.52 - -1.55

*Statistically significant result

4.5 Discussion

This study was the first to report on dietary intake, body composition and functional capacity (as measured by handgrip strength), in a population with bronchiectasis. Since its publication in 2021, there have been additional studies (reported in Chapter 2) exploring body composition measured through BMI and peripheral strength (Wang et al., 2022) and inflammation and BMI (Wang et al., 2021). Subsequently, aspects of nutrition were reported focusing on vitamin D status (Ali et al., 2022; Sami et al., 2021) compared with body composition and functional capacity (HGS and 6MWT). No subsequent publications, looking at nutritional intakes, exist. The results of the current study show that whilst BMI lay within normal to overweight ranges within the whole population and sub-groups, important functional, body composition and nutritional deficits exist. This is particularly so within a younger sub-group with PCD, who had impaired muscle function, when compared to other causal and associative diseases.

4.5.1 Anthropometry

Anthropometric measures of body composition including triceps skinfold thickness (TSF), mid upper arm circumference (MAC) and mid arm muscle circumference (MAMC) (a measure of somatic protein reserves) were comparable to normative values with no statistically significant differences between groups. This was reflected in BMI which remained in the normal or overweight range for the whole population and aetiological sub-groups. In contrast peripheral muscle strength, measured by handgrip strength, was impaired within the total population suggesting functional deficits are present. Previous studies have also shown a significant reduction in peripheral muscle strength (de Camargo et al., 2018; Ozalp et al., 2012) and exercise capacity (Ozalp et al., 2012) in bronchiectasis. It suggests peripheral muscle strength, measured by simple handgrip measures may have potential as an outcome measure for use in routine monitoring, pulmonary rehabilitation and risk stratification in clinical practice. The use of bio impedance analysis (BIA) could have served as a comparator to the anthropometric measures, with proven good association when compared, but can overestimate fat mass when considered against DXA (Beaumesnil et al., 2011). Whilst this is a limitation of the research undertaken here, the assessor was ISAK accredited which increases the validity of the measures further by accounting for the intra observer error and technical error of measurement (TEM), which serves as a marker of validity to the practice.

Similar findings have been reported in other respiratory diseases. In COPD, HGS is associated with CT-based markers of body composition, but not BMI (Martinez et al., 2017) and more recently in those with interstitial lung disease, severity is associated with upper limb muscle dysfunction and worse physical performance, independent of muscle mass (Guler et al., 2019). The presence of impaired muscle functionality, independent of muscle mass and BMI, aligns with the revised European consensus on definition and diagnosis of sarcopenia (Cruz-Jentoft et al., 2019). Here the definition of sarcopenia was extended, adding muscle function to previous classifications that relied on low muscle mass alone, recognising that strength is better than mass in predicting adverse outcomes. These findings support this, with approximately half (46%) of the total population having functional muscle impairment in the presence of adequate somatic protein reserve.

Although a reduction in peripheral muscle strength (functionality) was reflected across all aetiologies, it was significant in those with PCD where 96% of individuals failed to achieve normative values (>85%) and only 8% remained free of respiratory pathogens during the study period. The autosomal recessive nature of PCD, distinguishes it from other forms of bronchiectasis and in line with European registry data (Shoemark et al., 2018). PCD is characterised by earlier decline in lung function. These findings are supported by an earlier study in younger children with PCD who displayed deficits in exercise capacity and respiratory muscle strength as early as age 10 years (Firat et al., 2018). Impaired muscle strength and function may predate adulthood by many years in PCD indicating a need for closer group monitoring.

A positive association between HGS and lung function in the PCD population was also observed, not shown in other aetiologies but has been noted in both healthy (Son et al., 2018) and respiratory populations (Lima et al., 2019). In respiratory conditions such as COPD and Cystic fibrosis, the loss of muscle mass in patients with poorer nutritional status has been hypothesized to contribute to worsening of lung function as a result of increased metabolic demand from poor respiratory function (Cao et al., 2012; Sheikh et al., 2014) Potentially, these mechanisms may also be present in underweight patients with PCD. Within our own population, the lower strength parameters noted for those with low BMI (<18.5kg/m^2) would suggest that interventions to improve BMI might have a positive impact on lung function. Further research to understand longitudinal trends of weight, muscle functionality and its association with lung function and repeated infections is warranted.

4.5.2 Nutritional Intake

Muscle mass and function are both influenced by protein intake. All aetiologies met dietary protein reference values and the proportional intakes of energy by protein (15% of energy intake) recommended within national guidelines (Department of Health, 1991) This was sufficient to maintain muscle mass within normal range but could not maintain optimal muscle function, which relies on both protein intake and resistance exercise (Martone et al., 2017). This study did not assess physical activity levels which may have provided further insight into specific contributions of both factors, and activity has been reported as reduced in bronchiectasis compared with healthy peers (Jose et al., 2018). However, it suggests that adequate protein intakes were achieved when compared to reference nutrient intakes. Comparison of protein with adjusted requirements recommended by the PROTAGE study (Bauer et al., 2013) of 1g/kg/day show that targets of 1g/kg were almost met in the total population but not for those with bronchiectasis and asthma and PCD compounding the limited muscle function, especially in this younger PCD group.

Of note, protein distribution was similar at mealtimes across all aetiologies and increased with a skewed effect towards evening meal within aetiology. It has been suggested that an even distribution of more or equals to 30g protein intake per meal, achieves a greater net anabolic effect for muscle accrual than a skewed meal distribution (Deutz and Wolffe, 2013; Mamerow et al., 2014). However, mean intakes of more or equal to 30g protein per meal was not achieved at any mealtime within any of the aetiologies. It adds further weight to the suggestion that not only should protein be increased across aetiologies. This is of particular significance given that up to 36% of subjects within aetiology did not consume mid meal snacks. It adds further weight to the suggestion that not only should protein be increased across aetiologies but that efforts to redistribute protein across mealtimes should be tested.

Further work to assess and monitor nutritional intakes is needed to inform whether recommendations for other respiratory diseases such as COPD and Cystic Fibrosis (Brill et al., 2015, Turck et al., 2016) might also be required for PCD.

Of participants, 64% (n=81) of participants did not report intakes that could be considered habitual. EI:EE ratios reflected that at the lowest physical activity level of (1.35), their reported mean energy intakes would not sustain life in the longer term.

The largest category of under-reporting (39% participants) demonstrated energy deficits of 501-1000 kcals; mean deficits of 728kcals. Whilst daily variation

exists, and longer periods of data collection alongside use of technology may mitigate, it is an important to factor to consider as a limitation in this study. It is important to also note the limitations of applying the Goldberg cut offs with only extreme mis reporting being identified. Lack of physical activity data renders the application of any PAL limited by an assumption the population aligns to others in terms of physical activity. This is likely not the case in this population due to the impact of the respiratory condition on ability to engage in activity. It is also important to consider the degrees of disease severity that were also, not fully explored. Therefore, these reported values need to be considered with caution (Black, A.E., 2000). To this end Goldberg and Black (1998) have also considered the value of application of over reporting and suggested for a 7-day intake, an EI:BMR ratio of more than >2.82 is likely over reporting.

Vitamin D intakes were only 20% of dietary reference values for the whole population and similarly low for all aetiologies. The immunomodulatory role of vitamin D within lung disease is well established (Maes et al., 2020). From a mechanistic perspective Vitamin D is involved in the regulation of pathogen recognition receptors (PRRs) on the respiratory epithelial cells, which limit viral or bacterial spread and activation of the immune system, through the production of cytokines and anti-microbial peptides (AMPs). It is implicated in the enhancement of AMPs, reduction of antigen presenting capacity, suppression of T cell inflammation and reduction in B cell immunoglobulin production (Maes et al., 2020). Whilst serum levels were not measured here, a limitation of this study previous studies in bronchiectasis have reported high levels of deficiency (defined as <25nmol/l) ranging from 50-64% (Chalmers et al., 2013b; Ferri et al., 2019) with a recent systematic review in COPD concluding, those with lowest levels of <25nmol/l demonstrate the greatest benefits of supplementation in reducing chest exacerbations (Jolliffe et al., 2019, 2021). Dietary intake therefore appears suboptimal and would suggest strategies to improve intake through supplementation that could address previously identified deficiencies are required. Of note our PCD subgroup had similar or greater infection rates (3 exacerbations per year) compared to all other aetiological groups, despite being 30 years younger in age. In bronchiectasis, three or more exacerbations per year at baseline have been shown to be associated with worse quality of life, greater likelihood of future hospitalisation, increasing exacerbation frequency and mortality over a 5 year follow up period (Chalmers et al., 2018). Together these are powerful drivers to investigate potential strategies such as vitamin D supplementation and establish target levels that might address the greater risks associated with PCD. It would also suggest that routine annual monitoring is

required which would align with guidance from other respiratory conditions (Turck et al., 2016).

The lowest intakes for iron and calcium were also within this PCD group, although only iron intakes were suboptimal in terms of meeting recommendations. Together it illustrates that those with PCD have greater nutritional vulnerability, apparent at a significantly younger age.

4.6 Strengths and Limitations

The prospective nature of this study and large sample, reflected a true clinic population. The use of a single researcher, standard operating procedures for anthropometry and dietary recall helped to minimise error when measuring body composition and dietary intake. The high completion rate (98%) indicates strong adherence to the protocol adding rigour. Reliance on anthropometric data rather than DXA measures might be considered limiting but enabled high completion rates.

This study was limited by lack of data assessing physical activity. Establishing normal levels of activity can support evaluation of energy intakes and act as independent variables when considering health outcomes such as lung function and handgrip strength. Lack of this data also compromised use of the Goldberg cut offs (Black A.E., 2000) for energy in determining over reporting. Utilising generic cut offs for under reporting provides some insight into the lack of habitual intake and the range of energy deficit for all participants and by sex. Inclusion of assessment of physical activity should therefore be considered in future research, to assess associations and impact and enable appropriate methodological adjustments to reduce bias in reporting dietary intakes of populations.

4.7 Conclusion

In conclusion bronchiectasis is a condition requiring repeated medical intervention to enable clinical stability. Patients have limitations within normal daily living, which can be influenced by their nutritional status. Whilst seventy percent of the whole participant group had impaired handgrip measures when compared to normative values for sex and age this was statistically significant in those with PCD, identifying a younger but more nutritionally vulnerable group. Further research to understand nutritional needs and associated improvement in functionality and its influence on clinical outcomes and quality of life is warranted.

4.8 Future research

Further exploration of nutritional intakes over time with appropriate nutritional needs and intervention is required to begin to address some of the identified deficiencies in nutritional status and their impact on health and quality of life.

Analysis of nutritional data to determine further the role of micronutrients beyond those reported here should be reviewed.

Chapter 5
Micronutrient intakes of a population with Non-Cystic Fibrosis Bronchiectasis

5.1 Introduction

Within Chapter 4, dietary intake and nutritional status were characterised across defined aetiological groups within bronchiectasis and reported in an associated paper (King et al., 2021). Dietary intake of vitamin D was noted to be low across all groups and for those participants with PCD, iron intakes were also suboptimal. This chapter discusses further the micronutrient analysis of the recorded dietary intakes collected as part of the study in chapter 4.

Whilst Chapter 4 focused predominantly on macronutrient intake, interest in the role of micronutrients in disease processes is gaining traction (Berger et al., 2024). Their role within metabolic processes, immunity, appropriation of response to infection and inflammation is documented (Moreb et al., 2021). COVID-19 has also given a renewed focus on their role, in an attempt to establish adjunctive therapies in virus immune response (Gasmi et al., 2020) with specific micronutrients (A, C, D, E, B_{12}, B_6, B_2 folate, magnesium, zinc, copper, iron, and selenium) identified as essential in supporting immunity (Alpert, 2017; Maggini et al., 2018).

The role of micronutrients within metabolic processes, immunity, and the adaptive response to infection and inflammation (Gasmi et al., 2020; Gombart et al., 2020; Maggini et al., 2018; Moreb et al., 2021), therefore makes them a possible modifiable factor in disease progression. Unsurprisingly, micronutrient insufficiency has therefore been associated with increased susceptibility to pulmonary infections in wider respiratory disease (Luan et al., 2023), and to their duration (Wang et al., 2019), although evidence remains weak.

Micronutrient insufficiency has been shown to increase susceptibility to pulmonary infections (Luan et al., 2023), increase risk of morbidity and mortality in inflammatory conditions (zinc with vitamin D deficiency), disease severity and respiratory infections (Hejazi et al., 2016). Together it suggests that where nutritional intake is compromised, high risk individuals may benefit from supplementation for effective immune function, and reduction in risk of chronic lung disease (Agler et al., 2011).

Studies within bronchiectasis remain sparse and have so far focused solely on Vitamin D, and zinc as micronutrients of interest. Vitamin D has attracted

greatest attention; in part due to proven deficiency in other chronic lung diseases such as CF and COPD, but also in its multiple roles across immunomodulatory mechanisms, including respiratory epithelial cell antiviral response (Balla et al., 2020), and the presence of Vitamin D receptors on T-cells, B-cells and monocytes (Prietl et al., 2013).

Its role in neutrophil elimination and lowering of pro-inflammatory cytokine production also emphasise its potential in the modulation of bronchiectatic disease (Subramanian et al., 2017), Early reports by Chalmer's et al (2013) that indicated an association between Vitamin-D deficiency and chronic bacterial colonisation and disease severity in bronchiectasis, have since been confirmed by others (Mirra et al., 2015; Ferri et al., 2019; Niksarlıoğlu, et al., 2020). Collectively these studies reported a presence of deficiency/insufficiency that ranged from 64-93% (Chalmers et al., 2013; Mirra et al., 2015; Ferri et al., 2019; Niksarlıoğlu, et al., 2020).

Similarly, Zinc as an intracellular signalling molecule, has established roles in cell-mediated immune function and oxidative stress and in the regulation of oxidant/antioxidant balance (Maares and Haase, 2016). A recent review has explored zinc and its role in the pathogenesis of lung disease (Liu et al., 2022), exploring its involvement as a cofactor in metalloenzymes and metalloproteins and the role it exerts in phagocytosis, immunoglobulin and cytokine production in both health and disease. Zinc provides a distinctive function in two key areas; firstly, in supporting the anti-inflammatory response to inflammation and secondly in the inhibition of enzyme activation that enables viral replication following infiltration (Luan et al., 2023). If deficient, inflammatory markers may respond in an enhanced way, amplifying damage (Wessels et al., 2020). Understanding further dishomeostasis of zinc, through malnutrition, inadequate intake, or lung disease itself, is needed, to explore effective treatment strategies, with all populations requiring reference nutrient intakes (9.5mg/day men, 7mg/day women) (Department of Health, 1991)) as a minimum (Wessels et al., 2020). Research however is sparse and remains equivocal. Whilst Beeley et al., (1974) concluded that zinc status was normal in a cohort with bronchiectasis, Javadmoosavi et al., (2013) reported significantly lower values in a cohort with bronchiectasis compared to a corresponding control population. The significance of micronutrient intake in respiratory disease and specifically bronchiectasis, lies within associations with disease severity, specifically deficiency and requirements The investigation of any other micronutrients in bronchiectasis remains absent as does further exploration of malnutrition and

pro-inflammatory diets, which have been proposed as additional factors in disease progression and outcome across respiratory disease as a whole (Gea et al., 2018; de Araújo Morais et al., 2020). In a recent review of immune-nutrition and its role in bronchiectasis, Derbyshire and Calder (2021), proposed that wider study of all micronutrients involved in the immune process is warranted

Whilst specific roles and impact of micronutrients is not fully established in bronchiectasis, the greater reported episodes of exacerbation (Josè and Loebinger, 2021; Martinez-Garcia et al., 2013) and frequent cyclical endobronchial infection and inflammation (Rogers et al., 2014; Saleh et al., 2017) are a consideration for their influence. These exacerbations lead to progressive lung damage, reduced lung functionality and respiratory failure (Pasteur et al., 2010; Weyecker et al., 2005). Further scrutiny of micronutrients in addition to those already explored in bronchiectasis (Chalmers et al., 2013b; Sami et al., 2021; Zou et al., 2023) is supported (Chalmers et al., 2014; Chotirmall and Chalmers, 2018a; Dimakou et al., 2016; Martínez-García et al., 2014).

Cross sectional studies that establish micronutrient intake have a dual role; firstly, they can contextualise intakes for those with bronchiectasis according to general population norms, and secondly, they can provide a basis for early exploration of the association of micronutrients with key outcomes. In turn this can inform future targeted interventions.

5.2 Aim

The aim of this study was to examine micronutrient intakes in a population of bronchiectasis patients.

5.3 Objectives

- Identify potential deficiencies of micronutrients in recorded intakes by comparing with dietary reference values and the National diet and nutrition survey data.
- Explore any association of micronutrient intakes with body composition and strength parameters.
- Explore any association of micronutrient intakes with body mass index.
- Explore any association of micronutrient intakes with lung function ($FEV_1{}^{\%}$)

5.4 Methods

All methods used are those described in Chapter 4 but specifically.

5.4.1 Nutritional intake

A 24-hour dietary recall (using a multiple pass technique) was undertaken for each participant at 3 time points (baseline recruitment and each subsequent week for 2 weeks, until a total of 3 were retrieved) by a registered dietitian. Dietary recall interviews were undertaken face to face at the clinic appointment and then by telephone interview. Each dietary recall was coded and mean intakes of vitamins A, D, E, B_2, B_{12}, B_6, folic acid, selenium, zinc, and magnesium were recorded and used for analysis. Food records were analysed by the same dietitian using MyFood 24© (Carter et al., 2015) and compared to the Reference Nutrient Intakes (RNI) (Department of Health, 1991, SACN, 2011).

Micronutrient intakes were also compared to the National Diet and Nutrition Survey Data (NDNS). Participants were grouped as 16-64 years and 65+ years for direct comparison to values differentiated by the same age groups, as reported in the NDNS (Beverley et al., 2020).

5.4.2 Disease Aetiology

All participants were characterised by disease aetiology defined as Primary Ciliary Dyskinesia (PCD), Idiopathic cause, Bronchiectasis in association with Asthma and other (inclusive of Immunoglobulin, Post Infective, Auto–Immune, other Genetic Causes)

5.4.3 Stratification groups

The population were also stratified in groups according to predicted FEV_1 % quartiles (< 52%, 53-67%, 68-80%, > 81%) and Body Mass Index (BMI) (<18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, >30 kg/m^2), to determine differences in groups were categories of lung function and BMI can be qualified.

5.4.4 Statistical tests

Data was analysed using IBM SPSS statistics version 24 (IBM Corp, Armonk, N.Y. USA) by whole population and then grouped by aetiology. Data was checked for normality using the Shapiro Wilk test. Data variables were varied in their distribution. Data was therefore presented in a standard way as median and interquartile range (IQR). Pearson´s (r) or Spearman´s (rho) correlations were used to explore associations of lung function (FEV_1%) with anthropometric measures (MAMC, HGS, TSF, BMI, Weight) and nutrient intake (energy, protein, carbohydrate, fat, vitamin D, iron and calcium). Kruskal- Wallis was used to determine differences between the medians of values within groups, with the Dunn test applied (Bonferroni for non-parametric data) if determination of differences and groups required identification and adjustment for multiple comparisons (Type 1 error) for statistically significant differences is needed. Fishers-Freeman-Halton exact was used for comparison of differences between categorical variables. Statistical significance was set at a p-value less than 0.05 ($p<0.05$).

5.4.5 Ethics

The ethics process is reported in chapter 4. Health Research Authority granted ethical approval, by proportionate review at South Central Hampshire B Research Ethics Committee (IRAS 216351) (Appendix H.1).

5.5 Results

In total, 125 participants completed all nutritional recall interviews. The total population was predominantly female (66%) with most of the participants (56%) within the normal BMI range (18.5kg/m^2 – 24.9kg/m^2). The mean BMI of the total population was 25.1kg/m^2 (± 5.41). Characteristics of the cohort can be viewed in Chapter 4.

5.5.1 Micronutrient intakes

Micronutrient intakes by whole population and aetiological groups are shown in Table 14. As a whole population, the percentage Reference Nutrient Intake (RNI) was met for all micronutrients with the exception of vitamin A (77%), vitamin E (42%), selenium (50%), zinc (95%), and magnesium (81%).

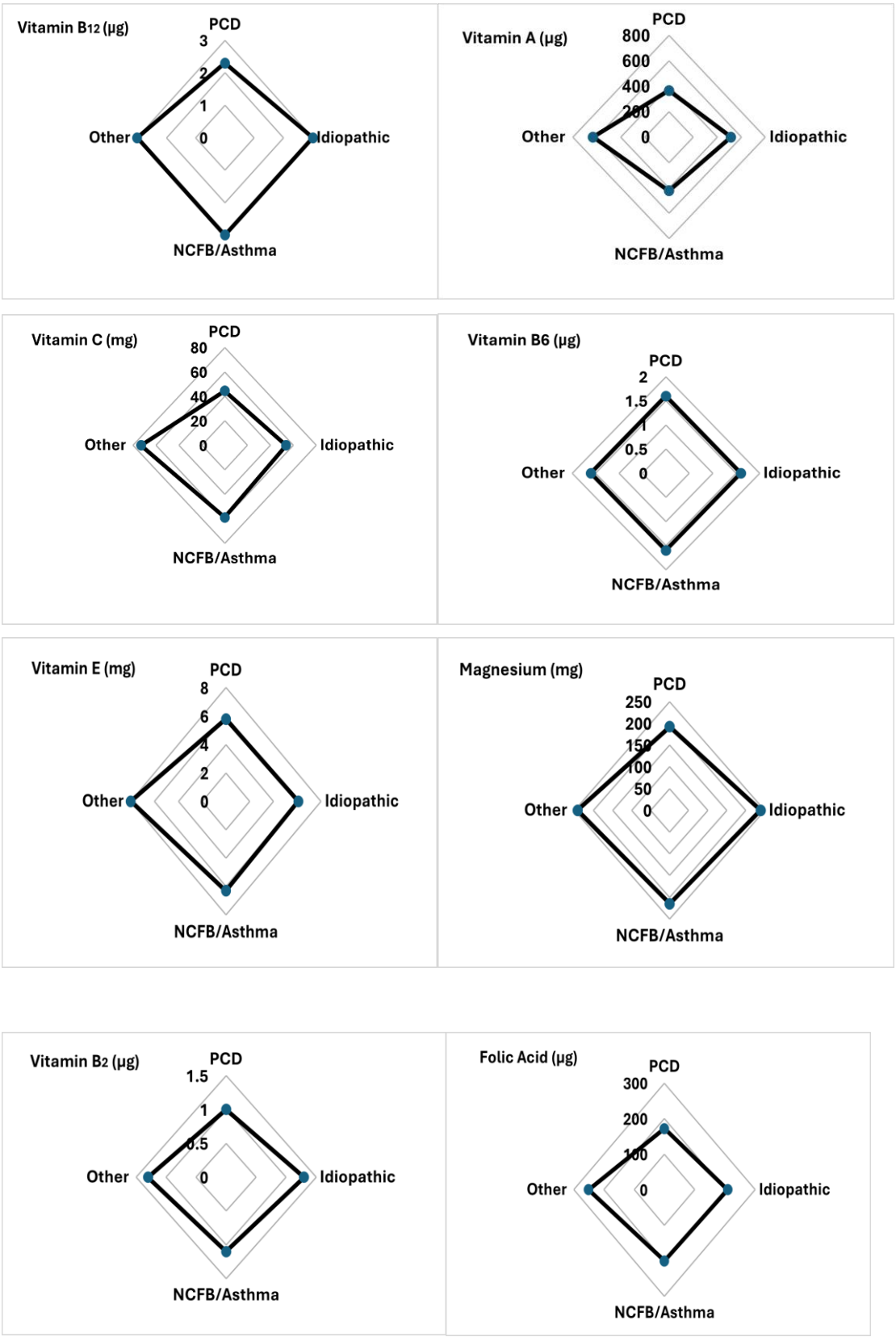
When micronutrient intake was presented by aetiological subgroup, participants with PCD, with the exception of vitamin B_6 and selenium, had the lowest overall

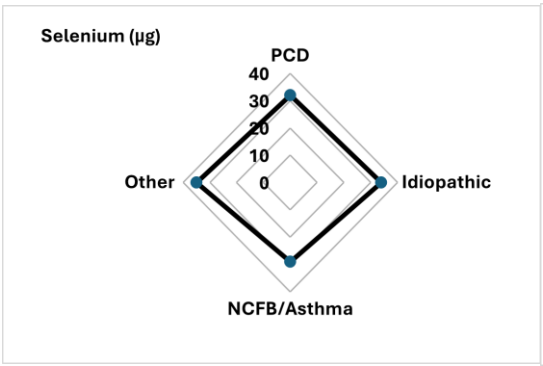
intakes of all analysed micronutrients when compared to other aetiological groups. Only intakes of vitamin E showed statistically significant differences between aetiological groups (5.8 mg [3.3-5.8], p =0.02) as well as all groups failing to meet age and sex adjusted % RNI (p = 0.02). This was lost overall following post hoc Bonferroni analysis between all groups for except for aetiological groups PCD and 'Other' Immunoglobulin Post Infective Auto – immune, other genetic) for both vitamin E intake (H = -2.962, p=0.018) and Vitamin E %RNI (H = -2.918, p= 0.017). Micronutrient intakes across aetiology groups have also been shown through radar graphs in a multifigure to demonstrate the distribution of micronutrient intakes (Figure 14)

When the total population was stratified by lung function (FEV_1 % quartiles) (Table 15), intakes of vitamin C, % RNI vitamin C, folic acid and % RNI folic acid were statistically significantly different between groups ([H (3), 12.8, p =0.005], [H (3), 12.8, p=0.005], [H (3), r = 9.0 p=0.029], [H (3), r = 8.93, p=0.030]) respectively. Following post hoc analysis this remained for both vitamin C and folic acid. The comparison between the first quartile group (FEV_1 [<52%]) and the fourth (FEV_1 [>81%]) (H = -3.445, p = 0.003), for vitamin C and between the first (FEV_1 [<52%]) and third quartile (FEV_1 [68-83%]) (H = -2.686, p=0.043) for folic acid. The second quartile group predicted FEV_1 (53% - 67%) had the lowest overall % of RNI values for vitamin E, folic acid, vitamin B_2, selenium, and magnesium. All other lowest values of micronutrients varied between quartile groups. The third quartile group (FEV_1, [68% - 80%]), had the highest intakes of micronutrients overall except for vitamin A, C and E which were highest in the fourth quartile of lung function (FEV_1, [>81%]).

When stratified by BMI categories (Table 16), significant differences were observed in vitamin E intake (H= 10.47, p=0.01) and %RNI vitamin E (H = 10.74 p = 0.01). these statistically significant differences between BMI groups were lost overall following post hoc analysis (Bonferroni) for multiple comparisons. They remained for comparison between BMI group (<18.5kg/m^2) and BMI group >30kg/m^2) for vitamin E intake (H = 2.997, p=0.016) and %RNI vitamin E (H = 3.009, p=0.016). Those classified as underweight consumed the greatest amounts of micronutrients across the four categories for vitamin A, C, E, B_{12}, B_6, folic acid, selenium, zinc and magnesium. Interestingly those classified as obese (BMI>30kg/m^2) consumed the least number of micronutrients across the four categories for vitamin A, E, B_2, B_6, folic acid, selenium, zinc and magnesium. Micronutrient intake across BMI categories (Figure 15) and lung function categories (Figure 16) are displayed in a multifigure of box and whisker plots, to show distribution of data.

Figure 14 Multifigure distribution of micronutrient intakes across disease aetiology




Selenium (µg)
PCD
40
30
20
10
0
Other
Idiopathic
NCFB/Asthma

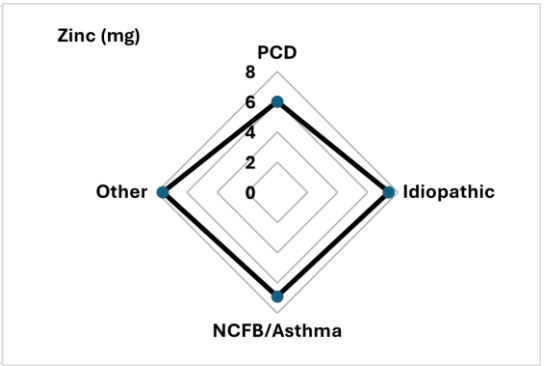

Zinc (mg)
PCD
8
6
4
2
0
Other
Idiopathic
NCFB/Asthma

Table 14. Micronutrient intakes of patients with bronchiectasis [whole population and by disease aetiology]

	Whole population Proportion (%) or median (Interquartile range)	PCD Proportion (%) or median (Interquartile range)	Idiopathic Proportion (%) or median (Interquartile range)	Bronchiectasis + asthma Proportion (%) or median (Interquartile range)	Other (Immunoglobulin Post Infective Auto – immune, other genetic) Proportion (%) or median (Interquartile range)	p value
Number	125	24 (19%)	48 (39%)	24 (19%)	29 (23%)	
Vitamin A (µg)	483 (321 – 845)	368 (187 -659)	514 (389 – 761)	422 (283 – 819)	631 (339 – 945)	p =0.19
Vitamin A (% RNI)	77 (51 – 126)	60.5 (31.2 – 100)	81 (60.7 – 118)	69.5 (46 – 127)	105 (51.5 – 153)	p =0.22
Vitamin C (mg)	58.0 (37.0 -99.5)	44.5 (20.5 – 92)	53.5 (36.2 – 88)	59 (35.7 – 95)	73 (58 -127)	p =0.05
Vitamin C (% RNI)	145 (92 – 248)	112 (52-230)	133 (90-220)	147 (89 – 237)	183 (145-317)	p =0.05
Vitamin E (mg)	6.3 (4.6 – 9.1)	5.8 (3.3-5.8)	6.1 (4.3 – 9.2)	6.3 (4.3 – 10.4)	8.0 (6.3 – 10.0)	p =0.02*
Vitamin E (% RNI)	42 (31-61)	38.5 (22-49)	41 (28-61)	42 (28 – 69)	53 (42-66)	p =0.02*
Vitamin B2 (µg)	1.3 (1.0-2.0)	1.0 (1.0-1.9)	1.3 (1.0-1.6)	1.4 (1.0-2.2)	1.3 (1.0 -2.0)	p = 0.33
Vitamin B2 (% RNI)	121 (90.0-153)	90 (79 – 152)	121 (90-151)	124 (90-204)	121 (90 – 180)	p =0.54
Vitamin B12 (µg)	3.0 (2.0 -4.1)	2.3 (1.3-4.9)	3.0 (2.0-4.0)	3.0 (2.0-4.9)	3.0 (2.0-4.0)	p =0.61
Vitamin B12 (% RNI)	200 (133-277)	155 (93 – 327)	200 (133 – 266)	200 (133 -330)	200 (133 – 266)	p =0.61
Vitamin B6 (µg)	1.6 (1.3 – 2.0)	1.6 (1.0-2.0)	1.6 (1.3-2.0)	1.6 (1.0 -2.2)	1.6 (1.0-2.0)	p =0.75
Vitamin B6 (% RNI)	138 (111-166)	138 (83 – 142)	138 (111 – 166)	138 (90 – 184)	138 (111 -166)	p =0.42
Folic Acid (µg)	208 (158 -276)	172 (119 – 290)	209 (163 – 251)	200 (170 – 323)	251 (178 -292)	p =0.11
Folic Acid (%RNI)	104 (78.5 – 137.5)	85 (59 – 145)	104 (79. – 125)	99 (85 – 161)	125 (88-146)	p =0.09
Selenium (µg)	33 (23.1 – 47.0)	32 (18-47)	34 (24 – 45)	29 (22-46)	35 (25 – 51)	p =0.62
Selenium (%RNI)	50 (73-121)	50 (28 – 75)	50 (38 – 73)	45 (37 – 75)	55 (38 – 75)	p =0.69
Zinc (mg)	7.3 (5.6 – 9.3)	6.0 (5.0- 7.6)	7.4 (6.3 -9.3)	6.9 (5.7 -9.8)	7.6 (5.6 – 8.6)	p =0.24
Zinc (%RNI)	95 (73-121)	78 (63 – 106)	99 (74 – 127)	95 (77 – 131)	85 (73 – 119)	p =0.18
Magnesium (mg)	229 (170 – 283)	192 (142 – 278)	239 (170 – 277)	215 (173 – 271)	242 (204 – 319)	p =0.22
Magnesium (%RNI)	81 (61-102)	69 (52 – 93)	85 (60 – 100)	79 (60 – 100)	88 (72 – 108)	p =0.27

*Statistically significant result p<0.05

Table 15. Micronutrient intakes [stratified by lung function]

	Predicted FEV_1 (%) quartiles				
	1st Quartile (<52%) Median (IQR)	2nd Quartile (53% -67%) Median (IQR)	3rd Quartile (68%-80%) Median (IQR)	4th Quartile (>81%) Median (IQR)	p value
Number	32	31	31	31	
Vitamin A (µg)	391 (246-635)	470 (283-956)	521 (392 – 709)	631 (387 – 1005)	p = 0.16
Vitamin A (% RNI)	60 (36-104)	77 (47-159)	86 (56 -115)	102 (60 -155)	p = 0.13
Vitamin C (mg)	37 (27-68)	60 (38 -101)	64 (47 -82)	69 (44-140)	p = 0.00*
Vitamin C (% RNI)	92 (70-172)	150 (95 -254)	160 (118 -205)	173 (110-351)	p = 0.00*
Vitamin E (mg)	6.3 (3.6-9.6)	6.0 (4.6- 9.0)	6.3 (4.3 – 8.0)	7.0 (5.6 – 10.0)	p = 0.54
Vitamin E (% RNI)	42 (24 -64)	40 (31 -60)	42 (28 -53)	46 (37 – 66)	p = 0.11
Vitamin B2 (µg)	1.3 (1.0-1.6)	1.0 (1.0-1.6)	1.6 (1.3-2.0)	1.3 (1.0-2.0)	p = 0.11
Vitamin B2 (% RNI)	102 (90-145)	90 (90-151)	151 (102-153)	102 (90-153)	p = 0.16
Vitamin B12 (µg)	3.0 (1.6 -4.4)	3.0 (2.0-4.3)	3.3 (2.0 – 5.0)	3.0 (2.0-4.0)	p = 0.67
Vitamin B12 (% RNI)	200 (111-297)	200 (133-288)	222 (133-333)	200 (133-266)	p = 0.67
Vitamin B6 (µg)	1.6 (1.0- 2.0)	1.6 (1.3-2.3)	1.6 (1.3-2.3)	1.6 (1.3-2.0)	p = 0.70
Vitamin B6 (% RNI)	138 (90-160)	138 (111-190)	138 (111-190)	138 (111 – 166)	p = 0.44
Folic Acid (µg)	186 (155 -244)	178 (142 – 276)	245 (205-289)	223 (170-258)	p = 0.02*
Folic Acid (%RNI)	92 (72 – 121)	89 (71 -138)	122 (102 – 140)	111 (85 -129)	p = 0.03*
Selenium (µg)	30 (22-45)	29 (21 -49)	34 (26 -49)	34 (25 -46)	p = 0.65
Selenium (%RNI)	49 (32 73)	46 (36 – 82)	55 (37 -76)	53 (40 -73)	p = 0.74
Zinc (mg)	7.3 (5.0 -9.3)	6.3 (5.0 -9.3)	8.3 (7.0-10.0)	7.0 (5.6-7.6)	p = 0.06
Zinc (%RNI)	87 (66 – 125)	85 (66 -129)	104 (95 – 128)	80 (73 109)	p = 0.07
Magnesium (mg)	231 (149 – 269)	185 (157 -284)	254 (215 – 302)	225 (170 -285)	p = 0.11
Magnesium (%RNI)	77 (53 -98)	68 (58 -105)	92 (74 -109)	80 (60-111)	p = 0.11

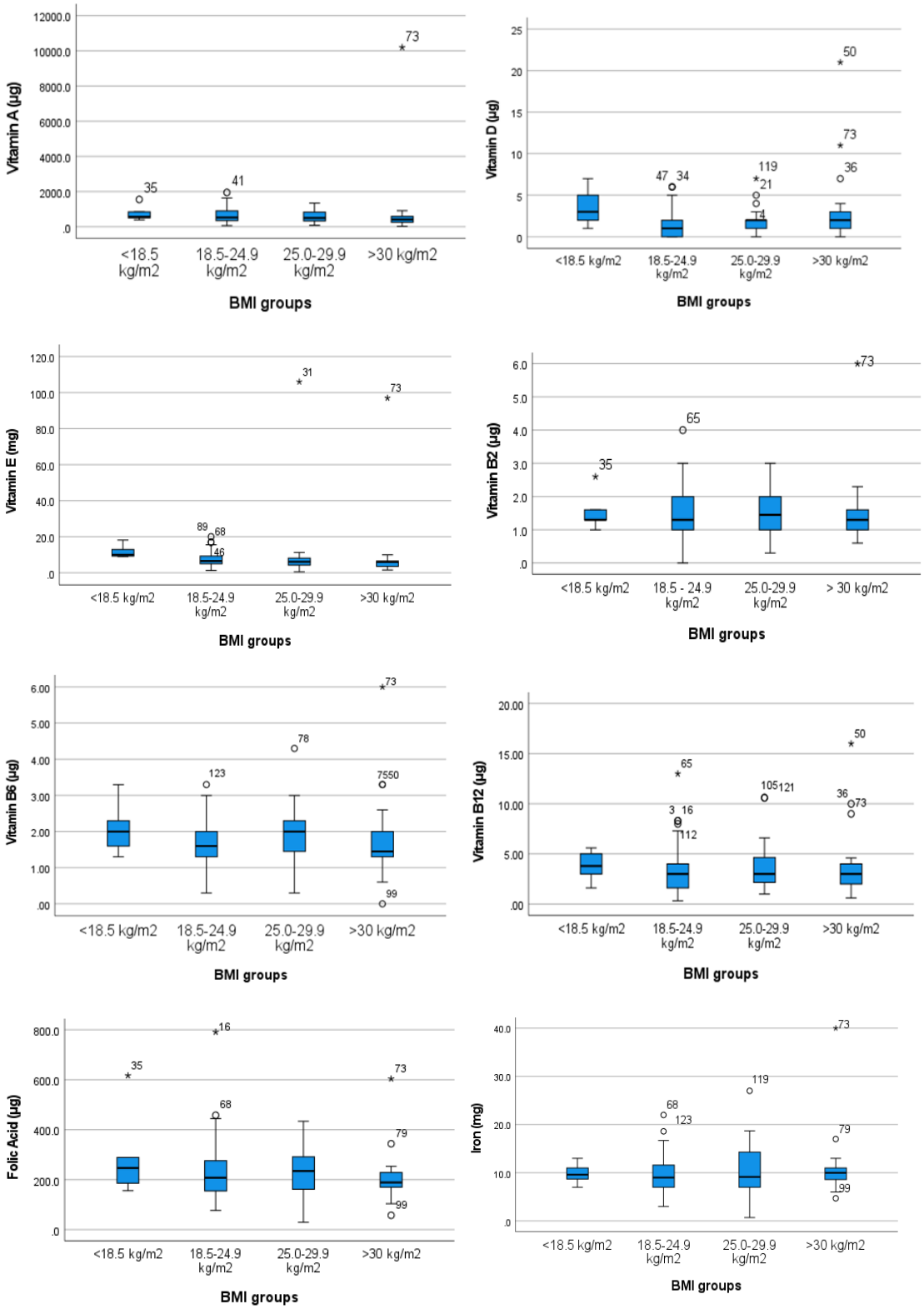
*Statistically significant result p<0.05

Table 16. Micronutrient intakes [stratified by BMI category]

	BMI Categories				
	Underweight (BMI<18.5 kg/m^2) Median (IQR)	Normal weight (BMI 18.5-24.9 kg/m^2) Median (IQR)	Overweight (BMI 25.0-29.9 kg/m^2) Median (IQR)	Obese (BMI >30 kg/m^2) Median (IQR)	p value
Number	5	70	28	22	
Vitamin A (µg)	566 (448 -1202)	529 (333 -913)	495 (329 -841)	409 (238 – 610)	p = 0.19
Vitamin A (% RNI)	94 (68 199)	86 (48 -146)	79 (53 – 119)	64 (34 – 101)	p = 0.19
Vitamin C (mg)	109 (48 -336)	69 (38 -102)	46 (30 -63)	47 (36 – 74)	p = 0.05
Vitamin C (% RNI)	272 (120 – 842)	173 (98 -258)	117 (75 – 157)	118 (92 -186)	p = 0.05
Vitamin E (mg)	10 (9.1 -15.6)	6.6 (4.9 -9.3)	6.1 (4.3 – 8.2)	6.0 (3.6 -6.7)	p = 0.01*
Vitamin E (% RNI)	66 (61 -106)	44 (32 -62)	41 (28 -54)	40 (24 -45)	p = 0.01*
Vitamin B2 (µg)	1.3 (1.1 -1.3)	1.3 (1.0 -2.0)	1.4 (1.0 -2.0)	3.0 (2.0 -4.0)	p = 0.75
Vitamin B2 (% RNI)	121 (97 -196)	111 (90 – 153)	124 (90 – 153)	102 (90 -151)	p = 0.19
Vitamin B12 (µg)	3.8 (2.3 -5.3)	3.0 (1.6-4.0)	3.0 (2.0-4.8)	3.0 (2.0-4.0)	p = 0.55
Vitamin B12 (% RNI)	255 (155 -355)	200 (11 – 271)	200 (138 -321)	200 (133 -266)	p = 0.55
Vitamin B6 (µg)	2.0 (1.4 – 2.8)	1.6 (1.3-2.0)	2.0 (1.3 – 2.3)	1.4 (1.3-2.0)	p = 0.19
Vitamin B6 (% RNI)	166 (124 -221)	138 (111-166)	142 (113 -184)	115 (111 – 166)	p = 0.02*
Folic Acid (µg)	247 (171 -453)	208 (155 -276)	235 (159 -296)	189 (167 -230)	p = 0.49
Folic Acid (%RNI)	123 (70 -226)	104 (77 -138)	117 (79 -148)	94 (83 -114)	p = 0.59
Selenium (µg)	39 (25 – 52)	31 (23 -49)	34 (22 -47)	27 (23 -44)	p = 0.88
Selenium (%RNI)	65 (42 -78)	50 (37 -76)	50 (30 -67)	46 (36 -63)	p = 0.76
Zinc (mg)	8.1 (6.8 -8.8)	7.3 (5.5 – 9.0)	7.3 (6.0 – 10.0)	6.6 (5.2 – 8.7)	p = 0.74
Zinc (%RNI)	114 (82 – 126)	95 (76 – 123)	80 (66 – 125)	92 (69 -110)	p = 0.65
Magnesium (mg)	242 (199-350)	238 (165 – 289)	229 (174 – 297)	217 (165 -258)	p = 0.61
Magnesium (%RNI)	85 (71 -129)	87 (61 -105)	76 (61 -105)	78 (56 -92)	p = 0.48

*Statistically significant result p<0.05

Figure 15 **Multifigure Box and Whisker plots for micronutrient intakes across BMI groups.**



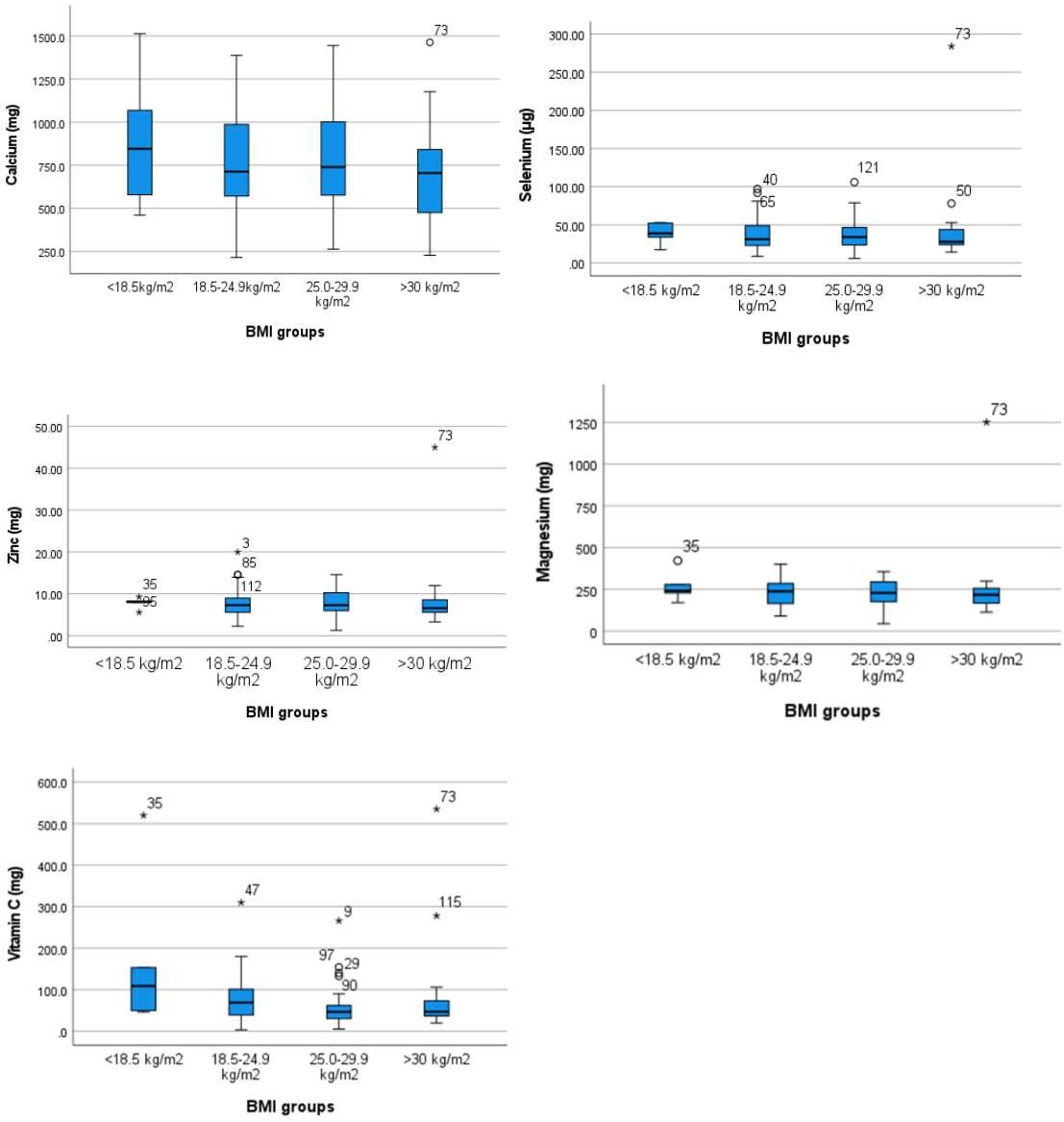
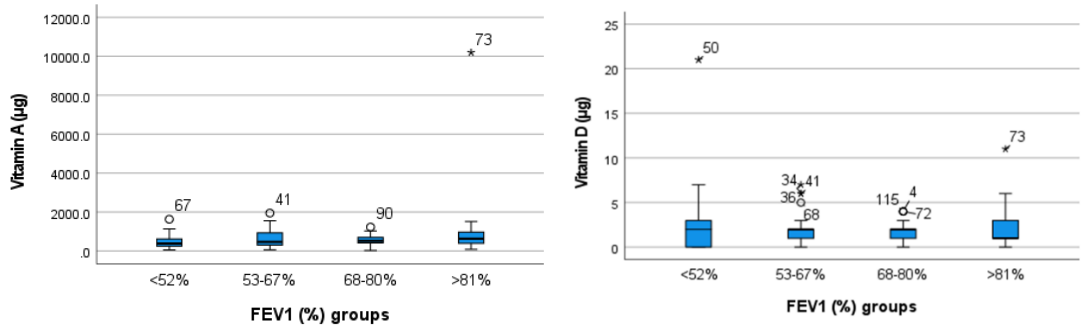
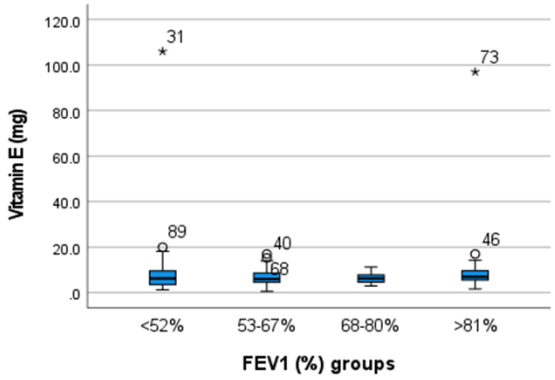
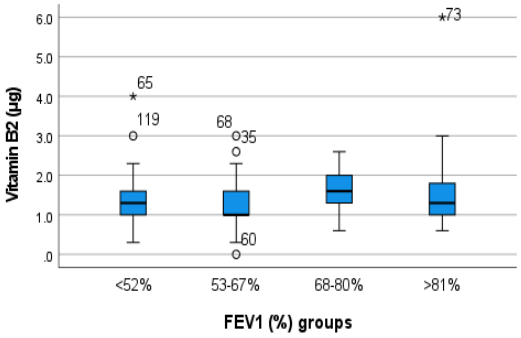
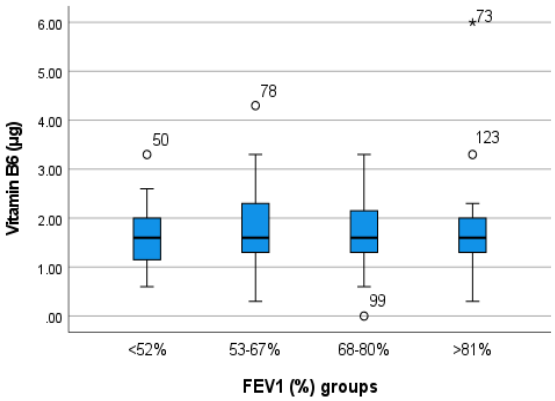


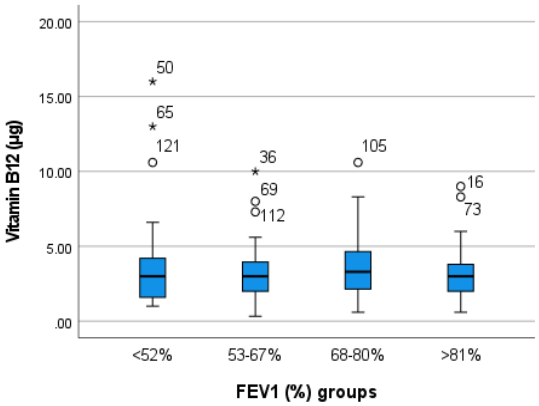
Figure 16 Multifigure Box and Whisker plots for micronutrient intakes across FEV_1% groups.

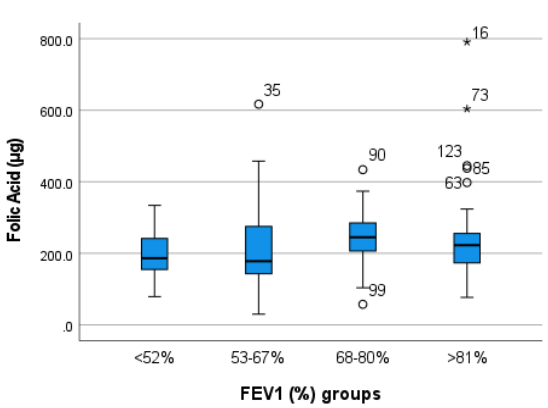


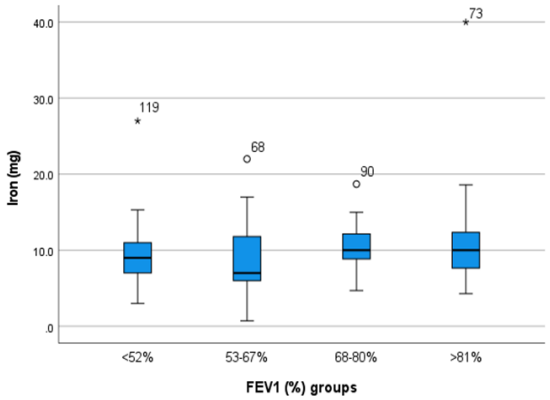

Vitamin E (mg)
120.0
100.0
80.0
60.0
40.0
20.0
.0
31
73
89
40
68
46
<52%
53-67%
68-80%
>81%
FEV1 (%) groups

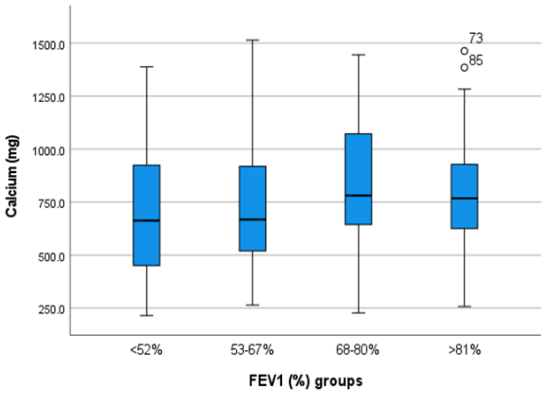

Vitamin B2 (µg)
6.0
5.0
4.0
3.0
2.0
1.0
.0
73
65
119
68
35
60
<52%
53-67%
68-80%
>81%
FEV1 (%) groups

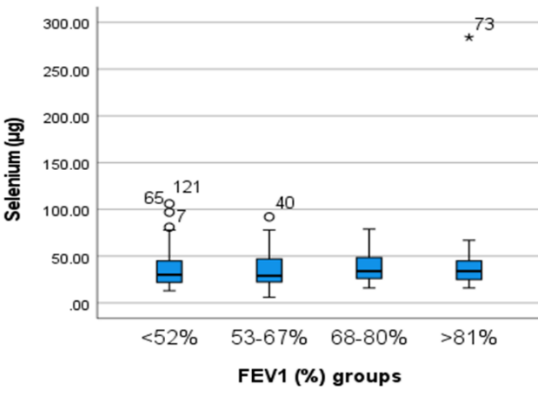

Vitamin B6 (µg)
6.00
5.00
4.00
3.00
2.00
1.00
.00
73
78
50
123
99
<52%
53-67%
68-80%
>81%
FEV1 (%) groups

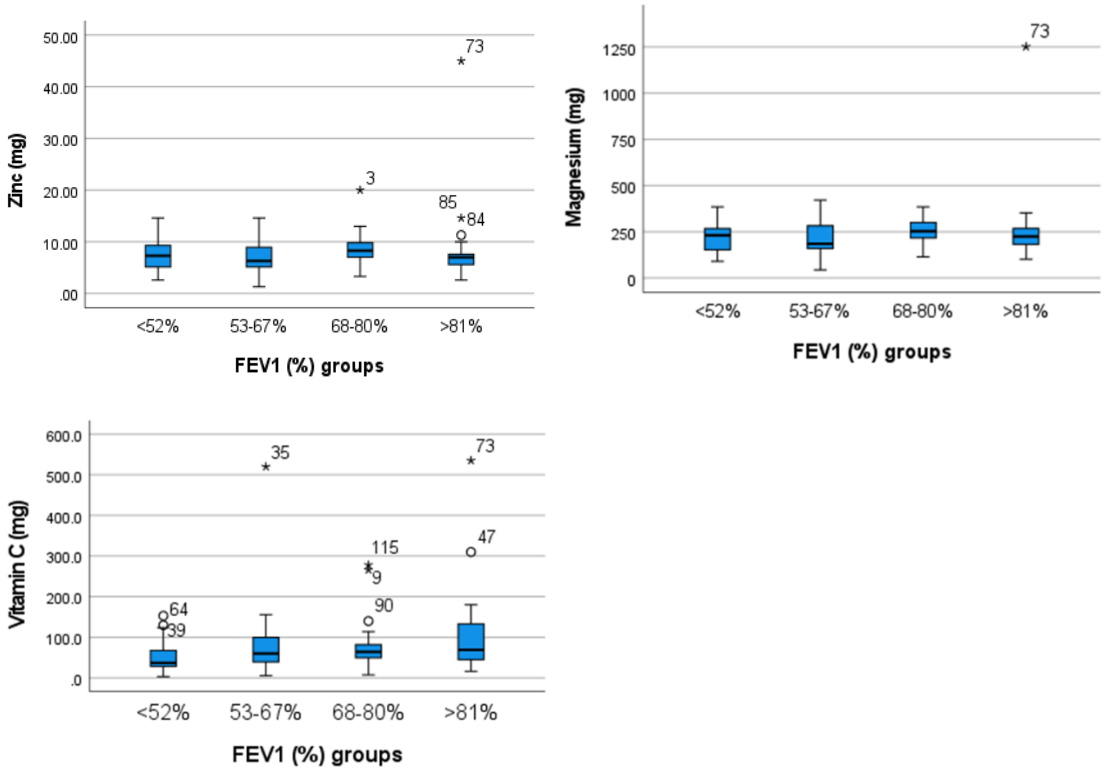

Vitamin B12 (µg)
20.00
15.00
10.00
5.00
.00
50
65
121
36
69
112
105
16
73
<52%
53-67%
68-80%
>81%
FEV1 (%) groups


Folic Acid (µg)
800.0
600.0
400.0
200.0
.0
16
73
35
90
123
85
63
99
<52%
53-67%
68-80%
>81%
FEV1 (%) groups


Iron (mg)
40.0
30.0
20.0
10.0
.0
73
119
68
90
<52%
53-67%
68-80%
>81%
FEV1 (%) groups


Calcium (mg)
1500.0
1250.0
1000.0
750.0
500.0
250.0
73
85
<52%
53-67%
68-80%
>81%
FEV1 (%) groups


Selenium (µg)
300.00
250.00
200.00
150.00
100.00
50.00
.00
73
121
65
87
40
<52%
53-67%
68-80%
>81%
FEV1 (%) groups



5.5.2 Micronutrient intakes compared with national diet and nutrition survey data (NDNS (2016/17-2018/19))

When compared to NDNS data the proportion of participants that did and did not meet the RNI for key micronutrients (A, C, D, E, Zinc, Selenium, and magnesium) are shown in Figure 17. Vitamin C was the only micronutrient that showed proportionally more of the participants met the RNI (70%). Median intakes of micronutrients were compared to specific median values from the NDNS data by their predefined age categories and are displayed in Figure 18. Vitamin E and Selenium were not reported due to lack of comparable data with NDNS.

Figure 17. P**roportion of participants meeting vs not meeting reference nutrient intakes (RNI) for micronutrients** (Vitamins A, C, D, E, Zinc, Selenium, Magnesium).

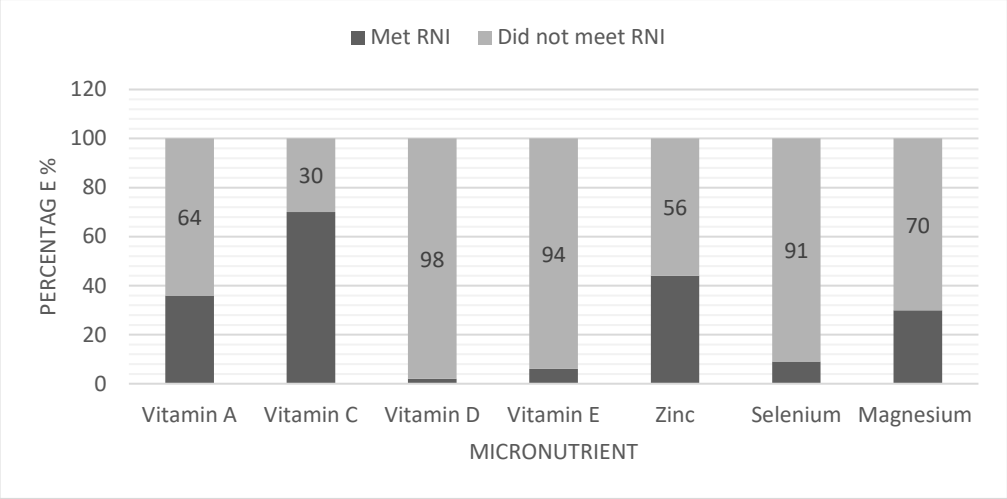
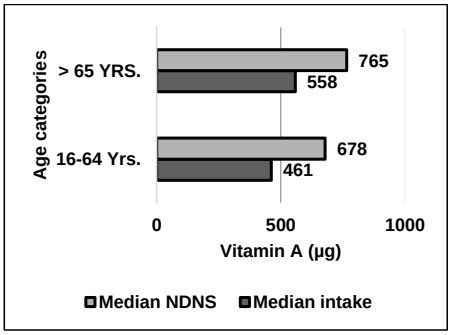
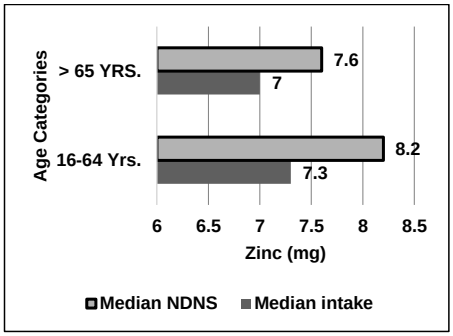
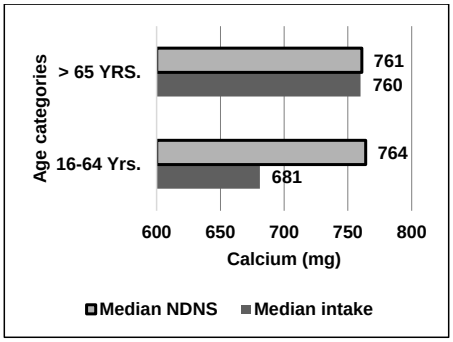
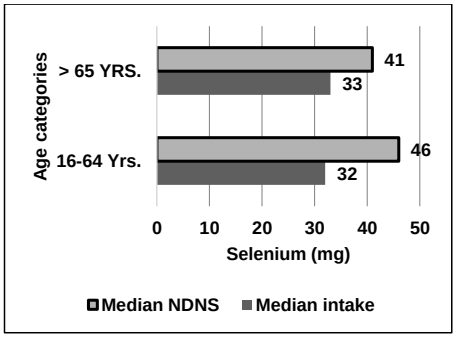


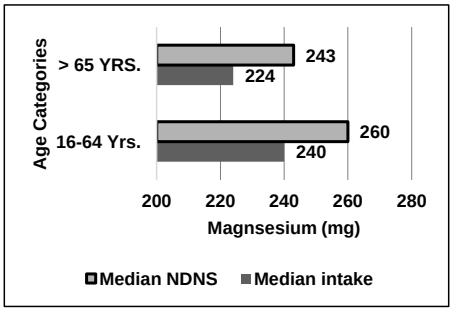
Figure 18 M**icronutrient intakes (Vitamin A, Zinc, Calcium, Selenium, magnesium, Folic acid, vitamin D, and iron) compared with NDNS data grouped by age categories (16-64 yrs. and >65 yrs.)**

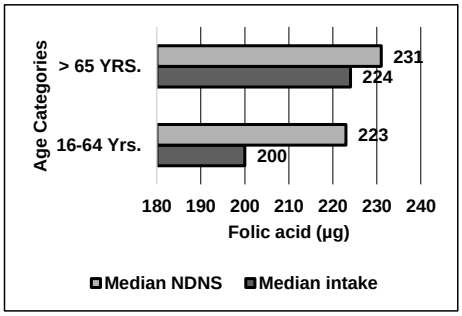


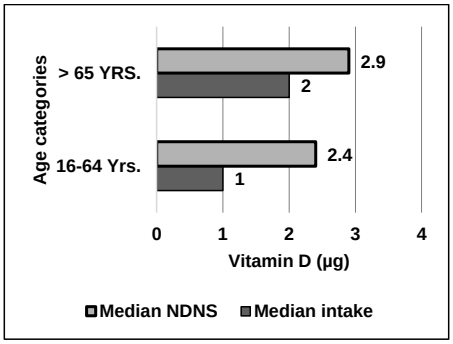


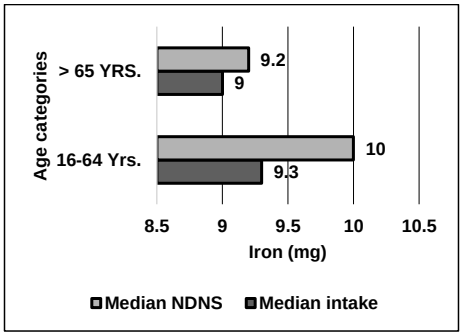












5.5.3 Micronutrient intakes and associations with strength parameters and clinical measures.

When comparing micronutrient intakes to % HGS norm, all were found to be statistically significantly associated except for vitamin C and E intakes. The strongest association was found with Zinc intakes ($r(123) = 0.412$ $p<0.001$) (Table 17). Triceps skinfold thickness (TSF) measures were negatively associated with all micronutrients with only vitamin B_{12}, C, and magnesium not reaching statistical significance. Statistically significant associations can be found in Table 17 with the stronger associations also expressed in Figures 20-25.

When comparing micronutrient intakes with number of infections, BMI, FEV_1 % and handgrip strength (HGS), significant negative and positive correlations are shown in correlation matrix (heatmap) (Figure 19) with the strongest positive correlations shown with progressively darker green and strongest negative correlations darker red.

Figure 19. Correlation matrix showing negative and positive correlations with clinical parameters

HGS (kg/f)	0.117	0.315	0.098	-0.125	0.214	0.362	0.312	0.222	0.37	0.269	0.213	0.416	0.286
FEV1 %	0.182	-0.04	0.051	0.278	0.044	0.029	-0.023	0.161	0.096	0.117	0.071	0.018	0.086
No of infections	-0.039	0.028	-0.007	0.078	-0.1	-0.014	-0.035	-0.053	-0.096	-0.135	-0.135	-0.063	-0.13
BMI (kg/m2)	-0.146	0.062	-0.209	-0.212	-0.029	-0.008	0.026	-0.127	0.027	-0.068	-0.068	-0.031	-0.103
	Vitamin A	Vitamin D	Vitamin E	Vitamin C	Vitamin B2	Vitamin B6	Vitamin B12	Folic Acid	Iron (Fe)	Calcium (Ca)	Selenium (Se)	Zinc (Zn)	Magnesium (Mg)

Table 17. Associations explored with micronutrient intakes, weight, and body composition.

Micronutrients	Body composition and weight parameters							
	Weight (kg)	P value	TSF (mm)	P value	Mean Handgrip (kg/f)	P value	Handgrip (% norm)	P value
Vitamin A (µg)	r = -0.149	p = 0.097	r = - 0.190	p = 0.034*	r = 0.117	p = 0.193	r = 0.250	p = 0.005*
Vitamin C (mg)	r = -0.153	p = 0.088	r = - 0.171	p = 0.053	r = -0.125	p = 0.164	r = -0.037	p = 0.678
Vitamin E (mg)	r = -0.125	p = 0.164	r = - 0.183	p = 0.041*	r = 0.098	p = 0.277	r = 0.124	p = 0.168
Vitamin B2 (µg)	r = 0.184	p = 0.040*	r = - 0.225	p = 0.012*	r = 0.214	p = 0.016*	r = 0.215	p = 0.016*
Vitamin B12 (µg)	r = 0.182	p = 0.042*	r = - 0.168	p = 0.062	r = 0.312	p <0.001*	r = 0.325	p <0.001*
Vitamin B6 (µg)	r = 0.195	p = 0.030*	r = - 0.244	p = 0.006*	r = 0.362	p <0.001*	r = 0.300	p <0.001*
Folic Acid (µg)	r = 0.048	p = 0.598	r = - 0.239	p = 0.007*	r = 0.222	p =0.013*	r = 0.256	p =0.004*
Selenium (µg)	r = 0.061	p = 0.500	r = - 0.201	p = 0.024*	r = 0.213	p =0.017*	r = 0.215	p =0.016*
Zinc (mg)	r = 0.147	p = 0.102	r = - 0.272	p = 0.002*	r = 0.416	p <0.001*	r = 0.412	p <0.001*
Magnesium (mg)	r = 0.062	p = 0.495	r = - 0.157	p = 0.056	r = 0.286	p =0.001*	r = 0.304	p <0.001*

*Statistically significant result p<0.05

Figure 20. Association between % handgrip and zinc intake.

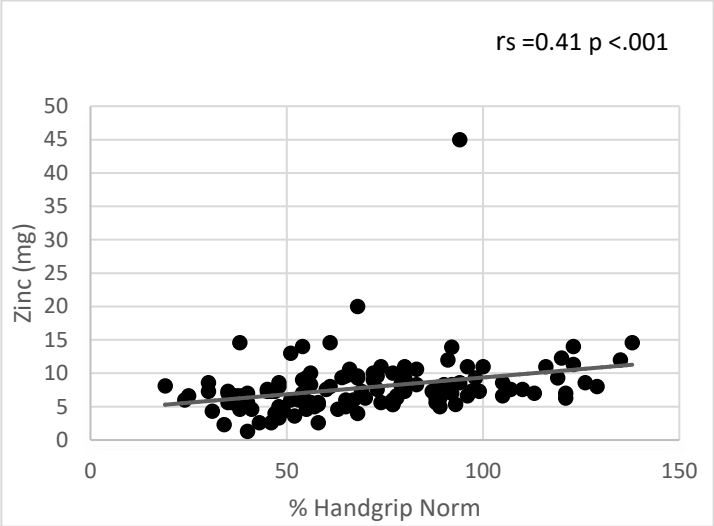


Figure 21. Association between % handgrip and magnesium intake.

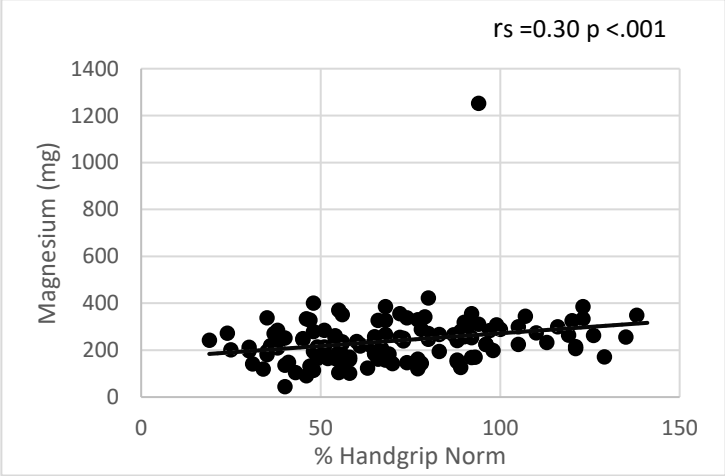


Figure 22. Association between % handgrip and Vitamin B_{12} intake.

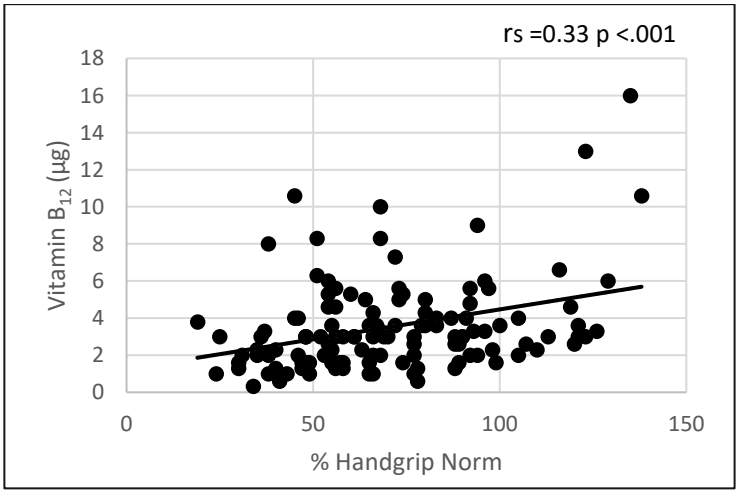


Figure 23. Association between % Handgrip and Vitamin B_6 intake.

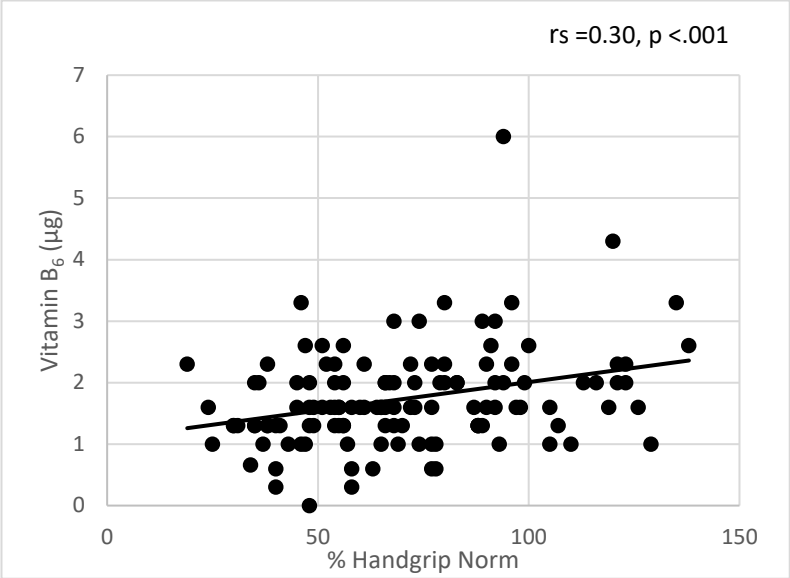


Figure 24. Association with TSF and zinc intake.

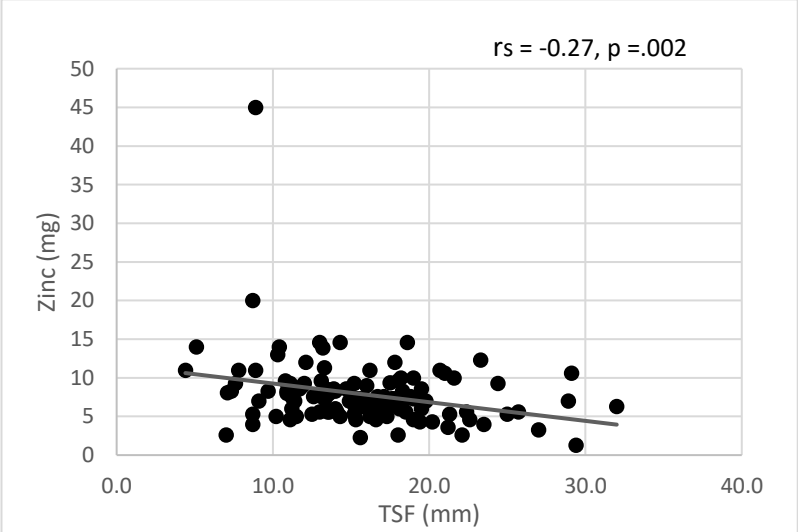
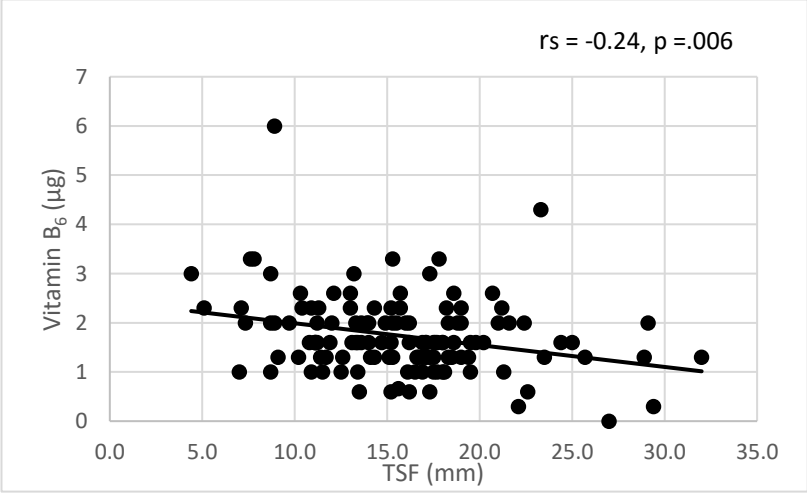


Figure 25. Association with TSF and Vitamin B_6 intake.



5.5.4 Micronutrient intakes and social index of deprivation

Indices of social deprivation were statistically significantly different between groups for vitamin A (H = 6.73, p = 0.034). This remained following Bonferroni correction for multiple testing but only between less deprived and the least deprived groups (H = -2.56, p= 0.031). Comparisons between the most deprived and less deprived, as well as most deprived and least deprived were lost. Zinc was also significantly different between social indexed groups (H = 6.19, p = 0.045) however this was lost following Bonferroni correction for multiple testing.

5.6 Discussion and conclusion

This is the first study, to the authors knowledge, that has analysed micronutrient intakes in a population with bronchiectasis with varying aetiologies.

5.6.1 Micronutrient intakes

In this cohort with bronchiectasis, it was shown that overall micronutrients intakes met the age and sex adjusted reference nutrient intakes, except for vitamin A, vitamin E, selenium, zinc, and magnesium, which are all key within inflammatory and immunomodulatory mechanisms and overall immunocompetence (Alpert, 2017; Gasmi et al., 2020; Maggini et al., 2018). In those with PCD, previously identified as a younger more vulnerable cohort, with impaired HGS, micronutrient intakes were lowest across all aetiologies, with the exception of vitamin B_6 and selenium. Long term insufficiency can increase susceptibility to infection (Black, 2003) and inflammation. The body is unable to maintain immunocompetence owing to an inability to manage oxidative stress, specifically in the older adult population and those with lung disease (Romieu, 2005). Further understanding of the specific role of micronutrients and their impact within bronchiectasis is required and adds to the knowledge of micronutrients that already exists in COPD (Scordotti et al., 2019), Cystic Fibrosis (McDonald et al., 2021b; Turck et al., 2016), and within the lung (Timoneda et al., 2018).

Intakes of micronutrients in bronchiectasis differed within BMI categories and within lung function categories (vitamin E, vitamin C, and folic acid respectively). This indicates that those with a BMI in the higher quartiles, consumed overall lower quantities of micronutrients. Prevalence of vitamin and mineral deficiencies have been reported in pre bariatric patients (Kaidar-Person et al., 2008) and in those living with obesity. Monitoring of serum and dietary

micronutrients in those living with obesity as part of care has been suggested (Kobylinska et al., 2022). It could be speculated that those with a higher BMI might have the poorest intakes or poorer dietary quality. Systematic review has reported an established inverse relationship with healthy eating index and obesity (Asghari et al., 2017). Healthy eating index measures the dietary intakes of individuals and groups against population or specific dietary requirements. The relationship observed reflects dietary intakes in those living with obesity does not meet population recommendations. Poor dietary quality has been reported as a key factor in assessing risk of developing obesity (Wolongevicz et al., 2010).

Greater impairment in lung function, may lead to an inability to consume sufficient micronutrient quantities. Evaluation of the relationship between dietary quality and lung function has been reported in a US population, where diet quality was independently associated with improved FEV_1 and FVC (Ducharme-Smith et al., 2021). The impact of symptoms on micronutrient intake and the evaluation of nutritional quality and quantity of diet and lung function needs exploration.

The difference observed in micronutrient intakes within the social indices groups is of interest. High levels of social deprivation, as measured by IMD, has been associated with lower overall dietary quality and lower consumption of fruits and vegetables compared with low levels of social deprivation (Irala-Estevez et al., 2000). This has been reported historically (Bates et al., 1999) and in review of dietary quality and social deprivation (Darmon and Drewnowski, 2008). Social deprivation may impact on food access, cost and dietary intake (Fougère et al., 2016), especially following COVID-19 (Mishra et al., 2021). Understanding further the relationship that may exist within identified social indices in those with bronchiectasis, may assist in considering tailored dietary advice that accounts for the influence of social deprivation.

Only intake of vitamin E was statistically significantly different across aetiological groups. However, mostly the lowest intakes of micronutrients were found in the younger, Primary Ciliary Dyskinesia (PCD) group with reported poorest handgrip (King et al., 2021). This has established an aetiological sub-group with poorer overall intakes of all micronutrients who fail to meet established Reference Nutrient intakes (RNI) (Department of Health, 1991) for their age and sex. It suggests that micronutrient deficiencies may exist and may impact immunity and susceptibility to infections. This is supported by studies that have established impaired growth in children with PCD (Goutaki et al., 2017; Svobodová et al., 2013). Understanding that vitamin D deficiency has also been reported (Ali et al., 2022; Marino et al., 2019) with insufficient dietary

intakes described in chapter 4 (King et al., 2021), strengthens the need to establish whether pathways leading to nutritional deficiencies in this sub-group exist.

5.6.2 Micronutrients and anthropometry

Within overweight and obese groups, micronutrients were noted to be low. In the whole population, micronutrients were also negatively associated with triceps skinfold thickness (TSF), as TSF increased, intake of micronutrients decreased (Figure 15 and 16). In this cohort, those with bronchiectasis and obesity, and/or greater levels of TSF may be consuming poorer micronutrient quality diets. Amplified inflammation is observed through production of adipokines e.g. TNF-α, IL-6, leptin, from adipocytes, present in those living with obesity (Khanna et al., 2022). Those with bronchiectasis have significant airway inflammation, resulting in impairment of lung function (Dente et al., 2015; Moldoveanu et al., 2009), which further exacerbates systems inflammation (McNeill et al., 2021). Combined, this may suggest those living with bronchiectasis and obesity have an overall greater level of inflammation. Future research should look to determine their characteristics, as a sub-group, and any association with micronutrient intakes, clinical and quality of life and inflammatory markers.

Of note, those classified underweight (n=5) (BMI <18.5kg/m^2) consumed the greatest micronutrient intakes across the BMI categories. Understanding diet quality index alongside micronutrient intakes in this group and its impact on markers of disease, will help to determine further, the role of micronutrients in optimising immunity in bronchiectasis.

5.6.3 Micronutrients and muscle strength parameters

Comparison of handgrip strength to normative values has revealed positive associations with micronutrient intakes, the strongest observed being zinc ($r = 0.412$ $p < 0.001$). The role of zinc in skeletal muscle metabolism is in muscle regeneration, activation of muscle cells and myogenesis (Hernández-Camacho et al., 2020) which favours improvement in strength. Intakes of zinc did not meet the RNI calculated for age and sex across aetiologies but are limited by lack of comparative serum levels. The role of zinc in the immune response is documented (Gasmi et al., 2020). It is required in both adaptive and innate immunity. Its role lies in T cell differentiation and proliferation, antigen cell function and antimicrobial activities (Maywald et al., 2017). It has been suggested that due to its association with lung disease it might be considered a

potential marker of disease (Liu et al., 2022; Gray et al., 2010). An early double-blind cross over trial, comparing individuals with bronchiectasis to healthy controls (Beeley et al., 1974) resulted in increased serum zinc levels but failed to establish whether deficiency existed or if zinc supplementation could achieve clinical improvements in patients. With only low numbers (n=65), this early work provides a basis for the role of zinc and other micronutrients in lung diseases. More recently Gray et al., (2010) reported participants with bronchiectasis had statistically significantly different elevated zinc levels in sputum, when compared with healthy subjects and those with COPD. Further, that zinc levels in sputum were associated with inflammatory markers and highlights zinc as a potential marker of inflammation in bronchiectasis. Recommendation for further trials to establish its therapeutic benefit (Javadmoosavi et al., 2013) that has been established in other lung diseases (Escobedo Monge et al., 2019) is called for. This study has reported reduced dietary intake of zinc when compared to national dietary survey levels. Considering the dual role both in lung immunity and muscle metabolism, dietary sources and supplementation of zinc should be explored in bronchiectasis. This population has shown dietary deficiency impaired hand grip strength and possible sarcopenia, where zinc may improve outcomes.

Magnesium intake was also found to be positively associated with handgrip strength in this cohort ($r = 0.30$, $p < 0.001$). In the body, it is involved in energy metabolism, and muscle contraction with deficiency leading to further oxidative stress which can damage muscle cells (Lukaski, 2004) this gives insight into this possible relationship. Presently, this is the only study to explore this in bronchiectasis, comparisons with COPD and magnesium intakes can be drawn from statistically significant associations with quality of life (St Georges Respiratory Questionnaire) ($p = 0.005$) and nutritional status markers (BMI, FFMI, FFM, HGS etc.). Whilst the latter was not statistically significantly different, higher values were seen in those with greater intake of magnesium (Ahmadi et al., 2022).

5.7 Strengths and Limitations

Whilst the collection of dietary intakes followed a validated and well-informed approach via 24-hour multiple pass recall, the data could be strengthened further by the inclusion of other methods of data collection that are specifically suited to considering frequency of consumption of micronutrients. Food frequency questionnaires do not capture dietary intake in its entirety (Thompson et al., 2015) but can be utilised to support and cross reference data on specific micronutrient intakes. Whilst this approach is considered in many data

assessment toolkits (Dao et al., 2019) the consideration of patient burden needs to be acknowledged. The use of multiple pass recall with additional food frequency might also be enhanced by utilisation of electronic methods for collection of this data. Future work that utilises a non-intrusive electronic device that can record dietary intake information should be considered (Thompson et al., 2010), along with triangulation of these methods that could improve accuracy of overall data collection. The limitations of nutrient databases have been discussed and outlined in chapter 3 but should be acknowledged here. Whilst limitations such as accuracy and completeness, cooking methods, and geographical location (Hannah et al., 2018), do exist the databases used, do house a considerable range of foods and their micronutrient content is utilised and created using comprehensive analytical methods and bio availability of those nutrients (Cade et al., 2019). To the authors knowledge there was no missing micronutrient data for the dietary intakes analysed. However, adjustments might include the addition of locally consumed foods and recipes. Where missing values exist the utilisation of other databases to match foods that have a comprehensive micronutrient list might also be considered (Lander et al., 2017).

Distribution of micronutrients across lung function and BMI groups were impacted by outliers. Outliers can impact on how the distribution appears and those that are considered due to measurement error, data entry or processing error. These should be removed. In this data, outliers observed were reviewed and remained in the data set, having been considered as true outliers with a natural variation to the population, in which case to remove them would have considerably increased type 1 error (Gress et al., 2018). Many alternative approaches might also be considered including statistical adjustments such as trimming or winsorisation. However, these methods can also be impactful on the true data sets. (Gress et al., 2018).

5.8 Conclusion

Whilst this study has not evaluated serum concentrations of micronutrients, it has clearly evidenced that specific micronutrient intakes do not meet current recommendations for RNI. These key micronutrients can attenuate inflammation, mucus secretions (de Boer et al., 2016; Marin-Hinojosa et al., 2021; Rodrigues et al., 2023) and within a balanced dietary intake, positively affect pulmonary function as seen in other respiratory diseases like COPD (Scoditti et al., 2019). Further work is now needed to consolidate these findings

in bronchiectasis and assess nutritional quality of intake, accounting for confounding factors such as social indices of deprivation (Gov.uk, 2020).

Strength and body composition assessment are associated with deficiency in micronutrient intakes, specifically zinc and magnesium. The impact of BMI and associated poorer dietary intake of micronutrients in those with bronchiectasis, requires further review. Considering the possibility of BMI masking potential sarcopenia, evidenced by poor HGS, is a further area if interest. Establishing whether sarcopenic obesity exists in bronchiectasis is required

This cross-sectional design is unable to infer causal relationships. However, future longitudinal studies are needed to explore dietary intakes further, quality of diet and serum micronutrient levels. The inclusion of body composition measures within studies, including HGS, may help in the evaluation of nutritional interventions and outcomes.

Chapter 6
Evaluating Hand Grip Strength as a prognostic tool in Bronchiectasis and Primary Ciliary Dyskinesia: A retrospective service study

6.1 Introduction

This study undertakes a retrospective service evaluation of hand grip strength (HGS) measures within the patient populations with bronchiectasis and Primary Ciliary Dyskinesia (PCD). In Chapter 4, a statistically significant impairment in HGS was reported (King et al., 2021), despite a mean BMI within the normal range, with over 70% of this group exhibiting reduced handgrip strength against normative values adjusted for age and sex. Consequently, the assessment of HGS using a handgrip dynamometer is incorporated as a standard care measure for all service users that attend the Leeds Regional Bronchiectasis and newly established PCD clinics, utilising the standard operating procedures discussed in Chapter 3. A standardised approach to measuring HGS, reduces variability and offers more homogeneous outcomes, as evidenced in a systematic review of 3 million participants (Núñez-Cortés et al., 2022).

HGS is gaining recognition in clinical settings for its role in identifying diminished nutritional status (Bohannon et al., 2019); its association with lung function in healthy (Mgbemma et al., 2022), and older populations, associated with morbidity, mortality, and activities of daily living (Lunt et al., 2021), it is also a component of the established definition of sarcopenia in the EWGSOP guidelines (Ackermans et al., 2022). This collectively demonstrates its value. It is also sensitive to changes in nutritional status responding more quickly to deficiency or repletion than measurement of overall muscle mass, (Norman et al., 2011).

Hand grip Strength assessment is recommended as a standard care measure in older adults (Lima et al., 2019) and is indicative of respiratory muscle strength in patients with bronchiectasis (Ozalp et al., 2012), and lung function in patients with COPD (Strandkvist et al., 2016, Suriyakul et al., 2022). In CF and COPD, it serves as a useful and simple tool to determine nutritional and functional parameters (Arinc et al., 2020; Contreras-Bolívar et al., 2021; Wu et al., 2019) with nutritional status and muscle wasting key prognostic and mortality indicators (Holden et al., 2021). The prevalence of sarcopenia is also significant in these conditions (Sepúlveda-Loyola et al., 2020), with relevance and use of

HGS in children and adolescents with CF promoted as an alternative to body composition for assessing nutritional status (Bouma et al., 2020; Cardoso et al., 2022). Initial exploration of HGS over time in a paediatric population with CF showed associations with vitamin D. It suggests further investigation into the role of HGS in nutritional assessment in paediatric CF populations is needed (Bellini et al., 2021).

The assessment of sarcopenia traditionally relied on direct measures via Magnetic Resonance Imaging (MRI), but the introduction of HGS assessment as part of the EWGSOP pathway, allows potential for sarcopenia screening at clinic or bedside, thus supporting early intervention strategies irrespective of BMI. It's association with respiratory muscle strength in hospitalised patients (Peterson et al., 2020) highlights its potential as a routine measure alongside promoting resistance training in older adults (Escriche-Escuder et al., 2021).

HGS is straightforward and quick to undertake utilising standardised procedures, minimising assessor variance and ensuring consistency in participant testing (Ha et al., 2018). Although, achieving consistently comparable outcomes remains challenging (Massierer et al., 2019). By incorporating HGS into standard care, and evaluating against standard assessment parameters, this study aims to elucidate further, the relationship between muscle strength and clinical outcomes in bronchiectasis and PCD. Additionally, it seeks to detect changes in HGS related to nutritional status and will enable identification of clinically relevant outcomes that inform intervention in areas of nutrition and muscle functionality. Determining if HGS is still impaired in this population (King et al., 2021) could help recognise vulnerable individuals and groups to establish the need for further investigation. Recognising the potential influence of HGS on disease severity could also lead to clinical consideration of tailored nutrition, which is currently lacking (Hill et al., 2019). This work could begin to contribute to the established body of work in bronchiectasis and identify a clinically relevant assessment, easy to complete at the bedside, that is not resource intensive but establishes early detection of possible interventional need.

This chapter will discuss the retrospective analysis of HGS data gathered, examining their adequacy compared to normative values over a one-year period. It is pertinent to note the impact of COVID-19 on delaying data collection and clinic access necessitating a retrospective rather than prospective study approach.

6.2 Aim

This retrospective study aims to assess HGS in a bronchiectasis and PCD cohort to establish the percentage of normative values and associations with other standard care outcomes.

6.3 Objectives

Primary Objectives

To examine retrospective values of muscle functionality, as measured by HGS in clinical populations of bronchiectasis and PCD against standard normative values for age and sex.

To assess retrospective HGS measures over a one-year period.

Secondary Objectives

To explore any associations of HGS to aetiology, lung function, BMI, number of infections, co morbidities and physiotherapy input.

To explore any associations with HGS over time to aetiology, lung function, BMI, number of infections, co morbidities and physiotherapy input.

6.4 Methods

A single site retrospective study within regional adult PCD and bronchiectasis services. Data were retrieved from clinical records recorded between October 2021 and October 2022 and included characteristics (age, sex, aetiology, and comorbidities (diabetes)) and the following clinical parameters (lung function (FEV_1%, FVC%), weight (kg), height (m), BMI (kg/m^2), HGS (Kg/f), HGS [% of normal value] as defined by Bohannon et al., (2006), number of exacerbations (requiring antibiotic treatment) within the study period, number of self-reported daily physiotherapy sessions and predominant microbiology. Data was extracted, coded and inputted into an excel spreadsheet for analysis. Any missing values were reported as zero where it was deemed appropriate for transferring to SPSS, these where then excluded from the data analysis.

All data was explored and analysed in accordance with reviewing the objectives of the study.

6.4.1 Statistical analysis

Data was analysed using IBM SPSS version 29 (IBM Corp, Armonk, N.Y. USA) for normality of distribution through Shapiro wilks. Non normally distributed data

were reported as percentages and median values with interquartile ranges (IQR), this was also applied were distribution differed. Kruskall-Wallis was used to determine differences between the medians of values, with the Dunn test applied if determination of differences and groups required identification. Fishers-Freeman-Halton exact was used for comparison of differences between categorical variables. Mann-Whitney U was applied for comparison between bronchiectasis and PCD groups and Wilcoxon for repeat measure comparisons within groups. Pearson´s (r) or Spearman´s (rho) correlations were used to explore associations of HGS with collected outcomes (lung function (FEV_1%), BMI, physiotherapy contacts and number of infections during data collection).

The total population of PCD and bronchiectasis clinic patients is approximately 350, accounting for a 5% margin of error and 95% confidence level, a sample size of 184 can be used to be able to determine any statistical significances in associations explored**.** Statistical results were deemed significant at <0.05.

6.4.2 Ethics

Due to the methodological nature of the study, analysing data as part of routine care, a Caldicott letter (Appendix H.3) was provided in support of analysing contact points against a standard measure (percentage handgrip compared to normative values) and exploring other standards of care measures collected throughout the duration. This exploration was not deemed to be generalisable via Health Research Authority and received University of Leeds Ethical approval on the 16$^{th\ of}$ February 2023.

6.5 Results

6.5.1 Total Population (n=201)

A total of 201 patient data were retrieved spanning the period October 2021 and October 2022. Each participant was reported as having PCD or bronchiectasis as the primary diagnosis. Sex distribution, age, weight, BMI, lung function, handgrip strength and handgrip strength compared to normative values, number of contacts, physiotherapy frequency, comorbidity, and number of infections in past year were collected and reported as characteristics in Table 18.

The population were predominantly female (55.7%) with the majority (70%) having bronchiectasis as the primary diagnosis. Median age was 53 years (IQR 17-88), with 70% of the population demonstrating impaired hand grip strength compared to adjusted normative values for age and sex.

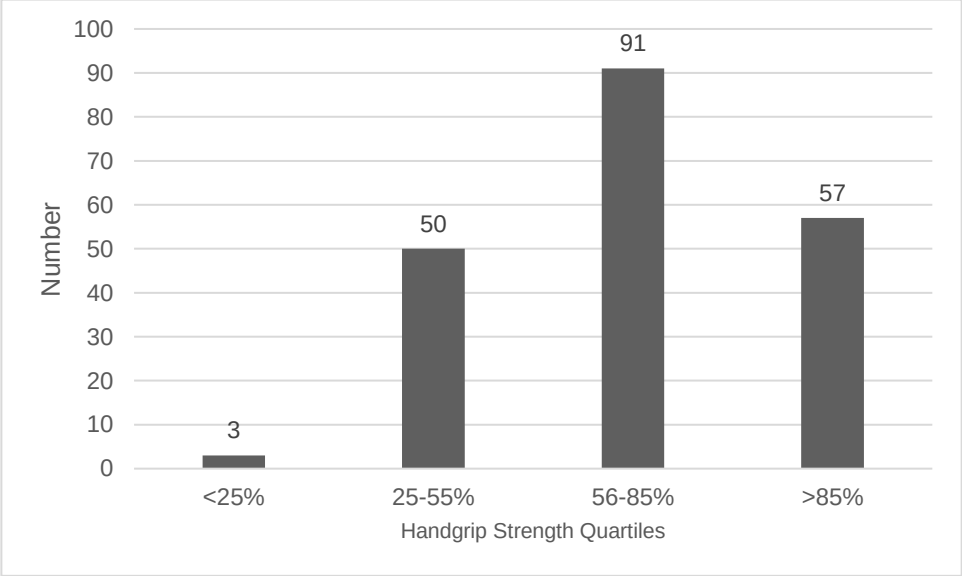
The group had a median number of two contacts within the study year and one contact with a physiotherapist, with only 7/201 (3.5%) having diabetes. The majority did not have microbiology isolated/reported (55.2%). Of o those who did have an isolated microbiology *Pseudomonas aeruginosa* was predominant (17.9%). The majority (37.8%) were from geographical areas considered to be in the highest deprivation, according to the Index of Multiple Deprivation (IMD) (GOV.UK, 2020), (Table 18)

Table 18. Characteristics of populations with Bronchiectasis and Primary Ciliary Dyskinesia (n=201)

	Number	Total participants Proportion (%) or median (Interquartile range)
Number (%)	201	201
Sex (M/F) %	201	91/110 (45.3)
Age (years)	201	53 (17-88)
Weight (kg)	200	68.5 (40.8-122.9)
BMI (Kg/m^2)	189	25.3 (15.1-40.4)
FEV_1 (%)	142	61.7 (22.2 – 112)
FVC (%)	141	75.0 (28.6 – 136)
Handgrip strength (Kgf)	200	22.3 (5.4 – 56.0)
Handgrip strength (% norm)	200	70.0 (19-134)
Aetiology • Bronchiectasis • Primary Ciliary Dyskinesia	201	 141 (70%) 60 (30%)
No of contacts (year)	201	2.0 (1-12)
Physio frequency (day)	144	1 (0-6)
Infections (number previous year)	138	0 (0 – 9)
Diabetes	201	7 (3.5%)
Microbiology n (%) ○ None isolated. ○ Haemophilus ○ Pseudomonas ○ Staph Aureus ○ Aspergillus ○ Other	201	 111 (55.2%) 17 (8.5%) 36 (17.9%) 14 (7.0%) 6 (3.0% 17 (8.5%)
Indices of multiple deprivation (IMD) • 1-3 high deprivation • 4-6 moderate deprivation • 7-10 low deprivation	201	 76 (37.8%) 66 (32.8%) 59 (29.4%)

When categorised by HGS % quartiles (Figure 26), 45.8% had HGS percentages between 56-85%, 24.8% had HGS percentages between 25-55% and 1.5% had percentage HGS compared to normative values ≤ 25%. In total, 71.6% of participants had impaired muscle functionality. This is combined with a median BMI of 25.3kg/m^2 (IQR 15.1– 40.4), identifying a population moving into the overweight classification.

Figure 26. Distribution of HGS % values within HGS quartiles (n = 201)



6.5.2 Handgrip strength over time (n=86)

A further sub-group of 86 participants were identified, where more than one handgrip measure was recorded throughout the period of study (one year), with the initial and end HGS taken for consistency across the participants. The characteristics of this group have been reported as a whole population (Table 19) and their clinical indices (Table 20).

Table 19 Population characteristics for (n=86) with baseline and follow-up HGS measures

Characteristic	Total population Proportion (%) or median (IQR)	p-value
Number	86	
Sex (M/F) %	41/45 (47.7% M)	0.83
Age (Yrs)	33 (26-58)	
No. contacts/year	3 (2-4)	
Diabetes n (%)	3 (3.5%)	
Microbiology n (%) • Non-isolated • Haemophilus • Pseudomonas • Staph Aureus • Aspergillus • Other	 23 (26.7%) 17 (19.8%) 24 (27.9%) 10 (11.6%) 2 (2.3%) 10 (11.6%)	<0.001*
Indices of multiple deprivation (IMD) n (%) • 1-3 high deprivation • 4-6 moderate deprivation • 7-10 low deprivation	 37 (43%) 27 (31.4%) 22 (25.6%)	0.13

Table 20 Changes in clinical indices from baseline to Year 1 for all participants (n=86) with longitudinal data

	Baseline	Year 1	p-value
Physio frequency (n/day)	2 (1-2)	2 (1-2)	0.53
Infections (number previous year)	1 (0-1.75)	0 (0-1.75)	0.67
BMI (kg/m^2)	24.6 (21.8-28.8)	25.0 (21.9-28.9)	0.89
FEV_1 (%)	59.5 (40.8-82.0)	61.0 (45.5-86.0)	0.09
Handgrip (Kgf)	22.8 (16.3-30.5)	23.3 (17.0-31.5)	0.16
Handgrip (% norm)	64 (51-80)	65 (50-84)	0.15

When the population was divided by their predominant diagnosis of Bronchiectasis and PCD (Table 21), 55% had a primary diagnosis of PCD with an almost 50/50 split for sex. There was a statistically significant difference between median ages when comparing bronchiectasis to PCD (55 years (±17-81)/27 years (±18 - 66), ($z = -5.2$, $p < 0.001$). No other statistically significant differences were observed between the primary diagnosis, except for initial FEV_1% ($z = 2.12$, $p = 0.03$). When comparing handgrip strength to normative values for age and sex there were no statistically significant differences between the baseline and end values (1 year) for the whole group (Table 19) and primary aetiology (Table 21). However, no median values reached the threshold of 85% of normative values (Madden and Smith, 2014).

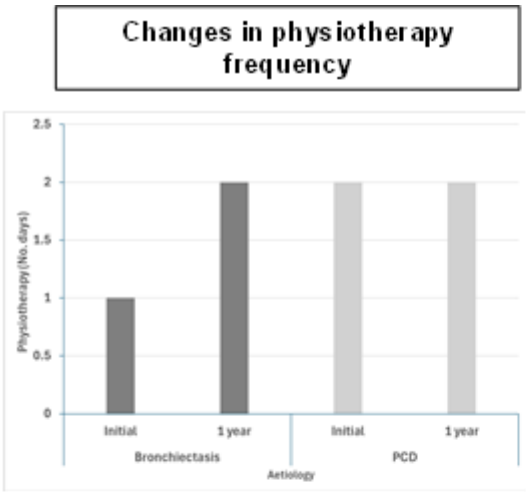
Table 21 Comparison of characteristics and longitudinal data (n=86) Bronchiectasis vs PCD

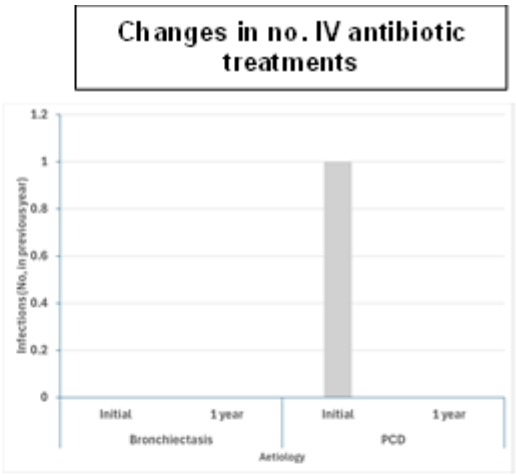
	Bronchiectasis (Proportion (%) or median (IQR))	PCD (Proportion (%) or median (IQR))	P value
Number (%)	39 (45%)	47 (55%)	
Sex (M/F) %	18/21 (46.2/53.9%)	23/24 (48.9/58.1%)	0.67
Age (Yrs.) (range)	55 (32-71)	27 (21-38)	<0.001**
No of contacts (yr.)	3 (2-9)	3 (2-12)	0.18
Diabetes	2	1	0.58
Microbiology n (%) • **None isolated.** • **Haemophilus** • **Pseudomonas** • **Staph Aureus** • **Aspergillus** • **Other**	 15 (38.5) 5 (12.8) 12 (30.8) 3 (7.7) 0 (0) 4 (10.3)	 8 (17) 12 (25.5) 12 (25.5) 7 (14.9) 2 (4.3) 6 (12.8)	0.13
Indices of multiple deprivation (IMD)			
• **1-3 high deprivation** • **4-6 moderate deprivation** • **7-10 low deprivation**	12 (30.8%) 14 (35.9%) 13 (33.3%)	25 (53.2%) 13 (27.7%) 9 (19.1%)	0.12
Physio frequency (No of days)			
Initial	1 (1-2)	2 (1-2)	0.66
1 year	2 (1-2)	2 (1-2)	0.83
Infections (number previous year)			
Initial	0	1	0.71
1 year	0	0	0.51
BMI (kg/m2)			
Initial	25.0 (21.9 – 29.7)	24.5 (21.8-28.8)	0.84
1 year	24.7 (22.0 – 28.7)	25.2 (21.5 -28.5)	0.83
FEV1%			
Initial	51.0 (22-102)	68.0 (26-112)	0.03*
1 Year	55.0 (18-96)	71.5 (23-112)	0.07
Handgrip (Kg/f)			
Initial	19.6 (12.8 – 30.4)	24.9 (18.5 -32.0)	0.12
1 Year	21.3 (16.5 – 28.5)	23.9 (17.4 -35.3)	0.36
Handgrip (% norm)			
Initial	62 (51 – 80)	65 (54 – 81)	0.29
1 year	66 (51 -85)	65 (50 – 84)	0.61

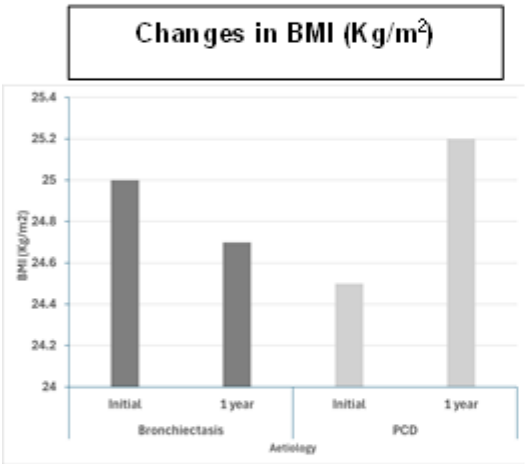
*Statistically significant p = <0.05 **Statistically significant p = <0.001

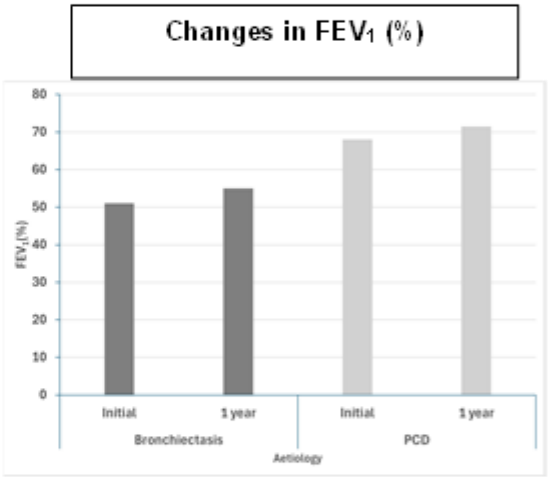
Change within aetiology is shown in Figure 27 and Table 22. No significant differences were observed from baseline to 1 year for any of the indices

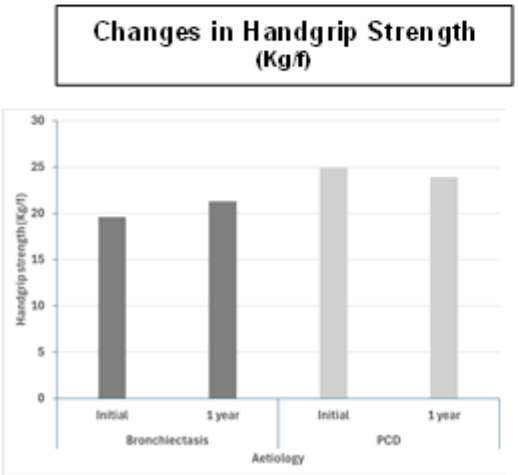
Figure 27 Changes in clinical measures within aetiological groups (Bronchiectasis and PCD) from baseline to 1 year.











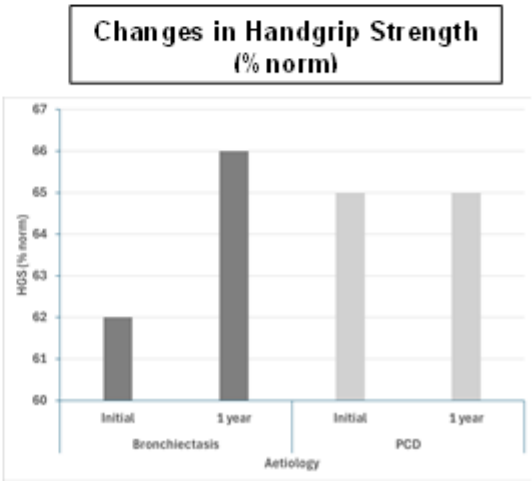


Table 22 Change in clinical characteristics at baseline and 1 year in bronchiectasis and PCD

	Bronchiectasis				Primary Ciliary Dyskinesia		
	Initial	1 year	P value		Initial	1 year	P value
Physio frequency (No of days)	1 (1-2)	2 (1-2)	0.32		2 (1-2)	2 (1-2)	0.26
Infections (number previous year)	0	0	0.78		1	0	0.46
BMI (kg/m^2)	25.0 (21.9 – 29.7)	24.7 (22.0-28.7)	0.28		24.5 (21.8 – 28.8)	25.2 (21.5 – 28.5)	0.57
FEV1%	51.0 (22.0 -102)	55.0 (18-96)	0.38		68.0 (26 – 112)	71.5 (23-112)	0.17
Handgrip (kg/f)	19.6 (12.8 – 30.4)	21.3 (16.5 – 28.5)	0.12		24.9 (18.5 – 32.0)	23.9 (17.4 – 35.3)	0.69
Handgrip (%norm)	62 (51 – 80)	66 (51 – 85)	0.15		65 (54 – 81)	65 (50-84)	0.59

6.5.2.1 Population (n=86) stratified by % of normative values

This population was also explored as stratified quartiles for percentage predicted handgrip strength (Table 23). This showed the majority (88.4%) had an impaired handgrip strength reflecting impaired muscle functionality (Smith and Madden, 2016), with only 10 participants having HGS considered not impaired (>85% of normative values).

Table 23 Characteristics of population (n=86) [stratified by HGS % norm quartiles]

	1st Quartile (<25%) Median (IQR)	2nd Quartile (25% -55%) Median (IQR)	3rd Quartile (56% - 85%) Median (IQR)	4th Quartile (>85%) Median (IQR)	p value
Number (%)	4 (4.7%)	27 (31.4%)	45 (52.3%)	10 (11.6%)	
Sex (M/F) %	1/3	11/16	24/21	6/4	0.47
Age (Yrs)	40.5 (25 – 64)	33.0 (26.0-68.0)	30.0 (22.0-54.0)	41.0 (22-72)	0.54
No of contacts (yr)	3.5 (2.25 – 7.75)	3.0 (2.0-6.0)	3.0 (2.0-4.0)	2.5 (2.0-3.75)	0.39
Diabetes	0	0	2	1	0.47
Microbiology n (%)					
○ **None isolated.**	1 (25%)	5 (19%)	9 (20%)	8 (80%)	
○ **Haemophilus**	0	9 (33%)	7 (16%)	1 (10%)	
○ **Pseudomonas**	2 (50%)	8 (30%)	13 (29%)	1 (10%)	0.004*
○ **Staph Aureus**	0	2 (7 %)	8 (18%)	0	
○ **Aspergillus**	1 (25%)	0	1 (2%)	0	
○ **Other**	0	3 (11%)	7 (16%)	0	
Indices of multiple deprivation (IMD)					
• **1-3 high deprivation**	1 (25%)	12 (44%)	22 (49%)	2 (20%)	
• **4-6 moderate deprivation**	0	8 (30%)	15 (31%)	5 (50%)	
• **7-10 low deprivation**	3 (75%)	7 (26%)	9 (20%)	3 (30%)	0.02*
Physio frequency (day)					
Initial	1.5	2.0	2.0	1.0	0.78
1 year	1.5	2.0	1.5	1.0	0.38
Infections (number previous year)					
Initial	0	0.5	1	1	0.99
1 year	0	0	0	1	0.72
BMI					
Initial	26.5 (23.3 – 34.2)	23.5 (21.5 – 27.0)	25.1 (21.4 – 28.6)	28.1 (25.9 -31.9)	0.11
1 year	26 (24.7 -33.2)	23.7 (21.3 – 25.5)	25.7 (21.2 – 28.3)	28.4 (25.7 – 31.6)	0.05
FEV1%					
Initial	61 (40.5 –86)	54.0(37.7-61.5)	70 (41 – 86)	74(51 – 103)	0.13
1 Year	74 (55.0- 74.0)	55.0 (36-62)	72 (45 -88)	74 (47-97)	0.10
Handgrip (Kgf)					
Initial	6.8 (5.8 -10.9)	14.4 (11.9 – 24.6)	25.4 (20.1 – 32.3)	41.2 (24.0-47.3)	<0.001**
1 Year	10.2 (7.5-22.7)	17.4 (13.1 – 24.9)	24.5 (20.4 -35.8)	38.4 (22.6 – 43.6)	<0.001**

***Statistically significance p = <0.05 **Statistically significance p = <0.001**

6.5.2.2 Association of HGS initial and end values with outcomes.

HGS values at baseline and end (1 year) within the 12-month period, showed some small statistically significant associations (Table 24).

Number of contacts (baseline) (r (84) = - 0.228, p=0.03) and physiotherapy contacts (baseline) (r = (84) - 0.266, p = 0.02) were found to be associated with HGS (baseline) (Table 24).

No statistically significant associations were seen in baseline values when comparing HGS to lung function (FEV_1%) and BMI (r (84) = 0.143, p = 0.22, r (84) = 0.197, p = 0.06 respectively).

When reviewing end (1 year) values for HGS and other care outcomes at 1 year, there were associations found with episodes of physiotherapy, which showed the strongest association (r = (84) -0.374 p = 0.001) with BMI (r = (84) 0.226, p=0.03), and also number of contacts (r = (84) -0.293 p = 0.006). All values are reported in Table 24.

6.5.2.3 Comparison of HGS % (norm) initial and end values with collected outcomes.

Exploration of the relationship associated with the baseline HGS % of normative values and outcomes FEV_1% can be found in Figure 28. This showed a very small statistically significant association with FEV_1% across the population (n=86), (r = (84) 0.234, p=0.04) with an 85% normative threshold line applied for comparison (Figure 28)

All other outcomes compared showed no statistically significant associations (BMI (r = (84) 0.205, p = 0.05), No of contacts (r = (84) -0.159, p = 0.14), physiotherapy contacts (r = (84) -0.126, p = 0.28) number of infections (r = (84) 0.01, p = 0.93)) (Table 24).

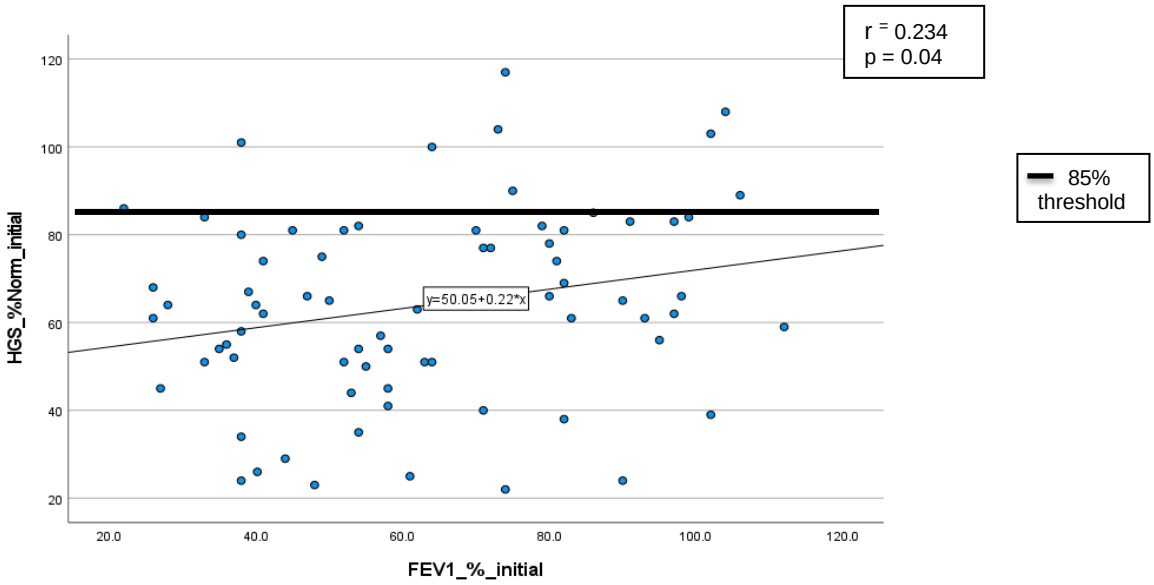
Reviewing the values at end (1 year) only number of contacts (r = (84) -0.349, p< 0.001) and physiotherapy contacts were associated (r = (84) -0.285, p=0.01) with HGS % of normative values (1 year).

Table 24 Associations of HGS and HGS % values and clinical indices (n=86)

	Baseline value		End (1 year)	
	HGS (kgf)	**HGS %**	**HGS (kgf)**	**HGS %**
FEV1% (Initial)	0.143 (p = 0.22)	0.234 (p = 0.04) *	0.154 (p = 0.19)	0.213 (p = 0.06)
FEV1% (1 year)	0.180 (p = 0.12)	0.192 (p = 0.10)	0.194 (p = 0.10)	0.213 9 (p = 0.07)
BMI (kg/m²) (Initial)	0.197 (p = 0.06)	0.205 (p = 0.05)	0.165 (p = 0.12)	0.167 (p = 0.12)
BMI (kg/m²) (1 year)	0.242 (p = 0.02) *	0.209 (p = 0.05)	0.226 (p = 0.03) *	0.199 (p = 0.06)
Physiotherapy contacts (Initial)	-0.266 (p= 0.02) *	-0.126 (p = 0.28)	-0.331 (p= 0.004)**	-0.244 (p = 0.03)*
Physiotherapy contacts (1 year)	-0.295 (p = 0.01) *	-0.155 (p = 0.19)	-0.374 (p = 0.001)**	-0.285 (p = 0.01)*
No of infections (Initial)	0.046 (p= 0.71)	0.011 (p = 0.93)	-0.015 (p= 0.90)	- 0.022 (p = 0.85)
No of infections (1 year)	-0.097 (p = 0.43)	-0.054 (p = 0.66)	-0.057 (p = 0.64)	-0.002 (p = 0.98)
No of contacts (Initial)	-0.228 (p=0.04)*	-0.159 (p = 0.14)	-0.293 (p= 0.006)**	-0.349 (p <0.001)**

***Statistically significance p = <0.05 **Statistically significance p = <0.001**

Figure 28. Scatterplot initial HGS % norm and initial FEV_1%.



6.6 Discussion

This retrospective study sought to determine if a population who attended either a bronchiectasis or Primary Ciliary Dyskinesia regional clinic still had impaired handgrip compared to adjusted values for age and sex, following implementation as a standard care measure in the clinic setting. In addition, as measures were collected over a period of one-year, longitudinal data was hoped to be able to compare changes in handgrip strength over time and with other clinical parameters, normally assessed as part of routine clinical care appointments in practice.

6.6.1 Handgrip strength measures compared to normative values.

Handgrip strength (HGS) measures of participants attending clinic showed that the majority (70%) still have impaired handgrip strength (HGS). This reflects the results discussed and published in chapter 4. Whilst no statistically significant difference was found between the 2 populations for HGS %, the median value still failed to meet the threshold of > 85% of normative values. HGS is emerging as a quick and useful tool to determine muscle impairment over time, its use in respiratory disease such as COPD and CF is established in systematic review and meta-analysis and associated with lung function and overall lower muscle strength (Holden et al., 2021; Wu et al., 2021). In bronchiectasis, Ozalp et al., (2012) reported HGS along with other outcomes such as respiratory muscle strength in determining outcome measures appropriate to assess following pulmonary rehabilitation programmes, reporting an association with respiratory muscle strength. Wang et al., (2022) found percentage handgrip strength in bronchiectasis was deficient when compared with controls. This research supports existing work to strengthen the consideration of its use as standard care measure within bronchiectasis and PCD. HGS as measure is now part of the European Working Group on Sarcopenia in Older People (EWGSOP) algorithm. It is included to assess for probable sarcopenia, and if identified as impaired, should trigger consideration of causes and intervention in isolation. Cut offs have been reported as 32kg for males and 22kg for females across all age groups (Bahat et al., 2016). The value HGS % compared to normative values adjusted (age and sex), reported in this study and the study in chapter 4, is useful in determining overall impairment of these groups. When reviewing respiratory disease and HGS, to the authors knowledge, this value is not reported. It does provide a ready reckoner at appointment and is inclusive of a range of values for determining impairment and subsequent changes as opposed to absolute values. Cut off values and overall HGS are useful to

observe changes over time when assessing individual regimens for influencing grip strength.

The measures collected for HGS utilised standard operating procedures (SOP's) for handgrip strength measure (Appendix C.3), which ensure consistency and accounts for variations in outcomes (Núñez-Cortés et al., 2022). Anthropometric assessment of HGS has shown SOP's require test-retest reliability (Karagiannis et al., 2020), and with the use of standard operating procedures in respiratory research globally, (Suriyakul et al., 2022), this embedding in care would ensure consistency in findings. Systematic review exploring handgrip strength and lung function, in both healthy adults and adults deemed as unhealthy, have shown statistically significant associations between the 2 measures, despite reported heterogeneous protocols in the research studied (Mgbemena, et al., 2022). This strengthens further, its reliability in this study when SOPs are utilised. Lower HGS is associated with poorer quality of life, increased morbidity, and likelihood of death in COPD (Holden et al., 2021) with similar findings in cystic fibrosis (Contreras-Bolívar et al., 2021) and therefore could have equal associations in this respiratory group.

Whilst the results from this retrospective evaluation are not generalisable, it supports the emerging role of HGS measures in local bronchiectasis and primary ciliary dyskinesia (PCD) populations, similar to other respiratory diseases, where relationships with lung function, and inspiratory and expiratory pressure and identified sarcopenia are emerging (Polastri et al., 2023). Clinical implications of not considering this as a useful tool for daily use as part of standard care could result in individuals with poorer outcomes not identified through traditional nutritional status measures such as BMI. Its value across many clinical areas (Scherbov et al., 2022, Luengpradidgun et al., 2022) is increasing and this evidence shows that impairment exists in the majority of the population which may have significant impact on clinical outcomes and associated quality of life (Barbosa et al., 2023).

Caution is needed when interpreting the data, confounders such as physical activity and medication (including steroids and beta blockers) were not adjusted for as this data was not collected as part of routine care and therefore could not be quantified in this retrospective methodology. Greater or lower physical activity can influence HGS results as can medication affecting muscle performance to a greater or lesser extent with further confounders including inflammation, motivation or effort when undertaking the test itself (Ribeiro et al., 2024). Whilst this was considered as part of the SOP, full demonstration of effort could not be assured as the researcher was not present at the time the measure was taken. This can be mitigated by increased frequency of

measurement and collection of physical activity data, through pedometer or other validated tools. Reporting of prescribed medication and inflammatory and frequency with adjustment through statistical analysis, would adjust for the influence of confounders associated with the HGS measure.

6.6.2 Handgrip strength and comparisons with infections, comorbidity, frequency of physiotherapy contact, no of contacts (year), BMI, and FEV_1%.

Only frequency of physiotherapy and number of contacts during the data collection period were statistically significantly associated with HGS. The relationship was inverse between the number of times individuals reported daily physiotherapy and their HGS value. This has also been seen in other respiratory diseases, were resistance training and physical activity are advocated to improve muscle functionality and improve overall health outcomes (Firat et al., 2022; O'Shea et al., 2009). Whilst frequency of physiotherapy (for clearing the chest of sputum) is needed for effective management of the condition, in this analysis, those who reported more episodes of physiotherapy, had a weaker HGS. This inverse association was also seen with number of contacts and HGS. An explanation for this might be that frequency of physiotherapy contact is initiated in response to clinical need, as are number of contacts within the clinic setting. Increased frequency of contact for both, may likely be associated with poorer health and wellbeing requiring greater numbers of contact, and more frequent episodes of illness or exacerbation. In turn, these increased episodes of illness may impact on strength and result in poorer nutritional status and therefore poorer handgrip strength. Although these results cannot infer a causal relationship, they begin to offer some insights into areas that require further study to determine any association and offer reason for why HGS was inversely associated with more frequent contact and physiotherapy. Exploration of this outcome in a clinic setting is important to further evaluate. Discussion of coordinated physiotherapy and dietetic treatment is also needed.

When reviewing data at the start of the collection period (baseline), no statistically significant associations were associated with HGS and the baseline values for infections during the study period, comorbidity of diabetes, lung function and BMI. This was not the case with BMI and data at the end of study (1 year). Measures reported at the end of the data collection period showed BMI at 1 year was weakly associated with HGS (both baseline and at 1 year), (r 0.226 p= 0.03). Further exploration and analysis are needed in greater numbers prospectively, to confirm if this is a true association and to understand the long-

term implications of impaired HGS on the measured clinical outcomes for this condition.

6.6.3 Handgrip strength as a percentage of normative values and comparisons with infections, comorbidity, frequency of physiotherapy contact, no of contacts throughout the year, BMI and FEV_1%.

When using values adjusted for age and sex, HGS % and FEV_1% was statistically significantly associated (r (84) 0.234, p=0.04), This relationship was also observed in Chapter 4 and may be a future clinical consideration. This relationship could also potentially impact on respiratory muscle affecting lung function over a prolonged period. Continued measurement of HGS at regular clinic appointments for effective surveillance is warranted. Those with bronchiectasis had worse HGS when compared with the PCD group (± 5.3kg/f) which contrasts with previous outcomes in this group (King et al., 2021). These sub optimal HGS values may be associated with age-related sarcopenia (Cruz-Jentoft et al., 2021) in the bronchiectasis group, coupled with impact of disease and deterioration in lung function. The younger PCD group still had impaired HGS when compared to normative values (65%). This retrospective data analysis has shown that again, HGS is a useful measure that could contribute to the overall clinical picture and progression of this under researched and vulnerable population, with potential to contribute to understanding of disease progression through its association with lung function. Where thresholds are not reached HGS could identify those at risk of sarcopenia and initiate appropriate and effective nutritional intervention to improve outcomes. HGS could be considered as a further measure that contributes to the bronchiectasis registry research network (EMBARC). Agreement on standard operating procedures, and clinical practice, along with protocols for intervention is needed.

6.6.4 Strengths and Limitations.

Strengths

This is the first study to review HGS over time in populations with Bronchiectasis and PCD. Measurements were conducted utilising standard operating procedures to ensure consistency in completion and recording. This was developed by an ISAK accredited dietitian which strengthens the results.

Participants were not recruited but included as part of previously agreed consent as part of ongoing research. This enabled analysis of data from

standard care that is recorded on the electronic patient record, allowing larger numbers of data to be accessed and strengthens the validity of the outcomes.

Limitations

Data was collected as part of routine care, without direct intervention by the researcher with participants. There were missing data points, which were excluded from analysis. When data points are absent assessment of their nature is key to determining how to manage them within the reporting (Popovich, D., 2025). Imputation can be utilised if data is missing at random (MAR). This was not the chosen method here as the data was deemed missing not at random (MNAR) and likely associated with attendance and engagement at clinic, reduced clinical need or inability of patient to undertake the required assessment. The deletion method can considerably reduce the analytical power of any statistical data presented (Dziadkowiec et al., 2020). This approach also limits consistency in the comparability of the results, accuracy against the objectives set, and it reduces sample size and representation.

Whilst employment of a standard operating procedure was undertaken, repeated random assessment of practice undertaken by the health care team was not completed due to COVID-19. This could result in inconsistencies and therefore validity in some measures. Potential measurement error needs to be considered in any conclusions drawn.

Normal clinic attendance is a minimal annual appointment. Contact is based on medically assessed clinical need at time of assessment, or early attendance based on presenting symptoms. In the sub population of 86 participants (studied due to having more than one contact with a recorded HGS), this could reflect a cohort that is more unwell and required more contact which could have skewed the results. This also resulted in participants with inconsistent numbers of HGS taken. Analysis may have yielded more significant outcomes if contact was a constant not intermittent factor.

A prospective approach would have resolved this challenge by introducing identified points for comparison over the period of a year e.g., 1,3,6,9 months but was limited by the impact of COVID-19. Lastly, whilst standard care measures are completed at each contact. There may have been varying reasons outside of the healthcare assessors' control for lack of completion e.g. pulmonary function test. This resulted in inconsistent numbers for the outcomes assessed and may have impacted on the results found.

Retrospective analysis by its nature also lacks a healthy control group to enable a direct comparison (Talari and Goyal, 2020). This population were older and therefore results could misrepresent others within the population e.g. younger

groups. Overall, this reduces generalisability. This data was also collected during a time of restrictive practice (COVID-19) that resulted in less face-to-face contacts. This may have influenced the results collected as those with greater clinical need may have attended. Comparison of this data to other times or when restrictions were lifted in settings would provide a greater understanding of any influence of restrictive practice.

6.7 Conclusion

This retrospective study is the first to review routinely collected data for HGS in regional Bronchiectasis and PCD population and confirms that HGS is still impaired (70%), 4 years on. Handgrip strength measures are associated with poorer lung function in COPD (Wu et al., 2019), Cystic Fibrosis (Holden et al., 2021) and Asthma (Hessleberg et al., 2023) and concerningly in children with PCD (Firat et al., 2022) and should be routinely measured in respiratory disease (Polastri et al., 2023) and specifically bronchiectasis (Wang et al., 2022). Exploration of nutritional and physical practices to improve HGS along with body composition changes is needed to develop appropriate and valid interventions to improve HGS and associated outcomes. Bronchiectasis and PCD populations are similarly affected, however the mechanism for impairment is likely different. The former are older and with poorer lung function due to ageing and disease progression and the latter, overall poorer lung function and handgrip strength despite being younger, this warrants further exploration to understand better the clinical implications and any associated impacts on quality of life. This retrospective data analysis confirms that handgrip strength is still a valid measure within the clinic setting and further investigation to improve these individual values is needed. HGS should be included in future research in bronchiectasis and PCD and continue to be monitored as part of routine care were appropriate treatment and intervention can be provided.

An example of an algorithm for assessment and decision making over support following handgrip strength measurement in clinic can be found in Figure 29. Subsequent intervention with physiotherapy and dietetics that are outlined would need to be specific to the individual, and consider many factors but should include the following key aspects as a baseline: -

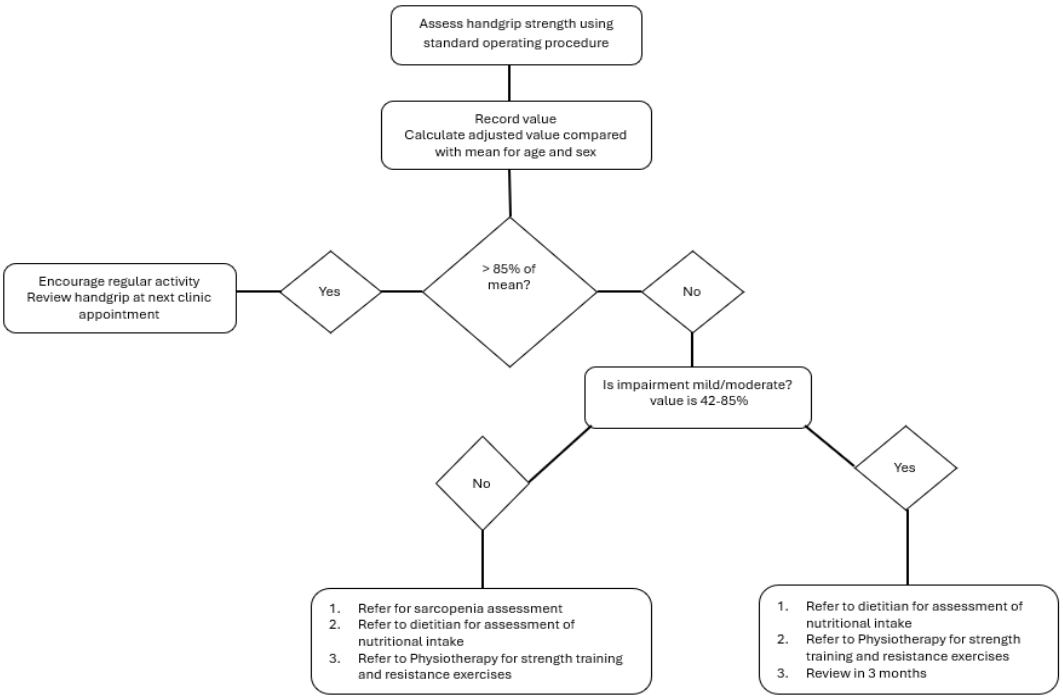
Physiotherapy

- Strength and resistance exercise such as those used in rehabilitation services (Labott et al., 2019, Silva Neto et al., 2022).

Dietetics

- Protein and energy intake
- Types of protein
- Protein distribution to determine regularity of intake (Jesperson and Agergard.,2021)
- Assessment of vitamin D intake and serum levels (Zhang et al., 2022)

Figure 29 Proposed clinical pathway for care following handgrip measurement



Its identification adds further the need to consider this a measure collected as part of routine care and an outcome within the European registry (EMBARC).

Chapter 7

Exploring consumption of nutritional supplements in primary ciliary dyskinesia: a feasibility study.

7.1 Introduction

In Chapter 4 and 5 population characteristics and dietary intakes, were reported in a subgroup with bronchiectasis, who had primary ciliary dyskinesia (PCD). The finding that handgrip strength (HGS) was impaired, in adults with PCD and that the measurement was a significant predictor of lung function resulted in the use of handgrip strength as a standard care measure within the PCD and Bronchiectasis regional clinics. In Chapter 6, a retrospective analysis identified a sustained impairment in HGS in individuals with PCD, despite this being a a predominantly younger cohort. These findings informed further exploration of nutritional and clinically relevant interventions to support the management of PCD.

PCD is a genetic autosomal recessive disorder, affecting approximately 1 in 7,500 people globally (Hannah et al., 2022). It is characterised by absent or dysfunctional cilia, that leads to impaired mucociliary clearance and suppurative lung disease. In turn this results in acute and chronic respiratory infections and energy intense breathing (King, 2009; Leigh et al., 2019) requiring repeated antibiotics and intensive physiotherapy (Kuehni and Lucas, 2017).

The focus of intervention has previously been on diagnostic criteria and disease pathology. However, a range of clinical manifestations are now emerging which contribute to knowledge of the disease (Goutaki et al., 2016). Whilst respiratory symptoms predominate (Kuehni et al., 2010), a recent systematic review and meta-analysis characterised the multitude of associated complications including congenital heart disease in 5% of cases (Goutaki et al., 2016), nasal polyps, sinusitis, situs anomalies, hearing loss and infertility (Bush et al., 2007; Rubbo et al., 2020; Shapiro et al., 2016).

As the clinical characteristics of PCD become more clearly defined, the potential role of nutrition in disease management has emerged. In a cross-sectional study from the international Primary Ciliary Dyskinesia Cohort, reduced growth was demonstrated across all age groups and low BMI noted in those < 9 years (Goutaki et al., 2017). Positive associations between BMI and lung function were also observed. These findings are supported by 2 further studies in smaller cohorts (Marino et al., 2018; Rubbo et al., 2020), which recommend that

early nutritional surveillance and intervention is warranted. In turn, it has given rise to analogies with Cystic Fibrosis, where similar associations between BMI and lung function are evident and early stratified nutritional interventions have been highly effective in improving clinical outcome (Calella et al., 2018; Woestenenk et al., 2013). Despite this no defined nutritional interventions are yet proposed for PCD, primarily due to a lack of evidence (Lam et al., 2022; Mirra et al., 2017).

In Chapter 6, a young population living with PCD with significant impaired handgrip strength was identified. These findings add to the previous research and prompted further exploration of effective nutritional interventions to improve HGS and lung function in PCD. There is growing interest in the role of protein, associated with muscle wasting and sarcopenia (Engelen et al.,2014; van Bakel et al., 2021). More specifically, increased quantities of leucine have been shown to contribute to improved muscle strength, physical performance, and overall lean mass in older adults with sarcopenia (Martinez-Arnau et al., 2019; Ispoglou et al., 2016). Evidence suggests that a synergistic impact of increased protein, in the form of a specific essential amino acid mixture high in leucine, alongside resistance exercise training, offsets an uncoupling of the mTOR signalling pathways (which controls cell growth), although mechanisms are not fully known (Rehman et al. 2023), this governs protein synthesis and breakdown. (Ispoglou et al., 2016). This may have additional significance in PCD, as the sarcopenic process in chronic respiratory conditions, is known to be exacerbated still further by the increased inflammatory response inherent within progressive disease pathways (Gea et al., 2018, 2020; Jones et al., 2015; van Den Borst et al., 2011). Sarcopenia has also been shown to correlate with systemic inflammation in COPD (Byun et al., 2017). Leucine supplementation may therefore offer benefits. This mechanism has not been explored in PCD, but its importance in prevention of muscle loss (Rehman al., 2023) through measurement of HGS is warranted.

When leucine supplementation can be combined with Vitamin D, there may be additional benefit and reduction in medication burden for patients. Increased inflammation within the lung is associated with vitamin D deficiency specifically within respiratory diseases (Ahmad et al., 2021; Ferri et al., 2019; Moustaki et al., 2017) due to its role in maintaining airway homeostasis and in the host defence within the lung (Chishimba et al., 2010). Vitamin D is part of both the innate and adaptive immune response. The essential anti-inflammatory role of Vitamin D Binding Protein (VDBP) is well documented. (Janssens et al., 2009; Hall and Agrawal, 2017). Insufficient serum levels have been associated with increased inflammation in the airway, increased exacerbations, and poor lung

function (Hall and Agrawal, 2017). Vitamin D deficiency has been documented extensively across respiratory disease (Chalmers et al., 2013b; Daley et al., 2019; Hall et al., 2010, Maes et al., 2020), with emerging development specifically in PCD, within paediatric populations (Sergi et al., 2021). The role of vitamin D supplementation in respiratory disease, and in preventing respiratory tract infections (Martineau et al., 2017) has been discussed extensively within Chapters 2,4, and 5 in this work and its inclusion, as supplementation within this feasibility study is warranted.

In the following chapter, the impact of nutritional supplementation on nutritional status is considered in PCD. The aim is to provide insight into the impact of a nutritional intervention, an area that has not been previously studied (Rubbo et al., 2020). The feasibility of consumption of leucine enriched amino-acid supplementation was considered appropriate to identify clinically important outcomes in PCD. Similar work has been undertaken in a small population of 60 older adults with bronchiectasis. In this study, the authors reported improvements in nutritional status and strength parameters with a supplement drink containing β-hydroxy-β-methyl butyrate (HMB), (a form of leucine) (Olveira et al., 2016).

7.1.1 Impact of COVID-19 pandemic

The COVID-19 pandemic impacted on the methodology in two ways; firstly, through the cessation of outpatient clinics and inability to attend in person for approximately one and a half years, and secondly the limitations associated with the gel supplement expiry date. The supplements were specifically manufactured prior to COVID-19 in preparation for the study. Delays imposed by the epidemic necessitated changes to the original duration of the study. A modified study was therefore proposed; the investigation becoming a feasibility study of 3 months duration. The aim was to establish tolerability of the supplement gel and potential impact on usual dietary intake and specific clinical and patient outcomes. This was a minimal timeframe to establish changes in clinical outcomes that might inform future research. In this chapter the feasibility and outcomes of the intervention are presented.

7.2 Aim

This study aimed to explore the feasibility, acceptability, and clinical impact of leucine enriched amino acid oral nutritional supplementation gels.

7.3 Objectives

1. To evaluate the acceptability and palatability of a leucine enriched amino acid oral nutritional supplement.
2. To evaluate nutritional intake at baseline and 3 months
3. To determine the impact of a specific amino acid supplement on lung Function (FEV1%), Body Mass Index (BMI) kg/m^2, Handgrip Strength (Kg/f) and Serum Vitamin D status (µmol)
4. To evaluate anthropometric and functional capacity measures at baseline and 3 months including Bio impedance analysis (BIA), Triceps Skinfold (TSF) (mm), Mid upper arm circumference (MUAC) (cm), Mid Upper Arm Muscle Circumference (MAMC) (cm)Quality of life (SF-36, SGRQ), Six-minute Walk test, Habitual Activity Estimation Scales (HAES)
5. To compare those participants consuming >50% v ≤50% supplements.

7.4 Materials and Methods

The following methods used as part of this study have been reported and discussed in Chapter 3 but are further outlined here as reference.

Study design: A feasibility study was chosen to enable assessment of the viability of a larger multi-site randomised trial. This included operational practicalities, the acceptability of supplementation, optimisation of resources and cost. Identifying the potential challenges and how risks are mitigated were key components of this approach, which was intended to underpin decision making for future costs and trial design. Initial recruitment of contained, smaller number of participants, allowed an ethical approach to answering these questions. The choice of a feasibility study also enabled the identification of appropriate and beneficial outcomes (Pearson et al., 2020), within a new and emerging area of research. These multiple factors, together with the use of a supplement, not yet trialled within a clinic population, informed the choice of a feasibility study as an appropriate approach that could determine clinically relevant future research and evaluations trial (Eldridge et al., 2016a). It is therefore an effective method to determine assessment of future use of the supplement (Rajadhyaksha, 2010).

Inclusion Criteria: Patients were eligible for inclusion if they were 17 years and over, were clinically stable, attended the regional PCD clinic, and had a confirmed diagnosis of PCD (nasal brushings).

Exclusion criteria: Patients were excluded if they were pregnant, had a malignancy, renal insufficiency, connective tissue, or immunoglobulin deficiency. The sample size was determined by recruiting until the expiry date of

the supplements, due to the impact of delay in COVID-19 pandemic and therefore this gave a finite window of 9 months.

Participant recruitment: Participants were recruited sequentially from consecutive clinics in a 9-month period (May 2021-November 2021), from a total clinic cohort of 54 patients. Each participant was screened by a lead consultant for the presence of established PCD and contacted via telephone by the researcher who outlined the study and provided participant information and contact for queries. Written participant information (Appendix I.3) was sent to all interested participants prior to their next scheduled clinic appointment. Participants were approached by the researcher at their next clinic appointment and written consent was obtained.

Supplement composition: The supplement formulation was a mix of leucine rich (40%) essential amino acids, with additional vitamin D (12.5 µg of vitamin D3 (cholecalciferol)) developed as a gel pouch (65g); the latter required as a supplement in a population with PCD (Mirra et al., 2015; Sergi, 2021). Each sachet (65g) contained 113.6 kcals and 7.5g of essential amino acids (Appendix J). This formulation was assured by VitritionTM (Vitrition UK, Ltd) who manufactured the product and completed microbial safety checks.

7.4.1 Intervention

Each participant was provided with 168 gel sachets (2/day; 1 post breakfast and 1 post lunch). Participants were instructed not to store the supplements near a heat source and recommended to place in the fridge to chill prior to consumption. An additional bag was provided to retain used sachets. Participants were asked to return any used and full sachets at the 3-month clinic appointment. Measures were collected at baseline in clinic in the initial recruiting appointment and at 3-month appointment (scheduled at baseline). Main outcomes of the study (palatability and acceptability scales and 24 hour recalls) were also collected at month one and two, via telephone appointments. The key steps in the pathway of the feasibility study can be found in the study flow chart (Figure 30). All recruited participants received the gel supplement as outlined above as part of the intervention, with toleration to the gel supplement considered at each contact point.

7.4.2 Outcome measures

The following measures were undertaken for this study at baseline, 1, 2 and 3 months to meet the objectives set.

Palatability and acceptability: Visual Analogue Scales (VAS) were used to determine overall ranking of visual appeal, smell, taste, aftertaste, and palatability. Individual and composite scores were calculated for overall palatability. The hedonic rating scale, ranking appearance, aroma, taste, sweetness, and texture/mouthfeel is a five-point reference scale (one = like a lot and five = dislike a lot). Median scores were calculated to give overall palatability. Both methods can be found in (Appendix G) and were used to determine if ranking differed dependent on the scale used.

Dietary intake: 24-hour recalls using multiple pass recalls technique (MPR) – were undertaken for each participant at, baseline, and then monthly for three months. Dietary recalls at baseline and three-month assessment were completed face to face in clinic with month one and two completed via telephone. Dietary recalls were analysed using Nutritics software (Nutritics, 2019) to determine, total energy intake and protein intake along with vitamin D. Baseline values were reported as collected, and 3-month values as a mean of month 1, 2, and 3, calculated with values from supplementation of gels as per protocol (2/day) and without to compare differences that adherence to protocol could have on intake. Vitamin D intakes were compared with national recommendations for intake (10µg/d) (SACN, 2016).

Calculated estimated requirements: Each participant's estimated energy requirements were calculated using fat free mass measures derived from BIA assessment (baseline and 3 months) (30 x FFM (kg) x PAL) (Todorovic and Marfrici, 2018). The level of reported activity from the Habitual Estimation Activity scale (HAES) was used to calculate the Physical Activity Level (PAL) for each participant. There is no existing evidence to recommend specific protein requirements in this population, therefore estimated protein requirements were calculated using two methods for comparison the first utilising FFM values as reflected in the calculation of energy requirements, FFM x 1.5g/d (Dekker et al., 2022), and the second using ESPEN guidelines 1.5g/kg/day (Duetz et al., 2014). Comparison of mean dietary intake of energy and protein at baseline to three months, with and without supplementation were compared to calculated estimated requirements. In addition, each participant Basal Metabolic Rate (BMR) was calculated using the Schofield equation to apply the Goldberg cut off to determine under reporting of energy intakes (Goldberg and Black., 1991)

The following nine measures were undertaken for this study at baseline, and 3 months: -

Pulmonary Function - spirometry ($FEV_1\%$) was assessed by means of standard spirometry using a Vitalograph Compact II Spirometer (Vitalograph Ltd, UK). FEV1 and FVC were compared with reference values and reported as the percentage of the predicted normal value (Stanojevic et al., 2022).

Body Mass Index (BMI) - Weight (kg) and height (m) were collected using calibrated SECA weighing scales (SECA 956 Class III, SECA, Birmingham. UK) and Leicester Height measure (MK II, SECA, Birmingham, UK). Body mass index (BMI) was calculated for each participant using the equation ($Weight/Height^2$).

Handgrip strength (peripheral muscle strength) - was evaluated using a Takei 5401 Handgrip dynamometer (Takei Scientific Instruments Co., Ltd, Tokyo, Japan). This was performed in accordance with the standard operating procedure (Appendix C.3). Values were expressed as a mean of all three measures. Measures were then compared to grip strength values adjusted for age and sex with values less than 85% of standard mean considered as impaired muscle function (Bohannon et al., 2006).

Triceps skinfold thickness - was measured using Harpenden skinfold callipers via the standard operating procedure that requests a mid-point be established between the acromion and olecranon processes to ascertain the site of the mid arm for the measurement. Mid arm muscle circumference (MAMC) was then calculated from mid upper arm circumference and TSF using a standard formula: MAMC = MUAC - (3.1415 × TSF). These measures are associated with fat mass (FM) and Fat Free Mass (FFM) respectively. They were compared with percentile cut offs (McDowell et al., 2008) to determine comparison with BIA measures.

Body composition (BC) - was measured following a SOP (Appendix C.5) using the seca medical body compositions analyser 515/514. It uses a four-point method via hand and foot electrodes and provided results for FM, FFM, and SMM. Results were compared with percentile cut offs for comparison to TSF and MAMC.

6-minute walk test (6MWT) - used extensively in research and recommended in assessment by the British Thoracic Society, (Hill et al., 2019). Participants are asked to walk between 2 measured points, over a period of 5 minutes and

the distance is recorded. In addition, the BORG scale for reporting exertion using descriptive exertion headings (no exertion (6), extremely light (7) to maximal exertion (20)) (Appendix C.6) and corresponding numbers was collected at the start and end of the test at baseline and three months.

Habitual activity estimation scales (HAES) - were completed by participants at baseline and 3 months at their scheduled clinic appointment, this tool has been used in similar populations and enables assessment of activity following intervention, treatment, or clinical condition. The responses to this also determining physical activity levels (PAL) for all participants to use in calculation of nutritional requirements. Overall levels and equivalent PAL's can be found in Appendix F.

Quality of life questionnaires – participants completed the validated St Georges Respiratory Questionnaire (SGRQ) (Appendix D) and the SF-36 (Appendix E) questionnaire at baseline and 3 months at their scheduled clinic appointments, in a quiet room with access to the researcher to ask any questions or if needed areas of clarification. These where then scored in accordance with their handbooks and scoring sheets (Jones et al., 1991; Ware et al., 1993; Ware. 2000).

Serum vitamin D – blood samples were obtained by nursing staff using a 4ml gold vacuette. Pathology analysis was reported in nmol/l and compared with National Institute for Health and Care Excellence (NICE) values for identification of vitamin D sufficiency and deficiency (NICE, 2022).

7.4.3 Adherence

Total consumption of gels over the three months was recorded utilising the number provided (168) and counting the returned empty and full sachets at the three-month appointment. Percentage adherence was calculated through the following equation: -

(Number of returned sachets/168) x 100.

7.4.4 Ethics

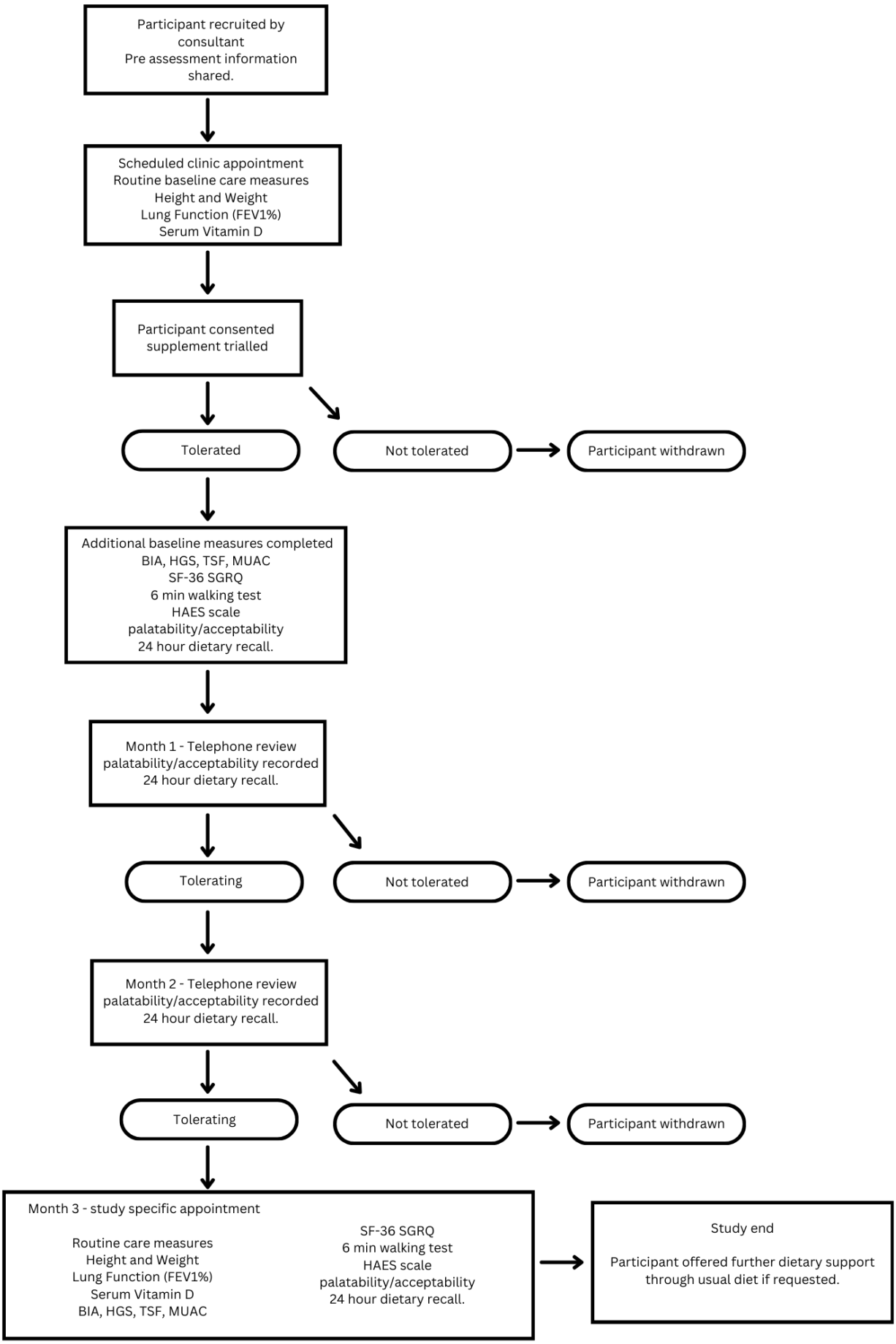
This study was approved on 24th December 2020 by South Central and Hampshire A, Health Research Authority (IRAS 222335) following attendance at

the Ethics committee on 10th November 2020 (Appendix H.2). To note the nutritional supplement does not exert pharmacological effects, and so its purpose falls outside of the Clinical Trials of Investigational Medicinal products (CTIMP).

7.4.5 Statistical analysis

Data was reported using descriptive statistics. Total numbers, proportion (%), and median values with interquartile ranges (IQR) were reported due to the low numbers recruited and non-normal distribution of the data. Baseline values and the mean values of 3 follow up appointments for energy and protein intakes were reported for each participant with the Goldberg cut off applied to determine non habitual intake (underreporting). Non-parametric, Wilcoxon rank test was used to determine any statistically significant differences between paired values at baseline and three-months. Mann Whitney U tests were used to compare values at baseline and 3 months for different groups (≤50% consumption and >50% consumption).

Figure 30 Study flow chart.



7.5 Results

A total of 15 participants were recruited between May 2021 and November 2021. One participant (6.6%) withdrew after consenting at baseline appointment as they could not tolerate the supplement and therefore all baseline data could not be collected. The remaining 14 had baseline data collected (Height, weight, lung function, serum vitamin D) and the additional study measures at baseline (BC, HGS, TSF, MUAC, SF-36, SGRQ, 6MWT, HAES activity scale). Four participants withdrew at different stages (26.6%) (one due to illness before first month appointment, one did not like the taste of the supplement at first month contact and the remaining two could not be reached when contacted in the first month). Characteristics of the 14 recruited participants can be found in Table 25. The participant group were predominantly male (64%) with a median age of 35 years (IQR 19-64) and median BMI 25.5 kg/m^2 (IQR 20.6 - 29.5).

Table 25. Baseline charactersitics of recruited participants (n = 14)

Characteristic	**Participants (14)**
Sex (M/F)	M 9 (64%)
Age yrs.(median)	35 (19-64)
	Median (IQR)
Weight (kg)	77.1 (55.6-86.9)
BMI (kg/m^2)	25.5 (20.6 – 29.5)
FEV_1%	71 (38.7 – 88)
Skeletal muscle mass (kg)	24.6 (17.6 – 30.2)
Fat free mass (kg)	50.9 (44.7-60.8)
Fat mass (kg)	21.3 (14.6 – 28.7)
MAMC (cm)	27.7 (23.8 – 30.6)
Triceps skinfold (mm)	11.7 (8.2 – 14.0)
Handgrip strength (kg/f)	21.9 (18.2 – 35.5)
% Handgrip strength	62 (48.5 – 72.0)
6 MWT (distance m)	364.3 (344.7-431.3)
Energy intake (kcal/d)	1612 (1365 – 2068)
Protein intake (g/d)	68.5 (57.5 – 90.2)
Serum Vitamin D (nmol/l)	52.5 (42.5 – 69.3)

Following withdrawals, the remaining participants (n=10), were predominantly male (70%) with a median age of 39.8 years (IQR 23-64) and median BMI 25.5 kg/m^2 (IQR 21.6 - 30.2) with further characteristics reported in Table 19.

Table 26. Baseline characteristics of recruited participants (n=10)

Characteristic	Participants (10)
Sex (M/F)	M 7 (70%)
Age yrs.(median)	39.8 yrs. (23-64)
	Median (IQR)
Weight (kg)	77 (62-87)
BMI (kg/m^2)	25.5 (21.6 – 30.2)
FEV_1%	76 (54.7 – 92.7)
Skeletal muscle mass (kg)	24.6 (20.4-30.2)
Fat free mass (kg)	50.9 (43.7 – 62.2)
Fat mass (kg)	21.3 (14.6 – 31)
MAMC (cm)	25.8 (23.8-30)
Triceps skinfold (mm)	11.6 (8.1-14.3)
Handgrip strength (kg/f)	28.5 (19-38)
% Handgrip strength	67.5% (56.7 – 79)
6 MWT (distance m)	392.1 (354.1 – 435.3)
Energy intake (kcal/d)	1651 (1527 -2068)
Protein intake (g/d)	82.0 (61 – 97)
Serum Vitamin D (nmol/l)	52.5 (41 -66)

Table 27 shows comparison of median values of all outcomes at baseline and three months (n=10), with handgrip strength statistically significantly different.

Table 27. Comparison of measured outcomes at baseline and 3 months

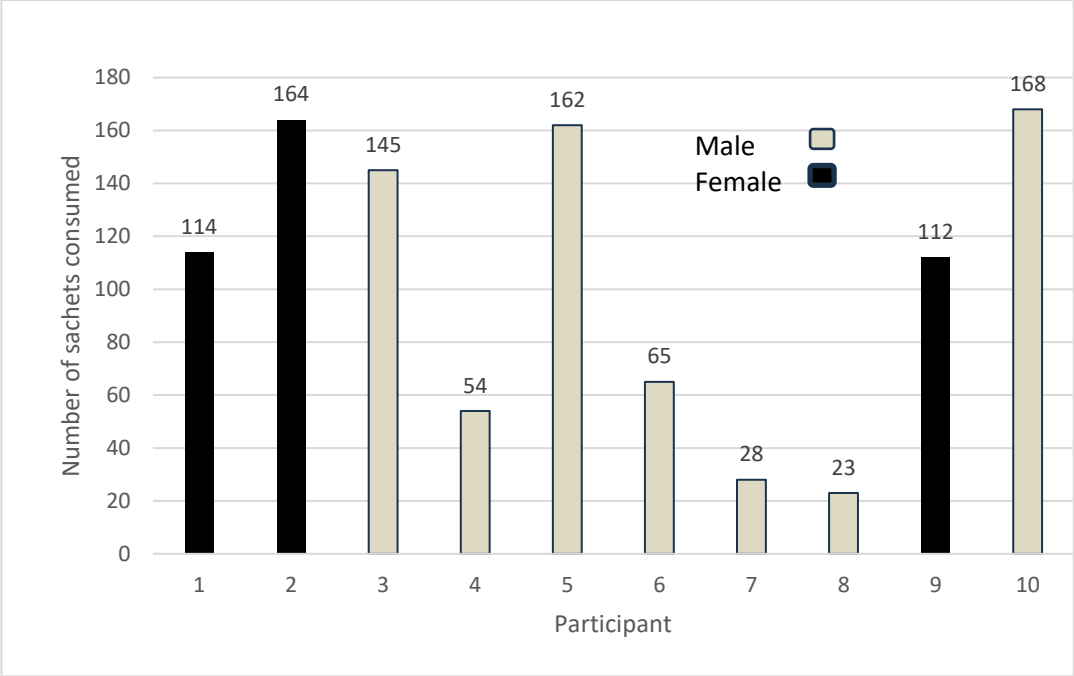
Measured outcome	Baseline assessment median (IQR)	3-month assessment (median IQR)	P value
Weight (kg)	77 (62-87)	77.5 (61-84)	0.87
BMI (kg/m^2)	25.5 (21.6 – 30.2)	26.2 (21.2 -30.0)	0.91
FEV_1%	76 (54.7 – 92.7)	75.5 (55.5 – 91.5)	0.95
Skeletal muscle mass (kg)	24.6 (20.4-30.2)	24.9 (20.5-29.9)	0.79
Fat free mass (kg)	50.9 (43.7 – 62.2)	50.5 (44.0 – 61.4)	0.72
Fat mass (kg)	21.3 (14.6 – 31)	22.9 (13.8 – 31.7)	0.72
MAMC (cm)	25.8 (23.8-30.0)	28.3 (25.0 -30.6)	0.64
Triceps skinfold (mm)	11.6 (8.1-14.3)	12.2 (10.2 – 14.7)	0.16
Handgrip strength (kg/f)	28.5 (19-38)	29.3 (24.5 – 40.9)	0.04*
% Handgrip strength	67.5% (56.7 – 79)	73.0% (59.7 – 87.5)	0.03*
6 MWT (distance m)	392.1 (354.1 – 435.3)	370.8 (351.2 -431.3)	0.28
Energy intake (kcal/d)	1651 (1527 -2068)	1552 (1421 – 1816)	0.26
Protein intake (g/d)	82.0 (61 – 97)	64.5 (50.2 – 87.2)	0.07
Serum Vitamin D (nmol/l)	52.5 (41 -66)	61 (38.7 – 73.5)	0.85

*Statistical significance $p<0.05$

7.5.1 Adherence and palatability (n=10)

Consumption of supplement gels over the study period ranged from 14% to 100%. Six participants consumed more than 50% of the supplement gels (68%, 71%, 86%, 96%, 97% and 100%), of these, 50% were female and total numbers of gel consumption can be seen in Figure 31. Those participants that consumed less than 50% of supplements were all male (100%).

Figure 31 Number of supplements consumed by each participant



*Sex distribution reported

Composite (baseline, month one, month two, and month three average) palatability scores for individuals using visual analogue scales are reported in Figures 32-36, with overall composite scores reported in Figure 37. Of the 10, participants 1,2,3,5,9 and 10 all consumed more than 50% (68-100%) of the supplements during the study period, participants 1,2 and 9 were female and 3,5 and 10 males. Those reporting lowest scores (participants 2 and 4) consumed 97% and 32% respectively, in contrast participant 7 reported the highest values for palatability but only consumed 16% of the supplements from baseline to three months.

Scores for palatability, taste and aftertaste were greater than scores for visual appeal and smell. Mean VAS scores for those who consumed > 50% of the supplement gel compared to ≤ 50% supplement were 29.6 - 76.0 mm versus 41.0 – 81.0 mm.

Figure 32. Composite scores for (visual appeal).

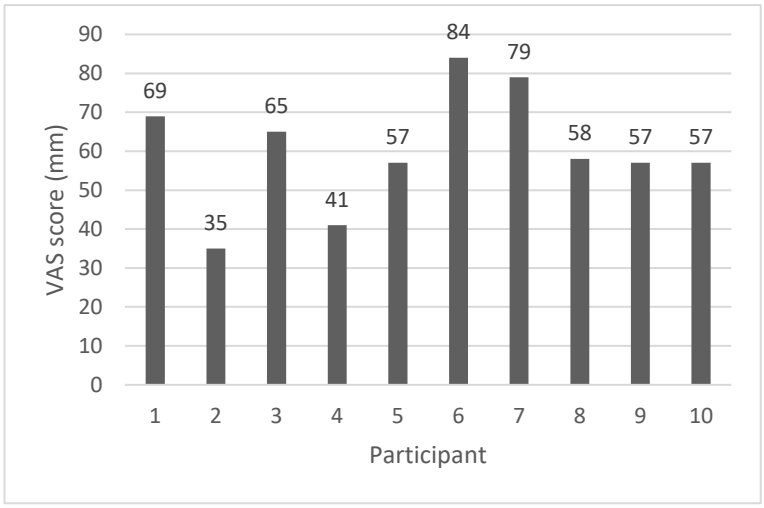


Figure 33. Composite scores for (smell)

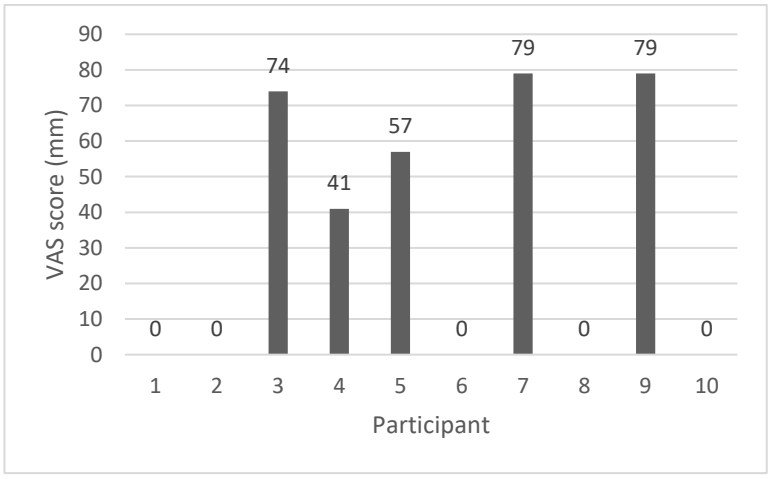


Figure 34. Composite scores (taste)

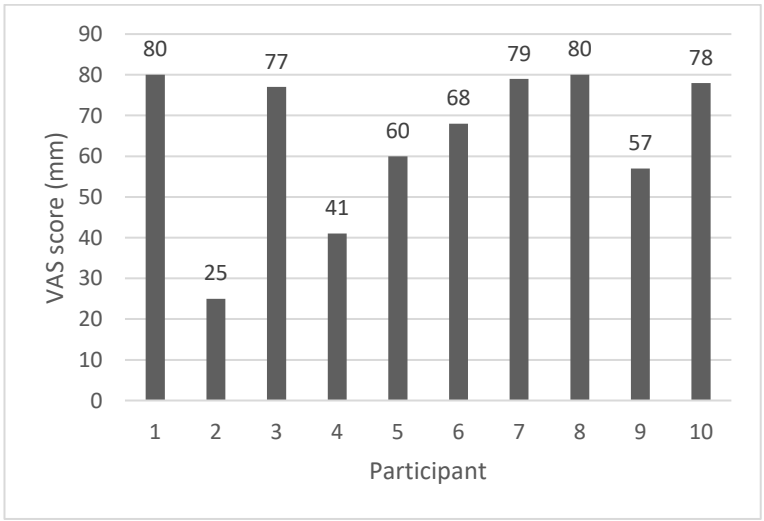


Figure 35. Composite scores (aftertaste)

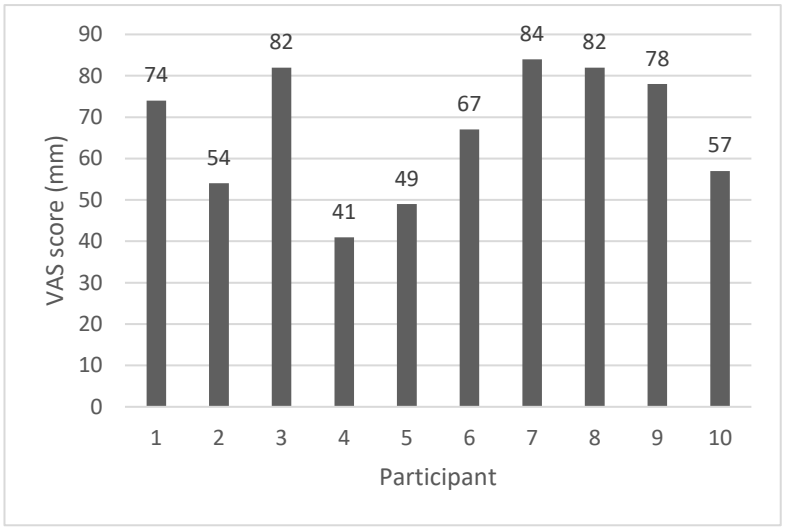


Figure 36. Composite score (palatability)

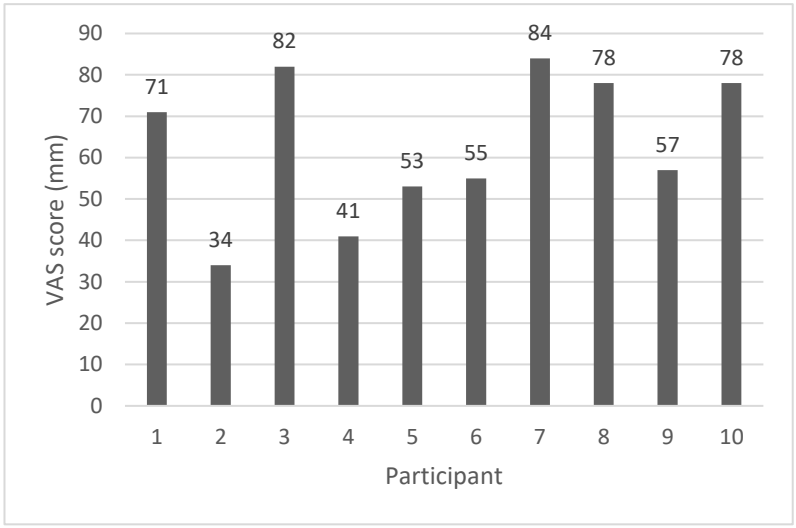
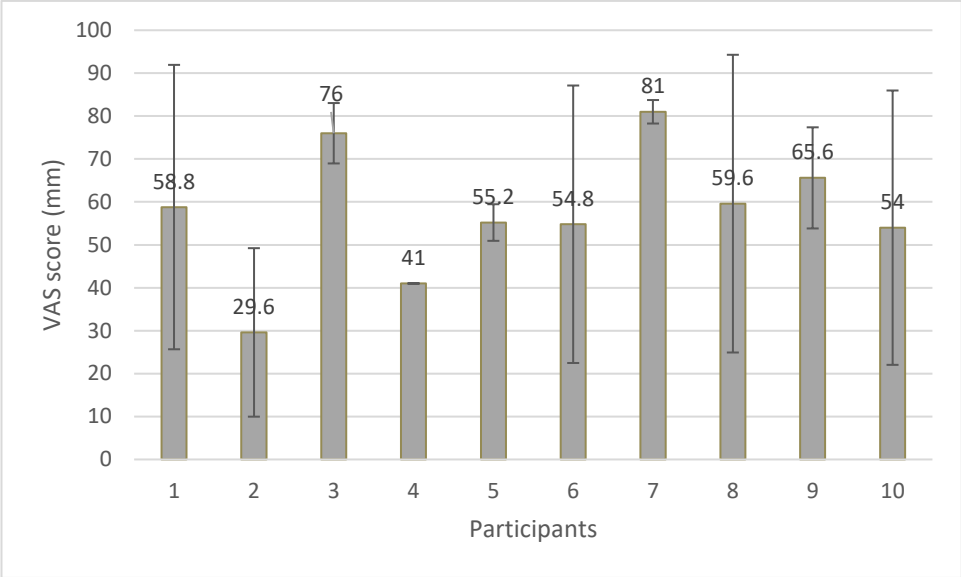


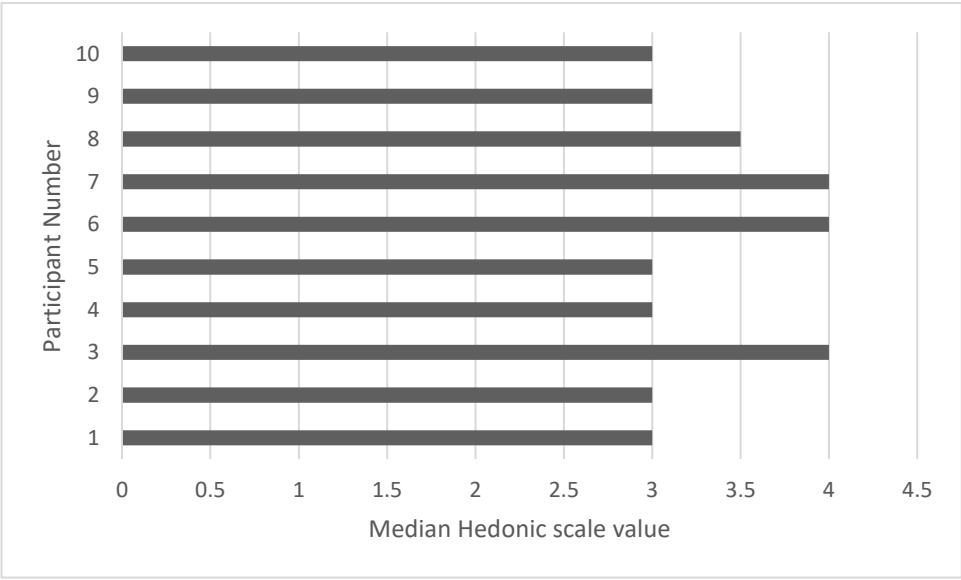
Figure 37. Overall mean composite palatability scores (n=10).



* With standard Deviation (SD) presented

Hedonic rating scales assessing acceptability of the gels (Figure 38) show the composite median scores of the 5-point scale (1 = Like a lot, 2= like a little, 3 = neither like nor dislike, 4 = dislike a little, 5 = dislike a lot). This showed the majority (60%) neither liked nor disliked the gel, and 30% expressed ‘a little’ dislike.

Figure 38. Median hedonic scale scores (n=10).



7.5.2 Dietary requirements and intake

Table 29 and 30 report the comparison of dietary energy and protein intakes (± supplementation) against estimated calculated requirements at baseline and 3 months. Statistically significant differences were observed between energy intake and estimated calculated requirement for energy at baseline ($z = -1.988$, $p = 0.04$), protein intake and estimated protein requirement using FFM at baseline ($z = -2.040$, $p = 0.04$) and protein intake and estimated protein requirement using ESPEN guidance at baseline ($z = -2.499$, $p = 0.01$). The difference between mean values of intake and estimated calculated requirements at 3 months were not statistically significantly different except when comparing protein intake and estimated calculated protein requirement using the ESPEN method ($z = -2.293$, $p = 0.02$).

When considering if energy intake met calculated requirements, 90% (n=9) of participants failed to meet calculated energy requirements. With supplementation, 80% (n=8) of participants still failed to meet their energy requirements. Energy deficits ranged from 0 -788 kcals.

When comparing estimated calculated protein requirements with intakes at baseline, 40% (n=4) did not achieve calculated requirements utilising FFM calculations. With supplementation 30% (n=3) still failed to meet these requirements. When comparing protein intake to estimated calculated requirements using the ESPEN guidance 90% (n=9) did not achieve there estimated calculated requirements at baseline. With supplementation 70% (n=7) still failed to meet their estimated requirement. Protein deficits/surplus ranged from -22g to +30g, when comparing to FFM calculation of protein requirements and -54g to -2g, when comparing to ESPEN estimated calculated protein requirement.

7.5.2.1 Application of Goldberg method

As physical activity levels were calculated from HAES activity (self-reported) questionnaires. This enabled calculation of a group specific lower cut off for determining non habitual intake (Figure 39). The mean PAL for the 10 participants was 1.37. Utilising the Goldberg formula (Goldberg et al., 1991) a lower cut of EI:BMR ratio of 1.23 can be applied to this group. Any EI:BMR ratio below this value, is likely to demonstrate non habitual intake (Table 28).

Figure 39 Goldberg equation for calculating population lower cut off EI:BMR ratio

Formula to calculate S (coefficient variation) (Goldberg)

$$s = \sqrt{\left[\frac{CViw^2}{k} + (CVb)^2 + (CVp)^2\right]}$$

Therefore, using a population of 10 participants and 4 days intake

$$s = \sqrt{\left[\frac{23^2}{4} + (8)^2 + (12 \cdot 5)^2\right]} = 18.77\%$$

To determine the cut off value the following equation should be used

$$PAL\ x\ exp\left[SDmin\ x \frac{S/100}{\sqrt{n}}\right]$$

Therefore

$$1.37\ x\ exp\left[-2\ x \frac{0.1877}{\sqrt{10}}\right]$$

$$1.37\ x\ exp[-0.118711903362721]$$

$$1.37\ x\ 0.88 = 1.23$$

Table 28 Characteristics following application of the Goldberg cut offs.

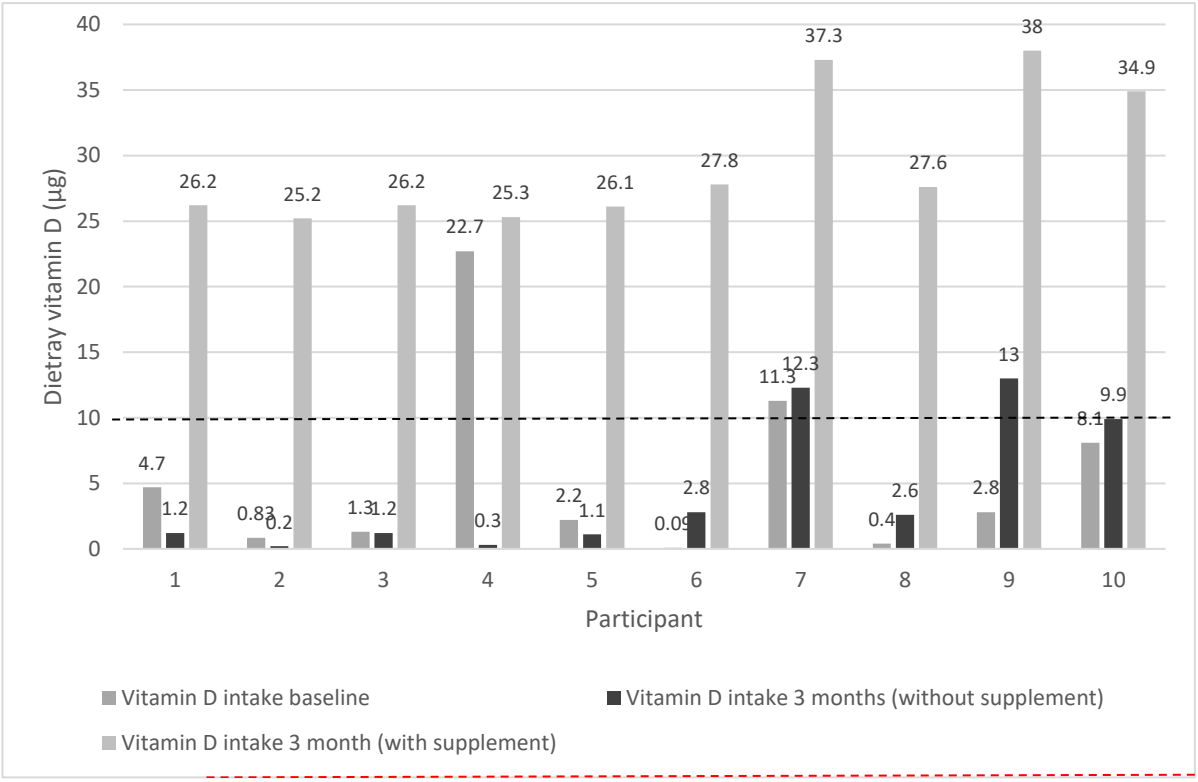
	Baseline EI: BMR <1.23	3 months EI: BMR <1.23	EI: BMR <1.23 (including supplement)
Number	5	7	5
Mean (range)	1.22 (0.82 -1.98)	1.10 (0.75 – 1.74)	1.26 (0.87 -1.46)
Sex (M/F)	3/2	5/2	5/0

7.5.3 Vitamin D serum values and dietary intakes

One participant (10%) had severe vitamin D deficiency (<25 nmol/l) with a baseline value of 20 nmol/l, three participants (30%) had insufficiency (25-50 nmol/l) and the remaining (60%, n= 6) were sufficient (>50nmol/l). At three months, four (40%) had increased serum levels, five (50%) had decreased serum levels and one (10%) had maintained their status. Of those participants with decreased Vit D serum concentrations at 3 months, three consumed less than 50% of their gel supplements [Participant 4 (14%), Participant 3 (16%), Participant 2 (38%)]. Conversely, the remaining two participants with decreased serum Vit D concentration at 3 months consumed 86% and 100% respectively.

Of the 10 participants, 80% (n= 8) failed to meet the recommended dietary intake of 10 µg/day at baseline. Consumption of Vitamin D was also calculated at 3 months via dietary records and included values solely derived from diet (without supplementation of 2 gels per day). These dietary intake values were then combined with Vitamin D derived from the prescribed 2 gels per day. Combined, the final intake of Vitamin demonstrated that all participants would have exceeded dietary requirements with supplementation of the gels. This can be seen in Figure 40.

Figure 40. Dietary vitamin D intakes at baseline and 3 months with and without supplementation (n=10)



----- = recommended dietary intake 10µg (SACN, 2016) presented

Table 29. Calculated requirements compared with intakes of actual, mean and with supplement for energy.

Participant	1	2	3	4	5	6	7	8	9	10
Energy requirement (kcal)										
Baseline	1727	1940	2663	2422	2441	2062	2059	2421	1168	1768
3 months	1665	1957	2683	2391	2402	2020	2067	2435	1168	1861
Energy intake (kcal)										
Baseline (actual intake) (Difference Energy intake to requirement)	1465 (±262)	1578 (±362)	2410 (±253)	1536 (±886)	2321 (±120)	1671 (±391)	1984 (±75)	1502 (±919)	1655 (±13)	1647 (±121)
3 months (mean) (Difference Energy intake to requirement)	1437 (±228)	1503 (±454)	1902 (±781)	1375 (±1016)	1763 (±639)	1880 (±140)	1607 (±460)	1233 (±1202)	1452 (±284)	1754 (±107)
+ supplement (Difference Energy intake to requirement)	1665 (±0)	1727 (±230)	2130 (±523)	1603 (±788)	1991 (±411)	2108 (±88)	1835 (±232)	1461 (±974)	1680 (±512)	1982 (±121)

Table 30. Calculated protein requirements compared to intakes with and without supplementation.

Participant	1	2	3	4	5	6	7	8	9	10
Protein requirement (g) (FFM x 1.5g/d)										
Baseline	66	69	95	93	94	74	79	81	42	63
3 months	64	70	96	91	92	72	80	81	42	67
Protein requirement (g) (1.5g/kg/d) (ESPEN)										
Baseline	88	101	107	125	129	96	114	104	65	87
3 months	85	95	110	126	129	93	120	107	63	87
Protein intake (g)										
Baseline (actual intake) (Difference protein intake to requirement FFM) (Difference protein intake to requirement ESPEN)	61 (±5) (±27)	47 (±22) (±54)	81 (±14) (±26)	123 (±30) (±2)	107 (±13) (±22)	70 (±4) (±26)	89 (±10) (±25)	83 (±2) (±21)	61 (±19) (±4)	94 (±31) (±7)
3 months (mean) (Difference protein intake to requirement FFM) (Difference protein intake to requirement ESPEN)	61 (±3) (±24)	40 (±30) (±55)	68 (±28) (±42)	99 (±8) (±27)	89 (±3) (±40)	79 (±7) (±14)	90 (±10) (±30)	52 (±29) (±55)	63 (±21) (±0)	92 (±25) (±5)
+ supplement (Difference protein intake to requirement FFM) (Difference protein intake to requirement ESPEN)	76 (±12) (±9)	55 (±15) (±40)	83 (±13) (±27)	114 (±23) (±12)	104 (±12) (±25)	94 (±22) (±1)	105 (±25) (±15)	67 (±14) (±40)	78 (±36) (±15)	107 (±40) (±20)

7.5.4 Secondary outcomes (n=10)

Hand grip strength alone was statistically significantly different from baseline to 3 months, (z = -1.988, p = 0.047) alongside percentage HGS compared to normative values (z = -2.091, p = 0.037). All other secondary measures were not statistically significantly different from baseline to 3 months (Table 25). When comparing measures from BIA and anthropometric indices using skinfold callipers, results reflected similar percentile positions. TSF, an indirect measure of fat mass, and FM measured through BIA were within the 50th - 75th percentile. MAMC, an indirect measure of fat free mass, and FFM measured through BIA were both <5th percentile.

7.5.5 Subgroup analysis (participants consuming ≤ 50% versus >50% of the amino acid supplementation gel)

Comparison of baseline and 3-month values for the group split by ≤ 50% and >50% can be found in Table 31. The six participants who consumed > 50% of the supplement gels, had a median age of 49 years. (IQR 33.7 – 58.7) and were equally split by sex. All female participants recruited in the feasibility study (n=3) consumed more than 50% of the amino acid gel supplement. The four participants who consumed ≤ 50% of the supplement gel had a median age of 29 years (IQR 23.2 – 39.3) and were all male (100%).

Table 31. Subgroup analysis (≤ 50% and >50% consumption of amino acid supplement gels) at baseline and 3 months.

Outcome	Consumption ≤ 50% (n = 4)	Consumption >50% (n = 6)		Consumption ≤ 50% (n = 4)	Consumption >50% (n = 6)	
	Baseline assessment median (IQR)	Baseline assessment median (IQR)	P value	3-month assessment median (IQR)	3-month assessment median (IQR)	P value
Weight (kg)	72.5 (64.8 – 81.3)	81.9 (53.8 – 90.9)	0.61	75.5 (64.2 -82.6)	79.7 (54.0 – 89.2)	0.76
BMI (kg/m^2)	24.4 (22.6 – 25.7)	28.7 (20.1 – 31.5)	0.48	25.3 (22.3 – 26.2)	28.6 (20.1 – 31.2)	0.48
FEV$_1$%	76.0 (47.5 – 99.2)	78.0 (51.5 -92.7)	0.91	74.0 (44.7 – 92.7)	82.0 (54.0-91.5)	1.00
Skeletal muscle mass (kg)	26.0 (24.0 – 29.0)	21.8 (16.4 – 31.5)	0.47	26.7 (24.1 – 29.0)	21.5 (17.5 – 31.0)	0.47
Fat free mass (kg)	53.3 (50.0 - 60.0)	45.2 (38.5 – 62.8)	0.47	53.5 (49.3 – 59.5)	45.5 (38.9 – 62.1)	0.47
Fat mass (kg)	17.3 (13.8 – 22.0)	26.6 (14.6 – 35.5)	0.25	18.4 (13.7 – 24.3)	27.9 (13.8 -33.9)	0.35
MAMC (cm)	25.6 (23.8 – 27.7)	27.0 (24.9 – 30.6)	0.47	27.3 (23.8 – 30.7)	28.8 (24.9 – 30.6)	1.00

Triceps skinfold (mm)	9.1 (7.9 – 12.4)	12.2 (9.1 – 18.1)	0.35	11.4 (9.6 – 13.4)	12.4 (9.7 – 17.4)	0.47
Handgrip strength (kg/f)	36.4 (24.8 – 40.5)	22.0 (21.3 – 36.5)	0.25	39.0 (30.7 – 41.0)	25.6 (21.3 – 36.5)	0.17
%Handgrip strength (kg/f)	72.5 (49.7 – 81.0)	64.5 (56.7 – 78.2)	0.91	76.5 (49.7 – 81.0)	67.5 (59.2 -102.2)	0.91
6 MWT (distance m)	411.7 (392.1-485.2)	361.3 (344.7– 435.4)	0.25	400.2 (368.4-468.8)	352.8 (333.2 –426.4)	0.17
Energy intake (kcal/d)	1603 (1510 -1905)	1651 (1549 –2343)	0.76	1565 (1149 -1821)	1552 (1434 -1936)	0.76
Protein intake (g/d)	86.0 (73.2 -114.5)	71.0 (57.5 – 97.2)	0.35	74.5 (43.0 – 91.7)	63 (47.0 – 84.5)	0.76
Serum Vitamin D(nmol/l)	52.5 (32.5 – 54.5)	55.0 (39.5 – 81.0)	0.76	38.5 *b (26.0 – 55.5)	66.0 *b (61.0 – 85.8)	0.02*

statistically significantly different values, * p<0.05, ** p<0.01, a = baseline values, b = 3-month values

No statistically significant differences were found between baseline and 3 months for the group with ≤ 50% consumption or the group with >50% consumption except for percentage fat mass (%FM) (U = 22.0, p= 0.038) at baseline and percentage fat free mass (%FFM) (U = 2.0, p = 0.038) at baseline. There was a statistically significant difference in the serum vitamin D level at 3-months between, those consuming ≤50% of the supplement and >50% supplement (U = 23.0, p=0.019). In the group that consumed >50% of the supplement, 50% (n=3) had increased serum vitamin D levels at 3 months [participant 9 (32%)], [participant 1, (175%)], [participant 2 (355%)]. Sixteen percent (n=1) (participant 5) had the same serum level at baseline and three months (62 nmol/l), with the remaining 32% (n=2), (participant 3 and 10) showing overall reductions in serum vitamin D of 29% and 11% respectively. In the ≤50 % consumption group, 75% (n=3) had decreased vit D serum values at 3 months [participant 6 (28%)], [participant 7, (29%)], [participant 8 (15%)] and 25% (n=1) had an increased vitamin D serum level of 17%. Increases in vitamin D serum levels were seen in those who consumed >50% of the amino acid supplement and a greater percentage increase was also shown compared with those who consumed ≤ 50% amino acid supplement gel.

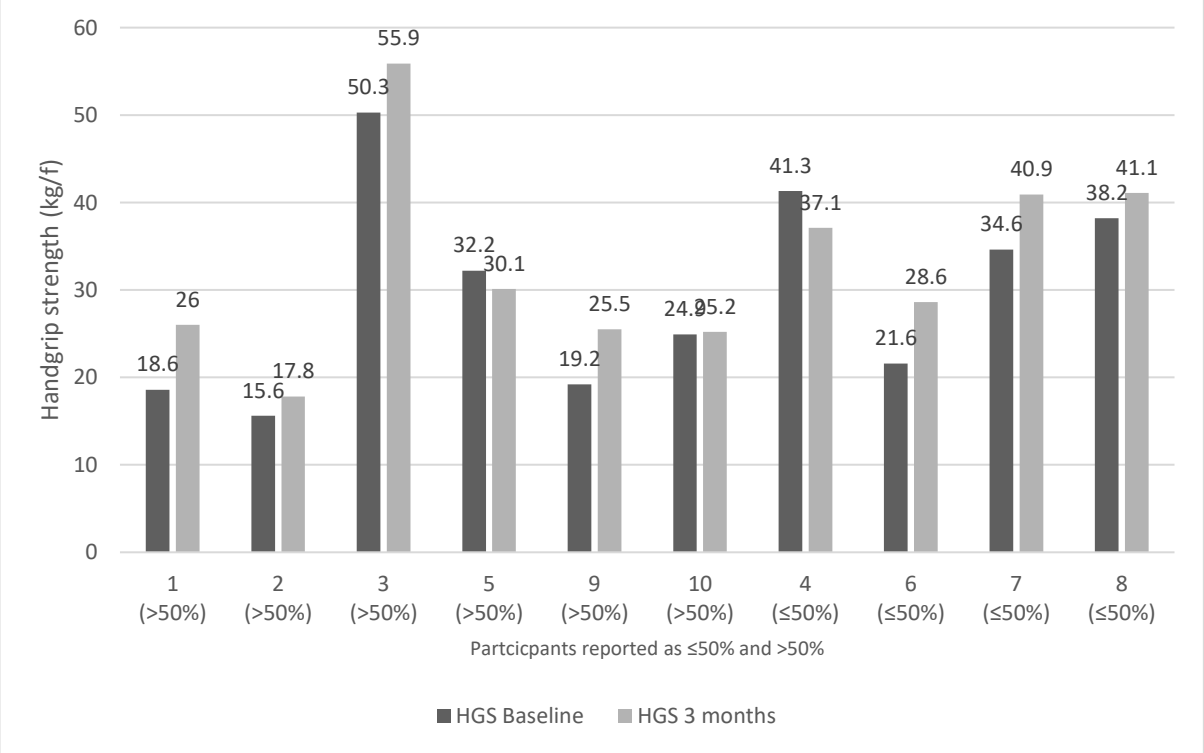
Actual changes in other parameters (weight, pulmonary function, skeletal muscle mass, [as measured by Bioelectrical Impedance Analysis (BIA)], triceps skinfolds, mid arm muscle circumference, energy intake, protein intake and 6 MWT distance) were small across both subgroups (≤ 50% consumption and >50%consumption). Whilst not statistically significant, the group consuming ≤50% of the amino acid supplement gel were younger, with a lower BMI, greater skeletal muscle mass, mid arm muscle circumference, and lower triceps skinfold thickness.

7.5.5.1 Handgrip strength comparison

Handgrip strength (HGS) an indicator of muscle strength, was noted to be higher in the group ≤50% consumption compared with the group consuming >50% of the gel at baseline and 3 months. When comparing actual values from baseline to 3 months those with ≤50% consumption, 75% (n=3) had increases in their HGS, with 25% (n=1) decreasing. Value changes in this group were + 6.3 kg/f, + 7.0 kg/f, +2.9 kg/f, and -9.6kg/f, (n=4) respectively. HGS changes in the >50% consumption group showed 83% (n=5) had an increase in HGS at 3 months, with 16% (n=1) reducing their HGS at 3 months (Figure 41). Value changes in this group were + 7.4 kg/f, + 2.2 kg/f, +5.6 kg/f, + 6.3 kg/f, + 0.3kg/f and – 2.1kg/f (n=6), respectively.

HGS values adjusted for age and sex showed that 100% (n=4) did not meet the adjusted threshold in the group with ≤50% consumption at baseline or 3 months and 83% (n=5) in the group with >50% consumption, with the remaining participant (17%, n=1) exceeding this (103% at baseline and 115% at 3 months). One participant (17%) in the >50% consumption group improved their HGS enough to exceed the 85% threshold (70% at baseline to 98% at 3 months). The average percentage increase in the group with ≤50% consumption was 10.6% and in the group with >50% consumption was 13.8%.

Figure 41. Handgrip strength measures at baseline and 3 months (≤ 50% and >50% consumption of amino acid supplement gels)



7.5.5.2 Activity outcomes (6MWT and HAES)

In assessing exertion using the BORG scale (measure perceived exertion), scores at baseline and three months for the 6MWT showed that participants' perceived exertion scale differences were smaller at 3 months than at baseline in those who consumed >50% of the amino acid supplement gel. Fifty percent (n=3) increased the distance they could walk without an accompanying rise in perceived exertion. These findings are visualised in Table 23, with changes in reported BORG Scale scores (6 = no exertion to 13 = somewhat hard). Those consuming ≤50% of the amino acid supplement gel showed 50% (n=2) had the same score difference and 50% (n=2) showed small differences from baseline to 3 months. In this group, 100% (n=4) walked less distance at 3 months compared with baseline.

Statistically significantly differences were observed for reported BORG scale exertion before the 6MWT test and after, in the whole group at baseline (n = 10) (z = -2.371, p = 0.018) and the group who consumed > 50% of supplements (n=6) (z = -2.032, p=0.042) but not at 3 months for the whole group (z = -0.638, p=0.524) nor those participants ≤ 50% consumption (z = -1.342, p =0.180) and >50% consumption (Table 32). When comparing start exertion scores at baseline and 3 months and end exertion scores at baseline and 3 months the whole population (n=10) (z = -2.375, p= 0.018) and the group with >50% consumption (n=6) had statistically significant differences in pretest exertion scores (z = -2.214, p= 0.027) (Table 33). Changes in values from start and end of test at baseline and three months can be viewed in Table 34.

Table 32. Median scores at start and end of test at baseline, 3 months for whole population and ≤ 50% and >50% consumption of amino acid supplement gels.

	BORG exertion scores (baseline)			BORG exertion scores (3 months)		
	Start of test median score (IQR)	End of test median score (IQR)	P value	Start of test Median score (IQR)	End of test median score (IQR)	P value
Whole population n=10	6.8 (6.0-7.2)	9.0 (6.7 – 11.5)	P= 0.01	10.5 (7.0-11.5)	10.5 (7.0 – 12.2)	P= 0.52
Group consumed <50% supplements (n=4)	7.0 (6.2 – 7.7)	8.0 (6.25-9.0)	P= 0.18	7.0 (6.2 – 9.2)	8.0 (7.0-9.7)	P= 0.18
Group consumed >50% supplements (n=6)	6.0 (6.0-7.5)	11.0 (8.2 – 13.0)	P=0.04	11.0 (10.5 – 13.0)	11.5 (10.0-13.0)	P= 1.00

Table 33 Comparison of median start of test at baseline and end of test at 3 months

	BORG exertion scores (baseline and 3 months)			BORG exertion scores (baseline and 3 months)		
	Start of test median score (IQR)	Start of test Median score (IQR)	P value	End of test median score (IQR)	End of test median score (IQR)	P value
Whole population n=10	6.8 (6.0-7.2)	10.5 (7.0-11.5)	P= 0.02	9.0 (6.7 – 11.5)	10.5 (7.0 – 12.2)	P= 0.08
Group consumed <50% supplements (n=4)	7.0 (6.2 – 7.7)	7.0 (6.2 – 9.2)	P= 0.32	8.0 (6.25-9.0)	8.0 (7.0-9.7)	P= 0.15
Group consumed >50% supplements (n=6)	6.0 (6.0-7.5)	11.0 (10.5 – 13.0)	P=0.02	11.0 (8.2 – 13.0)	11.5 (10.0-13.0)	P= 0.19

Table 34. 6MWT reported exertion scores (BORG) diffrerences at baseline and 3 months (≤ 50% and >50% consumption of amino acid supplement gels)

Participant	Baseline 6MWT			3 months 6MWT		
	BORG Scale	BORG Scale	Change	BORG Scale	BORG Scale	Change
Group consumed >50% supplement						
1	9	13	+6	13	13	0
2	6	11	+5	6	7	+1
3	6	9	+3	11	11	0
5	7	11	+4	11	13	+2
9	6	11	+5	9	11	+2
10	6	13	+7	13	12	-1
Group consumed ≤50% supplement						
4	6	6	0	6	7	+1
6	7	7	0	7	7	0
7	7	9	+2	7	9	+2
8	8	9	+1	10	10	0

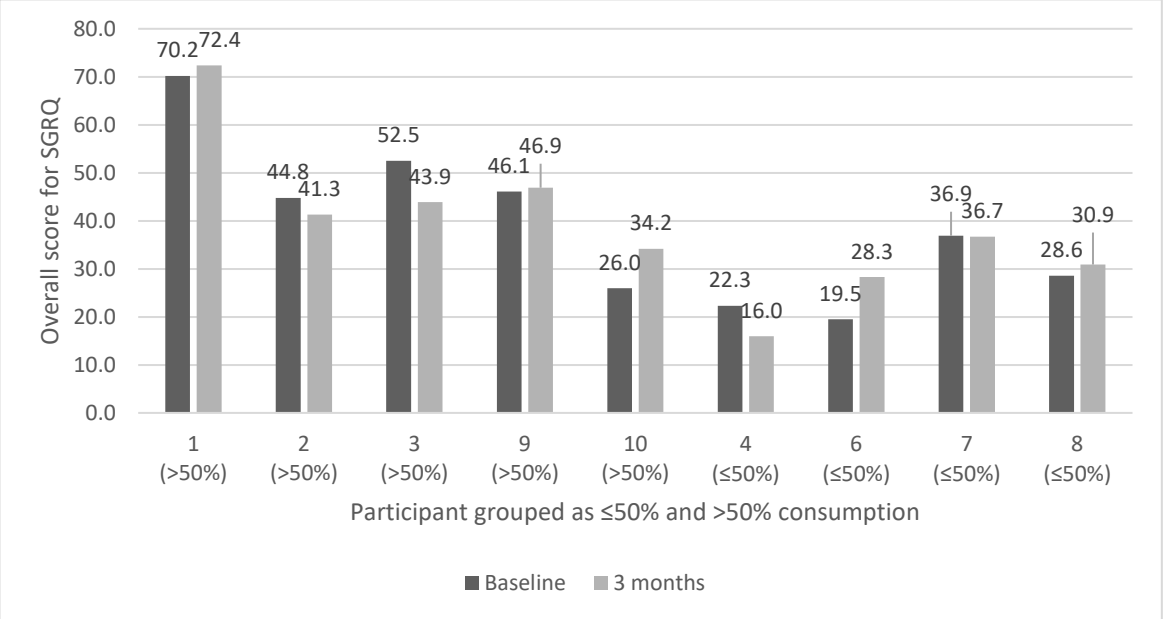
Habitual Activity Estimation Scales (HAES) in the group with >50% amino acid consumption showed 83% (n=5) reported their daily activity to be 'somewhat active' with 17% (n=1) reporting their overall activity to be 'somewhat inactive'. In the group who consumed ≤50% of the amino acid supplement, 50% (n=2) reported being somewhat inactive, and 50% (n=2) somewhat active. There were no changes in reported levels of activity between baseline and 3 months.

7.5.5.3 Quality of life measures

St Georges Respiratory Questionnaire (SGRQ) validated scores are reported for 83% (n=5) in the group consuming >50% of the gel compared to 100% (n=4) for those consuming ≤50% due to an incomplete questionnaire by participant five.

In the group with >50% consumption, 60% (n=3) participants reported worse respiratory health at three months (lower to higher score), and 40% (n=2) two reported better health (higher to lower score). This was also reflected in the group with ≤50% consumption, where 50% (n=2) reported worst health and 50% (n=2) reporting better health from baseline to 3 months (Figure 42).

Figure 42. Reported SGRQ scores baseline and 3 months (≤ 50% and >50% consumption of amino acid supplement gels)

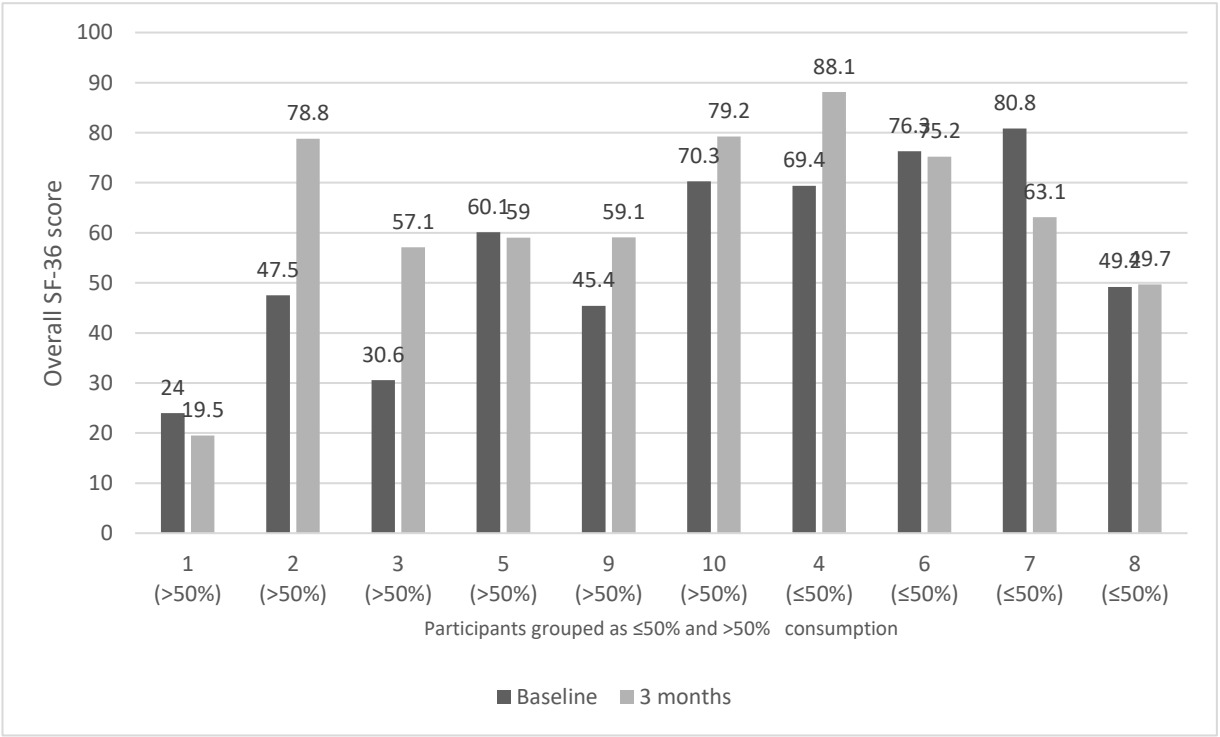


SF-36 health questionnaire results showed similar patterns from baseline to 3 months (Figure 43). Participants who consumed >50% of the amino acid supplement gel 33% (n=2) reported worse health scores (greater score = better health) at 3 months, with 66% (n=4) recording better health scores. In the group consuming ≤50% of the amino acid gel supplement, 50% (n=2) reported

improved scores at 3 months. Median scores for those with ≤50% consumption showed a greater median at baseline (72.9), compared with those consuming >50% (46.5) indicating that the group with >50% consumption reported a greater impact of disease on health. This was also reflected at 3 months. However, those consuming >50% of the gel supplements, improved their median value score for quality of life (from 46.1 - 59.1) and those consuming ≤50% showed a decrease in quality of life (from 72.9 - 69.2).

One participant [participant 10] in the group consuming >50% of the gel supplement reported an improvement in health in the SF-36 (70.3 at baseline and 79.2 at 3 months) but worsening health in the SGRQ (26.0 at baseline and 34.2 at 3 months). One participant in the ≤50% consumption group [participant 7] reported worse scores in the SF-36 (80.8 at baseline and 63.1 at 3 months) and remained stable in the SGRQ (36.9 at baseline to 36.7 at 3 months).

Figure 43. Reported SF-36 scores at baseline and 3 months (≤ 50% and >50% consumption of amino acid supplement gels)



7.5.6 Subgroup analysis of participants that withdrew (n=4)

Of the 4 participants who withdrew, 50% were male with a median age of 31yrs. (19-39yrs.). As only baseline measures were collected, key characteristics have been reported for interest (Table 33).

All median outcome measures are lower than those reported in participants who competed the study (n=10), except for triceps skinfold thickness and mid arm muscle circumference. Of specific note is the poor pulmonary function (FEV_1%) and handgrip strength which are 47.5% and 18.4 kg/f compared with 76% and 28.5 kg/f, reflecting a compromised group with poorer lung function. In addition, the overall energy and protein intakes were the lowest at baseline when compared with those that completed.

Table 35. Characteristics of participants that withdrew (n=4)

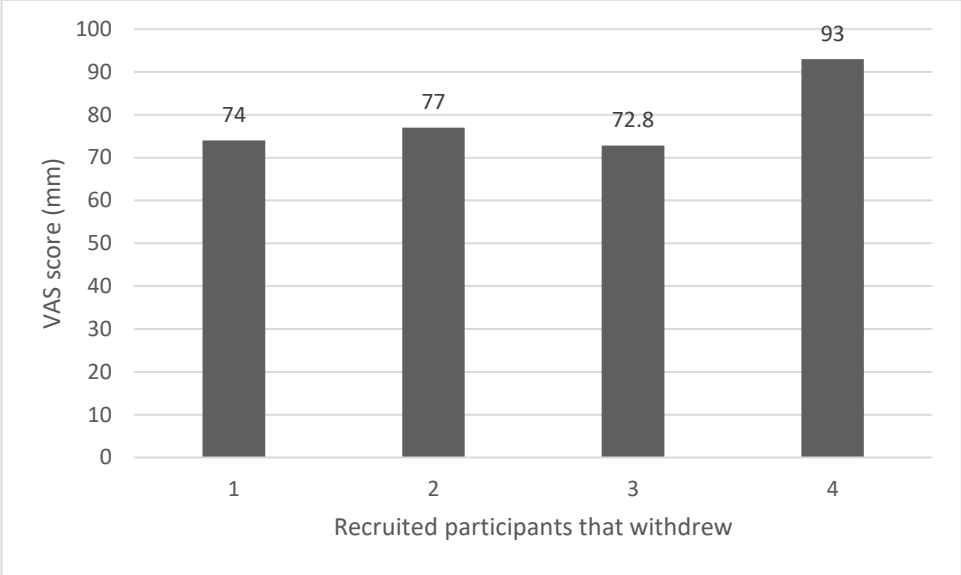
Characteristic	**Participants (4)**
Sex (M/F)	M 2 (50%)
Age yrs.(median)	31 (19-39)
	Median (IQR)
Weight (kg)	65.8 (47.9 – 89.4)
BMI (kg/m^2)	24.7 (19.9 – 29.2)
FEV_1%	47.5 (38 -72)
Skeletal muscle mass (kg)	21.6 (14.0 – 30.8)
Fat free mass (kg)	44.4 (33.7 – 56.9)
Fat mass (kg)	21.4 (13.9 – 27.6)
MAMC (cm)	30.3 (24.8 – 31.6)
Triceps skinfold (mm)	12.5 (9.0 – 14.8)
Handgrip strength (kg/f)	18.4 (16.5 – 21.6)
% Handgrip strength	48 (41.7 – 60.2)
6 MWT (distance m)	328.71 (262.3 – 360.2)
Energy intake (kcal/d)	1053 (1029 – 2120)
Protein intake (g/d)	48.9 (32.5 – 66.0)
Serum Vitamin D (nmol/l)	57 (36.0 -100.5)

7.5.6.1 Palatability scores for recruited participants that withdrew.

Of those who withdrew, 75% (n=3), did not record a value for smell as part of the VAS scoring and 25% (n=1) that could, rated this as poor (80 mm). Composite scores reported in Figure 44, show that when compared to the 10 participants who completed the full study, all scores were toward the upper end of the scale (poorly accepted). This group also had the highest reported value (93mm) of all scores reflecting poor palatability. Mean score for taste in this group (n=4) was the highest when compared to the mean score from the group of 10 (64.5 mm compared with 84 mm). This reflects that the participants who

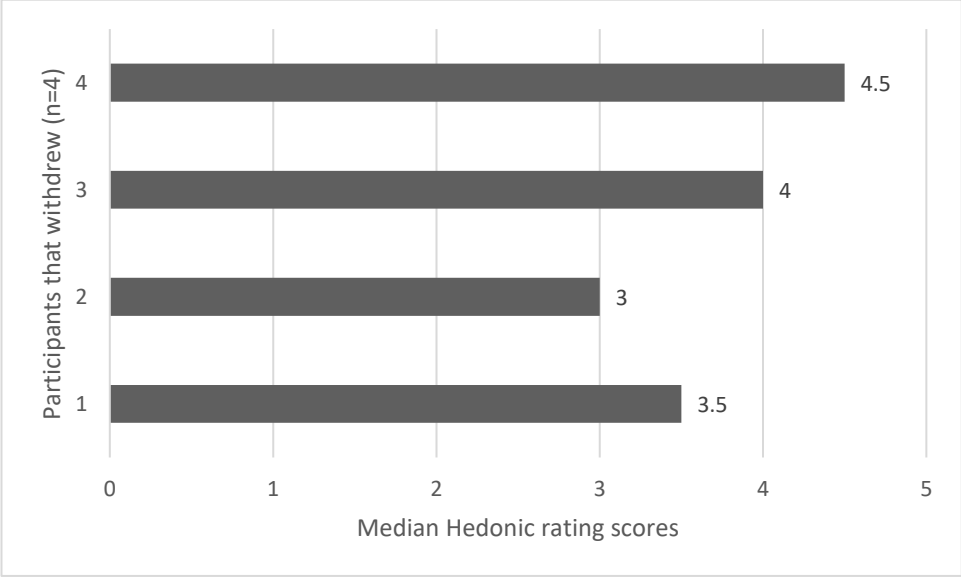
withdrew (n=4) rated taste as worse than the participants who completed the study (n=10).

Figure 44. Overall mean composite palatability scores for withdrawn participants (n=4)



Median scores from the baseline hedonic rating scale are displayed in Figure 45 and show similar results when comparing to those who completed the study (n=10). In this group, 25% (n=1) had the greatest median hedonic rating score of 4.5, with 25% (n=1) neither liked nor disliked the gel and 50% (n=2) expressing a ‘little dislike’.

Figure 45. Overall median hedonic scores for withdrawn participants (n=4)



7.6 Discussion

7.6.1 Nutritional supplementation consumption

This is the first feasibility study to explore the consumption of a leucine enriched amino acid gel supplement in PCD. The study found that 60% of participants were able to consume more than 50% of the supplements over a 3-month period. In contrast to male recruits, all female participants (30%), consumed more than 50% of the supplements. This likely reflects previous reports where increased adherence to medication and higher utilisation of supplementation was reported among women (Alhazami et al., 2020; Dickinson and Mackay, 2014). Adherence to such regimens can be challenging, with few studies focusing on adherence to nutritional supplementation alone. While good adherence was defined as >50%, in our study, adherence levels to nutritional supplementation varies between diseases (de Oliveira et al., 2021) ranging from 32% - 100%. This is similar to previously published adherence to medication in multiple health conditions (36.8% - 72.3%) (Briesacher et al., 2008). There is presently no clear evidenced based cut-off ranges to differentiate good, moderate, and poor adherence. Hommel et al., (2019) reported an adherence rate of 60% to prescribed nutritional supplementation in a cohort of paediatric CF patients with ‘good adherence’ defined >80%. Similar findings have been reported in COPD where mean compliance was 78% (37%-100%) reflecting good tolerability to ONS (Hubbard et al., 2012). Similar to this feasibility study, good adherence was stated as >50% consumption of nutritional supplementation in pre- and post-surgical patients, but no clear justification for the 50% cut off was reported (Kerr et al., 2022). In contrast, adherence to other therapeutic treatments, such as physiotherapy (Low et al., 2020) and medications (Bhattarai et al., 2020) show overall poor adherence in bronchiectasis and COPD with rates being as low as 20%.

Variation in adherence criteria and the lack of studies defining ‘good adherence’, limit the comparability of this feasibility study with other adherence research. Historically, definition of good adherence has been >80%. Established in antihypertensive trials (Haynes et al., 1980), it is a cut-off point that is frequently used but has no clear rationale (Gellad et al., 2017). Consideration of adherence thresholds exploring appropriate outcomes in supplementation is advocated in a systematic review (Baumgartner et al., 2018) and should be included in future research that involves supplementation.

This feasibility study provides a preliminary evaluation of adherence to nutritional supplementation in adults with PCD and supports recommendations that adherence should be a reported outcome in this disease (Gahlentier et al.,

2022; Shoemark and Harman, 2021). Greater than 50% adherence was used in this study due to the small sample size and reflects previous reported adherence to medications of around 53% in patients with bronchiectasis (Thornton et al., 2022) and 50% or less reported in systematic review evidence for those consuming supplements in the home setting (Gea Cabrera et al., 2019).

7.6.2 Palatability and acceptability

Palatability and acceptability were similar across both the VAS and hedonic scales. Despite a range of consumption, overall palatability was rated towards the poorer end of each scale. This was specifically reflected in the taste and aftertaste of the amino acid supplement. There was no relationship between palatability rating and percentage consumption. Notably, those participants who consumed ≤50% of the amino acid supplement gel reported better ratings for taste and aftertaste. It suggests firstly that non-consumption is not related to its taste properties and secondly that duration of daily supplementation may cause taste fatigue. The latter has been established in respiratory disease (Spencer et al., 2021; Valizadeh et al., 2023), oncology treatment (Ravasco, 2005) and more recently in COVID-19 and should be addressed by introducing flavour variety, smell training and zinc supplementation to ameliorate altered taste. (Risso et al., 2020)

Fifty percent of participants were unable to record ‘smell’ on the VAS scale which reflects a high prevalence of anosmia. This reflects the well-recognised association between nasal obstruction, sinus disease and PCD (Pifferi et al., 2018). This absence of smell will also impact on taste and alter perception of palatability of the supplement. The impact of anosmia on flavour perception, flavour loss, and reduced stimulation of appetite (Hunter and Dalton, 2022) should be considered when designing future trials and the addition of a variety of flavours could maximise future palatability. This is recommended in a systematic review of oral nutritional supplementation (Hubbard et al., 2012). It has also been suggested that taste panels and testing within specific clinical populations such as PCD should be undertaken prior to trial interventions; a factor considered in previous interventional studies (Ispoglou et al., 2016)

The presence of taste fatigue was not addressed in this study and may have been a contributing factor to supplement uptake. This has been reported in previous research reviewing adherence to oral nutritional supplements in participants with cancer. Bolton et al., (1992) reported 19% of participants listed flavour fatigue as the reason for withdrawal. However, this study demonstrated

that the consumption of two gels per day, was achievable in the short term. Despite shorter term feasibility, longer duration of consumption could be potentially challenging. Factors that affect adherence and intake of oral nutritional supplements include personal preference, palatability, social factors and more (Nieuwenhuizen et al., 2010). Inclusion of semi structured interviews or focus groups to qualify the impact of the gel supplement on overall dietary intake, taste and tolerability should be considered for future research.

7.6.3 Dietary intake

The impact of supplementation on dietary intake over 3 months did not indicate a compensated reduction in normal dietary intake. Improvements in dietary intake were observed with the addition of the gel supplement, enabling individuals to improve their intakes, but not always to meet their calculated requirements. This is supported by a systematic review and meta-analysis which explored protein supplementation in healthy adults (Ben-Harchache et al., 2021). The authors found that energy intake was not compromised by longer term protein supplementation, despite this, 80% still failed to meet estimated calculated requirements, similar to the findings in this feasibility study. Nutritional interventions in pulmonary rehabilitation in COPD, have been shown to improve energy and protein intakes, but deficits of 23% for energy and 17% for protein, still remined (Beck et al., 2023). Calculating estimated requirements, provide individual energy and protein needs at point of assessment. This also enabled a review of individual EI:BMR ratio to determine non habitual intakes. This may have provided a more accurate record of underreporting of energy intakes due to the addition of physical activity data collection. More robust methods for collecting data on nutritional intake are needed to support a true understanding of any underreporting that may be present in this population for future research.

Requirements are adjusted based upon the presenting clinical situation, which can fluctuate in PCD during periods of exacerbation, and repeated treatment for bacterial colonisation. (Shapiro et al., 2016). Evidence is lacking exploring longer term supplementation, of more than 3 months. Systematic review in COPD suggests further research that establishes impact before, during and after exacerbation on outcomes such as QoL, body composition, HGS and dietary intake, (Beijers et al., 2023). Regular monitoring over time is therefore essential and has been suggested to improve adherence (Hopanci Bickali et al., 2017).

In this study, fat free mass (rather than total body weight) was used to calculate personalised values for estimating energy requirements. In doing so, it provided

a more accurate value in clinical settings, where indirect and direct calorimetry are unavailable (Todorovic and Marfrici, 2018). Similar arguments hold true for protein requirements where fat free mass and ESPEN equations were used to calculate estimated protein requirement (Dekker et al., 2022). Two methods were utilised in an effort to address the inflammatory influence of the disease (Brill et al., 2015; Aghasafari et al., 2019), and the limitations associated with estimation using a single measure. Using ESPEN guidance (Deutz et al., 2014), the deficit for protein was greater and did not reach requirements in some participants when compared to the method utilising fat free mass. Advocation for use of the greater value (ESPEN) to mitigate for losses in protein, that cannot be accounted for through calculations. This optimises identified protein need, without compromise of kidney function (Deutz et al, 2014). Whilst the impact longer term of using either equation remains unresolved, the need to monitor and evaluate the outcomes associated with either method is required. In this way, optimal intakes with sufficient provision of protein can be established. This ensures effective improvements in outcomes, reported by Bernardes et al., (2023) in a systematic review and meta-analysis in COPD and establishing optimal levels of protein need and intake is essential in cystic fibrosis (Engelen et al., 2014).

The amino acid formulation used, was a leucine enriched (40%) amino acid mixture that has been shown to augment protein synthesis and was initially tested in older healthy adults (Ispoglou et al, 2016, Ispoglou et al., 2021). Robinson et al., (2019) reviewing current UK evidence, advocate for investigation into the role of supplementation, therapeutic actions of diet and dietary patterns that may influence effective muscle strength in combination with physical activity, reinforced further by meta-analysis, which highlights the synergistic role of protein and exercise in sarcopenic older adults (Kirwan et al., 2022). Systematic review evidence has also explored the use of dairy products as a dietary source of leucine, in improving appendicular muscle mass (Hanach et al., 2019) to improve quality of life. Whilst, this could be promising, feasibility of consumption of sufficient amounts of dairy products needs to be established and may not be achievable, in a PCD population experiencing cyclical infections, and excessive sputum production which add further challenges to achieving optimal dietary intakes.

In COPD, improvements in skeletal muscle, overall strength, and inspiratory muscle strength, in those receiving leucine and vitamin D (Jonker et al., 2017; van de Bool et al., 2017), suggests that it may play a similar role in bronchiectasis and PCD. Whilst supplementation did not impact dietary intake, it was noted that dietary intakes were sub optimal in most participants, (reported

in chapter 4). Amino-acid supplementation may therefore be a more practical way to achieve required protein intakes than asking individuals to consume additional food products and may simultaneously increase energy intakes.

Whilst the controlled formulation and low volume gel supplement could induce taste challenges, its merits are that it is a simple and practical supplemental alternative. Systematic review evidence supports the role of leucine and similar compounds to improve muscle function and mitigating skeletal muscle loss (Phillips et al., 2022b). To address inconsistencies in the research, a more homogeneous approach to determining effective outcomes has also been proposed (Bernardes et al., 2022). This feasibility study begins to establish a route for further research to address the gap in nutritional needs and benefit of additional protein, for patients with PCD and bronchiectasis specifically.

7.6.4 Secondary outcomes

Spirometry, reported as FEV_1%, as an indicator of lung function decline, showed no statistically significant changes from baseline to three months in all 10 participants. However, reported improvements in functional capacity (6MWT) and perceived exertion, suggest that lung function should not be used in isolation. These practical outcomes for participants suggest that they have merit for inclusion as a primary outcome in future trials. These two measures, along with inflammatory markers of disease, may then provide a more holistic picture that enables effective phenotypic grouping of individuals. Together with genotype, sub-populations can then be better characterised for effective treatments. This is supported by a review by Goutaki and Pederson, (2021) and mirrors the establishment of endotypes in bronchiectasis (Flume et al., 2018; Martins et al., 2023) and COPD (Huang et al., 2022). This could contribute to addressing research gaps in PCD. Narrative review suggests that incorporating clearly defined sub-group of disease helps to support progress to bespoke prescriptive treatments (Goutaki et al., 2016), it may also provide a clear rationale for exploring markers to determine such classification; an approach that is further endorsed by the BEAT-PCD consensus statement 2024 (Kos et al., 2024).

In this feasibility study SGRQ, showed improvements in 40% of the participants that consumed more than 50% of the supplements and 50% in those that consumed less than 50%, with similar results reflected in the generic SF-36. Established impact and appropriate measures of HRQoL in COPD (Hurst et al., 2021) and bronchiectasis (McLeese et al., 2021) show the influence that these conditions have on outcomes and validates their use here. Whilst HRQoL outcomes were inconclusive in this current feasibility study, their use in

measuring outcomes in PCD populations has been recommended and is supported by expert consensus (Kos et al, 2024). Of note and aligned with bronchiectasis (Dudgeon et al., 2018), quality of life deteriorates for all age groups in PCD, and when compared to family members without disease, are poorer (Behan et al., 2017b). This study shows that it is feasible to collect QoL data at clinical appointments (95% completion rate) and this should be incorporated within larger studies to determine longer term impact of nutritional supplementation. This is lacking across clinical provision currently.

7.6.5 Anthropometry

Handgrip strength (HGS) in this population continues to show impairment in comparison to normative values. This has been a consistent finding in chapter 4 and 6. A significant improvement in hand grip strength was found in 90% of participants, over the 3-month period and has been shown to be associated with lung function in PCD (King et al., 2021). It is associated with poorer outcomes overall in healthy and unhealthy individuals, other respiratory disease, and inflammation (Mgbemena et al., 2022, Tuttle et al., 2020). The benefits of handgrip strength are its ease of use in the clinical setting and ability to identify potential sarcopenia. HGS has been identified as an essential tool in prediction of lung function in healthy adults (Mgbemena et al., 2022) but requires further study to understand the impact on lung function in PCD. Its use as an important tool and association with clinical outcomes is reported in CF (Contreras-Bolivar et al., 2021) and COPD (Holden et al, 2021).

The inclusion of this practical measure may help to address the gap in bespoke nutritional recommendations for this population group, through its role in identifying the extent of muscle impairment and monitoring changes in muscle strength. Inclusion of HGS as a monitoring method in PCD, may then be used to inform a more personalised approach to macronutrient manipulation, and consideration of dietary intake beyond existing whole population recommendations. Current guidelines advocate macronutrient intakes that equate to 50% carbohydrate, 30 - 35% fat and 15-20% protein. Coelho-Junior et al., (2022), following systematic review and meta-analysis, reported intakes of protein are lower in older adults with sarcopenia. Enhancing the nutritional status of this PCD population further, through dietary manipulation and supplementation is of interest. The impact of nutrition on HGS has been reported in older adults in meta-analysis (Veronese et al., 2019; Robinson et al., 2019).

Systematic review evidence considering sarcopenia in older adults, report greater protein intakes have positive effect on lean muscle mass (Rogeri et al., 2021). Changes in body composition, that can be measured easily through HGS, may improve clinically relevant outcomes.

Measurement of muscle mass through BIA, showed an increase in skeletal muscle mass for two (20%) of the 10 participants although there were no statistically significant differences between baseline and 3-month values. This study has recorded some changes in body composition with statistically significant baseline differences in %FM and %FFM but not post consumption of supplements. These findings are in agreement with those from a recent meta-analysis, which determined the consumption of HMB did not change body composition (Jakubowski et al., 2020). Overall, BIA provides an indirect measure of body composition and may have value in larger longitudinal research for PCD. This feasibility study indicates similar results comparing BIA and anthropometric measures, both reflecting similar percentiles, and suggests that in the absence of BIA these assessment methods are viable alternatives in a clinic setting. The use of anthropometric measures in PCD is more commonly seen within paediatric populations where monitoring of growth and development are essential (Kos et al., 2024; Marino et al., 2019). There is lack of evidence to support its use as a standard clinical measure in adults with PCD but continued inclusion in trials will help to solidify its role, mirroring already established recommendations in other respiratory disease (Contreras-Bolívar et al., 2021; Holden et al., 2021).

7.6.6 Further dietary considerations

The positive anti-inflammatory properties of vitamin D in lung disease has been well established (Chishimba et al., 2010) with appropriate supplementation being recommended as part of standard care in bronchiectasis (Chalmers et al., 2013b; Ferri et al., 2019; Sami et al., 2021) COPD (Joliffe et al., 2019; Minter et al., 2023) COVID-19 (Pereira et al., 2022) and CF (Daley et al., 2019). However, it is still not part of standard care within PCD (Sergi, 2021). Vitamin D status of participants in this feasibility study showed varying results when compared with NICE guidance for proposed levels of sufficiency and insufficiency (NICE 2020). Overall, mean dietary intakes were insufficient to meet the dietary reference value of 10µg per day, and whilst supplementation consumption varied, those that had reported the greatest adherence (>50%) were consuming between 25-38 µg in total. This exceeds recommendations but lies within the safe limits established by SACN (2016). There did not appear to

be a relationship between supplementation and serum Vitamin D levels, and no statistically significant changes were observed in the 3-month period. Importantly, the consumption of these gels spanned the winter months when serum vitamin D levels are often at their lowest. This could have influenced the results. Further inclusion of this and other essential micronutrients to determine longer term impacts of sufficiency and insufficiency and its role in PCD is justified. Further evaluation of the impact of dose and duration of supplementation, dependent on comorbidity, age and baseline serum values have also been proposed (Bliezgys, 2021). Optimal dosing in PCD has not been established.

7.6.7 Withdrawn participants.

Recruited participants who did not complete the 3-month study had the lowest median outcome values compared with any other group reviewed, except for TSF and MAMC. The analysis of factors associated with withdrawal from the study showed that the participants who withdrew had a significantly lower median baseline energy intake (1400 kcal compared to 1600 kcal for those who completed the study) and protein intake (55 g compared to 70 g for completers). These participants also had a median FEV_1% of 47.5% and a HGS of 18.4 kg/f, compared to 76% and 28.5 kg/f in those who completed the study, respectively. This is of specific note as the FEV_1% values reflect severe pulmonary impairment (Pellegrino et al., 2005) and impaired handgrip strength. It suggests a group who would have gained greater benefit from supplementation. The withdrawal of these participants therefore impacted the overall study outcomes, as the characteristics of those who withdrew were considerably different from those who completed the study. This resulted in a potentially skewed understanding of the supplement's effects, highlighting the need for strategies to improve retention in future studies. Study retention strategies such as communication touch points, clear and patient centred participant information, use of technology (where appropriate) and non-financial incentives should be considered (Chaudhari et al., 2020). Effective planning and personalised care can also improve retention (Poongothai et al., 2023). A Delphi survey and further systematic review of UK researchers, reported a list of retention strategies, ranked by clinical trial units (Kearney et al., 2017). Careful consideration and future research should assess effectiveness of the suggested strategies that are specific to the research being conducted.

7.7 Strengths and limitations

Strengths

Secondary measures undertaken in this feasibility study utilised standard operating procedures (SOP) to ensure consistency in methods of data collection and conducted by the same researcher. When undertaking the anthropometrical skinfold measures the assessor had gained ISAK accreditation, improving reliability of results and reducing standard error. Whilst feasibility is unable to infer causal relationships it has been able to establish key outcomes that could be valuable in exploring in further research trials.

This feasibility study has reinforced the value of HGS as a simple bedside measure that was improved following supplementation and cements its use as a standard measure in the regional clinic population.

The fundamental nature of a feasibility study enables areas of bias that may exist through design or selection to be reviewed and considered prior to further multicentre research. Measurement bias was reduced by having standard operating procedures for physical measurements such as HGS, and specialist measures were undertaken by one researcher which provides consistency in approach. All equipment utilised in measurements were validated and/or calibrated were appropriate which provides consistency and accuracy in measurements.

Limitations

The limitations of this feasibility study lie in its attrition rate and the imprecise nature of adherence measures to the gel supplement. Reason for attrition was related to non-engagement and inability to tolerate the supplement gel. Those in this group where characteristically different than those that completed the feasibility study, and this may have affected the results seen.

All participants were provided with expected pre-assessment guidance prior to clinic appointment for measures undertaken e.g. BIA, however this was not checked beyond questioning, as there was no feasible way of ensuring participants followed this guidance. Bringing prospective participants in to discuss further the requirements may safeguard adherence to the required pre assessments.

Whilst the research focused on key functional outcomes, changes in body composition, lung function, BMI, and Handgrip Strength and the final uptake of supplements. Earlier qualitative interviews might have yielded shorter term patient centred outcomes around the lived experience of the feasibility study

itself. Introducing this qualitative perspective as a formal part of a future trial design would be important.

Finally, there was no option of reporting reasons for non-adherence, although some participants did offer further insight without prompt. Future research should consider mixed methods approach to establish this aspect in greater depth.

Small sample sizes, by their nature result in limitations of outcomes reviewed. Whilst some consideration of what this study has found and that can inform future research, numbers closer to 20 would have provided stronger evidence for proposals, and so a limitation to consider here.

7.8 Conclusion

The results of this feasibility study have shown that consumption of supplementary gels twice daily, in a respiratory population that experience overall poor health can reach 100%. Palatability lies within reported poorer ranges. A leucine and vitamin D enhanced amino acid gel has been shown to improve dietary intake, whilst avoiding a compensatory reduction in food intake. To improve retention within future trials, the development of enhanced palatability and supplement adherence strategies in this younger population group should now be considered. Hand grip strength has been shown to be a practical measure and important outcome. Further key parameters identified as important for future research include spirometry, 6MWT, measurement of body composition and quality of life, which are all advocated by BEAT-PCD consensus statements (Kos et al, 2024). This study informs future research within longitudinal and multicentre trials, that determine the impact, of leucine rich amino acid supplementation.

7.9 Future research

This study provides important early findings to inform future multicentre clinical trials, with appropriate outcomes of interest to assess. Key areas of note are:

1. Adherence – understanding and establishing reason for non-adherence through semi structured interviews to address participant retention and engagement.
2. Palatability – completion of qualitative focus groups through patient and public involvement to establish appropriate flavour profiles. Taste panels to address challenges with anosmia and palatability of supplementation,

alongside appropriate dosing, and formulation considering deficits in energy and protein through normal diet.

3. Quality-of-life - Incorporation of measures that provide important patient perspective to determine impact of disease and nutritional intervention e.g. QoL-PCD.
4. Standard use of HGS - to address the gap in research and determine muscle functionality and prescriptive dietary needs of this population. This would require recruitment nationally to reach greater numbers of participants.
5. Body composition – measuring beyond BMI to consolidate distribution of FM/FFM in adults with PCD and the influence this has on outcomes specifically QoL and exacerbations.

Chapter 8
Discussion of the collective work within this thesis

8.1 Overview

The following chapter will draw together the key findings of this novel body of work and its impact and contribution to current and future research. This chapter's aim is to synthesise the main findings and consider collective interpretation of the research undertaken.

The aims of the thesis were to review the current evidence for nutritional characterisation of bronchiectasis, determine the nutritional status and dietary intake of a clinical cohort and exploring the feasibility of consumption for leucine enriched amino acid supplementation. These aims were addressed in 4 linked studies.

Study 1 (chapter 2) was a novel narrative review that established the role of BMI in predicting morbidity and mortality in bronchiectasis. Overall, a lack of studies characterising nutritional intake and status was identified. The review pulled together the small amount of data on clinical body composition, specifically fat mass, fat free mass and Hand grip Strength (HGS) beyond Body Mass Index (BMI), and the emerging role of vitamin D in bronchiectasis. The narrative review informed chapters 4 and 5 which sought to characterise dietary intake in a clinical cohort with bronchiectasis for the first time and evaluate anthropometric measures of body composition additional to BMI. In a cohort with bronchiectasis and sub-group with PCD, the proportion of individuals with normative HGS values assessing muscle strength, was established, and their association with standard care outcomes reported. In chapter 6, anthropometric measures (specifically HGS) were further assessed in a retrospective study. Repeating assessment of muscle strength and standard care outcomes over a period of one year and considering changes over time with association of reported standard care measures. The final study (Chapter 7) explored through feasibility, the acceptability and palatability of a leucine enriched amino acid gel in a population with PCD. The impact of supplementation on dietary intake, clinical and functional outcomes over a 3-month period were explored.

8.2 Chapter summaries

8.2.1 Narrative review (Study 1)

A novel exploration of the impact of nutritional intake, nutritional status, and body composition on clinical outcomes in NCFB was undertaken in Chapter 1. Despite a Cochrane review that had examined all systematic reviews to that date within NCFB (Welsh et al., 2015), none had focused on nutrition. Findings from the narrative review therefore contributed new evidence and informed further studies within the thesis.

Fifteen studies were included in the review and showed diversity in study measures, outcomes, geographical location, and population. Despite this, the review highlighted some common findings that informed Chapters 4,5,6 and 7. The impact of low BMI was shown to be consistently associated with poorer outcomes in bronchiectasis. In those categorised as underweight (BMI < 18.5kg/m^2), BMI was associated with higher incidence of NCFB (Yang et al., 2021), poorer lung function (Despotes et al., 2020; Qi et al 2015; Sami et al., 2021) and increased all cause and respiratory related mortality (Lee et al., 2021; Qi et al., 2015). It suggested that BMI remains a practical screening measure that can identify more vulnerable sub-groups of NCFB.

The lack of standard outcome measures limited comparison between studies. To obviate this, a Cochrane umbrella review (Welsh et al., 2015) has proposed that standard measures including lung function, QoL, and exacerbations should be included in all future trials in bronchiectasis. Whilst lung function was uniformly collected across the 15 studies, QoL and/or exacerbations were included in only five (Contreras- Bolivar et al., 2019; Despotes et al., 2021; Olveira et al, 2014; Olveira et al, 2016; Qi et al., 2015). These outcome measures were subsequently considered within the feasibility study (Chapter 7).

As an adjunct measure of nutritional status (and outcome) handgrip strength (HGS) has been established as an easy and useful indicator of muscle functionality in lung disease (Mgbemena et al., 2022). There was limited evidence prior to and within this review on the role of HGS in bronchiectasis. This contrasts with COPD and CF where its association with exacerbation and reduced lung function has been established (Contreras-Bolivar et al., 2021; Holden et al., 2021). Clinically, it is effectively utilised in liver disease (Luengpradidgun et al., 2022), oncology (Victoria-Montesinos et al., 2023), older adults (Strandkvist et al., 2021) and advocated as measure of overall health (Vaishya et al., 2024) and predictor of disease (Lopez-Bueno et al., 2022).

Findings of the narrative review also indicated that with the exception of vitamin D, characterisation of nutritional intake in bronchiectasis was lacking. Cumulatively such studies have helped to inform nutritional guidance in other respiratory disease conditions such as CF and COPD and improve disease outcome (Collins et al., 2019; Turck et al., 2016;). Within the review, early studies had focused on vitamin D alone identifying that vitamin D intake and serum levels were suboptimal in bronchiectasis, lower when compared to controls (Ali et al., 2022; Chalmers et al 2013), and contributed to high levels of 73% insufficiency (Sami et al., 2021). It suggested that fuller exploration of macro and micronutrient intakes was warranted and informed study 2 (Chapter 3)

In summary the findings of the narrative review informed emerging areas of research requiring exploration; namely studies examining dietary intake in bronchiectasis (including vitamin D), studies establishing the utility of HGS as a further measure of body composition and whether supplementation can improve muscle function and nutrient status (specifically vitamin D).

8.2.2 Characterisation study (Study 2)

Chapters 4 and 5 characterised nutritional intake, nutritional status and body composition in bronchiectasis and provided the first detailed study of nutritional intake (King et al., 2021) in a local bronchiectasis population. At the start of the thesis, nutritional status had been characterised by BMI alone (Despotes et al., 2020; Li et al., 2020b; Qi et al., 2015). There was no research to establish overall dietary intakes in bronchiectasis and limited evidence for the utility of further body composition measures. The work within Chapter 4 and 5 presented for the first time a detailed cohort analysis of nutrient intake in bronchiectasis and further differentiated nutritional intake according to distinct sub-groups of a clinic population. Findings indicated a group with variable severity of lung function and Body Mass Index (BMI), which lay predominantly within normal and overweight categories. This is reflective of other bronchiectasis cohorts within Europe (Chalmers et al., 2013b; Contreras-Bolivar et al., 2019; King et al., 2021; Lee et al., 2021; Olveira et al., 2012; Olveira et al., 2016; Sami et al., 2021; Wang et al., 2021)

Original findings also revealed a sub-group of patients with PCD who were younger, had lower BMI, high prevalence of low HGS (96%) and the lowest intakes of vitamin D, calcium, iron, and protein compared to other sub-groups. Whilst nutritional requirements were sub-optimal for vitamin D and iron alone, it was notable that those with PCD were significantly younger by 4-5 decades compared to other aetiological groups. For the first time a younger and more

vulnerable adult group were identified, who might benefit from early, targeted nutritional monitoring and intervention. Such interventions have already been introduced across other respiratory diseases such as CF (Turck et al., 2016) and COPD (Scordotti et al., 2019), where nutritional risk profiling is established. The monitoring of body composition (using BIA) and vitamin D is already advocated in paediatric populations (Marino et al., 2019), but is not yet established in adults, but identification as a vulnerable group supports continued measures of HGS and nutritional surveillance.

Novel findings within the chapter also show that energy intakes were uniformly sub optimal across the cohort as a whole and within each aetiological sub-group. The achievement of only 71-81% of estimated average energy requirements (chapter 4), may require a more nutrient dense diet to achieve macro and micronutrient requirements. If sustained it can compromise nutritional status. Consideration of those that are likely under reporting needs effective and triangulated assessment of nutritional intake, including digitally recorded multiple pass recall and food frequency questionnaires that focus on key nutrients over a longer period of time to mitigate this. Notably, specific sub-groups failed to achieve recommended reference nutrient intakes for some vitamins. Those categorised as overweight and obese had reduced micronutrient intakes compared with those of normal or low BMI; findings that are reflected in systematic review evidence (Asghari et al., 2017; Wolongevicz et al., 2010). Suboptimal intakes of vitamin D and vitamin E were particularly significant and provided new evidence to suggest a more proactive approach to monitoring and supplementation should be considered. This approach is further supported by knowledge that vitamin E is integral to both the inflammatory response (Gasmi et al., 2022; Luan et al., 2023; Martín Giménez et al., 2021) and muscle function (Hernández-Camacho et al., 2020; JavadMoosavi et al., 2013).

The analysis of micronutrient intakes in chapter 5 identified a positive relationship between HGS and zinc intake in bronchiectasis. These findings were plausible as zinc affects muscle cell activation and is associated with muscle mass and strength (Hernández-Camacho et al., 2020). Corrective supplementation of low serum levels in bronchiectasis has previously been shown to reduce disease progression (JavadMoosavi et al., 2013) and alongside Vitamin D has also been shown to play a role in attenuating inflammation and infection in bronchiectasis (Derbyshire and Calder, 2021). Evaluation of nutritional intake in bronchiectasis (Chapter 4 and 5) and the subsequent publication of this new data (King et al., 2021) provided new insight

and additions to the literature. Together it informed further evaluation of HGS in Study 4 (Chapter 6).

8.2.3 Study on HGS (Study 3)

In Chapter 6, HGS was retrospectively observed over one year. This study was informed by study 2 where significant impairment in HGS, measures of muscle strength, had shown that muscle strength impairment was present in 70% of the total cohort and 96% of a sub-group with PCD.

In Study 3 (Chapter 6), these findings were extended further to show that sustained impairment in HGS (muscle strength) was present over a one-year period in distinct populations with bronchiectasis and PCD. Those with PCD were confirmed to have an accelerated decline in muscle strength, with HGS measures similar to a comparator cohort with bronchiectasis who were almost three decades older. Longitudinal measures of HGS had not previously been reported in bronchiectasis and these new findings further confirmed that the measurement of BMI alone masks the presence of persistent muscle impairment and possible sarcopenia in this population. It again confirmed a more vulnerable population with PCD.

The importance of these findings is linked to previous reports of poor respiratory muscle strength in bronchiectasis (Wang et al., 2022). Hand grip strength is associated with inspiratory muscle strength in a variety of older cohorts (Kim, 2018; Martínez-Arnau et al., 2020; Pegorari et al., 2018) and has also been noted in COPD and CF (Samarghandi et al., 2020; Sovtic et al., 2018), although the extent of this relationship remains unclear. The degree of respiratory muscle impairment in this bronchiectasis population in those with impaired HGS was unknown. However, the association of HGS, adjusted for age and sex with lung function, suggests that use of HGS should be continued in the clinical setting. The findings of this study also strengthened the rationale to support a practical nutritional intervention that might mitigate and/or improve HGS in Study 4 (Chapter 7)

8.2.4 Feasibility study (Study 4)

In Chapter 7, the consumption of a leucine enriched amino-acid gel was evaluated in a sub-group of patients with PCD, previously identified as younger, with poorer nutritional intakes, lower BMI and lung function, and an accelerated decline in muscle strength. This study built on findings from Chapter 2,4,5, and

6 and a study by Olveira et al., (2016) and was unique within a PCD population. Whilst a previous study had examined use of a leucine derivative in a prospective randomised study in bronchiectasis, the current study extended this work to PCD alone and offered new insight to inform future trials.

It considered that body composition measures (FFM, HGS, MAMC) can be improved with focused nutritional supplementation in PCD. The study rationale was also underpinned by the knowledge that HGS had already been shown to be impaired (Study 2), sustained over time (study 6) and associated with lung function and sub optimal dietary intake - specifically vitamin D, zinc, and vitamin E.

Findings indicated that nutritional supplementation was tolerated in 60% of participants, although varying palatability scores and adherence were noted. Importantly gel supplement intake did not reduce oral food intake, suggesting it exerts an additive effect. Supplementation demonstrated improvements in HGS and Vitamin D serum measures over 3 months. Key outcomes such as 6MWT and QoL were also shown to be feasible in future trial design shown through 100% adherence to protocols and 98% adherence in the completion of QoL questionnaires. Use of the 6MWT in chronic respiratory diseases is validated (Singh et al., 2014) and predominantly used in paediatric PCD populations (Firat et al., 2022; Gut et al., 2023). Its use is supported as a standard outcome measure for research in adults with PCD (Kos et al., 2024). Adherence to physical paper copies of QoL versus completion of digital tools is a consideration for future research. Digital QoL tools have advantages over paper with good completion rates and improved data quality (Meirte et al., 2020) and are advocated in larger studies. This study has validated further the use of QoL and 6MWT that are emerging as key outcomes for assessing daily activity and quality of life in those living with respiratory disease. The utilisation of both methods in PCD is advocated within the BEAT-PCD consensus statements as key outcome for consideration in future research (Kos et al., 2024).

The feasibility study further consolidated the value of HGS measures within PCD, highlighting that improvement in HGS can be achieved with supplementation in 83% of those that consumed more than 50% of the supplements over the study period (3 months). Importantly the study also highlighted the need for effective retention strategies, through the analysis of participants who withdrew indicating that they were significantly more unwell at baseline.

This study has found that a low volume supplement gel, twice a day, with a leucine enriched amino acid formula, despite poor evaluation of palatability can

be tolerated over a period of 3 months. This adds knowledge to adherence of supplementation and provides clear outcomes that are valuable for future research. The feasibility study also identified outcomes that should be considered in any future research. The lack of duration of disease, degree of severity through study period and exacerbations, and medications throughout the study period should be considered to ensure confounders are accounted for.

This study provided insight into the successful completion of valuable assessments of physical activity and included outcomes such as quality of life assessments to determine lived experiences of those with Primary ciliary dyskinesia and its impact.

A key focus of future research should include an enhanced approach to collection of physical activity with the use of equipment that can also measure the physical activity undertaken such as a pedometer, with a programme of activity that includes strength training to accentuate the impact/effect of any leucine supplementation (Rehman et al. 2023). It has also identified some of the limitations associated with the dietary assessment approach and again further enhancement via digital technology that may improve accuracy of reporting and provide data over longer periods of time. It offers some contribution to the existing evidence that supplementation is feasible in respiratory diseases and influences key outcomes (Aldhahir et al., 2020, Collins et al., 2012). This is the first to be undertaken in PCD. It contributes to a considerable change in clinical focus to influence patient outcomes. There is benefit in long-term dietary surveillance with a focus on protein intake and its distribution throughout meal episodes. All these aspects have been considered within the design of a proposed clinal trial outline below.

8.3 Research strengths and limitations.

8.3.1 Strengths

In undertaking this programme of research several key strengths emerged. As an ‘orphan disease’ there has been little nutritional research that could directly inform clinical practice. This has had two benefits. Firstly, the thesis findings have provided specific and relevant findings that are directly applicable within the clinical setting. Secondly it has directly contributed to better understanding of nutritional and functional outcome for aetiological groups such as PCD and those underweight, overweight and obese. These findings can inform, future more targeted approaches to nutritional screening and care and better use of staff resource.

In study 2, (chapter 4 and 5), participant engagement and completion rates of 100% and 98% was high. This resulted in comprehensive data sets and minimal dropout and missing data values. The rigor of data collection and originality of the study contributed to the production of an abstract at both national (King et al., 2016) and regional conference level (King et al., 2020). The publication of findings part way through the thesis has provided further opportunity for dissemination of findings and impact (King et al., 2021). The study has subsequently been cited within a further publication (Zhang et al., 2022) indicating an early contribution to further research in NCFB.

The high recruitment and retention rates in Study 2 and Study 3 resulted from a number of strategies implemented by the lead researcher and minimised study bias that might be introduced through attrition. Attrition rates in clinical trials can exceed 20% (Bell et al., 2013; Poongothai et al., 2022). Cross sectional studies such as study 2, can by their nature reduce patient burden associated with follow-up but may still be impacted. Processes to mitigate attrition included participant involvement in designing study 2 and study 4. Patients were approached and recruited (3 for study 2 and 2 for study 4) to discuss the key aspects of the attitudes and determine from their lived experience, strengths, and areas for development both in the concept of the studies and the practical implications. Patients were consulted about feasibility and achievability of completing the measures and the practicality of implementing them within their clinic settings. Best practice participant consent procedures that provided hard copy information for participants and direct engagement with the researcher at early stages were also used (Poongothai et al., 2022).

To minimise bias further, each study was strengthened by the utilisation of standard operating procedures (SOP's) as part of nutritional assessment. The researcher underwent formal training in anthropometric measurement (ISAK level 1 accreditation) which maximised the consistency and validity of measures, including TSF, MAMC, and HGS. Standard operating procedures were then created specifically for the patient group attending the clinic settings, used in study 2,3, and 4. In addition, training was provided to all healthcare professionals on SOP's, to be used within each of the studies. This enabled engagement and consistency from the clinical team and maximised the accuracy of measures obtained.

The utilisation of a patient electronic clinical record throughout study 2, 3 and 4, ensured that supplementary demographic and clinical data was collected accurately in real time. The use of ECR has already been noted to have significant benefits for the conduct of research (Peckham et al., 2014), enabling easy stratification of aetiologic groups, systematic analysis of trends, and the

use of accurate retrospective data collected in real time. This was exemplified in Chapter 6, a longitudinal study which utilised retrospective data for HGS collated from the ECR.

Lastly, the introduction of a feasibility trial of supplementation (Study 4) was also considered a strength. It provided the opportunity to evaluate supplement palatability research burden, adherence, and the feasibility of collecting a broad range of clinical dietary and anthropometric measures. Together these provided practical insight into factors that might affect adherence and retention in future trials, specifically extended clinic appointment times to undertake additional measures, practicality of transporting supplements and storing them in participants homes, and engagement in pre assessment protocols.

8.3.2 Limitations

Whilst many strengths are already reported, some key limitations of the methodological approach are also important to report. Cross-sectional study design (Study 1 and 2) provides a firm basis for establishing association, but not causal effect. The retrospective longitudinal nature of Study 3 (Chapter 6) relied on routinely collected clinical data but also introduced the bias of missing values. This meant that the study (n=201) contained a self-selected population (n=86) who had 2 time points for measurements. A prospective longitudinal study would have enabled more complete data collection, a greater sample size and the avoidance of potential of selection bias. In the final study (study 4), the feasibility of a future RCT was assessed. Small in number and by necessity (impacted by COVID-19), short in time length of 3 months, this impacted on the magnitude of study findings and also the ability to determine true differences from the small sample size and adjust for key factors such as length of diagnosis, exacerbations and FEV1 (%)

Recruitment was undertaken at a regional centre. Whilst this provides an established cohort and regional clinical management expertise, this is not a model of care available throughout the UK. The approach of convenience sampling could also have influenced the population under investigation. Those recruited may have more interest in their own health and wellbeing and those may be more interested in nutrition. As such they may recall more detail than those who do not have a similar relationship with food.

Interview bias is a consideration with sub conscious assumptions made by the interviewer, and possible influence that can lead to both social desirability bias and recall bias. All of these factors can influence responses. These can be mitigated by standardisation of the interview process and in future research the

use of digital tools that may help to mitigate the risk of recall bias. Increasing recruited numbers may also mitigate.

A further limitation is the presence of under and overreporting. Underreporting was identified for 80% of the recruited sample. Compounded by database limitations that include differing or absence of recipe information, may further bias nutritional data, resulting in under or overestimation of dietary intake. To mitigate this the recruitment of correct sample sizes to note a true difference is important as is the use of digital platforms for data collection (dietary intake and physical activity data). Lastly, implementing longer study periods allows that include interim measurement points, enables better identification of time points where changes might occur and observation of longitudinal change. This would allow for further consideration of fatigue or enhanced longer term changes to muscle functionality and body composition that were not immediately seen in a small sample with limited time.

The occurrence of the COVID-19 pandemic (March 2020) influenced the conduct and timing of the research considerably. This limited the availability of clinics and subsequent access to participants. This inability to control the environment limited the availability of data by reducing the number of face-to-face patient contacts, limiting contact to those who required immediate review, and those willing to attend and those who might be more engaged in their healthcare. It therefore excluded those who were more well, or who might be fearful of attending clinic, reducing access and engagement of these participants. Limitations associated with a pandemic greatly influenced the potential of the outcomes, due to timing.

Clinic lists were reduced; to minimise face to face attendance and contact and instead patients were given the option of telephone review. In addition, considerably greater levels of PPE were mandated due to bronchiectasis being a respiratory disease. At the beginning of the lifting of the restrictions from lockdown, contact with participants was reduced and only essential healthcare professionals were able to engage directly. This paused any research in the setting between March 2020 until May 2021 until further restrictions were lifted.

The impact of this delay primarily influenced the feasibility study (study 4). Due to this delay and the limitations imposed by the supplement 'use by date', the duration of study 4 was reduced to nine months overall and the implementation period for each participant. This in turn affected recruitment numbers, collection of data (limited to 3 months) and limited the ability to address confounding factors such as seasonal vitamin D.

Vitamin D levels fluctuate throughout the year, primarily due to changes in sunlight exposure. Adjustments to confound for this include season specific baselines, with serum levels to be collected over longer periods of time. Two main considerations exist: firstly, that respiratory disease has been shown to require vitamin D in an immunomodulatory role and secondly that the older population over 60 years requires supplementation (NICE,2022). The baseline data collection of vitamin D serum levels within study 4, enabled a winter value that would confirm likely absolute lowest levels during winter months. Repeated measures over winter and summer months could be considered in the next research trial to account for potential within year variation (Chalmers et al., 2013b; Sergi., 2021)

Lack of inclusion of qualitative data collected as part of study 4 limited greater understanding associated with adherence and palatability of the supplements. If interviews or focus groups with all participants had been considered as part of the study this may have provided the support and contact that can contribute to more effective retention (Poongathai et al, 2022) and would have provided rich data that could inform any future changes to improve supplement palatability and participant information. Public and patient involvement in these studies included involvement in preparation and oversight of information which is one specific measure that is proposed (Sacristán et al., 2016). Involving those with lived experience enables embedding of health research, economic and cost improvements, fosters holistic approaches and promotes relevance and inclusivity (Aries et al., 2021; Holmes et al., 2019).

As identified in in a Cochrane review (Welsh et al., 2015) the collection of reported exacerbation alongside lung function and quality of life are advocated as key outcomes in bronchiectasis. This was limited in this research by the lack of collection of inflammatory markers within study 2 and 4. Whilst review of infections, as part of exacerbation, were considered in study 2 further inflammatory markers may have provided specific insight about associations with the novel findings here namely micronutrients and HGS.

The duration and length of the period of study is a limitation to the presentation of the studies and the contributions to the existing evidence base. This period of study has spanned 8 years (total). Enrolment in the programme of study was undertaken on a part time basis, due to existing work commitments and the clinical NHS changes imposed by the introduction of COVID-19, further impacted on duration. This leads to anomalies in timelines e.g. the need for a 2-phase narrative review, availability of data prolonged due to COVID-19 and further consideration of discoveries in this research, superseded by further

research. Whilst this area of research is still novel, this is still a noteworthy limitation.

8.4 Implications for future research

Several considerations for future research have been proposed in each of the chapters throughout this thesis. Key research should include the following.

It is essential that any future research should include patient and public involvement (PPI) in a more robust way. PPI is a key NHS driver that fosters involvement from both the public and patients with lived experiences of specific conditions. They are key to providing insight into achievable and important future research development. Primary ideas can be presented and developed in a collaborative way utilising the principles of the strategy (NHSE, 2022). Patient involvement was undertaken as part of study 2 and 4 (chapter 7), but not in the other research discussed. It was limited to trail practicalities in the preparation and oversight of ideas and reinforced that the studies were achievable and appropriate for the potential participants.

Study 2 has identified a vulnerable population with bronchiectasis and PCD, that are younger and have impaired HGS. This was corroborated in study 3 (chapter 6) which established that HGS impairment was sustained. The current cohort of patients with PCD registered in the regional clinical is estimated at approximately 100-130. The previously recruited numbers therefore represent less than 50% of the current population. Characterising this regional adult population more fully, would extend and consolidate early research findings in this cohort which is currently recommended in the paediatric cohort (Firat et al., 2022).

Study 2 has also identified a vulnerable bronchiectasis group with impaired HGS. Utilising the newly collected HGS measures as part of clinical practice HGS in the older population merits review, including categorisation according to the EWGSOP thresholds (Bahat et al., 2016). Assessment of body composition through BIA and dietary intakes, utilising longitudinal design e.g. over 1 year through collection of multiple pass recalls at specific time points. This will provide essential data to determine the incidence of sarcopenia and sarcopenic obesity within this population and determine the influence of dietary intake. This will address the potential masking of BMI, that may exist in this group and enable identification for appropriate dietary and physical interventions, either through pulmonary rehabilitation or though individual dietetic consultation. Additional measures that are considered standard in bronchiectasis – including exacerbation (inflammatory markers), serum vitamin and mineral levels, HGS

and quality of life using the QoL-B questionnaire (Welsh et al., 2015) should be incorporated to enable standardised outcomes and comparability of the study with other research.

The feasibility study in chapter 7 (study 4), confirmed that supplementation is achievable, but challenging in terms of palatability and sustaining intakes over time. A clinical trial outlined below is suggested to qualify the feasibility outcomes and determine influence of nutritional supplementation in PCD. It accounts for the learning acquired from the feasibility. The following study design is advocated in a review (Goutaki et al., 2024) and the key outcomes are identified in the BEAT-PCD consensus statement (Kos et al., 2024).

8.4.1 Integration of findings into future research

The studies combined, identified several areas of focus for future research. Qualitative study designs using focus groups for those with PCD, would enable a more detailed understanding of factors that limit adherence to the use of nutritional supplements and to the research protocol itself. This was a key finding from the feasibility study and would ensure that a future RCT is underpinned and informed by patient involvement. It might also inform outcomes important to patients that might not be evident to the research team.

Adherence remains a major obstacle to treatment, both in the clinical and research setting. Areas to consider include adherence of 2 gels daily over a 6-month period, understanding its impact in daily life and the consideration of different flavour profiles, explored through taste panels specifically suited to this population. This would reduce overall costs and waste.

Using digital technology to collect data for physical activity provides opportunity to reduce recall bias, selection and social desirability bias. However, its use within specific age groups and aetiologies requires further evaluation. Use of digital food diaries and pedometers are two examples where there is potential to collect data in ‘real time’ and subsequently reduce recall bias further.

The choice of study design is crucial. Qualitative underpinning has already been discussed. A number of follow-on trial designs are available, including randomised cross-over trial design where treatments are compared by after subjects have received more than one intervention in a randomized sequence. Its advantage lies in its ability to enable within-subject comparisons and minimise between-subject variability

In contrast a full-scale randomised controlled trial determines the effectiveness of an intervention according to comparison of randomly assigned arms of treatment. For smaller populations including PCD, to achieve the correct power

and sample size to observe differences, this is better achieved as a multicentre study.

Regional PCD centres in the UK will be approached and included in this study to enable a large enough population to extrapolate results to the UK PCD population.

Proposed RCT

Multisite randomised, double-blind trial to assess efficacy of leucine enriched oral nutritional supplement gel in patients with Primary Ciliary Dyskinesia (PCD).

Regional PCD centres in the UK will be approached and included in this study to enable a large enough population to extrapolate results to the UK PCD population.

Overall Aim:

To evaluate the impact of a leucine enriched oral nutritional supplement gel (ONS-Gel) on lung function, disease severity, dietary intake, vitamin D status, body composition (BIA), Handgrip strength (HGS), physical activity and quality of life in participants with Primary Ciliary Dyskinesia

Study Design:

- Duration**:** 24 weeks
- Participants**:** Adults with a confirmed diagnosis of Primary Ciliary Dyskinesia (genetics reported)
- Blinding**:** Double-blind (both participants and investigators are unaware of the treatment allocation)
- randomisation**:** Participants will be randomized in a 1:1 ratio to either:
    1. Intervention group**:** ONS-Gel (nutritional supplement) and resistance exercise programme
    2. Control group**:** Placebo Gel (no active nutritional components) and resistance exercise programme

Inclusion Criteria:

- Adults (17-100 years)
- Diagnosed with primary ciliary dyskinesia with confirmed genetics

- Stable or mild-to-moderate disease (no exacerbation in the last 4 weeks)

Exclusion Criteria:

- Severe disease (e.g., requiring hospitalisation)
- Active systemic infections (identified through clinical markers of infection)
- Pregnant or breastfeeding women
- Chronic diseases affecting metabolism (e.g., cancer, severe liver or kidney disease)

Primary Outcomes

- Lung function – Spirometry measuring FEV_1 (a measure of airflow obstruction) and FVC (volume of forcibly exhaled air). Also recorded FEV_1% predicted (FEV_1/FVC) at baseline, week 6, 12, 18 and 24.
- Hand grip strength – measurement through handgrip dynamometry at baseline, week 6, 12, 18 and 24.
- Body composition by bio-electrical impedance –FM, FFM, Skeletal muscle mass) at baseline, week 6, 12, 18 and 24 with body composition analyser e.g. SECA
- Exacerbations - The number of exacerbations experienced during the 24-week trial based on clinical markers and microbiological data.

Secondary Outcomes

- Dietary intake –dietary intake recorded via an on online dietary analysis programme. Recording of 4 days intake (including 1 weekend day) at week 1, 6 12, 18 and 24.
- Vitamin D status - Serum 25-Hydroxyvitamin D Levels: Blood tests to measure baseline and changes in vitamin D status (25(OH)D) at baseline, week 6, 12, 18, and week 24.
- Physical Activity –
    - Step count using a pedometer or other wearable device to track daily activity
    - 6MWT to determine endurance and exercise capacity at baseline week 6, 12, 18, and week 24.
- Quality of life – QoL – PCD, a validated tool to be undertaken at baseline week 6, 12, 18 and 24.
- Adherence – Consumption of supplement as per protocol to measure percentage consumption.

Additional data collection at baseline for all participants to determine characteristics include the following–

Sex, ethnicity, age, year of diagnosis, predominant microbiology, genotype and existing co morbidities.

Hypothesis - Consumption of a supplement gel with additional leucine over a period of 24 weeks results in with improved lung function, improved handgrip strength, changes in body composition and reduction in exacerbations

Null Hypothesis - Consumption of a supplement gel with additional leucine over a period of 24 weeks does not result in with improved lung function, improved handgrip strength, changes in body composition and reduction in exacerbations

Sample size

UK population of PCD approximately 3000, therefore with a 2% margin of error and 95% confidence interval the study should recruit 1334 participants.

Data analysis

Consider stratification by BMI (low, medium, overweight)

Consider adjustment for length of diagnosis, FEV1%, HGS and frequency of exacerbation.

8.5 Integration of findings for clinical practice

The findings in this research are highly relevant in a clinical population and have been discussed in each previous section. The research underpins the following key areas of clinical practice, which have been expanded below to identify practical ways to apply them in clinical practice under immediate, medium-, and long-term application

8.5.1 Immediate implementation of research findings.

Hand grip strength measures should remain as a standard care measure in the clinic setting for those with bronchiectasis and PCD. To facilitate this the standard operating procedure (SOP) should be embedded and update training sessions should be provided to all healthcare practitioners that are involved in assessing service users. To facilitate this the author of this thesis will deliver the training as an ISAK accredited practitioner. To ensure quality is embedded throughout routine annual audit to evaluate data and relevant interventions and identifying changes over time should be undertaken.

Routine annual monitoring of Vitamin D (Winter level) to assess the need for further supplementation and to assess trends should be implemented. Nutritional surveillance utilising electronic databases for capture in ‘real time’ should be part of routine care providing the ability to assess when intervention is required and establish longitudinal trends The introduction of BIA or DEXA annually is also key. This will enable monitoring of body composition changes. Coupled with longer term dietary surveillance it will enable more personalised approaches to nutrition counselling.

8.5.2 Medium-term implementation of findings.

Integration of the HGS values which provide alerts to facilitate data gathered in a timely way to be discussed in ward round and MDT situations. Formulation of work streams that identifies key research across regional clinics to capture larger data sets and enable wider evaluation of cohorts and subgroups. Considering the reporting of HGS values annually, this could contribute to the EMBARC registry enabling multicentre and larger cohort evaluation. Consideration of potential increase in workload associated with continued implementation of HGS in clinic settings.

Greater use of the ECR – to code data and retrieve this for clinical comparison and analysis. Allowing early identification of vulnerable sub-groups, to prompt intervention. Combined use of the EMBARC registry and use of the ECR to gain regional and national collaboration between clinics – particularly for PCD

8.5.1 Longer term implementation of findings.

Introducing QoL measures as part of an annual review process, would provide an opportunity for patients to report their own perceptions of health and outcomes. Suitable tools may include the validated QoL-B tool. Implemented in clinic, this may add additional time to the appointment or increase patient burden, which should be considered. Provision of a digital platform that can be utilised pre or post appointment to observe completion rates and advocate self-management may mitigate some of this burden.

This research contributes novel concepts that are considered within existing effective pulmonary rehabilitation programmes within other lung diseases such as COPD (dietary and physical assessment). Pulmonary rehabilitation has been effective in the short term in bronchiectasis (Lee et al., 2017) but not considered in PCD. Exploration of these programmes for those with bronchiectasis and PCD is an area that could be considered in the future as a potential means of reducing exacerbations.

8.6 Conclusion

In summary, the aim of this programme of research was to determine the nutritional status and dietary intake of a clinical cohort and explore the feasibility of consumption of leucine enriched amino acid supplementation. To achieve this, 4 studies were undertaken, culminating in a feasibility study to evaluate the feasibility of consumption of leucine enriched amino acid supplementation. impact of contributed to a growing body of work and confirms that HGS is an important outcome to assess as part of routine care in bronchiectasis and specifically PCD.

This research provides an original contribution to the evidence base, in an area of limited research. This is the first work to analyse and report in detail the dietary intakes of those with bronchiectasis and identify those with PCD as a nutritionally vulnerable sub-group of the population. This analysis has also found that the role of protein, vitamin D, Vitamin E, zinc and magnesium requires further exploration to determine specific influence on muscle strength, body composition, inflammation, and lung function in populations with bronchiectasis and PCD.

This work is the first to examine HGS, nutritional intake and feasibility of consumption of an oral leucine enriched amino-acid gel supplement twice a day. As a result, it has established new findings that identify a population with bronchiectasis have poor muscle functionality through impaired handgrip strength; determining that this persists over time and should be explored further as a potentially important clinical outcome that is highly clinically relevant.

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Appendix A Prospero confirmation

Dear Mrs King,

Thank you for submitting details of your systematic review "Dietary interventions, nutritional status and body composition in patients with non-cystic fibrosis bronchiectasis: a systematic review" to the PROSPERO register. We are pleased to confirm that the record will be published on our website within the next hour.

Your registration number is: CRD42019138143

You are free to update the record at any time, all submitted changes will be displayed as the latest version with previous versions available to public view. Please also give brief details of the key changes in the Revision notes facility and remember to update your record when your review is published. You can log in to PROSPERO and access your records at https://www.crd.york.ac.uk/PROSPERO.

Comments and feedback on your experience of registering with PROSPERO are welcome at crd-register@york.ac.uk

Is your team looking for a platform to conduct data extraction for your systematic review? SRDR-Plus is a free, powerful, easy-to-use systematic review data management and archival tool. You can get started here: http://srdrplus.ahrq.gov.

Best wishes for the successful completion of your review.

Yours sincerely,

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Appendix B Data tables SR

Database	Search terms	Inclusion detail	Number of results	Number kept after reading titles and abstracts	Number retained after inclusion/exclusion criteria	Number included (after duplicates removed)	Name of papers
MEDLINE	(Non cyst* fibros* Bronchiectasis and (Nutri* or Diet* or food or intake or supp*) and (body mass or body composition or lean* or fat* or muscle*)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx, tc, id, tm]	2000-2018	127	12	4	4 (2 body composition only 1 Nutrition and body composition 1 dietary)	Qi et al 2015 Olveira et al 2012 Olveira et al 2016 Chalmers et al 2015
EMBASE	(Non cyst* fibros* Bronchiectasis and (Nutri* or Diet* or food or intake or supp*) and (body mass or body composition or lean* or fat* or muscle*)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx, tc, id, tm]	2000-2018	1333	37	8 (2 duplicate, 1 letter, 4 abstracts)	1 (1 nutrition only)	Olveira et al 2014
CINAHL	TX Non cyst* fibros* Bronchiectasis AND TX (Nutri* or Diet* or food or intake or supp*) AND TX (body mass or body composition or lean* or fat* or muscle*)	2000-2018	1310	2	2 (both duplicates)	0	

PUBMED	Non cyst* fibros* Bronchiectasis AND (Nutri* or Diet* or food or intake or supp*) AND (body mass or body composition or lean* or fat* or muscle*)	2000-2018	13	2	2 (both duplicates)	0	
PSYCHINFO	(Non cyst* fibros* Bronchiectasis and (Nutri* or Diet* or food or intake or supp*) and (body mass or body composition or lean* or fat* or muscle*)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx, tc, id, tm]	2000-2018	30	2	2 (both duplicates)	0	
WEB OF SCIENCE	ALL=(Non cyst* fibros* Bronchiectasis AND (Nutri* or Diet* or food or intake or supp*) AND (body mass or body composition or lean* or fat* or muscle*))	2000-2018	13	3	2 (1 only focused on exercise, 1 duplicate)	0	

Database	Search terms	Inclusion detail	Number of results	Number kept after reading titles and abstracts	Number retained after inclusion/exclusion criteria	Number included (after duplicates removed)	Name of papers
MEDLINE	(Non cyst* fibros* Bronchiectasis and (Nutri* or Diet* or food or intake or supp*) and (body mass or body composition or lean* or fat* or muscle*)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx, tc, id, tm]	01-01-2019 – 31-12-2022	84	9	8 (1 could not differentiate between CF bronchiectasis and Non CF Bronchiectasis)	8	Li et al 2020 Yang et al 2021 Lee et al 2021 Wang et al 2021 Wang et al 2022 Despotes et al 2020 Sami et al 2021 King et al 2021
EMBASE	(Non cyst* fibros* Bronchiectasis and (Nutri* or Diet* or food or intake or supp*) and (body mass or body composition or lean* or fat* or muscle*)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx, tc, id, tm]	2019-2022	626	10	10 (6 duplicates removed, 1 conference abstract, 1 did not differentiate)	2	Contreas-Bolivar et al 2019 Ali et al 2022
CINAHL	TX Non cyst* fibros* Bronchiectasis AND TX (Nutri* or Diet* or food or intake or supp*	2019-2022	3	1	1 (duplicate)	0	

	) AND TX (body mass or body composition or lean* or fat* or muscle*)						
PUBMED	Non cyst* fibros* Bronchiectasis AND (Nutri* or Diet* or food or intake or supp*) AND (body mass or body composition or lean* or fat* or muscle*)	2019-2022	11	6	6 (all duplicates)	0	
PSYCHINFO	(Non cyst* fibros* Bronchiectasis and (Nutri* or Diet* or food or intake or supp*) and (body mass or body composition or lean* or fat* or muscle*)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx, tc, id, tm]	2019-2022	13	0	0	0	
WEB OF SCIENCE	ALL=(Non cyst* fibros* Bronchiectasis AND (Nutri* or Diet* or food or intake or supp*) AND (body mass or body composition or lean* or fat* or muscle*))	2019-2022	24	7	7 (all duplicates)	0	

Appendix C Quality assessment traffic lights and CASP forms

Question Number CASP checklists	Olveira et al., 2012	Chalmers et al., 2013	Olveira et al., 2014	Qi et al., 2015	Olveira et al., 2016	Contreras-Bolivar et al., 2019	Despotes et al., 2020	Li et al., 2020	Yang et al., 2021	Sami et al., 2021	King et al., 2021	Wang et al., 2021	Lee et al., 2021	Wang et al., 2022	Ali et al., 2022
1															
2															
3															
4															
5a															
5b															
6a															
6b															
7															
8															
9															
10															
11															
12															

Key

Yes	
No	
Can’t tell	
Not Applicable	

CASP
Critical Appraisal Skills Programme

Paper for appraisal and reference: Qi et al., 2015

Section A: Are the results of the study valid?

1. Did the study address a clearly focused issue?

Yes	X
Can't Tell	
No	

HINT: A question can be 'focused' in terms of
- the population studied
- the risk factors studied
- is it clear whether the study tried to detect a beneficial or harmful effect
- the outcomes considered

Comments
BMI and disease severity association

2. Was the cohort recruited in an acceptable way?

Yes	X
Can't Tell	
No	

HINT: Look for selection bias which might compromise the generalisability of the findings:
- was the cohort representative of a defined population
- was there something special about the cohort
- was everybody included who should have been

Comments
Convenience sampling all those that met inclusion criteria were approached and included all bronchiectasis differentiated between CF and non CF

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5. (a) Have the authors identified all important confounding factors?

Yes	X
Can't Tell	
No	

HINT:
- list the ones you think might be important, and ones the author missed

Comments: Yes

5. (b) Have they taken account of the confounding factors in the design and/or analysis?

Yes	X
Can't Tell	
No	

HINT:
- look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

Comments: Some confounders considered

6. (a) Was the follow up of subjects complete enough?

Yes	X
Can't Tell	
No	

HINT: Consider
- the good or bad effects should have had long enough to reveal themselves
- the persons that are lost to follow-up may have different outcomes than those available for assessment
- in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort

6.(b) Was the follow up of subjects long enough?

Yes	X
Can't Tell	
No	

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3. Was the exposure accurately measured to minimise bias?	Yes		HINT: Look for measurement or classification bias: • did they use subjective or objective measurements • do the measurements truly reflect what you want them to (have they been validated) • were all the subjects classified into exposure groups using the same procedure
	Can't Tell	X	
	No		

Comments: no exposure as observational

4. Was the outcome accurately measured to minimise bias?	Yes		HINT: Look for measurement or classification bias: • did they use subjective or objective measurements • do the measurements truly reflect what you want them to (have they been validated) • has a reliable system been established for detecting all the cases (for measuring disease occurrence) • were the measurement methods similar in the different groups • were the subjects and/or the outcome assessor blinded to exposure (does this matter)
	Can't Tell	X	
	No		

Comments: not clear – multicenter trial therefore observation of results across different areas.

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9. Do you believe the results?

Yes	X
Can't Tell	
No	

HINT: Consider
- big effect is hard to ignore
- can it be due to bias, chance or confounding
- are the design and methods of this study sufficiently flawed to make the results unreliable
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Comments: Whilst looking for associations here they have been fully adjusted and projected in terms of possible outcomes and associations with

Section C: Will the results help locally?

10. Can the results be applied to the local population?

Yes	
Can't Tell	
No	X

HINT: Consider whether
- a cohort study was the appropriate method to answer this question
- the subjects covered in this study could be sufficiently different from your population to cause concern
- your local setting is likely to differ much from that of the study
- you can quantify the local benefits and harms

Comments: No the population has different cut offs for BMI than the UK population and so cannot be generalize however adds to understanding of the role of BMI on works in populations and because they were adjusted similar observation may be seen

11. Do the results of this study fit with other available evidence?

Yes	X
Can't Tell	
No	

Comments: Low BMI determined to be associated with poorer survival and other markers of disease severity whilst confounding for duration of disease, sex, smoking exacerbations etc.

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Comments: As prospective observation of a population this was over a 9 year period to be able to determine change over time

Section B: What are the results?

7. What are the results of this study?

HINT: Consider
- what are the bottom line results
- have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference
- how strong is the association between exposure and outcome (RR)
- what is the absolute risk reduction (ARR)

Comments: BMI negatively correlated with acute exacerbations CRP, ESR, radiographic extent of bronchiectasis and chronic colonisation with P.Aeruginosa. Positive correlation found with pulmonary function. Lower BMI leads to more likelihood of acute exacerbations, worse pulmonary function amplified inflammation and chronic colonisation of pseudomonas.

8. How precise are the results?

HINT:
- look for the range of the confidence intervals, if given

Comments: appropriate analysis was conducted survival rates determined and associations within BMI categories reported

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12. What are the implications of this study for practice?

Yes	X
Can't Tell	
No	

HINT: Consider
- one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- for certain questions, observational studies provide the only evidence
- recommendations from observational studies are always stronger when supported by other evidence

Comments: low BMI poorer outcomes. Although considered limitation of understanding body composition and nutritional status

Critical Appraisal Skills Programme

CASP Checklist:
For Cohort Studies

During critical appraisal, never make assumptions about what the researchers have done. If it is not possible to tell, use the "Can't tell" response box. If you can't tell, at best it means the researchers have not been explicit or transparent, but at worst it could mean the researchers have not undertaken a particular task or process. Once you've finished the critical appraisal, if there are a large number of "Can't tell" responses, consider whether the findings of the study are trustworthy and interpret the results with caution.

Study Chalmers et al., 2013

Section A: Are the results valid?	
1. Did the study address a clearly focused issue?	**X** Yes ☐ No ☐ Can't Tell Vitamin D levels and associations outcomes 3 yar follow up
CONSIDER: *A question can be 'focused' in terms of* • *the population studied* • *the risk factors studied* • *is it clear whether the study tried to detect a beneficial or harmful effect* • *the outcomes considered*	
2. Was the cohort recruited in an acceptable way?	**X** Yes ☐ No ☐ Can't Tell Yes convenience sampling
CONSIDER: • *Look for selection bias which might compromise the generalisability of the findings:* • *was the cohort representative of a defined population*	

• *was there something special about the cohort* • *was everybody included who should have been*	
3. Was the exposure accurately measured to minimise bias?	**X** Yes ☐ No ☐ Can't Tell Appropriate for the study
CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)* • *were all the subjects classified into exposure groups using the same procedure*	
4. Was the outcome accurately measured to minimise bias?	**X** Yes ☐ No ☐ Can't Tell Limitations are outlined including different ways of assessing supplementation
CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)* • *has a reliable system been established for detecting all the cases (for measuring disease occurrence)* • *were the measurement methods similar in the different groups* • *were the subjects and/or the outcome assessor blinded to exposure (does this matter)*	
5. (a) Have the authors identified all important confounding factors?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *list the ones you think might be important, and ones the author missed*	
b) Have they taken account of the confounding factors in the design and/or analysis?	☐ Yes ☐ No **X** Can't Tell
CONSIDER: • *look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors*	
6. a) Was the follow up of subjects complete enough?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *the persons that are lost to follow-up may have different outcomes than those available for assessment* • *in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort*	

b) Was the follow up of subjects long enough?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *the good or bad effects should have had long enough to reveal themselves*	
Section B: What are the results?	
7. What are the results of this study?	**X** Yes ☐ No ☐ Can't Tell Vitamin D deficient and associated with poor lung function
CONSIDER: • *what are the bottom line results* • *have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference* • *how strong is the association between exposure and outcome (RR)* • *what is the absolute risk reduction (ARR)*	
8. How precise are the results?	**X** Yes ☐ No ☐ Can't Tell Vitamin D deficiency is common and correlates with markers of disease severity however the mechanism of the association is not clear.
CONSIDER: • *look for the range of the confidence intervals, if given*	
9. Do you believe the results?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *big effect is hard to ignore* • *can it be due to bias, chance or confounding* • *are the design and methods of this study sufficiently flawed to make the results unreliable* • *Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)*	
Section C: Will the results help locally?	
10. Can the results be applied to the local population?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *Is a cohort study the appropriate method to answer this question*	

• *If the subjects covered in this study could be sufficiently different from your population to cause concern* • *If your local setting is likely to differ much from that of the study* • *If you can quantify the local benefits and harms*

11. Do the results of this study fit with other available evidence?	**X** Yes ☐ No ☐ Can't Tell
12. What are the implications of this study for practice?	**X** Yes ☐ No ☐ Can't Tell Vitamin D supplementation is important in NCFB

CONSIDER: • *one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making* • *for certain questions, observational studies provide the only evidence* • *recommendations from observational studies are always stronger when supported by other evidence*

CASP Checklist:
For Descriptive/Cross-Sectional Studies

During critical appraisal, never make assumptions about what the researchers have done. If it is not possible to tell, use the "Can't tell" response box. If you can't tell, at best it means the researchers have not been explicit or transparent, but at worst it could mean the researchers have not undertaken a particular task or process. Once you've finished the critical appraisal, if there are a large number of "Can't tell" responses, consider whether the findings of the study are trustworthy and interpret the results with caution.

Paper for appraisal Olveira et al., 2012

Section A: Are the results valid?	
1. Did the study address a clearly focused issue?	**X** Yes ☐ No ☐ Can't Tell FFM depletion explored independently in NCFB and CF bronchiectasis
CONSIDER: *A question can be 'focused' in terms of* • *the population studied* • *the risk factors studied* • *is it clear whether the study tried to detect a beneficial or harmful effect* • *the outcomes considered*	
2. Did the authors use an appropriate method to answer their question?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *Is a descriptive/cross-sectional study an appropriate way of answering the question* • *did it address the study question*	
3. Were the subjects recruited in an acceptable way?	**X** Yes ☐ No ☐ Can't Tell Convenience sampling associated with clinic
CONSIDER: *We are looking for selection bias which might compromise the generalisability of the findings:* • *Was the sample representative of a defined population* • *Was everybody included who should have been included*	
4. Were the measures accurately measured to reduce bias?	**X** Yes ☐ No ☐ Can't Tell

CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)*	
5. Were the data collected in a way that addressed the research issue?	**X** Yes ☐ No ☐ Can't Tell Disease severity and aetiology
CONSIDER: • *if the setting for data collection was justified* • *if it is clear how data were collected (e.g., interview, questionnaire, chart review)* • *if the researcher has justified the methods chosen* • *if the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews were conducted?)*	
6. Did the study have enough participants to minimise the play of chance?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *if the result is precise enough to make a decision* • *if there is a power calculation. This will estimate how many subjects are needed to produce a reliable estimate of the measure(s) of interest.*	
7. How are the results presented and what is the main result?	**X** Yes ☐ No ☐ Can't Tell Results were controlled for BMI, Age and Intake These patients presented with a high percentage of fat free mass depletion independent of Aetiology FFM and IL6 useful
CONSIDER: • *if, for example, the results are presented as a proportion of people experiencing an outcome, such as risks, or as a measurement, such as mean or median differences, or as survival curves and hazards* • *how large this size of result is and how meaningful it is* • *how you would sum up the bottom-line result of the trial in one sentence*	
8. Was the data analysis sufficiently rigorous?	**X** Yes ☐ No ☐ Can't Tell All appropriate findings reported
CONSIDER: • *if there is an in-depth description of the analysis process* • *if sufficient data are presented to support the findings*	
9. Is there a clear statement of findings?	**X** Yes ☐ No ☐ Can't Tell

CONSIDER: • *if the findings are explicit* • *if there is adequate discussion of the evidence both for and against the researchers' arguments* • *if the researchers have discussed the credibility of their findings* • *if the findings are discussed in relation to the original research questions*	
10. Can the results be applied to the local population?	**X** Yes ☐ No ☐ Can't Tell Spanish population extrapolate too as European
CONSIDER: • *the subjects covered in the study could be sufficiently different from your population to cause concern.* • *your local setting is likely to differ much from that of the study*	
11. How valuable is the research?	**X** Yes ☐ No ☐ Can't Tell Contributes further to understanding of the role of body composition in NCFB not just BMI
CONSIDER: • *one descriptive/cross-sectional study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making* • *if the researcher discusses the contribution the study makes to existing knowledge (e.g., do they consider the findings in relation to current practice or policy, or relevant research-based literature?)* • *if the researchers have discussed whether or how the findings can be transferred to other populations*	

CASP Checklist:
For Descriptive/Cross-Sectional Studies

During critical appraisal, never make assumptions about what the researchers have done. If it is not possible to tell, use the "Can't tell" response box. If you can't tell, at best it means the researchers have not been explicit or transparent, but at worst it could mean the researchers have not undertaken a particular task or process. Once you've finished the critical appraisal, if there are a large number of "Can't tell" responses, consider whether the findings of the study are trustworthy and interpret the results with caution.

Paper for appraisal Olveira et al., 2014

Section A: Are the results valid?	
1. Did the study address a clearly focused issue?	**X** Yes ☐ No ☐ Can't Tell Mediterranean diet and depression
CONSIDER: *A question can be 'focused' in terms of* • *the population studied* • *the risk factors studied* • *is it clear whether the study tried to detect a beneficial or harmful effect* • *the outcomes considered*	
2. Did the authors use an appropriate method to answer their question?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *Is a descriptive/cross-sectional study an appropriate way of answering the question* • *did it address the study question*	
3. Were the subjects recruited in an acceptable way?	**X** Yes ☐ No ☐ Can't Tell Convenience sampling associated with 4 Spanish centres
CONSIDER: *We are looking for selection bias which might compromise the generalisability of the findings:* • *Was the sample representative of a defined population* • *Was everybody included who should have been included*	
4. Were the measures accurately measured to reduce bias?	**X** Yes ☐ No ☐ Can't Tell Used validated tools to assess QOL and intake of med diet

CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)*	
5. Were the data collected in a way that addressed the research issue?	**X** Yes ☐ No ☐ Can't Tell Through validate questionnaires
CONSIDER: • *if the setting for data collection was justified* • *if it is clear how data were collected (e.g., interview, questionnaire, chart review)* • *if the researcher has justified the methods chosen* • *if the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews were conducted?)*	
6. Did the study have enough participants to minimise the play of chance?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *if the result is precise enough to make a decision* • *if there is a power calculation. This will estimate how many subjects are needed to produce a reliable estimate of the measure(s) of interest.*	
7. How are the results presented and what is the main result?	**X** Yes ☐ No ☐ Can't Tell NCFB, have higher symptoms of depression and anxiety compared with the general population, Exacerbation frequency, dyspnoea and Charlson morbidity index. Those with higher depression and anxiety scores also had lower PREDIMED scores
CONSIDER: • *if, for example, the results are presented as a proportion of people experiencing an outcome, such as risks, or as a measurement, such as mean or median differences, or as survival curves and hazards* • *how large this size of result is and how meaningful it is* • *how you would sum up the bottom-line result of the trial in one sentence*	
8. Was the data analysis sufficiently rigorous?	**X** Yes ☐ No ☐ Can't Tell All appropriate findings reported and confounders considered in the results and analysis
CONSIDER: • *if there is an in-depth description of the analysis process* • *if sufficient data are presented to support the findings*	
9. Is there a clear statement of findings?	**X** Yes ☐ No ☐ Can't Tell

CONSIDER: • *if the findings are explicit* • *if there is adequate discussion of the evidence both for and against the researchers' arguments* • *if the researchers have discussed the credibility of their findings* • *if the findings are discussed in relation to the original research questions*	
10. Can the results be applied to the local population?	☐ Yes ☐ No **X** Can't Tell Considered QoL and dietary intakes, some aspects may influence future intervention but limited here
CONSIDER: • *the subjects covered in the study could be sufficiently different from your population to cause concern.* • *your local setting is likely to differ much from that of the study*	
11. How valuable is the research?	☐ Yes ☐ No **X** Can't Tell some aspects may influence future intervention but limited here
CONSIDER: • *one descriptive/cross-sectional study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making* • *if the researcher discusses the contribution the study makes to existing knowledge (e.g., do they consider the findings in relation to current practice or policy, or relevant research-based literature?)* • *if the researchers have discussed whether or how the findings can be transferred to other populations*	

Critical Appraisal Skills Programme

CASP Checklist:
For Randomised Controlled Trials (RCTs)

During critical appraisal, never make assumptions about what the researchers have done. If it is not possible to tell, use the "Can't tell" response box. If you can't tell, at best it means the researchers have not been explicit or transparent, but at worst it could mean the researchers have not undertaken a particular task or process. Once you've finished the critical appraisal, if there are a large number of "Can't tell" responses, consider whether the findings of the study are trustworthy and interpret the results with caution.

Olveira et al., 2016

Section A Is the basic study design valid for a randomised controlled trial?	
1. Did the study address a clearly formulated research question?	X Yes ☐ No ☐ Can't Tell
CONSIDER: *Was the study designed to assess the outcomes of an intervention?* *Is the research question 'formulated' in terms of:* • *Population studied* • *Intervention given* • *Comparator chosen* • *Outcomes measured?*	
2. Was the assignment of participants to interventions randomised?	X Yes ☐ No ☐ Can't Tell

CONSIDER: • *How was randomisation carried out? Was the method appropriate?* • *Was randomisation sufficient to eliminate systematic bias?* • *Was the allocation sequence concealed from investigators and participants?*	
3. Were all participants who entered the study accounted for at its conclusion?	X Yes ☐ No ☐ Can't Tell
CONSIDER: • *Were losses to follow-up and exclusions after randomisation accounted for?* • *Were participants analysed in the study groups to which they were randomised (intention-to-treat analysis)?* • *Was the study stopped early? If so, what was the reason?*	
Section B Was the study methodologically sound?	
4. (a) Were the participants 'blind' to intervention they were given?	☐ Yes X No ☐ Can't Tell
(b) Were the investigators 'blind' to the intervention they were giving to participants?	☐ Yes X No ☐ Can't Tell
(c) Were the people assessing/analysing outcome/s 'blinded'?	☐ Yes X No ☐ Can't Tell
5. Were the study groups similar at the start of the randomised controlled trial?	X Yes ☐ No ☐ Can't Tell
CONSIDER: • *Were the baseline characteristics of each study group (e.g. age, sex, socio-economic group) clearly set out?* • *Were there any differences between the study groups that could affect the outcome/s?*	

6. Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?	X Yes ☐ No ☐ Can't Tell
CONSIDER: • *Was there a clearly defined study protocol?* • *If any additional interventions were given (e.g. tests or treatments), were they similar between the study groups?* • *Were the follow-up intervals the same for each study group?*	
Section C: What are the results?	
7. Were the effects of intervention reported comprehensively?	X Yes ☐ No ☐ Can't Tell
CONSIDER: • *Was a power calculation undertaken?* • *What outcomes were measured, and were they clearly specified?* • *How were the results expressed? For binary outcomes, were relative and absolute effects reported?* • *Were the results reported for each outcome in each study group at each follow-up interval?* • *Was there any missing or incomplete data?* • *Was there differential drop-out between the study groups that could affect the results?* • *Were potential sources of bias identified?* • *Which statistical tests were used?* • *Were p values reported?*	
8. Was the precision of the estimate of the intervention or treatment effect reported?	☐ Yes X No ☐ Can't Tell
CONSIDER: • *Were confidence intervals (CIs) reported?*	
9. Do the benefits of the experimental intervention outweigh the harms and costs?	X Yes ☐ No ☐ Can't Tell
CONSIDER: • *What was the size of the intervention or treatment effect?* • *Were harms or unintended effects reported for each study group?* • *Was a cost-effectiveness analysis undertaken? (Cost-effectiveness analysis allows a comparison to be made between different interventions used in the care of the same condition or problem.)*	

Section D: Will the results help locally?	
10. Can the results be applied to your local population/in your context?	X Yes ☐ No ☐ Can't Tell
CONSIDER: • *Are the study participants similar to the people in your care?* • *Would any differences between your population and the study participants alter the outcomes reported in the study?* • *Are the outcomes important to your population?* • *Are there any outcomes you would have wanted information on that have not been studied or reported?* • *Are there any limitations of the study that would affect your decision?*	
11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	X Yes ☐ No ☐ Can't Tell
CONSIDER: • *What resources are needed to introduce this intervention taking into account time, finances, and skills development or training needs?* • *Are you able to disinvest resources in one or more existing interventions in order to be able to re-invest in the new intervention?*	

CASP Checklist:
For Cohort Studies

During critical appraisal, never make assumptions about what the researchers have done. If it is not possible to tell, use the "Can't tell" response box. If you can't tell, at best it means the researchers have not been explicit or transparent, but at worst it could mean the researchers have not undertaken a particular task or process. Once you've finished the critical appraisal, if there are a large number of "Can't tell" responses, consider whether the findings of the study are trustworthy and interpret the results with caution.

Study Despotes et al., 2020

Section A: Are the results valid?	
1. Did the study address a clearly focused issue?	**X** Yes ☐ No ☐ Can't Tell BMI and disease severity outcomes
CONSIDER: *A question can be 'focused' in terms of* • *the population studied* • *the risk factors studied* • *is it clear whether the study tried to detect a beneficial or harmful effect* • *the outcomes considered*	
2. Was the cohort recruited in an acceptable way?	**X** Yes ☐ No ☐ Can't Tell Retrospective longitudinal multicentre study (5 years)
CONSIDER: • *Look for selection bias which might compromise the generalisability of the findings:* • *was the cohort representative of a defined population*	

• *was there something special about the cohort* • *was everybody included who should have been*	
3. Was the exposure accurately measured to minimise bias?	**X** Yes ☐ No ☐ Can't Tell Appropriate for the study
CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)* • *were all the subjects classified into exposure groups using the same procedure*	
4. Was the outcome accurately measured to minimise bias?	**X** Yes ☐ No ☐ Can't Tell Limitation of study reported including the impact of data collection of retrospective study
CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)* • *has a reliable system been established for detecting all the cases (for measuring disease occurrence)* • *were the measurement methods similar in the different groups* • *were the subjects and/or the outcome assessor blinded to exposure (does this matter)*	
5. (a) Have the authors identified all important confounding factors?	**X** Yes ☐ No ☐ Can't Tell All confounders that could be observed have been
CONSIDER: • *list the ones you think might be important, and ones the author missed*	
b) Have they taken account of the confounding factors in the design and/or analysis?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors*	
6. a) Was the follow up of subjects complete enough?	☐ Yes **X** No ☐ Can't Tell
CONSIDER: • *the persons that are lost to follow-up may have different outcomes than those available for assessment* • *in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort*	

b) Was the follow up of subjects long enough?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *the good or bad effects should have had long enough to reveal themselves*	
Section B: What are the results?	
7. What are the results of this study?	**X** Yes ☐ No ☐ Can't Tell BMI associated with decrease in lung function
CONSIDER: • *what are the bottom line results* • *have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference* • *how strong is the association between exposure and outcome (RR)* • *what is the absolute risk reduction (ARR)*	
8. How precise are the results?	**X** Yes ☐ No ☐ Can't Tell Underweight patients had lower lung function (FEV1 %) compared to the other groups p = 0.02 no other significant differences between groups for other markers assessed (exacerbations frequency or hospitalisation). Majority of patients displayed stable BMI over 5 years
CONSIDER: • *look for the range of the confidence intervals, if given*	
9. Do you believe the results?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *big effect is hard to ignore* • *can it be due to bias, chance or confounding* • *are the design and methods of this study sufficiently flawed to make the results unreliable* • *Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)*	
Section C: Will the results help locally?	
10. Can the results be applied to the local population?	☐ Yes **X** No ☐ Can't Tell Likely not as American review
CONSIDER:	

• *Is a cohort study the appropriate method to answer this question* • *If the subjects covered in this study could be sufficiently different from your population to cause concern* • *If your local setting is likely to differ much from that of the study* • *If you can quantify the local benefits and harms*	
11. Do the results of this study fit with other available evidence?	☐ Yes ☐ No **X** Can't Tell No they are in contrast
12. What are the implications of this study for practice?	**X** Yes ☐ No ☐ Can't Tell BMI alone is not a marker in US population BC is needed
CONSIDER: • *one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making* • *for certain questions, observational studies provide the only evidence* • *recommendations from observational studies are always stronger when supported by other evidence*	

CASP Checklist:
For Descriptive/Cross-Sectional Studies

During critical appraisal, never make assumptions about what the researchers have done. If it is not possible to tell, use the "Can't tell" response box. If you can't tell, at best it means the researchers have not been explicit or transparent, but at worst it could mean the researchers have not undertaken a particular task or process. Once you've finished the critical appraisal, if there are a large number of "Can't tell" responses, consider whether the findings of the study are trustworthy and interpret the results with caution.

Paper for appraisal King et al., 2021

Section A: Are the results valid?	
1. Did the study address a clearly focused issue?	**X** Yes ☐ No ☐ Can't Tell Nutritional status and intake in NCFB
CONSIDER: *A question can be 'focused' in terms of* • *the population studied* • *the risk factors studied* • *is it clear whether the study tried to detect a beneficial or harmful effect* • *the outcomes considered*	
2. Did the authors use an appropriate method to answer their question?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *Is a descriptive/cross-sectional study an appropriate way of answering the question* • *did it address the study question*	
3. Were the subjects recruited in an acceptable way?	**X** Yes ☐ No ☐ Can't Tell Consecutive sampling associated with clinic
CONSIDER: *We are looking for selection bias which might compromise the generalisability of the findings:* • *Was the sample representative of a defined population* • *Was everybody included who should have been included*	
4. Were the measures accurately measured to reduce bias?	**X** Yes ☐ No ☐ Can't Tell

CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)*	
5. Were the data collected in a way that addressed the research issue?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *if the setting for data collection was justified* • *if it is clear how data were collected (e.g., interview, questionnaire, chart review)* • *if the researcher has justified the methods chosen* • *if the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews were conducted?)*	
6. Did the study have enough participants to minimise the play of chance?	**X** Yes ☐ No ☐ Can't Tell Power calculation included
CONSIDER: • *if the result is precise enough to make a decision* • *if there is a power calculation. This will estimate how many subjects are needed to produce a reliable estimate of the measure(s) of interest.*	
7. How are the results presented and what is the main result?	**X** Yes ☐ No ☐ Can't Tell BMI significant predictor of lung function, impaired HGS poor in whole population and significant in PCD. Population failed to meet Vit D intake RNI consistently <35%
CONSIDER: • *if, for example, the results are presented as a proportion of people experiencing an outcome, such as risks, or as a measurement, such as mean or median differences, or as survival curves and hazards* • *how large this size of result is and how meaningful it is* • *how you would sum up the bottom-line result of the trial in one sentence*	
8. Was the data analysis sufficiently rigorous?	**X** Yes ☐ No ☐ Can't Tell All appropriate findings reported
CONSIDER: • *if there is an in-depth description of the analysis process* • *if sufficient data are presented to support the findings*	
9. Is there a clear statement of findings?	**X** Yes ☐ No ☐ Can't Tell

CONSIDER: • *if the findings are explicit* • *if there is adequate discussion of the evidence both for and against the researchers' arguments* • *if the researchers have discussed the credibility of their findings* • *if the findings are discussed in relation to the original research questions*	
10. Can the results be applied to the local population?	**X** Yes ☐ No ☐ Can't Tell UK population, one of only 2
CONSIDER: • *the subjects covered in the study could be sufficiently different from your population to cause concern.* • *your local setting is likely to differ much from that of the study*	
11. How valuable is the research?	**X** Yes ☐ No ☐ Can't Tell Novel concept of HGS by aetiology and contributes to BMI and lung function association
CONSIDER: • *one descriptive/cross-sectional study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making* • *if the researcher discusses the contribution the study makes to existing knowledge (e.g., do they consider the findings in relation to current practice or policy, or relevant research-based literature?)* • *if the researchers have discussed whether or how the findings can be transferred to other populations*	

CASP Checklist:
For Cohort Studies

During critical appraisal, never make assumptions about what the researchers have done. If it is not possible to tell, use the "Can't tell" response box. If you can't tell, at best it means the researchers have not been explicit or transparent, but at worst it could mean the researchers have not undertaken a particular task or process. Once you've finished the critical appraisal, if there are a large number of "Can't tell" responses, consider whether the findings of the study are trustworthy and interpret the results with caution.

Study Lee et al., 2020

Section A: Are the results valid?	
1. Did the study address a clearly focused issue?	**X** Yes ☐ No ☐ Can't Tell Explored BMI as a predictor of mortality in NCFB population-based study
CONSIDER: *A question can be 'focused' in terms of* • *the population studied* • *the risk factors studied* • *is it clear whether the study tried to detect a beneficial or harmful effect* • *the outcomes considered*	
2. Was the cohort recruited in an acceptable way?	**X** Yes ☐ No ☐ Can't Tell Consecutive recruitment of those diagnosed with NCFB over 2 year period
CONSIDER: • *Look for selection bias which might compromise the generalisability of the findings:* • *was the cohort representative of a defined population*	

• *was there something special about the cohort* • *was everybody included who should have been*	
3. Was the exposure accurately measured to minimise bias?	X Yes ☐ No ☐ Can't Tell Yes this was accurately measured over a period of time
CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)* • *were all the subjects classified into exposure groups using the same procedure*	
4. Was the outcome accurately measured to minimise bias?	X Yes ☐ No ☐ Can't Tell Limitation of study including aetiology some data not retrieved e.g. lung function this is acknowledged
CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)* • *has a reliable system been established for detecting all the cases (for measuring disease occurrence)* • *were the measurement methods similar in the different groups* • *were the subjects and/or the outcome assessor blinded to exposure (does this matter)*	
5. (a) Have the authors identified all important confounding factors?	X Yes ☐ No ☐ Can't Tell All confounders that could be conserved have been
CONSIDER: • *list the ones you think might be important, and ones the author missed*	
b) Have they taken account of the confounding factors in the design and/or analysis?	X Yes ☐ No ☐ Can't Tell Smoking activity comorbidities etc.
CONSIDER: • *look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors*	
6. a) Was the follow up of subjects complete enough?	X Yes ☐ No ☐ Can't Tell
CONSIDER: • *the persons that are lost to follow-up may have different outcomes than those available for assessment*	

• *in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort*	
b) Was the follow up of subjects long enough?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *the good or bad effects should have had long enough to reveal themselves*	
Section B: What are the results?	
7. What are the results of this study?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *what are the bottom line results* • *have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference* • *how strong is the association between exposure and outcome (RR)* • *what is the absolute risk reduction (ARR)*	
8. How precise are the results?	**X** Yes ☐ No ☐ Can't Tell Cox proportional hazards model HR of underweight for mortality was 2.60 (95% CI, 1.92-3.54 compared to normal weight (1.00). Kaplan-Meier survival curves 1-, 5- and 10-years survival rates in bronchiectasis was 98.9%, 93.8% and 86.5% respectively. Lowest in the underweight group 5 yr. survival 76.4%
CONSIDER: • *look for the range of the confidence intervals, if given*	
9. Do you believe the results?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *big effect is hard to ignore* • *can it be due to bias, chance or confounding* • *are the design and methods of this study sufficiently flawed to make the results unreliable* • *Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)*	
Section C: Will the results help locally?	
10. Can the results be applied to the local population?	☐ Yes **X** No ☐ Can't Tell Population have different cut offs for BMI so unable to generalise to other populations

CONSIDER: • *Is a cohort study the appropriate method to answer this question* • *If the subjects covered in this study could be sufficiently different from your population to cause concern* • *If your local setting is likely to differ much from that of the study* • *If you can quantify the local benefits and harms*	
11. Do the results of this study fit with other available evidence?	☐ Yes ☐ No **X** Can't Tell Minimal studies like this to be able to confirm
12. What are the implications of this study for practice?	**X** Yes ☐ No ☐ Can't Tell Low BMI impacts survival
CONSIDER: • *one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making* • *for certain questions, observational studies provide the only evidence* • *recommendations from observational studies are always stronger when supported by other evidence*	

CASP Checklist:
For Descriptive/Cross-Sectional Studies

During critical appraisal, never make assumptions about what the researchers have done. If it is not possible to tell, use the "Can't tell" response box. If you can't tell, at best it means the researchers have not been explicit or transparent, but at worst it could mean the researchers have not undertaken a particular task or process. Once you've finished the critical appraisal, if there are a large number of "Can't tell" responses, consider whether the findings of the study are trustworthy and interpret the results with caution.

Paper for appraisal Wang et al., 2021

Section A: Are the results valid?	
1. Did the study address a clearly focused issue?	**X** Yes ☐ No ☐ Can't Tell Nutritional status and inflammatory markers in NCFB
CONSIDER: *A question can be 'focused' in terms of* • *the population studied* • *the risk factors studied* • *is it clear whether the study tried to detect a beneficial or harmful effect* • *the outcomes considered*	
2. Did the authors use an appropriate method to answer their question?	**X** Yes ☐ No ☐ Can't Tell Used cross sectional multicentre
CONSIDER: • *Is a descriptive/cross-sectional study an appropriate way of answering the question* • *did it address the study question*	
3. Were the subjects recruited in an acceptable way?	**X** Yes ☐ No ☐ Can't Tell Recruited through 43 centres
CONSIDER: *We are looking for selection bias which might compromise the generalisability of the findings:* • *Was the sample representative of a defined population* • *Was everybody included who should have been included*	
4. Were the measures accurately measured to reduce bias?	**X** Yes ☐ No ☐ Can't Tell

CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)*	
5. Were the data collected in a way that addressed the research issue?	**X** Yes ☐ No ☐ Can't Tell Considered impact of body composition on associated outcomes
CONSIDER: • *if the setting for data collection was justified* • *if it is clear how data were collected (e.g., interview, questionnaire, chart review)* • *if the researcher has justified the methods chosen* • *if the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews were conducted?)*	
6. Did the study have enough participants to minimise the play of chance?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *if the result is precise enough to make a decision* • *if there is a power calculation. This will estimate how many subjects are needed to produce a reliable estimate of the measure(s) of interest.*	
7. How are the results presented and what is the main result?	**X** Yes ☐ No ☐ Can't Tell Lung function, exercise capacity CRP significantly reduced in NCFB compared with healthy controls
CONSIDER: • *if, for example, the results are presented as a proportion of people experiencing an outcome, such as risks, or as a measurement, such as mean or median differences, or as survival curves and hazards* • *how large this size of result is and how meaningful it is* • *how you would sum up the bottom-line result of the trial in one sentence*	
8. Was the data analysis sufficiently rigorous?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *if there is an in-depth description of the analysis process* • *if sufficient data are presented to support the findings*	
9. Is there a clear statement of findings?	**X** Yes ☐ No ☐ Can't Tell

CONSIDER: • *if the findings are explicit* • *if there is adequate discussion of the evidence both for and against the researchers' arguments* • *if the researchers have discussed the credibility of their findings* • *if the findings are discussed in relation to the original research questions*	
10. Can the results be applied to the local population?	**X** Yes ☐ No ☐ Can't Tell Spanish cohorts therefore considered within Europe comparison
CONSIDER: • *the subjects covered in the study could be sufficiently different from your population to cause concern.* • *your local setting is likely to differ much from that of the study*	
11. How valuable is the research?	**X** Yes ☐ No ☐ Can't Tell Explores considerable associations with body composition and markers and the differences between men and women against healthy cohorts. Useful for contribution to research
CONSIDER: • *one descriptive/cross-sectional study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making* • *if the researcher discusses the contribution the study makes to existing knowledge (e.g., do they consider the findings in relation to current practice or policy, or relevant research-based literature?)* • *if the researchers have discussed whether or how the findings can be transferred to other populations*	

CASP Checklist:
For Descriptive/Cross-Sectional Studies

During critical appraisal, never make assumptions about what the researchers have done. If it is not possible to tell, use the "Can't tell" response box. If you can't tell, at best it means the researchers have not been explicit or transparent, but at worst it could mean the researchers have not undertaken a particular task or process. Once you've finished the critical appraisal, if there are a large number of "Can't tell" responses, consider whether the findings of the study are trustworthy and interpret the results with caution.

Paper for appraisal Sami et al., 2021

Section A: Are the results valid?	
1. Did the study address a clearly focused issue?	**X** Yes ☐ No ☐ Can't Tell Vitamin D status in non-CF bronchiectasis
CONSIDER: *A question can be 'focused' in terms of* • *the population studied* • *the risk factors studied* • *is it clear whether the study tried to detect a beneficial or harmful effect* • *the outcomes considered*	
2. Did the authors use an appropriate method to answer their question?	**X** Yes ☐ No ☐ Can't Tell Used cross sectional snapshot
CONSIDER: • *Is a descriptive/cross-sectional study an appropriate way of answering the question* • *did it address the study question*	
3. Were the subjects recruited in an acceptable way?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: *We are looking for selection bias which might compromise the generalisability of the findings:* • *Was the sample representative of a defined population* • *Was everybody included who should have been included*	
4. Were the measures accurately measured to reduce bias?	☐ Yes ☐ No **X** Can't Tell

CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)*	
5. Were the data collected in a way that addressed the research issue?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *if the setting for data collection was justified* • *if it is clear how data were collected (e.g., interview, questionnaire, chart review)* • *if the researcher has justified the methods chosen* • *if the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews were conducted?)*	
6. Did the study have enough participants to minimise the play of chance?	☐ Yes ☐ No **X** Can't Tell Power calculation not reported limited power
CONSIDER: • *if the result is precise enough to make a decision* • *if there is a power calculation. This will estimate how many subjects are needed to produce a reliable estimate of the measure(s) of interest.*	
7. How are the results presented and what is the main result?	**X** Yes ☐ No ☐ Can't Tell Vitamin D insufficiency 73% Low vit D is associated with respiratory dysfunction Pulmonary dysfunction positively was correlated with more body fat and less skeletal muscle mass
CONSIDER: • *if, for example, the results are presented as a proportion of people experiencing an outcome, such as risks, or as a measurement, such as mean or median differences, or as survival curves and hazards* • *how large this size of result is and how meaningful it is* • *how you would sum up the bottom-line result of the trial in one sentence*	
8. Was the data analysis sufficiently rigorous?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *if there is an in-depth description of the analysis process* • *if sufficient data are presented to support the findings*	
9. Is there a clear statement of findings?	**X** Yes ☐ No ☐ Can't Tell

CONSIDER: • *if the findings are explicit* • *if there is adequate discussion of the evidence both for and against the researchers' arguments* • *if the researchers have discussed the credibility of their findings* • *if the findings are discussed in relation to the original research questions*	
10. Can the results be applied to the local population?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *the subjects covered in the study could be sufficiently different from your population to cause concern.* • *your local setting is likely to differ much from that of the study*	
11. How valuable is the research?	**X** Yes ☐ No ☐ Can't Tell Explores considerable associations with body composition and specifically associated with vitamin D status
CONSIDER: • *one descriptive/cross-sectional study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making* • *if the researcher discusses the contribution the study makes to existing knowledge (e.g., do they consider the findings in relation to current practice or policy, or relevant research-based literature?)* • *if the researchers have discussed whether or how the findings can be transferred to other populations*	

CASP Checklist:
For Descriptive/Cross-Sectional Studies

During critical appraisal, never make assumptions about what the researchers have done. If it is not possible to tell, use the "Can't tell" response box. If you can't tell, at best it means the researchers have not been explicit or transparent, but at worst it could mean the researchers have not undertaken a particular task or process. Once you've finished the critical appraisal, if there are a large number of "Can't tell" responses, consider whether the findings of the study are trustworthy and interpret the results with caution.

Paper for appraisal Li et al., 2020

Section A: Are the results valid?	
1. Did the study address a clearly focused issue?	**X** Yes ☐ No ☐ Can't Tell This was considered nutritional status in non-CF bronchiectasis
CONSIDER: *A question can be 'focused' in terms of* • *the population studied* • *the risk factors studied* • *is it clear whether the study tried to detect a beneficial or harmful effect* • *the outcomes considered*	
2. Did the authors use an appropriate method to answer their question?	**X** Yes ☐ No ☐ Can't Tell Some limitations but retrospective cross sectional assessment of nutritional status
CONSIDER: • *Is a descriptive/cross-sectional study an appropriate way of answering the question* • *did it address the study question*	
3. Were the subjects recruited in an acceptable way?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: *We are looking for selection bias which might compromise the generalisability of the findings:* • *Was the sample representative of a defined population* • *Was everybody included who should have been included*	
4. Were the measures accurately measured to reduce bias?	☐ Yes ☐ No **X** Can't Tell

CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)*	
5. Were the data collected in a way that addressed the research issue?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *if the setting for data collection was justified* • *if it is clear how data were collected (e.g., interview, questionnaire, chart review)* • *if the researcher has justified the methods chosen* • *if the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews were conducted?)*	
6. Did the study have enough participants to minimise the play of chance?	☐ Yes ☐ No **X** Can't Tell Power calculation not reported
CONSIDER: • *if the result is precise enough to make a decision* • *if there is a power calculation. This will estimate how many subjects are needed to produce a reliable estimate of the measure(s) of interest.*	
7. How are the results presented and what is the main result?	☐ Yes ☐ No **X** Can't Tell BMI considered but limited by use of albumin as marker of nutritional status as period of disease not reported
CONSIDER: • *if, for example, the results are presented as a proportion of people experiencing an outcome, such as risks, or as a measurement, such as mean or median differences, or as survival curves and hazards* • *how large this size of result is and how meaningful it is* • *how you would sum up the bottom-line result of the trial in one sentence*	
8. Was the data analysis sufficiently rigorous?	☐ Yes ☐ No **X** Can't Tell Sufficient data reported but limited by the underpinning although associations are statistically strong and data is presented appropriately
CONSIDER: • *if there is an in-depth description of the analysis process* • *if sufficient data are presented to support the findings*	
9. Is there a clear statement of findings?	**X** Yes ☐ No ☐ Can't Tell

CONSIDER: • *if the findings are explicit* • *if there is adequate discussion of the evidence both for and against the researchers' arguments* • *if the researchers have discussed the credibility of their findings* • *if the findings are discussed in relation to the original research questions*	
10. Can the results be applied to the local population?	☐ Yes **X** No ☐ Can't Tell
CONSIDER: • *the subjects covered in the study could be sufficiently different from your population to cause concern.* • *your local setting is likely to differ much from that of the study*	
11. How valuable is the research?	☐ Yes ☐ No **X** Can't Tell Limited as only evidence utilising this approach to disease severity and nutritional status included to consider BMI relationship
CONSIDER: • *one descriptive/cross-sectional study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making* • *if the researcher discusses the contribution the study makes to existing knowledge (e.g., do they consider the findings in relation to current practice or policy, or relevant research-based literature?)* • *if the researchers have discussed whether or how the findings can be transferred to other populations*	

CASP Checklist:
For Descriptive/Cross-Sectional Studies

During critical appraisal, never make assumptions about what the researchers have done. If it is not possible to tell, use the "Can't tell" response box. If you can't tell, at best it means the researchers have not been explicit or transparent, but at worst it could mean the researchers have not undertaken a particular task or process. Once you've finished the critical appraisal, if there are a large number of "Can't tell" responses, consider whether the findings of the study are trustworthy and interpret the results with caution.

Paper for appraisal Wang et al., 2022

Section A: Are the results valid?	
1. Did the study address a clearly focused issue?	**X** Yes ☐ No ☐ Can't Tell Resp and peripheral muscle weakness BC
CONSIDER: *A question can be 'focused' in terms of* • *the population studied* • *the risk factors studied* • *is it clear whether the study tried to detect a beneficial or harmful effect* • *the outcomes considered*	
2. Did the authors use an appropriate method to answer their question?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *Is a descriptive/cross-sectional study an appropriate way of answering the question* • *did it address the study question*	
3. Were the subjects recruited in an acceptable way?	**X** Yes ☐ No ☐ Can't Tell Consecutive recruitment matched to healthy controls
CONSIDER: *We are looking for selection bias which might compromise the generalisability of the findings:* • *Was the sample representative of a defined population* • *Was everybody included who should have been included*	
4. Were the measures accurately measured to reduce bias?	**X** Yes ☐ No ☐ Can't Tell

CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)*	
5. Were the data collected in a way that addressed the research issue?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *if the setting for data collection was justified* • *if it is clear how data were collected (e.g., interview, questionnaire, chart review)* • *if the researcher has justified the methods chosen* • *if the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews were conducted?)*	
6. Did the study have enough participants to minimise the play of chance?	☐ Yes ☐ No **X** Can't Tell It is not clear if the 150 recruited supported significance values but were compared to healthy cohort
CONSIDER: • *if the result is precise enough to make a decision* • *if there is a power calculation. This will estimate how many subjects are needed to produce a reliable estimate of the measure(s) of interest.*	
7. How are the results presented and what is the main result?	**X** Yes ☐ No ☐ Can't Tell Women with NCFB have less quadricep force than men, lower BMI, FFM and FFMI than healthy matched controls (women) HGS was significantly reduced in NCFB compared with healthy controls gender differences exist with regards severity of disease and FFM
CONSIDER: • *if, for example, the results are presented as a proportion of people experiencing an outcome, such as risks, or as a measurement, such as mean or median differences, or as survival curves and hazards* • *how large this size of result is and how meaningful it is* • *how you would sum up the bottom-line result of the trial in one sentence*	
8. Was the data analysis sufficiently rigorous?	**X** Yes ☐ No ☐ Can't Tell All appropriate findings reported limitations presented
CONSIDER: • *if there is an in-depth description of the analysis process* • *if sufficient data are presented to support the findings*	
9. Is there a clear statement of findings?	**X** Yes ☐ No ☐ Can't Tell

	HGS impactful as a measure
CONSIDER: • *if the findings are explicit* • *if there is adequate discussion of the evidence both for and against the researchers' arguments* • *if the researchers have discussed the credibility of their findings* • *if the findings are discussed in relation to the original research questions*	
10. Can the results be applied to the local population?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *the subjects covered in the study could be sufficiently different from your population to cause concern.* • *your local setting is likely to differ much from that of the study*	
11. How valuable is the research?	**X** Yes ☐ No ☐ Can't Tell Contributes to further understanding of BC and NCFB
CONSIDER: • *one descriptive/cross-sectional study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making* • *if the researcher discusses the contribution the study makes to existing knowledge (e.g., do they consider the findings in relation to current practice or policy, or relevant research-based literature?)* • *if the researchers have discussed whether or how the findings can be transferred to other populations*	

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Paper for appraisal and reference: Ali et al 2022

Section A: Are the results of the trial valid?

1. Did the study address a clearly focused issue?

Yes	✔
Can't Tell	
No	

HINT: An issue can be 'focused' In terms of
- the population studied
- Whether the study tried to detect a beneficial or harmful effect
- the risk factors studied

Comments:

2. Did the authors use an appropriate method to answer their question?

Yes	✔
Can't Tell	
No	

HINT: Consider
- Is a case control study an appropriate way of answering the question under the circumstances
- Did it address the study question

Comments:

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Is it worth continuing?

3. Were the cases recruited in an acceptable way?

Yes ☑
Can't Tell ☐
No ☐

Comments:

HINT: We are looking for selection bias which might compromise validity of the findings
- are the cases defined precisely
- were the cases representative of a defined population (geographically and/or temporally)
- was there an established reliable system for selecting all the cases
- are they incident or prevalent
- is there something special about the cases
- is the time frame of the study relevant to disease/exposure
- was there a sufficient number of cases selected
- was there a power calculation

4. Were the controls selected in an acceptable way?

Yes ☑
Can't Tell ☐
No ☐

Comments:

HINT: We are looking for selection bias which might compromise the generalisability of the findings
- were the controls representative of the defined population (geographically and/or temporally)
- was there something special about the controls
- was the non-response high, could non-respondents be different in any way
- are they matched, population based or randomly selected
- was there a sufficient number of controls selected

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5. Was the exposure accurately measured to minimise bias?

Yes ☐
Can't Tell ☐
No ☑

HINT: We are looking for measurement, recall or classification bias
- was the exposure clearly defined and accurately measured
- did the authors use subjective or objective measurements
- do the measures truly reflect what they are supposed to measure (have they been validated)
- were the measurement methods similar in the cases and controls
- did the study incorporate blinding where feasible
- is the temporal relation correct (does the exposure of interest precede the outcome)

Comments:

6. (a) Aside from the experimental intervention, were the groups treated equally?

HINT: List the ones you think might be important, that the author may have missed
- genetic
- environmental
- socio-economic

List: Yes

6. (b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?

Yes ☑
Can't Tell ☐
No ☐

HINT: Look for
- restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

Comments:

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Section B: What are the results?

7. How large was the treatment effect?

HINT: Consider
- what are the bottom line results
- is the analysis appropriate to the design
- how strong is the association between exposure and outcome (look at the odds ratio)
- are the results adjusted for confounding, and might confounding still explain the association
- has adjustment made a big difference to the OR

Comments:

Vitamin D deficiency is associated with more frequent pulmonary exacerbations chronic pseudomonas infection and worsening lung function.
NCFB vitamin D deficiency 45% of population compared with controls 10% ($p<0.001$). Vit D deficiency associated with more frequent exacerbations statistically significant between groups NCFB/CF and NCFB/control.
Also found no differencves in %RDA means. Suggests more Vit D needed to supplement use in in immune response in this group

8. How precise was the estimate of the treatment effect?

HINT: Consider
- size of the p-value
- size of the confidence intervals
- have the authors considered all the important variables
- how was the effect of subjects refusing to participate evaluated

Comments: Reported significant differences between cohorts

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9. Do you believe the results?

Yes ✔
No

HINT: Consider
- big effect is hard to ignore!
- Can it be due to chance, bias, or confounding
- are the design and methods of this study sufficiently flawed to make the results unreliable
- consider Bradford Hills criteria (e.g. time sequence, does-response gradient, strength, biological plausibility)

Comments:

Section C: Will the results help locally?

10. Can the results be applied to the local population?

Yes ✔
Can't Tell
No

HINT: Consider whether
- the subjects covered in the study could be sufficiently different from your population to cause concern
- your local setting is likely to differ much from that of the study
- can you quantify the local benefits and harms

Comments: Afircan population but could be considered to apply to UK

11. Do the results of this study fit with other available evidence?

Yes ✔
Can't Tell
No

HINT: Consider
- all the available evidence from RCT's Systematic Reviews, Cohort Studies, and Case Control Studies as well, for consistency

Comments: other studies i deficincy of vitmain D also found simiar results in adults

Remember One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making. However, for certain questions observational studies provide the only evidence. Recommendations from observational studies are always stronger when supported by other evidence.

CASP Checklist:
For Descriptive/Cross-Sectional Studies

During critical appraisal, never make assumptions about what the researchers have done. If it is not possible to tell, use the "Can't tell" response box. If you can't tell, at best it means the researchers have not been explicit or transparent, but at worst it could mean the researchers have not undertaken a particular task or process. Once you've finished the critical appraisal, if there are a large number of "Can't tell" responses, consider whether the findings of the study are trustworthy and interpret the results with caution.

Paper for appraisal Contreras Bolivar et al., 2022

Section A: Are the results valid?	
1. Did the study address a clearly focused issue?	X Yes ☐ No ☐ Can't Tell Exploration of BMD muscle strength with NCFB and nutritional intake and status.
CONSIDER: *A question can be 'focused' in terms of* • *the population studied* • *the risk factors studied* • *is it clear whether the study tried to detect a beneficial or harmful effect* • *the outcomes considered*	
2. Did the authors use an appropriate method to answer their question?	X Yes ☐ No ☐ Can't Tell
CONSIDER: • *Is a descriptive/cross-sectional study an appropriate way of answering the question* • *did it address the study question*	
3. Were the subjects recruited in an acceptable way?	X Yes ☐ No ☐ Can't Tell Convenience sampling associated with clinic
CONSIDER: *We are looking for selection bias which might compromise the generalisability of the findings:* • *Was the sample representative of a defined population* • *Was everybody included who should have been included*	
4. Were the measures accurately measured to reduce bias?	☐ Yes X No ☐ Can't Tell

CONSIDER: *Look for measurement or classification bias:* • *did they use subjective or objective measurements* • *do the measurements truly reflect what you want them to (have they been validated)*	
5. Were the data collected in a way that addressed the research issue?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *if the setting for data collection was justified* • *if it is clear how data were collected (e.g., interview, questionnaire, chart review)* • *if the researcher has justified the methods chosen* • *if the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews were conducted?)*	
6. Did the study have enough participants to minimise the play of chance?	**X** Yes ☐ No ☐ Can't Tell
CONSIDER: • *if the result is precise enough to make a decision* • *if there is a power calculation. This will estimate how many subjects are needed to produce a reliable estimate of the measure(s) of interest.*	
7. How are the results presented and what is the main result?	**X** Yes ☐ No ☐ Can't Tell 62.8% and 62.5% (men/women respectively had normal BMD, 30.2% and 22.2% had osteopenia and 7% and 15% osteoporosis Those with decreased bone mass had significantly lower HGS Max expiratory volume and vit D level
CONSIDER: • *if, for example, the results are presented as a proportion of people experiencing an outcome, such as risks, or as a measurement, such as mean or median differences, or as survival curves and hazards* • *how large this size of result is and how meaningful it is* • *how you would sum up the bottom-line result of the trial in one sentence*	
8. Was the data analysis sufficiently rigorous?	**X** Yes ☐ No ☐ Can't Tell Considered seasonal variation although number were low to draw conclusions
CONSIDER: • *if there is an in-depth description of the analysis process* • *if sufficient data are presented to support the findings*	
9. Is there a clear statement of findings?	**X** Yes ☐ No ☐ Can't Tell

CONSIDER: • *if the findings are explicit* • *if there is adequate discussion of the evidence both for and against the researchers' arguments* • *if the researchers have discussed the credibility of their findings* • *if the findings are discussed in relation to the original research questions*	
10. Can the results be applied to the local population?	**X** Yes ☐ No ☐ Can't Tell Spanish cohorts therefore considered within Europe comparison
CONSIDER: • *the subjects covered in the study could be sufficiently different from your population to cause concern.* • *your local setting is likely to differ much from that of the study*	
11. How valuable is the research?	**X** Yes ☐ No ☐ Can't Tell Contributes further to understanding of nutritional status an intake and vitamin D in bronchiectasis. Adds to the body of evidence
CONSIDER: • *one descriptive/cross-sectional study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making* • *if the researcher discusses the contribution the study makes to existing knowledge (e.g., do they consider the findings in relation to current practice or policy, or relevant research-based literature?)* • *if the researchers have discussed whether or how the findings can be transferred to other populations*	

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3. Was the exposure accurately measured to minimise bias?

Yes	X
Can't Tell	
No	

HINT: Look for measurement or classification bias:
- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- were all the subjects classified into exposure groups using the same procedure

Comments: Development of Bronchiectasis in larger free-living population and association with BMI

4. Was the outcome accurately measured to minimise bias?

Yes	X
Can't Tell	
No	

HINT: Look for measurement or classification bias:
- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- has a reliable system been established for detecting all the cases (for measuring disease occurrence)
- were the measurement methods similar in the different groups
- were the subjects and/or the outcome assessor blinded to exposure (does this matter)

Comments: Limitations were reported reliable due to length of study an number of subjects as prospective observational

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Paper for appraisal and reference: Yang et al., 2021

Section A: Are the results of the study valid?

1. Did the study address a clearly focused issue?

Yes	X
Can't Tell	
No	

HINT: A question can be 'focused' in terms of
- the population studied
- the risk factors studied
- is it clear whether the study tried to detect a beneficial or harmful effect
- the outcomes considered

Comments
Exploring data related to BMI and risk of developing bronchiectasis

2. Was the cohort recruited in an acceptable way?

Yes	X
Can't Tell	
No	

HINT: Look for selection bias which might compromise the generalisability of the findings:
- was the cohort representative of a defined population
- was there something special about the cohort
- was everybody included who should have been

Comments
Korean study utilizing healthcare database to observe a population over considerable period of time 6,329,838 aged 20-40 years

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5. (a) Have the authors identified all important confounding factors?

Yes	X
Can't Tell	
No	

HINT:
- list the ones you think might be important, and ones the author missed

Comments: limitations outlined of data collected were discussed within the paper
Age of population

5. (b) Have they taken account of the confounding factors in the design and/or analysis?

Yes	X
Can't Tell	
No	

HINT:
- look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

Comments:
Utilised appropriate cut offs for Asian population for BMI therefore considered here

6. (a) Was the follow up of subjects complete enough?

Yes	X
Can't Tell	
No	

HINT: Consider
- the good or bad effects should have had long enough to reveal themselves
- the persons that are lost to follow-up may have different outcomes than those available for assessment
- in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort

6.(b) Was the follow up of subjects long enough?

Yes	X
Can't Tell	
No	

Comments: As prospective observation of a population

Section B: What are the results?

7. What are the results of this study?

HINT: Consider
- what are the bottom line results
- have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference
- how strong is the association between exposure and outcome (RR)
- what is the absolute risk reduction (ARR)

Comments: Risk of Bronchiectasis was (fully adjusted model) significantly higher in underweight category (HR 1.36 (CI 1.30-1.42) compared with the normal BMI category.

8. How precise are the results?

HINT:
- look for the range of the confidence intervals, if given

Comments: precise

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9. Do you believe the results?

Yes	X
Can't Tell	
No	

HINT: Consider
- big effect is hard to ignore
- can it be due to bias, chance or confounding
- are the design and methods of this study sufficiently flawed to make the results unreliable
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Comments: Whilst looking for associations here they have been fully adjusted

Section C: Will the results help locally?

10. Can the results be applied to the local population?

Yes	
Can't Tell	
No	X

HINT: Consider whether
- a cohort study was the appropriate method to answer this question
- the subjects covered in this study could be sufficiently different from your population to cause concern
- your local setting is likely to differ much from that of the study
- you can quantify the local benefits and harms

Comments: No the population has different cut offs for BMI than the UK population and so cannot be generalize however adds to understanding of the role of BMI on works in populations and because they were adjusted similar observation may be seen

11. Do the results of this study fit with other available evidence?

Yes	
Can't Tell	X
No	

Comments: only 1 of 2 studies like this and so has identified risk of developing bronchiectasis but limited

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12. What are the implications of this study for practice?

Yes	
Can't Tell	X
No	

HINT: Consider
- one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- for certain questions, observational studies provide the only evidence
- recommendations from observational studies are always stronger when supported by other evidence

Comments: No reported change could be considered for clinical practice only that low BMI could result in developing bronchiectasis over 7.46 year period

Appendix D Standard Operating Procedures

D.1 Standard operating procedure for weight to determine BMI.

The Leeds Teaching Hospitals NHS Trust

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Leeds Regional Bronchiectasis Clinic

Standard Operating procedure: Measuring Weight

Version and Date v1 21/11/2016

Author Linsey King RD PhD Student

Weight measure is used as part of assessment of clinical outcome and is required in the determination of Body Mass Index (BMI). Weight should be measured using calibrated scales on an even surface in order to ensure exact measurement.

This Standard Operating Procedure has been created for use in the Leeds Regional Bronchiectasis clinic as part of clinical research undertaken.

It is the responsibility of the staff involved in the clinical research to read and use the standard operating procedure to measure the weight of study participants (SP) to ensure continuity.

Equipment required – Calibrated Digital Scales

Procedure:

1. Explain to the SP the procedure for measuring their weight and ensure the scales or positioned on a flat surface and are turned on
2. Ask the SP to remove their shoes and to stand on the scales.
3. Wait until the digital value has settled and record the reading.
4. Measure to the nearest 0.1kg
5. Record the measure on the appropriate data collection form
6. Ask the SP to step off the scales and explain the recording is complete

References

National Health and Nutrition Examination Survey (NHANES), 2013, Anthropometry Procedure Manual, last accessed 21/11/2016 available at: http://www.cdc.gov/nchs/data/nhanes/nhanes_13_14/2013_Anthropometry.pdf

D.2 Standard operating procedure for height to determine BMI.

The Leeds Teaching Hospitals NHS Trust

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Leeds Regional Bronchiectasis Clinic

Standard Operating procedure: Measuring Height

Version and Date v1 21/11/2016

Author Linsey King RD PhD Student

Height measure is usually used as part of the assessment of body composition and is required for calculating Body Mass Index (BMI). Height is measured using a stadiometer and positioning is essential to accurate measurements.

This Standard Operating Procedure has been created for use in the Leeds Regional Bronchiectasis clinic as part of clinical research undertaken.

It is the responsibility of the staff involved in the clinical research to read and use the standard operating procedure to measure the height of study participants (SP) to ensure continuity.

Equipment required – Height Measure/Stadiometer

Procedure:

1. Explain to the SP the procedure for measuring their height and ensure the measuring plate is high enough before inviting the SP to stand
2. Ask the SP to remove their shoes and stand on the plate of the stadiometer with their back to the height measure
3. The SP should stand up straight, as tall as they can, arms and shoulders relaxed with their feet flat on the floor and heels together. Their head, shoulder blades, buttocks and heels should make contact with the back board. N.B. In some cases this is not possible e.g. due to kyphosis
4. Move the head plate down so that it rests on the top of the head firmly. The head should be aligned in the Frankfort Horizontal plane. This is determined by observing that an imaginary horizontal line exists between the external auditory meatus (ear canal) and the lower border of the orbit of the eye. These should be parallel to the floor and perpendicular to the backboard.
5. The reading should be taken from as level position as possible, therefore if required a small step or a stoop may be required to ensure that the eyeline of the assessor is level with the measure

6. Measure to the nearest 0.1cm
7. Record the measure on the appropriate data collection form

References

National Health and Nutrition Examination Survey (NHANES), 2013, Anthropometry Procedure Manual, last accessed 21/11/2016 available at: http://www.cdc.gov/nchs/data/nhanes/nhanes_13_14/2013_Anthropometry.pdf

University of Exeter Clinical Research standard operating procedure: Measuring Height, last accessed 21/11/2016 available at: https://ctsn.exeter.ac.uk/web/content/standard-operating-procedures

Sheffield Clinical Research Facility Standard Operating Procedure, Measuring Height (2011), last accessed 21/11/2016 available at: https://www.sheffield.ac.uk/polopoly_fs/1.218530!/file/sop_crfc106_measuring_height.pdf

D.3 Standard Operating Procedure Hand grip dynamometry

The Leeds Teaching Hospitals NHS Trust

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Leeds Regional Bronchiectasis Clinic

Standard Operating procedure: Measuring Handgrip Dynamometry

Version and Date v1 21/11/2016

Author Linsey King RD PhD Student

This standard operating procedure is to be used to measure Hand Grip Strength in Study Participants (SP) as part of clinical research carried out at the Leeds Regional Bronchiectasis clinic. This test has been shown to be a predictor of health outcomes.

Measurements are taken using the Takei Digital dynamometer

Procedure:

1. Wash your hands and use an alcohol wipe to clean the dynamometer
2. Check with the patient if they have any issues with their hands that could impact on them taking the test
3. If the SP is able to ask them to remove any watches and or bracelets on their dominant hand
4. If the SP is able to stand ask them to do so with their feet, hip width apart. If not they can sit in a chair.
5. At this point show the SP the position to stand or sit and how to hold the dynamometer and show them how to squeeze and the result that is shown.
6. Ask the SP to hold the dynamometer and check with them that it feels comfortable in their hand. Adjust the positioning of the dynamometer at this point if required.
7. Turn the dynamometer on and hand it to the SP and ask them to have a practice squeeze. Ask them not to hold their breath during this.
8. The SP should now be ready to carry out the dynamometry test. Ask them to squeeze on the dynamometer and count for 5 seconds.
9. Ask the SP to stop and then record the result to the nearest 0.1kg
10. Repeat this 3 times to gain an average

References

National Health and Nutrition Examination Survey (NHANES), 2011, Muscle Strength Procedures Manual, last accessed 25/11/2016 available at: https://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/muscle_strength_proc_manual.pdf

Sheffield Clinical Research Facility Standard Operating Procedure, Grip Strength testing (2010), last accessed 25/11/2016 available at: https://www.shef.ac.uk/polopoly_fs/1.218558!/file/sop_crfc130_grip_strength_testing.pdf

D.4 Standard operating procedure for measuring triceps skinfold thickness.

The Leeds Teaching Hospitals NHS Trust

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Leeds Regional Bronchiectasis Clinic

Standard Operating procedure: Measuring Tricep Skinfold Thickness

Version and Date v1 30/11/2016

Author Linsey King RD PhD Student

This standard operating procedure is to be used to measure Tricep Skinfold Thickness in Study Participants as part of clinical research carried out at the Leeds Regional Bronchiectasis clinic. This test is shown to support measurement to determine Mid-arm muscle circumference to estimate muscle mass in adults shown to be a predictor of health outcomes.

Measurements are taken using standard tape measure and skinfold calipers

Procedure:

1. Wash your hands and use an alcohol wipe to clean the calipers
2. Check with the patient if they are happy to go ahead with the test and explain that their non-dominant arm will be used in this procedure.
3. Take the tape measure and ask the participant to bend their elbow to 90 degrees.
4. Identify the acromion process and the olecranon process, take the tape measure, and mark the mid-point between the two with a non-toxic marker.
5. Ask the participant to hang the arm loosely by their side.
6. Take the tape measure and measure the circumference of the arm at the point identified and record the result.
7. Repeat this 3 times to gain an average measure.
8. At this point grasp a vertical fold of skin and fat at the back of the arm, 1cm above the mark, taking care to separate fat from muscle.

9. Use the calipers to measure the skinfold at the mid-point mark read the dial and record the measure measurement
10. Repeat this procedure 3 times to gain an average.

References

National Health and Nutrition Examination Survey (NHANES), 2009, Anthropometry Procedure Manual, last accessed 21/11/2016 available at: http://www.cdc.gov/nchs/data/nhanes/nhanes_13_14/2013_Anthropometry.pdf

D.5 Standard operating procedure Bio-Electrical Impedance analysis (BIA)

The Leeds Teaching Hospitals NHS Trust

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Feasibility study exploring supplementation nutritional gels in participants with Primary Ciliary Dyskinesia

Pre Assessment guide and Standard Operating Procedure: Measuring Body composition using Bioelectrical Impedance Analysis (BIA)

Version and Date v1 08/03/2020

Author Linsey King RD PhD Student

BIA is a useful way to assess composition of the body and determine Fat Mass (FM) Fat Free Mass (FFM). It is considered safe and minimally invasive. This Pre assessment guide and SOP has been created for use in the Primary Ciliary Dyskinesia clinic as part of clinical research undertaken.

Equipment required – SECA BIA machine

Pre assessment guidance and SOP

Study Participants (SP) should follow this guidance prior to this measure being taken. Success at all points will be recorded at the beginning of the test. The test will still be completed recording if any of the pre test guidance have not been completed

Pre test instructions

1. Avoid vigorous activity 8 hours before the test
2. No eating and drinking within 4 hours of the test (where possible).

Standard Operating procedure

1. Study Participant cannot complete the test if they have an electrical device (pacemaker, metal plate, cochlear implant)
2. Ensure hands and feet are clean with alcohol wipes
3. Remove Shoes, Socks, tights before completing the test
4. Stand on the metal foot plates and place hands on the metal hand positions.
5. Enter the required measures in accordance with the manual instruction
6. When the machine is measuring advise SP to remain still for the duration of the measure.
7. Save output and record results.

D.6 Standard operating procedure for 6-minute walk test (6MWT)

The Leeds Teaching Hospitals NHS Trust

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Feasibility study exploring supplementation nutritional gels in participants with Primary Ciliary Dyskinesia

Pre-Assessment guide and Standard Operating Procedure: Six Minute walk test (6MWT)

Version and Date v1 10/03/2020

Author Linsey King RD PhD Student

The 6MWT is used extensively in research and is identified as a tool for determining change following interventions in patients with lung diseases. It can be used as measure of functional status and a predictor of morbidity and mortality.

This Pre assessment guide and SOP has been created for use in the Primary Ciliary Dyskinesia clinic as part of clinical research undertaken.

Equipment required.

Timer/stopwatch
Lap counter
2 chairs that can be moved easily
Markers such as small cones to note the turnaround points
Access to a defibrillator
Access to oxygen

Pre assessment guidance and SOP

Study Participants (SP) should follow this guidance prior to this measure being taken. Technicians should use this guidance to complete the 6MWT safely and correctly

Pre-test instructions

1. Avoid vigorous activity within 2 hours of the test
2. Appropriate shoes and comfortable clothing should be worn for walking
3. SP's should use their usual walking aids during the test e.g. walker, walking stick

Standard Operating procedure

1. Explain to the SP what they will be required to do over the duration of the test. Then demonstrate to the SP how to walk around the cones.

2. Explain to the participant that they need to rate their dyspnoea using the BORG scale and record the result
3. Ask the SP to move to the start and ask them to begin and walk at their own pace until they are instructed to stop or they feel they cannot continue. Start the timer and begin to track the number of laps completed.
4. Encouragement should be offered to the SP during the test.
5. When the timer reaches 15 seconds before the end instruct the SP that you will ask them to stop in a moment.
6. Mark where the patient stops and record the distance to the nearest meter. Repeat the BORG scale dyspnoea measure.

The BORG scale is a measure of perceived exertion using a tabled scale (see below) (Borg G., 1998) and is utilised standard in the 6MWT

Rating	Perceived Exertion
6	No Exertion
7	Extremely light
8	
9	Very Light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very Hard
18	
19	Extremely Hard
20	Maximal Exertion

Appendix E 24 hour dietary multiple pass recall

The Leeds Teaching Hospitals NHS Trust

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Leeds Regional Bronchiectasis Clinic **IRAS 216351**

Version and Date v1 24/02/2017

24 Hour recall **Participant ID Number**

Time of day	Food and Drink Consumed	Quantity

Date agreed for telephone 24 hr Recall

24 hr recall 1	**Date agreed**	**No for contact**
24 hr recall 2	**Date agreed**	**No for contact**

Appendix F St George's Respiratory Questionnaire

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ORIGINAL ENGLISH VERSION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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continued…

St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have had over the past 3 months.

Please tick (✔) *one box for each question*:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 3 months, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 3 months, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 3 months, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 3 months, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 3 months how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✔) *one*:

- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✔) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 3 months, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✔) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✔) *one*:

- No ☐
- Yes ☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your chest condition?

Please tick (✔) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✔) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless these days.

Please tick (✔) in ***each box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

	Please tick (✔) in ***each box*** that applies to you ***these days***: True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

	Please tick (✔) in ***each box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

	Please tick (✔) in ***each box*** that applies to you ***these days***: True	False
My medication does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My medication interferes with my life a lot	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

Please tick (✔) in ***each box*** that applies to you ***because of your breathing***:

	True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

Please tick (✔) in ***each box*** that applies to you ***because of your chest trouble***:

	True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, pub, club or place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

.....

.....

.....

.....

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐

It stops me doing one or two things I would like to do ☐

It stops me doing most of the things I would like to do ☐

It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

Appendix G SF-36 questionnaire

SF-36 QUESTIONNAIRE

Name:_____ **Ref. Dr:**_____ **Date:** _____

ID#: _____ **Age:** _____ **Gender: M / F**

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:
In general, would you say your health is:
Excellent Very Good Good Fair Poor

Compared to one year ago, how would you rate your health in general now?
Much better now than one year ago
Somewhat better now than one year ago
About the same
Somewhat worse now than one year ago
Much worse than one year ago

LIMITATIONS OF ACTIVITIES:
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
Yes, Limited a lot Yes, Limited a Little No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Lifting or carrying groceries
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Climbing several flights of stairs
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Climbing one flight of stairs
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Bending, kneeling, or stooping
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking more than a mile
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking several blocks
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking one block
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Bathing or dressing yourself

◯Yes, Limited a Lot ◯Yes, Limited a Little ◯No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities

◯Yes ◯No

Accomplished less than you would like

◯Yes ◯No

Were limited in the kind of work or other activities

◯Yes ◯No

Had difficulty performing the work or other activities (for example, it took extra effort)

◯Yes ◯No

EMOTIONAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities

◯Yes ◯No

Accomplished less than you would like

◯Yes ◯No

Didn't do work or other activities as carefully as usual

◯Yes ◯No

SOCIAL ACTIVITIES:

Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

◯Not at all ◯Slightly ◯Moderately ◯Severe ◯Very Severe

PAIN:

How much bodily pain have you had during the past 4 weeks?

◯None ◯Very Mild ◯Mild ◯Moderate ◯Severe ◯Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

◯Not at all ◯A little bit ◯Moderately ◯Quite a bit ◯Extremely

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- ◯ All of the time
- ◯ Most of the time
- ◯ A good Bit of the Time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the Time

Have you been a very nervous person?
- ◯ All of the time
- ◯ Most of the time
- ◯ A good Bit of the Time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- ◯ All of the time
- ◯ Most of the time
- ◯ A good Bit of the Time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the Time

Have you felt calm and peaceful?
- ◯ All of the time
- ◯ Most of the time
- ◯ A good Bit of the Time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the Time

Did you have a lot of energy?
- ◯ All of the time
- ◯ Most of the time
- ◯ A good Bit of the Time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the Time

Have you felt downhearted and blue?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time

GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

I am as healthy as anybody I know
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

I expect my health to get worse
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

My health is excellent
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

Appendix H Habitual Activity Estimation scale

THE HAES (HABITUAL ACTIVITY ESTIMATION SCALE)

This questionnaire will ask you questions about your daily activities. Please read all of the instructions carefully and answer each question as truthfully as you can.

Participant Number :

_____

Date: _____

INSTRUCTIONS (please read!)

Please recall the activities of *one typical weekday* (choose from Tuesday, Wednesday or Thursday) and *one typical Saturday* within the past 2 weeks. For each given time period, please estimate the percentage of time that you spent in each of 4 different activity levels. For each of the time periods, the total time spent in all activity levels must add up to 100%.

The different activity levels are described below:

ACTIVITY LEVEL DESCRIPTIONS

These descriptions give you examples of activities that are typical of each activity level. You should refer back to these descriptions as often as you need when completing your estimates.

e) **inactive** – *lying down*, sleeping, resting, napping

f) **somewhat inactive** – *sitting*, reading, watching television, playing video games, time in front of the computer, playing games or activities which are mostly done sitting down

g) **somewhat active** – *walking*, shopping, light household chores

h) **very active** – *running*, jumping, skipping, bicycling, skating, swimming, games that require lots of movement and make you breathe/sweat hard

Following is a sample of a completed time period:

SAMPLE

From when you finished breakfast until when you started lunch, please estimate the percentage of time that you spent in each of the following activity levels:	
a) inactive	5% (i.e., having a nap)
b) somewhat inactive	60% (i.e., watching TV)
c) somewhat active	25% (i.e., shopping)
d) very active	10% (i.e., riding a bicycle)
TOTAL	100%

WEEKDAY ACTIVITY

For *one typical weekday in the past 2 weeks*, (choose from one of Tuesday, Wednesday or Thursday), please estimate the percentage of time that you spent in each activity level.

1. After getting out of bed until starting breakfast:

a) inactive _____ %

b) somewhat inactive _____ %

c) somewhat active _____ %

d) very active _____ %

TOTAL 100%

2. After finishing breakfast until starting lunch:

a) inactive _____ %

b) somewhat inactive _____ %

c) somewhat active _____ %

d) very active _____ %

TOTAL 100%

3. After finishing lunch until starting supper:

a) inactive _____ %

b) somewhat inactive _____ %

c) somewhat active _____ %

d) very active _____ %

TOTAL 100%

4. After finishing supper until bedtime:

a) inactive _____ %

b) somewhat inactive _____ %

c) somewhat active _____ %

d) very active _____ %

TOTAL	100%

For the *typical weekday* that you are referring to, please answer the following questions as accurately as possible in the spaces provided.

5. At what time did you get out of bed in the morning? _____

6. At what time did you start eating breakfast? _____

7. How long did you spend eating breakfast? _____ minutes

8. At what time did you start eating lunch? _____

9. How long did you spend eating lunch? _____ minutes

10. At what time did you start eating supper? _____

11. How long did you spend eating supper? _____ minutes

12. At what time did you go to bed that evening? _____

13. For the *typical weekday* that this questionnaire has asked you about, please rate your <u>overall</u> level of activity (please circle one response only):

a) very inactive
b) inactive
c) somewhat inactive
d) somewhat active
e) active
f) very active

14. Is this "typical" Tuesday, Wednesday or Thursday that you described in this questionnaire (please circle one response only):

a) a lot like most weekdays
b) a little bit like most weekdays
c) a little bit different from most weekdays
d) a lot different from most weekdays

SATURDAY ACTIVITY

For *one typical Saturday in the past 2 weeks*, please estimate the percentage of time that you spent in each activity level.

15. After getting out of bed until starting breakfast:

a) inactive _____ %

b) somewhat inactive _____ %

c) somewhat active _____ %

d) very active _____ %

TOTAL	100%

16. After finishing breakfast until starting lunch:

a) inactive _____ %

b) somewhat inactive _____ %

c) somewhat active _____ %

d) very active _____ %

TOTAL	100%

17. After finishing lunch until starting supper:

a) inactive _____ %

b) somewhat inactive _____ %

c) somewhat active _____ %

d) very active _____ %

TOTAL	100%

18. After finishing supper until bedtime:

a) inactive _____ %

b) somewhat inactive _____ %

c) somewhat active _____ %

d) very active _____ %

TOTAL	100%

For the *typical Saturday* that you are referring to, please answer the following questions as accurately as possible in the spaces provided.

19. At what time did you get out of bed in the morning? _____

20. At what time did you start eating breakfast? _____

21. How long did you spend eating breakfast? _____ minutes

22. At what time did you start eating lunch? _____

23. How long did you spend eating lunch? _____ minutes

24. At what time did you start eating supper? _____

25. How long did you spend eating supper? _____ minutes

26. At what time did you go to bed that evening? _____

27. For the *typical Saturday* that this questionnaire has asked you about, please rate your overall level of activity (please circle one response only):

a) very inactive
b) inactive
c) somewhat inactive
d) somewhat active
e) active
f) very active

28. Is the "typical" Saturday that you described in this questionnaire (please circle one response only):

a) a lot like most Saturdays
b) a little bit like most Saturdays
c) a little bit different from most Saturdays
d) a lot different from most Saturdays

29. If you have any comments about your activity patterns that you think are important, please mention them on the back of this page. Thank-you.

Appendix I Acceptability and Palatability scales

The Leeds Teaching Hospitals NHS Trust

UNIVERSITY OF LEEDS

Feasibility study exploring supplementation nutritional gels in participants with Primary Ciliary Dyskinesia

Palatability and acceptability of nutritional supplements scales

Initial month 1, month 2 and end point.

Participant Number _____

Does the participant have any allergies? YES/NO

Checked against nutritional supplement ingredients is participant able to consume supplement YES/NO

If yes move on to trial supplement if no unable to continue in study

Questions on palatability of test gel supplement

Visual Appeal	Good	——|——|——|——	Bad
Smell	Good	——|——|——|——	Bad
Taste	Good	——|——|——|——	Bad
Aftertaste	Good	——|——|——|——	Bad
Palatability	Good	——|——|——|——	Bad

Hedonic Rating Scale

	Like a lot	Like a little	Neither like nor dislike	Dislike a little	Dislike a lot
Appearance					
Aroma					
Taste					
Sweetness					
Texture mouthfeel					

Appendix J Ethical approval documents

J.1 Characteristics study – Chapter 4 and 5

NHS
Health Research Authority

Mrs Linsey King
Senior Lecturer/Dietitian
Leeds Beckett University
CL413
City Campus
Leeds
LS1 3HE

Email: hra.approval@nhs.net

19 April 2017

Dear Mrs King

Letter of HRA Approval

Study title:	**A study to investigate the characteristics, anthropometry and dietary intakes of a group of patients with bronchiectasis. The results of this will allow stratification of the group to inform further research including effects of a tailored amino acid supplemented intervention on clinical outcomes and functionality**
IRAS project ID:	**216351**
REC reference:	**17/SC/0131**
Sponsor	**University of Leeds**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.

- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

IRAS project ID	216351

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **216351**. Please quote this on all correspondence.

Yours sincerely

Beverley Mashegede
Assessor

Email: hra.approval@nhs.net

Copy to: Sponsor contact
Anne Gowing, Lead NHS R&D Contact

IRAS project ID	216351

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	*Version*	*Date*
Contract/Study Agreement [Statement of Activities]		15 March 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance certificate]		08 September 2016
IRAS Application Form [IRAS_Form_01032017]		01 March 2017
IRAS Application Form XML file [IRAS_Form_01032017]		01 March 2017
IRAS Checklist XML [Checklist_07042017]		07 April 2017
Letter from sponsor [Sponsor letter]		14 February 2017
Other [Schedule of Events]		15 March 2017
Other [Standard Operating Procedure Handgrip]	1	21 November 2016
Other [Standard Operating Procedure Height]	1	21 November 2016
Other [Standard Operating Procedure Weight]	1	21 November 2016
Other [Standard Operating Procedure Tricep]	1	30 November 2016
Other [Data Collection workbook]	2	03 March 2017
Other [24 Hour recall]		24 February 2017
Other [Sponsor email]		14 February 2017
Other [PIS - with tracked changes]	4	22 March 2017
Other [Consent form with tracked changes]	3	22 March 2017
Other [Covering letter response to REC]		07 April 2017
Research protocol or project proposal [Protocol v4]	4	03 March 2017
Summary CV for Chief Investigator (CI) [CV]		05 January 2017
Summary CV for supervisor (student research) [Supervisor CV]		01 February 2017

IRAS project ID	216351

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations*, *capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Not named
Tel: 01133437587
Email: governance-ethics@leeds.ac.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	The sponsor intends to use a Statement of Activities as the form of agreement with participating NHS organisations.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this research study.

IRAS project ID	216351

Section	HRA Assessment Criteria	Compliant with Standards	Comments
4.3	Financial arrangements assessed	Yes	No application for external funding made. No funds will be provided to the participating organisation to support this study.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	Provisional Opinion issued 21 March 2017. Further Information Favourable Opinion issued 19 April 2017.
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

IRAS project ID	216351

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
This is a non-commercial student (PhD) study and there is one site type. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.
Participating NHS organisations in England **will be expected to formally confirm their capacity and capability to host this research**. • Following issue of this letter, participating NHS organisations in England may now confirm to the sponsor their capacity and capability to host this research, when ready to do so. How capacity and capacity will be confirmed is detailed in the *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* section of this appendix. • The Assessing, Arranging, and Confirming document on the HRA website provides further information for the sponsor and NHS organisations on assessing, arranging and confirming capacity and capability.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A PI is expected at the participating organisation. GCP training is not a generic training expectation, in line with the HRA statement on training expectations.

IRAS project ID	216351

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
Where arrangements are not already in place, network staff (or similar) undertaking any research activities that may impact on the quality of care of the participant, would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance. For research team members undertaking activities that do not impact on the quality of care of the participant (for example, administering questionnaires), a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Phase 1 study **Linsey King PhD Student** **University of Leeds**

Date 03/03/2017 **IRAS 216351** **Version 4**

Protocol

Title – a prospective cross-sectional study to establish baseline characteristics of a bronchiectasis patient group to assess nutritional status and disease associated outcomes and stratify populations.

Aim – To capture data including aetiology, sputum volumes, nutritional intake, lung function, antibiotic treatments, MRC score and anthropometrics to report on findings comparing nutritional status with lung function, recurrent infection, exercise tolerance and functionality and their interplay. In addition to determine and establish stratified sub populations.

Objectives

- To collect standard data using EMIS web platform of all patients with bronchiectasis attending the Leeds Regional bronchiectasis clinic within the time period outlined
- To collect 3 dietary snapshots using 24 hour recall dietary assessment methods with all patients recruited within the study time period
- To establish functional ability through handgrip dynamometry on all patients recruited within the study time period
- To collect tricep skinfold measurements to determine body composition

Evidence outline

Bronchiectasis, a respiratory condition with many causes both acquired and congenital, is associated with a dearth of evidence characterising the population and establishing their current dietary needs. Guidelines for management of patients with Bronchiectasis were produced by the British Thoracic Society utilising limited evidence and research (Pasteur et al, 2010). Previous considerations for intervention, diagnosis and assessment were fundamentally based upon empirical data and at present prevalence in the UK is unknown (Pasteur et al, 2010).

There is a dearth of evidence on the relationship between nutritional status and clinical outcomes in this patient group. Oliveira in 2012 outlined that 1/3rd of these patients have significant fat free mass depletion. In addition, Oliveira et al 2014, utilised the Mediterranean diet and found those who had greater adherence to the Mediterranean diet approach had lower likelihood of symptoms of depression and anxiety. Investigation into the role of nutrition with further functional and clinical outcomes is lacking. A multicentre study was undertaken in 2015 by Qi et al that found those patients with Bronchiectasis with lower BMI’s were prone to developing more acute exacerbations of

bronchiectasis and poorer pulmonary function. Although not conducted in the UK or Europe this research reflects some of the potential relationship between poor nutritional status and clinical outcomes. In addition, and more specifically there is growing interest in the role of vitamin D specifically in the protection against inflammation and recurrent infections within this patient group (Bartley et al, 2013).

Rationale

The nutritional characterisation of bronchiectasis is lacking and there is limited evidence for understanding body composition and associated dietary intake in this patient group. This study would assess the incidence of infection and lung function compared with dietary intakes, anthropometry, muscle functionality and exercise tolerance and their interplay to effectively determine associations with nutrition and clinical outcomes. The data collected will also allow sub populations to be identified for further stratification to be established for future research studies intended.

Methodology

Inclusion criteria

- People aged 17 or over with a confirmed diagnosis of bronchiectasis
- People with bronchiectasis who are clinically stable -not requiring acute admission to hospital
- People who attend the Leeds Regional Clinic

Exclusion criteria

- People who are pregnant
- Those with existing co-morbidities such as malignancy

The study design will be cross-sectional, and data will be collected on each participant at presentation in the Leeds Regional Bronchiectasis Clinic. Routine data as part of the patient care pathway will be collected using standard operating procedures where appropriate and will be collected by Research Nurses linked with the clinic. Additional data outside of the standard patient care pathway (24 recall, tricep skinfold and hand grip dynamometry) will be collected by the researcher who is trained in collection of such data. This will be done within the clinical appointment. There will be 2 other points for each participant were they will be contacted via telephone of 2 further 24 hr recalls in order to gain an average. These will be agreed with the participant at the time of collecting other data in the clinic setting. Patients will be recruited by the Primary researcher, research nurses and consultants as part of the clinic appointment who will offer information and collect consent for the researcher to follow up at the clinic appointment.

Secondary Outcomes

- Assessment of association between dietary intake and infection incidence/lung function/Dyspnoea scale
- Assessment of association between anthropometry and infection incidence/lung function/Dyspnoea scale
- Assessment of association between functionality and infection incidence/lung function/Dyspnoea scale
- Determine interplay between dietary intake, anthropometry and functionality with infection incidence/lung function/Dyspnoea scale

Sample/Study Size

The study size was determined according to the following calculation, assuming a margin of error of 5% and a confidence level of 95%:
Sample Size = (Distribution of 50%) / (Margin of Error% / Confidence Level Score) 2 = (0.5 x (1-0.5)) / (0.05/1.96)2
= 384.16.
A finite population correction was then applied for the total population sample of 200 patients True Sample = (Sample Size x Population) / (Sample Size + Population – 1) = study size. Sample size = 384.16 x 188/ 384.16 + 188 – 1 = **126 participants**

Statistical analysis

The statistical analysis will explore associations of the data collected between BMI, functional ability and body composition with lung function, incidence of infection and dyspnoea score (MRC) amongst others using Pearson's correlation or Spearman's dependant on normality of the data collected.

In addition, ordinal regression analysis will be used to explore associations of predictions of functional ability, BMI, Muscle mass and dyspnoea MRC score and lung function

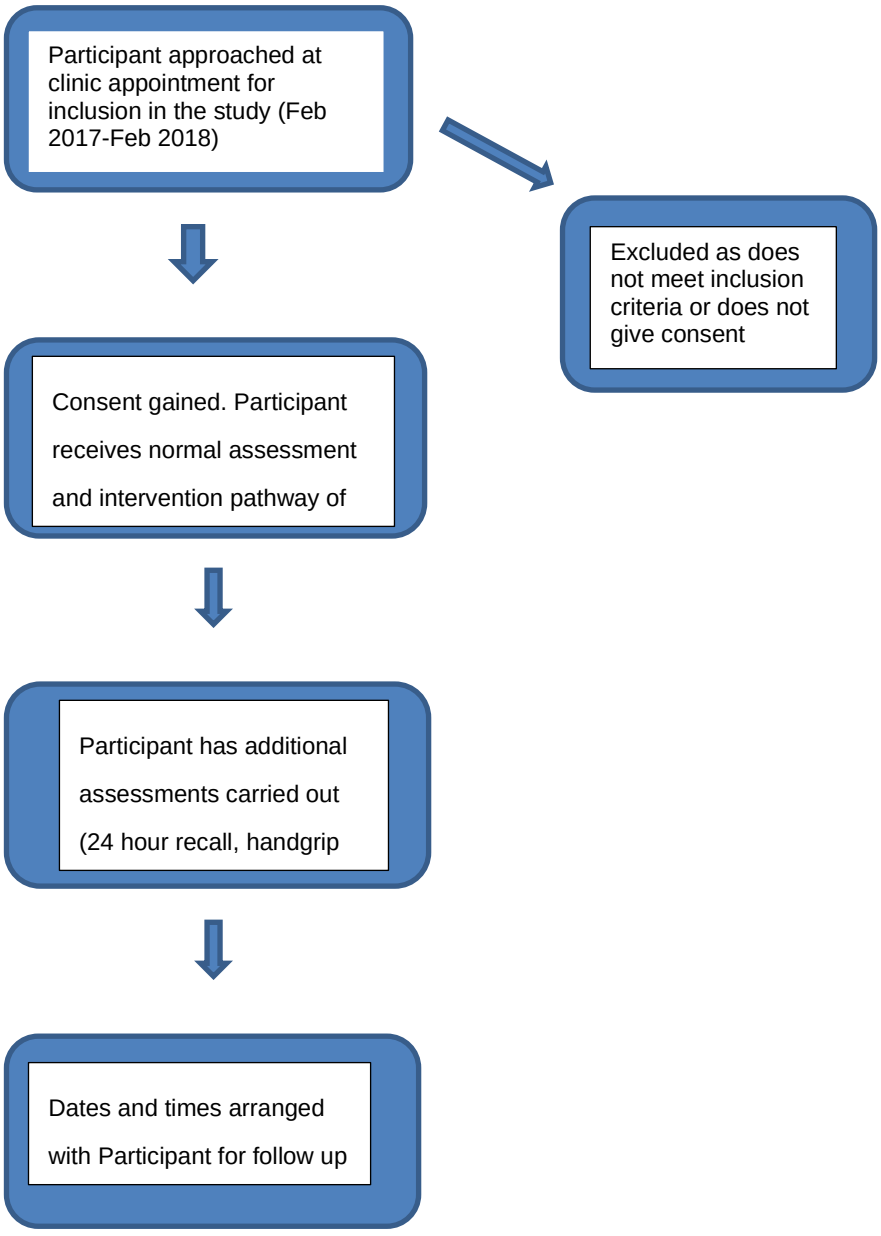
Pilot Study

Standard data collection will not be piloted as a system already exists to record the patient care pathway. Anthropometrical and nutritional data collection tools used are using validated methods already established in many research streams (Warren and Stephen, 2009) and therefore piloting of these would not be required.

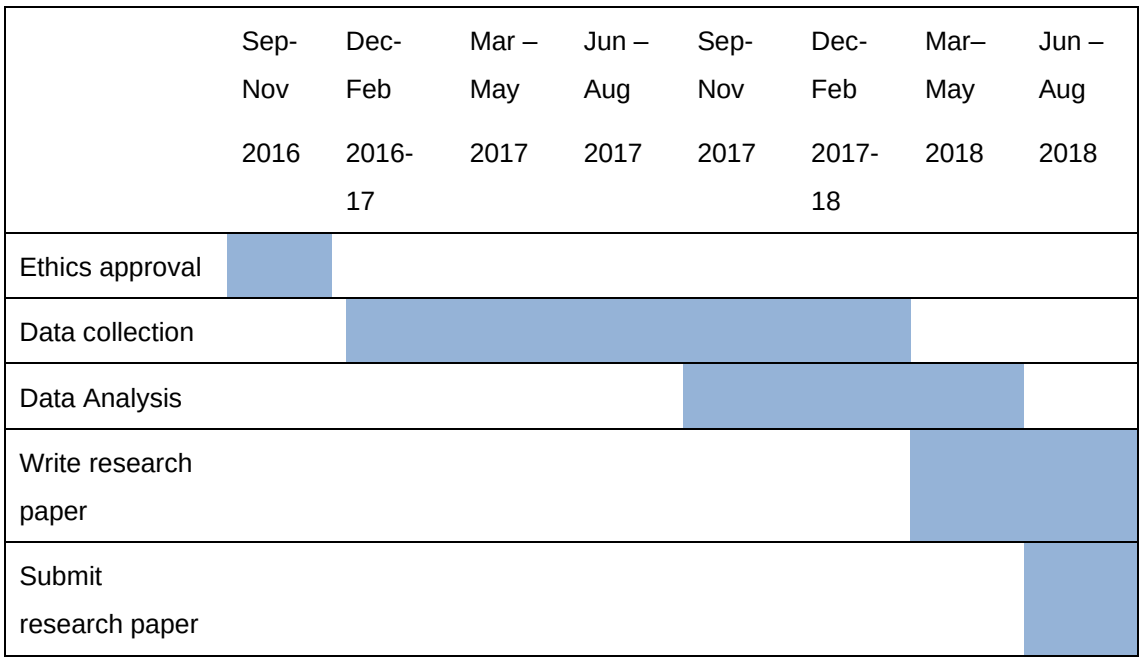
Ethical Considerations

Question burden on the participants, time associated with extra measurements. Recall burden associated with 24-hour recall. Data confidentiality of participant data would be avoided by using a pseudonymised approach to participant information allocating an ID number to ensure that their data is not identifiable by name but is able to be tracked through with 24-hour recall follow up.

Flow chart data collection



GANTT chart



References

Bartley, J., Garrett, J. Grant, C.C., and Camargo, C.A, (2013), Could Vitamin D have a Potential Anti-Inflammatory and Anti-Infective Role in Bronchiectasis?, **Curr Infect Dis Resp,** 15, 148-157

Olveira, G., Olveira, C., Gaspar, I., et al, (2012), Fat Free mass depletion and inflammation in patients with Bronchiectasis**, Journal of Academy of Nutrition and Dietetics,** 112, 12, 1999-2006

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Qi,Q., Li, T., Li, J.C. and Li, Y., (2015), Association of Body Mass Index with Disease severity and prognosis in patients with non-cystic fibrosis bronchiectasis, **Brazilian Journal of Medical and Biological Research**, 48, (8),715-724

Warren, J.M., and Stephen, A.M., Ed. (2009), Dietary Assessment at the end of life's spectrum, **Eur J Clin Nutr,** 63 S1-S4; doi:10.1038/elcn.2008.58

confirmation os sponsorship

Jean Uniacke

Tue 2/14/2017 9:20 AM

To: Linsey King <umlmk@leeds.ac.uk>;

1 attachments (374 KB)

University of Leeds 2016 17 Liability Confirmation Letter.pdf;

Dear Linsey,

We can now confirm University of Leeds sponsorship in principle for this study, 'Characterisation of Bronchiectasis patients' (IRAS 216351).
We will therefore proceed with electronic authorisation via IRAS. Please use the governance-ethics@leeds.ac.uk address for this.

A copy of the University Indemnity certificate is attached to this email.

As a condition of sponsorship, a full set of the HRA approved documents for this study are to be kept by the Chief investigator in the Site file and made available to the sponsor for audit or monitoring purposes when requested.
In addition, once HRA approval has been granted please send copies of all of the final HRA approved documents attached to an email to governance-ethics@leeds.ac.uk.

Role of the Research Sponsor under the Research Governance Framework for Health & Social Care (2005, 2nd Ed) and the Medicines for Human Use (Clinical Trials) Regulations 2004

I hereby confirm that the University of Leeds would be prepared to accept the role of research sponsor as currently defined in the *Research Governance Framework for Health & Social Care Version 2 (DoH 2005)* and the *Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031),* in relation to the study:

Characterisation of Bronchiectasis Patients

I have been informed that this study will be conducted by Mrs Linsey King, a PhD student at the University of Leeds under the supervision of Professor Daniel Peckham of the University of Leeds.

Sponsorship is conditional upon review and approval of the research by appropriate ethics, NHS and regulatory bodies.

To enable the sponsor to meet their responsibilities as listed in section 3.8 of the Research Governance Framework, Chief Investigators are required to adhere to their responsibilities as outlined in section 3.6 of the Framework www.dh.gov.uk/research. In line with this requirement Professor Peckham must ensure that all

involved in the research project understand and discharge their responsibilities in accordance with the agreed protocol and any relevant management, ethical and regulatory approvals.

If you have any queries about sponsorship of this project then please address them to Mrs Clare Skinner, at governance-ethics@leeds.ac.uk or 0113 343 4897.

Yours,

Jean Uniacke

On behalf of Clare Skinner, Faculty Head of Research and Innovation Support.

J.2 Feasibility study - Chapter 7

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Mrs Linsey King
1 Westwinn View
LS14 2HY

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

24 December 2020

Dear Mrs King

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**A study to explore the feasibility of consumption of essential complex amino acid supplementation in the form of an oral gel with additional leucine (40%) and vitamin D in patients with Primary Ciliary Dyskinesia: a feasibility study.**
IRAS project ID:	**222335**
Protocol number:	**N/A**
REC reference:	**20/SC/0413**
Sponsor	**University of Leeds**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **222335**. Please quote this on all correspondence.

Yours sincerely,
Damilola Odunlami

Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: Jean Uniacke

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsor insurance]		
Interview schedules or topic guides for participants [Pre-test guidelines]	Version 1	10 March 2020
Interview schedules or topic guides for participants [pres test guidance for BIA]	Version 1	08 March 2020
IRAS Application Form [IRAS_Form_23102020]		23 October 2020
Letter from sponsor [Email confirmation of sponsorship]	Version 1	15 September 2020
Organisation Information Document [OID]	Version 3	15 September 2020
Other [Email for confirming EMIS]	1	
Other [Professional Indemnity]	1	
Other [Ethics Committee response letter]	1	
Other [Confirmation of supplement delivery]	Version 1	15 September 2020
Other [Supplement gel content list]	Version 1	15 September 2020
Other [Standard Operating Procedure Skinfold]	Version 1	06 March 2020
Other [Standard Operating Procedure weight]	Version 1	06 March 2020
Other [Standard Operating Procedure height]	Version 1	06 March 2020
Other [Standard Operating Procedure Handgrip]	Version 1	06 March 2020
Participant consent form [Consent form]	Version 2	02 July 2020
Participant information sheet (PIS) [Participant information sheet]	4	07 December 2020
Research protocol or project proposal [Protocol]	4	30 November 2020
Sample diary card/patient card [Dietary collection sheet]	Version 1	27 April 2020
Sample diary card/patient card [Supplement tolerance scales]	Version 1	15 September 2020
Schedule of Events or SoECAT [Schedule of events]	Version 3	15 September 2020
Summary CV for Chief Investigator (CI) [Curriculum Vitae]	Version 1	15 September 2020
Summary CV for student [CV]	Version 1	15 September 2020
Summary CV for supervisor (student research) [CV]	Version 1	15 September 2020
Summary CV for supervisor (student research) [H White CV]	1	27 October 2020
Summary CV for supervisor (student research) [T Ispoglou CV]	1	27 October 2020
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Flow diagram]	Version 1	15 September 2020
Validated questionnaire [Quality of life SF-36]	Version 1	15 September 2020
Validated questionnaire [Disease specific quality of life]	Version 1	15 September 2020
Validated questionnaire [activity scale]	Version 1	15 September 2020

IRAS project ID	222335

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
There is only one participating NHS organisation therefore there is only one site type.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	An Organisation Information Document has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	Study funding will be provided to sites as per the Organisation Information Document.	A Principal Investigator should be appointed at study sites.	No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, network staff (or similar) undertaking any of the research activities listed in the research application (except for administration of questionnaires or surveys), would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an
					NHS to NHS confirmation of pre engagement - checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance. For research team members only administering questionnaires or surveys, a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated they do not intend to apply for inclusion on the NIHR CRN Portfolio.

The Leeds Teaching Hospitals NHS Trust

UNIVERSITY OF LEEDS

Full Title:

A study to explore the feasibility of consumption of specific complex amino acid supplementation in the form of an oral gel with additional leucine (40%) and vitamin D in patients with Primary Ciliary Dyskinesia: a feasibility study.

Short Title:

Feasibility of consumption of nutritional supplementation in Primary Ciliary Dyskinesia (PCD)

This protocol has regard for the HRA guidance and order of content

RESEARCH REFERENCE NUMBERS:

IRAS ID: 222335

SPONSOR NUMBER:

PROTOCOL VERSION NUMBER: 2.0

PROTOCOL DATE VERSION DATE: 15/09/2020

SPONSOR

Claire E Skinner, Head of research Integrity and Governance, Faculty of Medicine and Health Research Office, Room 9.29, Level 9, Worsley Building, University of Leeds, Clarendon Way, Leeds, LS2 9NL

Governance-ethics@leeds.ac.uk 01133434897

This protocol will be completed as part of a PhD project for Linsey King (Chief Investigator/study coordinator).

Declaration

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:
...../...../.....
.....

Name: University of Leeds

.....
.....

Position:
.....
.....

Chief Investigator:

Signature: Date:
..../...../.....
.....

Name: Mrs Linsey King

.....
.....

KEY STUDY CONTACTS

Director of Studies	Professor Daniel Peckham, Professor of Respiratory Medicine and Cystic Fibrosis, Leeds Teaching hospitals NHS trust, Centre for respiratory medicine, St James' University Hospital, Beckett Street, Leeds LS9 7TF 01132433144 Daniel.peckham@nhs.net d.g.peckham@leeds.ac.uk
Chief Investigator and Study Co-ordinator	Linsey King PhD Student Clinical Sciences Building University of Leeds St James' University hospital, Beckett Street, Leeds, LS9 7TF umlmk@leeds.ac.uk
Sponsor	Claire E Skinner Head of Research Integrity and governance, Faculty of Medicine and Health Research Office, Room 9.29, Level 9, Worsley Building, Clarendon Way, Leeds, LS2 9NL Governance-ethics@leeds.ac.uk 01133434897
Key Protocol Contributors	Professor Daniel Peckham Professor of Respiratory Medicine and Cystic Fibrosis Leeds Teaching hospitals NHS trust Centre for respiratory medicine St James' University Hospital Beckett Street Leeds LS9 7TF

	Daniel.peckham@nhs.net D.G.Peckham@leeds.ac.uk 01132433144 Dr Helen White Subject Group Head Nutrition and Dietetic Group School of Clinical and Applied Sciences CL615a, Calverley Building, City site Leeds Beckett University Leeds LS1 3HE h.white@leedsbeckett.ac.uk 01138124994 Dr Theocharis Ispoglou Reader in Nutrition and Muscle Health SARCA group Lead Carnegie School of Sport Headingly Campus Leeds T.Ispoglou@leedsbeckett.ac.uk 01138128603

LIST OF ABBREVIATIONS

CI	Chief Investigator
FEV1	Forced Expiratory Volume in 1 second
6MWT	6-minute walk test
PIS	Participant Information Sheet
PCD	Primary Ciliary Dyskinesia
SOP	Standard Operating Procedure
HAES	Habitual activity estimation scale
MUAC	Mid Upper Arm Circumference
TSF	Tricep Skinfold
HGS	Hand Grip Strength
BIA	Bio Impedance Analysis

Study Title	A study to explore the feasibility of consumption of specific complex amino acid supplementation in the form of an oral gel with additional leucine (40%) and vitamin D in patients with Primary Ciliary Dyskinesia: a feasibility study.
Internal ref. no. (or short title)	Feasibility of consumption of nutritional supplementation in Primary Ciliary Dyskinesia (PCD)
Study Design	This study aims to explore the feasibility of consumption of a specific amino acid oral nutritional supplementation gel twice each day containing 7.5g of essential amino acids (40% leucine) and 500 IU/d vitamin D (daily total 15g EAA and 1000 IU vitamin D) over a 3-month period using validated feasibility/tolerability assessment measures and impact upon nutritional intake through 24 hour recalls alongside establishing habitual activity estimation scales. Secondary outcomes will explore the feasibility of collecting routine measures (lung function (FEV1%), number of exacerbation's during study period, vitamin D status), additional body composition measurements via Bio impedance analysis (BIA), skin-fold measures (e.g. Triceps Skin-fold (TSF), Mid upper arm circumference (MUAC)) and handgrip strength using Handgrip dynamometer in patients who attend for their annual check-up clinic and an additional study specific visit. This study will also explore feasibility of collecting quality of life impact through validated questionnaires and establish effect on exercise tolerance through 6-minute walking tests at baseline (routine appointment) and 3 months (study specific visit). These secondary outcomes are required to enable understanding of engagement from participants and to identify possible important outcome measures that may need further exploration through future clinical trials.
Study Participants	Those with Primary Ciliary Dyskinesia (PCD)
Planned Size of Sample (if applicable)	Total planned sample is up to 20 participants
Follow up duration (if applicable)	3 months
Planned Study Period	1 year from date of commencement dependent on current COVID-19 situation

Research Question/Aim(s)	**Objectives**	**Outcomes**
	1. To explore acceptability of an oral nutritional gel supplement containing 7.5g of essential amino acids (leucine 40%) and Vitamin D (500 IU) per gel.	1. Measurement of acceptability and palatability of supplement gels
	2. To evaluate impact on nutritional intake using twenty-four-hour dietary recall	2. Measurement and comparison of intake at baseline, end of month one, two and three.
Secondary Outcomes	1. To collect data from routine measures as part of standard care at usual clinic appointment and end of study appointment at 3 months	1. Lung Function (FEV1%, FVC%) to determine if any changes occur during 3-month period of supplementation 2. Height and weight to calculate body mass index to determine any changes during supplementation period 3. MRC score (breathlessness scale) determine any changes during supplementation period 4. Vitamin D levels determine any changes during supplementation period 5. Exacerbations during study period (3 months) determine any changes during supplementation period
	2. To explore feasibility of completion of the following measures from baseline and on completion of the study at 3 months and explore associated changes.	1. Quality of life will be collected through validated questionnaires to determine ease of completion and determine impacts of supplementation during study period (QoL- ST George's/SF36) 2. Muscle functionality measured by Handgrip strength (HGS) 3. Skinfold Measures (Triceps Skinfold (TSF), Mid upper arm circumference (MUAC) 4. Exercise capacity (6MWT) 5. Bio electrical impedance analysis (BIA) measures specific components of body

		composition (lean tissue, fat mass)

ROLE OF STUDY SPONSOR

The sponsor has no role in trial design, analysis, interpretation, or manuscript writing. The sponsor is responsible for overseeing the conduct of the study. The funder may be involved in dissemination and publication of results and will be regularly updated on study progress, as per funding requirement.

STUDY FLOW

1. Participant is screened via patient online data system EMIS by lead consultant's and contacted via telephone to outline study and provide information and contact for queries. PIS and pre-test guidance to be sent to participant prior to next scheduled clinic appointment.
2. Participant attends usual scheduled clinic appointment where routine care measures are collected by healthcare assistants and lead consultants

   Height and Weight to determine BMI
   Lung Function (FEV1%, FVC %)
   MRC score
   Blood samples including CRP and vitamin D level

3. Participant is approached by study co-ordinator to answer any questions and collect consent for additional measures and use of results of routine care measures.
   Anthropometry BIA, HGS, TSF, MUAC, MAMC
   Quality of Life HRQoL questionnaire (EQ-5D) ST Georges Respiratory questionnaire
   Physical activity 6 min walking test and HAES scale
   Supplement trial palatability/acceptability recorded
   Dietary intake 24-hour dietary recall.

4. Consent recorded and supplement is trialled whist completing palatability and acceptability record. If tolerated by participant all other additional measures are recorded. There is no preferred order of their completion. If not tolerated participant is excluded from the study and no further measures are taken.

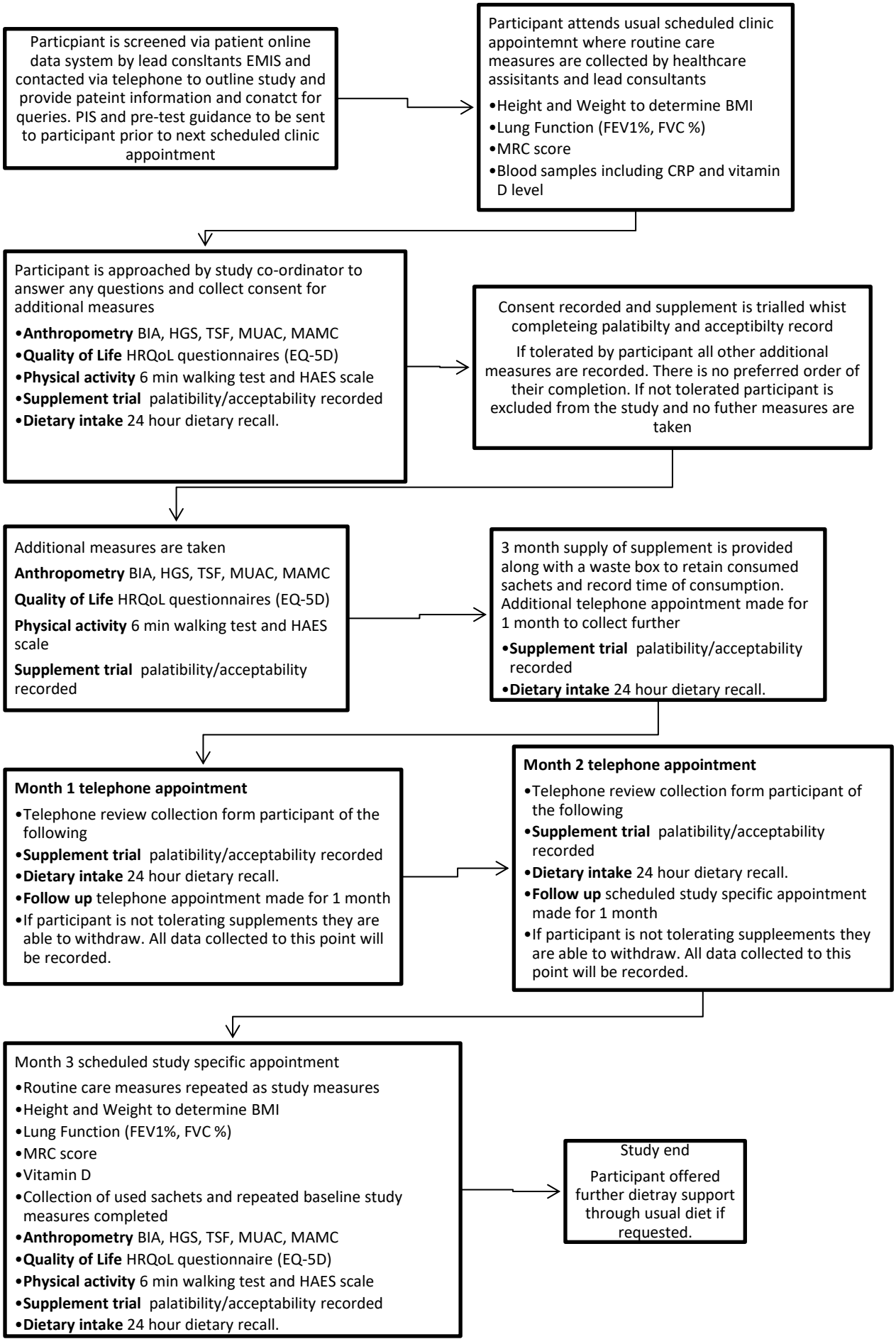
5. 3 month supply of supplement is provided along with consumption instructions (consume 1 at breakfast and 1 at lunch) a waste box to retain consumed sachets and record time of consumption. Additional telephone appointment made for 1 month to collect further
   Supplement trial palatability/acceptability recorded
   Dietary intake 24-hour dietary recall.

6. **Month 1 telephone appointment**
   Telephone review collection form participant of the following
   Supplement trial palatability/acceptability recorded
   Dietary intake 24-hour dietary recall.
   Follow up telephone appointment made for 1 month
   If participant is not tolerating supplements, they are able to withdraw at this point. All data collected to this point will be recorded.

7. **Month 2 telephone appointment**
   Telephone review collection form participant of the following
   Supplement trial palatability/acceptability recorded
   Dietary intake 24-hour dietary recall.
   Follow up scheduled study specific appointment made for 1 month
   If participant is not tolerating supplements, they are able to withdraw. All data collected to this point will be recorded.

8. **Month 3 scheduled study specific appointment, routine care measures repeated as study measures**
   Height and Weight to determine BMI
   Lung Function (FEV1%, FVC %)
   MRC score Vitamin D
   Anthropometry BIA, HGS, TSF, MUAC, MAMC
   Quality of Life HRQoL questionnaire (EQ-5D) ST Georges Respiratory questionnaire
   Physical activity 6 min walking test and HAES scale
   Supplement trial palatability/acceptability recorded **Dietary intake** 24 hour dietary recall.

STUDY FLOW CHART


Particpiant is screened via patient online data system by lead consltants EMIS and contacted via telephone to outline study and provide pateint information and conatct for queries. PIS and pre-test guidance to be sent to participant prior to next scheduled clinic appointment
Participant attends usual scheduled clinic appointemnt where routine care measures are collected by healthcare assisitants and lead consultants
•Height and Weight to determine BMI
•Lung Function (FEV1%, FVC %)
•MRC score
•Blood samples including CRP and vitamin D level
Participant is approached by study co-ordinator to answer any questions and collect consent for additional measures
•Anthropometry BIA, HGS, TSF, MUAC, MAMC
•Quality of Life HRQoL questionnaires (EQ-5D)
•Physical activity 6 min walking test and HAES scale
•Supplement trial palatibility/acceptability recorded
•Dietary intake 24 hour dietary recall.
Consent recorded and supplement is trialled whist completeing palatibilty and acceptibilty record
If tolerated by participant all other additional measures are recorded. There is no preferred order of their completion. If not tolerated participant is excluded from the study and no futher measures are taken
Additional measures are taken
Anthropometry BIA, HGS, TSF, MUAC, MAMC
Quality of Life HRQoL questionnaires (EQ-5D)
Physical activity 6 min walking test and HAES scale
Supplement trial palatibility/acceptability recorded
3 month supply of supplement is provided along with a waste box to retain consumed sachets and record time of consumption. Additional telephone appointment made for 1 month to collect further
•Supplement trial palatibility/acceptability recorded
•Dietary intake 24 hour dietary recall.
Month 1 telephone appointment
•Telephone review collection form participant of the following
•Supplement trial palatibility/acceptability recorded
•Dietary intake 24 hour dietary recall.
•Follow up telephone appointment made for 1 month
•If participant is not tolerating supplements they are able to withdraw. All data collected to this point will be recorded.
Month 2 telephone appointment
•Telephone review collection form participant of the following
•Supplement trial palatibility/acceptability recorded
•Dietary intake 24 hour dietary recall.
•Follow up scheduled study specific appointment made for 1 month
•If participant is not tolerating suppleements they are able to withdraw. All data collected to this point will be recorded.
Month 3 scheduled study specific appointment
•Routine care measures repeated as study measures
•Height and Weight to determine BMI
•Lung Function (FEV1%, FVC %)
•MRC score
•Vitamin D
•Collection of used sachets and repeated baseline study measures completed
•Anthropometry BIA, HGS, TSF, MUAC, MAMC
•Quality of Life HRQoL questionnaire (EQ-5D)
•Physical activity 6 min walking test and HAES scale
•Supplement trial palatibility/acceptability recorded
•Dietary intake 24 hour dietary recall.
Study end
Participant offered further dietray support through usual diet if requested.

STUDY PROTOCOL

A study to explore the feasibility of consumption of specific complex amino acid supplementation in the form of an oral gel with additional leucine (40%) and vitamin D in patients with Primary Ciliary Dyskinesia: a feasibility study.

BACKGROUND

PCD is a rare autosomal recessive genetic disorder which presents as a specific phenotype. This condition results in uncoordinated or absent cilia within the respiratory system which reduces the lungs ability to effectively clear sputum resulting in repeated infections. As a result PCD patients can develop bronchiectasis, resulting in cyclical infective episodes requiring repeated intravenous antibiotics and intensive physiotherapy (Kuehni and Lucas, 2017) Bronchiectasis is a debilitating respiratory condition, which can be acquired or congenital. The aetiology of Non Cystic Fibrosis Bronchiectasis (NCFB) is unknown in up to 50% of cases but the condition is associated with many underlying diseases including childhood infections (Measles, Whooping cough), pneumonia, tuberculosis, rheumatoid arthritis, aspiration, environmental exposure, immunodeficiency, Cystic Fibrosis and Primary Ciliary dyskinesia (PCD) (Hill et al., 2019) Resulting chronic inflammation and repeated immune stimulation can influence effective utilisation and attainment of nutrition leading to increased gluconeogenesis and compromised nutritional status (Brill et al., 2015, Boyton and Altmann, 2016).

Recent unpublished preliminary research within a regional clinic population, has identified this group has having statistically significant impaired handgrip strength (HGS), (57.76 %, ±15.56 p= 0.004), despite mean BMI within the normal range (23.20 Kg/m^2, ±3.49). HGS as a marker of muscle functionality has been shown to respond more quickly to deficiency or repletion than overall muscle mass assessed through BMI. (Norman et al., 2011). In addition, the diverse NCFB population also showed impaired (<85%) HGS when compared with normative values for age and gender, despite seemingly adequate nutritional intakes, identifying a need for further investigation of tailored nutrition support despite BMI within normal ranges.

Evidence is limited in establishing nutritional status or body composition of this population and its impact on clinical outcomes such as lung function. Research exploring bronchiectasis is lacking and particularly sub analysis by aetiology. Research in PCD is sparse but emerging themes show poorer nutritional status and growth in childhood (Goutaki et al., 2017) with identification of higher nutritional risk in children and lower vitamin D requiring monitoring. Despite weak associations with lung function and nutritional status in this PCD

paediatric population, recommendations for nutritional strategy and intervention are warranted (Marino et al., 2018). Oliveira et al (2012), reported that a 1/3rd of patients with NCFB had significant fat free mass depletion. These findings were supported by a multicentre study concluding patients with Bronchiectasis with lower BMI's were prone to developing more acute exacerbations of bronchiectasis and poorer pulmonary function (Qi et al., 2015). These studies did not differentiate changes by aetiology.

Recommended treatment of nutritional depletion in this population is also lacking. Emerging evidence for the role of concentrated amino acids with particular attention to Leucine, in supplement form, has been shown to improve lean tissue mass in diagnosed sarcopenia, in free living elderly populations (Ispoglou et al., 2016). Evidence is limited in exploring if this approach can transpose to long term chronic conditions such as PCD. A Spanish study explored the role of supplement drinks with additional β-Hydroxy-β - Methylburtyrate (a metabolite of leucine) to affect lean tissue mass (LTM) investigating its role in improving clinical and patient reported outcomes in combination with pulmonary rehabilitation (PR) (Olveira et al., 2016). Olveira combined oral supplement drinks with 1.5g HMB and pulmonary rehabilitation in normally nourished bronchiectasis participants of varying aetiology. This Spanish Bronchiectasis population were comparative to the investigated Leeds population for mean FEV^1 % (66.1% SD ± 23.6 and 66.6% SD ± 20.6) BMI (26.6 kg/m^2 SD ±4.7, 25.1kg/m^2 SD ± 5.4) Age (56yrs SD±13 and 57 ±21.3) and weight (69.5 kg, 67.5kg). Whilst difference in mean handgrip of 10kgf (28.2 kgf, 18kgf) reflects a group more nutritionally compromised with poorer muscle function, the Spanish research found improvements in lean tissue mass and HGS. It is not clear what proportion of their population had PCD only that they were categorised as normally nourished by the authors using BMI as their marker. This study did not blind researchers to either arm of the trial or determine subgroup aetiology analysis. Measurement of BMI is a useful indicator of total boy mass but does not determine composition. Whilst crude anthropometric measures are a useful bedside tool, more reliable analysis such as Bio electrical impedance is needed in order to determine if such assessment should be part of standard care in this population. In addition, and more specifically there is growing interest in the role of vitamin D in immunomodulation and associated inflammation as a result of recurrent infections within this patient group (Bartley et al., 2013). Further work around impact of supplementation of vitamin D_3 in this group has shown increase in concentration with daily supplementation and improvement in Health-Related Quality of Life (HRQoL) measures (Bartley et al., 2018).

RATIONALE

NCFB is a lifelong, suppurative and infective cyclical condition. Recurrent infections and poor immunity with continued exposure to antibiotic therapy result in raised inflammatory markers and associated deterioration in nutritional status. PCD patients are susceptible to development of NCFB, having poorer nutritional status and specifically functional ability. Body composition and more accurately LTM and fat free mass (FFM) are shown to be important factors more widely in COPD (Costa et al., 2015) Costa et al., 2018) but with limited work in PCD. Nutritional interventions that might impact body composition/ infective exacerbations and management of the condition, require investigation. Exploration of the possible role and feasibility of complex amino acid supplementation with higher concentrations of leucine and Vitamin D, is justified to establish if nutritional intervention could improve clinical and patient reported outcome measures in the longer term. This feasibility study aims to determine if such supplementation is tolerated and if there are any initial changes to body composition and other clinical outcome measures.

RESEARCH QUESTION/AIM(S)

This study aims to explore the feasibility of consumption of a specific amino acid oral nutritional supplementation gel with 40% leucine and 500 IU/d vitamin D, twice a day, over a 3-month period using validated feasibility/tolerability assessment measures and impact upon nutritional intake through 24 hour recalls alongside establishing habitual activity estimation scales.

Primary Objectives

1. To explore acceptability of an oral nutritional gel supplement containing essential amino acids, additional leucine (40%) and Vitamin D.

2. To evaluate impact on nutritional intake using twenty-four-hour dietary recall

Hypothesis

Patients with PCD can successfully consume 2 gel supplements per day for a period of 3 months with no effect on dietary intake.

Secondary Objectives

1. To collect data from routine measures as part of standard care at usual clinic appointment and end of study appointment at 3 months

2. To explore feasibility of completion of the following measures from baseline and on completion of the study at 3 months and explore associated changes.

Outcomes

Primary

a. Measurement of acceptability and palatability of supplement gels
b. Measurement and comparison of intake at baseline, end of month one, two and three.

Secondary

a. Lung Function (FEV1%, FVC%) to determine if any changes occur during 3-month period of supplementation
b. Height and weight to calculate body mass index to determine any changes during supplementation period
c. MRC score (breathlessness scale) determine any changes during supplementation period
d. Vitamin D levels determine any changes during supplementation period
e. Exacerbations during study period (3 months) determine any changes during supplementation period
f. Quality of life will be collected through validated questionnaires to determine ease of completion and determine impacts of supplementation during study period (QoL- PCD/EQ5D)
g. Habitual activity estimation scales (HAES) questionnaire to determine usual activity
h. Muscle functionality measured by Handgrip strength (HGS)
i. Skinfold Measures (Triceps Skinfold (TSF), Mid upper arm circumference (MUAC)
j. Exercise capacity (6MWT)
k. Bio electrical impedance analysis (BIA) measures specific components of body composition (lean tissue, fat mass)

STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

Feasibility study to understand and gain preliminary information on tolerability and palatability of an oral nutritional supplement gel in a clinical Primary Ciliary Dyskinesia population. To determine if dietary intake is affected by the consumption of the nutritional supplement.

Explore possible future outcome measures that could be important in determining impact of this nutritional intervention on this patient group.

Study Setting

This is a single site study taking place with the Leeds Adult Primary Ciliary Dyskinesia service

Study Group

Patients with Primary Ciliary Dyskinesia

Sampling/Study size

As this is a feasibility study a sample size calculation is not required.

The PCD population within the regional clinic is currently 54. All patients with PCD will be approached for inclusion in this pilot/ feasibility if they meet the above inclusion criteria until minimum number of 15 and maximum of 20 is reached.

Recruitment

Inclusion criteria

- People aged 17 or over with a confirmed diagnosis of Primary ciliary dyskinesia PCD (nasal brushings)
- People who attend the Leeds Regional PCD Clinics
- People who have capacity to give informed consent

Exclusion criteria

- People who are pregnant
- Those with existing co-morbidities such as malignancy
- People with connective tissue disorders and immunoglobulin deficiencies
- People with renal insufficiency
- Participants will complete only aspects of the feasibility study they are able to, dependent upon the limitations and risk assessments completed as part of the participant pre-test guidelines e.g. metal plate or pacemaker for Bio-Electrical Impedance

Consent

Eligible participants will be contacted via telephone and given information about the study (participant information sheet) from the lead consultant. Participant information sheets have been produced that are user friendly and provided in a simple format

Participants will then be approached at their usual clinic appointment by the study investigator to explore if they have any questions about the study. Patients will then be required to consent if they wish to take part.

A proportion of patients with Primary Ciliary Dyskinesia are of South East Asian origin. We will assess the participant and carer ability to understand the study and consent on an individual basis. An interpreter is rarely required however if this is needed and the family member present is able, they will be utilized to discuss the study and seek consent whilst they are present for usual clinic. If not, they will be excluded from the study.

Study Procedures

All participants will have had routine care measures taken including

Height and Weight to determine BMI

- These measurements are taken routinely for patients with Primary Ciliary Dyskinesia at every clinic appointment and are required for accuracy of data analysis.

Lung Function (FEV_1, FVC, FEV_1%, FVC %)

Participants will perform spirometry (test to measure lung function) using their normal technique this usually includes:

- Sitting upright or standing.
- They are instructed to take a big breath in and then breathe out as hard and fast as possible into the spirometer that is connected to a computer.
- The measurements are usually repeated until 3 acceptable and repeatable ones have been obtained.

Clinical data as part of routine care

- MRC (Medical Research Council) score is checked at each clinic appointment. Patients are asked to rate their level of breathlessness against a scale attributed to a described activity.

Grade	Degree of breathlessness related to activity
1	Not troubled by breathless except on strenuous exercise
2	Short of breath when hurrying on a level or when walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking 100 yards, or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing/undressing

- Routine Bloods include many different measures, but C-Reactive protein and Vitamin D level are standard measures at clinic appointments

Supplement trial

Participants will be given 1 sample of the nutritional gel and asked to complete palatability and acceptability scales. This will determine if the participant is able to consume and tolerate the gels. If at this point, they are unable to no further measures will be completed, and the participant will be withdrawn from the study. The data collected to this point will be used as contribution to feasibility.

Study additional measures

Each consented participant who can tolerate the gel supplement at this point will undergo measurement of the following at baseline and end of study period (3 months)

Bio Impedance Analysis (BIA) scans to determine body composition

BIA is a useful way to assess composition of the body and determine Fat Mass (FM) Fat Free Mass (FFM). It is considered safe and minimally invasive. A Pre assessment guide and Standard Operating Procedure (SOP) has been created for use in the Primary Ciliary Dyskinesia clinic as part of clinical research undertaken. Each participant will complete the following at baseline and endpoint (3 months)

Study Participant cannot complete the test if they have an electrical device (pacemaker, metal plate, cochlear implant). Remove Shoes, Socks, tights before completing the test and ensure hands and feet are clean with alcohol wipes. Participants will stand on the metal foot plates and place hands on the metal hand positions. The test requires them to stand until the measurement is complete which takes approximately 1 minute, and the output is then recorded.

Quality of life St Georges Respiratory questionnaire (quality of life measure), Generic quality of life measure EQ-5D and habitual activity estimation scales

The first 2 are questionnaires used to determine quality of life indicators and outcomes associated with clinical disease. The disease specific St Georges questionnaire contains questions pertaining directly to respiratory disease and so comparisons can be made to other respiratory diseases. The EQ-5D measure is generic and can be used to compare PCD to many other clinical diseases based on their comparative quality of life scores. The habitual activity estimation scale is a questionnaire to determine baseline activity levels and assess perceived changes. These questionnaires are all completed at baseline and end of study.

A 6-minute walking test (6 MWT) to establish baseline measures and end of study

The 6MWT is used extensively in research and is identified as a tool for determining change following interventions in patients with lung diseases. It can be used as measure of functional status and a predictor of morbidity and mortality. A pre-assessment guide and SOP has been created for use in the Primary Ciliary Dyskinesia clinic as part of clinical research undertaken. Initially the requirement and where to walk is shown to the participant and they will be asked to rate their dyspnoea using the BORG scale at the start and end of the test. The participant should walk at their own pace and until instructed to stop or they feel that they cannot continue. The distance walked is then measured and the BORG scale repeated

The BORG scale is a measure of perceived exertion using a tabled scale (see below)

Rating	Perceived Exertion
6	No Exertion
7	Extremely light
8	
9	Very Light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very Hard
18	
19	Extremely Hard
20	Maximal Exertion

Handgrip strength measure

Hand grip measure is used in many clinical areas and used as a measure of health outcomes. It has been shown to be a strong predictor of outcomes in other respiratory diseases such as COPD. Participants will be required to take the dynamometer and using the non-dominant arm squeeze for 5 seconds and then the measure is recorded. This is repeated 3 times to gain an average.

Skinfold measures

These enable bedside measurement of fat and fat free mass comparing to international data tables as predictive cut offs. These will be taken as an alternative comparator to the BIA to establish methodological quality of results and success of measure with participants. Two measures will be taken Mid upper arm circumference (MUAC) and triceps skinfold thickness (TSF) and a

third calculated from both measures. Standard operating procedures have been created. Participants may need to remove clothes to enable access to the non-dominant arm in order to complete the measures

Measures collected at baseline, monthly contact points and end of study period

Supplement palatability and acceptability scales will be completed at baseline, monthly contact points. will be completed. Participants will receive 3 months' supply of nutritional supplement in the form of a gel and will be required to consume 2/day. Each participant will be requested to record the time of consumption of the nutritional supplements and to retain the empty sachets to return at end of study

To determine approximate intakes and possible effect on dietary intake a 24-hour recall will be collected by a qualified dietitian at baseline, monthly and end points.

End of study

The end of the study will be when the last participant undergoes their last measures at their 3-month appointment.

Withdrawal criteria

Participants can withdraw from the study at any point without giving any reason. Any data collected from them up until that point can be used in analysis.

Statistics and data analysis

Sampling/Study size

As this is a feasibility study a sample size calculation is not required.
The PCD population within the regional clinic is currently 54. All patients with PCD will be approached for inclusion in this feasibility if they meet the inclusion criteria until minimum number of 15 and maximum of 20 is reached.

Statistical analysis

Data collected as part of this study will be tabulated and checked for anomalies or missing data points. Descriptive statistics will be used for population characteristics. Variables reviewed will include

Continuous outcomes
Weight
BMI
Lung function
Binary Outcomes
Sex
Ethnicity

Primary outcome measures

The feasibility of the supplementation will be measured by number of consumed gels and verified by number of returned sachets along with data from the questionnaires.

Dietary recalls will be compared over time from start to end of study and analysed for changes to macronutrient intakes

Secondary outcome measures

All other measures will be explored to determine clinical suitability and acceptability as a method for collecting data and attempting to identify the most important outcome measures to determine future clinical trials. To determine this associations and changes between baseline and end point will be explored using inferential statistics to determine relationships with lung function.

ETHICAL AND REGULATORY CONSIDERATIONS

Assessment and management of risk

Participants data will not be easily identifiable to an individual as once entered into the study they will be assigned a number, and all data becomes pseudonymised and stored in accordance with General data protection regulation and in concordance with the data protection act (2018). The research data will be stored on university of Leeds computers and password protected. Any associated identifiable data will be stored in a locked filing cabinet within the main recruitment and research site (Seacroft Hospital) where only the Primary Researcher (CI) and direct care team have access.

Patient questionnaire burden associated with completion of HRQoL questionnaires on the participants. To mitigate for this the shortened versions of the questionnaires will be used to avoid survey fatigue.

Recall burden associated with 24-hour recall. This will be carried out by an experienced dietitian able to utilise effective communication skills to support efficient data collection.

Toleration of nutritional supplementation and completion of the 3-month consumption. Participants will be contacted by telephone to check progress following initial palatability and acceptability scales. Participants will not be included or given the nutritional supplements if they are unable to tolerate them.

Assessing hand grip strength will also require the participant to hold and grip a piece of equipment (3 times) which if not done correctly may cause discomfort.

The measurement of the upper arm requires access which may result in moving of clothes. Details of this requirement will be in the participant information sheet

Additional blood sample of vitamin D levels. Participants have routine measures undertaken as part of routine care. The final blood sample of vitamin D will be in addition and so may cause additional discomfort. Participants will be made aware of the additional need for this blood test in the participant information sheet

Participants will be made aware of all risks associated with 6-minute walk test and bio electrical impedance analysis. Assessments will be stopped if any of the risk assessment measures are breached, or the participant feels they are unable to continue. The level and measure will be recorded at that point

Regulatory Review & Compliance

Research Ethics (REC) approval

Before the start of the study, approval will be sought from a REC for the protocol, informed consent forms and other relevant documents. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study. All correspondence with the REC will be retained in the PI Site File. It is the Chief Investigator's responsibility to produce the annual reports as required. The Chief Investigator will notify the REC of the end of the study. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Amendments

If an amendment to the REC application or supporting documents is required, then the study team will discuss this with the sponsor. The sponsor will be responsible for decided whether this is a substantial or non-substantial amendment. A valid notice of amendment will be submitted to the REC for consideration.

Amendments will be notified to the national coordinating function of the UK country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site.

After any amendment, dates and version numbers on any documents that have required amendment will be updated. Previous versions will be archived

Peer review

Internal peer review by the named research team within University of Leeds has continually occurred to produce this

Patient & Public Involvement

Potential eligible participants (2) were approached in PCD clinic on Thursday 2nd May 2019 at routine clinical appointments to discuss feasibility of engagement in the study. This has resulted in refinement to the methodology to enhance engagement and completion

Data protection and patient confidentiality

Participants will be given an individual participant number following consent, and this will be recorded on the consent form. In addition, a telephone contact number will also be recorded for further contact at one monthly points. All of this information will be kept securely at the local hospital site where the clinic is held in a locked filing cabinet with only the chief investigator (PhD student) and direct care team (including director of studies) can access. If consent is not obtained, then nothing will be recorded.

Data collection Spreadsheet

The full study data spreadsheet will hold data from all participants using only their individual participant number as the identifier. Results will be collated and analysed from this form. The full study data form will be stored on a password-protected University drive, secure and encrypted.

Only the Chief investigator and lead consultant (director of studies) will have access to both the paper consent document and the computer database, in order to identify participants. Paper consent forms will be locked away. Data will be stored securely after the study has ended to allow for analysis.

The data custodian is the Director of studies, Professor Daniel Peckham

Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

Indemnity

University of Leeds insurance will apply to meet the potential legal liability of the sponsor for harm to participants arising from the management of the research.

University of Leeds insurance will apply to meet the potential legal liability of the sponsor or employer for harm to participants arising from the design of the research.

NHS indemnity apply to meet the potential legal liability of investigators arising from harm to participants in the conduct of the research.

Access to the final study dataset

The study coordinator (CI) will have access to the full dataset. Once the study is completed then only the Study Coordinator (CI) and custodian of the data, Professor Daniel Peckham will have access, as the data is stored.

DISSEMINIATION POLICY

The Study Coordinator (CI) will own the data arising from the study. On completion of the study, the data will be analysed and tabulated, and a Final study Report prepared as part of a PhD thesis. The full study report will be accessed from the University of Leeds password protected computers. Only the Study Coordinator (CI) and director of studies will coordinate publication of data.

It will not be routine for participants to obtain individual results however these can be made available should they be requested. The study results will be written up and published in leading peer-reviewed journals and as part of PhD. Feedback to participants can be done informally, for example: during clinic visits.

Authorship eligibility guidelines and any intended use of professional writers

The study team will have authorship on the final trial report. Criteria for individually named authors will be met.

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The Leeds Teaching Hospitals
NHS Trust
Pathology CSU

Pathology R&D
Old Medical School
Leeds General Infirmary
Thoresby Place
LS1 2BY
(0113) 392 2915
Leedsth-tr.PathologyRD@nhs.net
Date: 10/03/2021

Linsey King
Cardio-respiratory medicine

Dear Dr King

Re: DYSKINESIA
Protocol number:
Local Project Number: RM20/137548
Pathology Ref: STP993
IRAS: 222335

I confirm that I am aware of the above research project and agree that it can take place within the Pathology CSU. I am satisfied that there is the capacity within the CSU to host this study and the financial implications of the study have been considered and agreed.

LTHT Pathology can support the testing of:
Vitamin D

Yours sincerely

Organisation Information Document – Non-Commercially Sponsored Studies

(Template version: 1.5)

Guidance on Using This Document

Please use this document to create the outline Organisation Information Document/s that you will submit with your IRAS Form. In most instances the Organisation Information Document should be localised before sharing with participating NHS / HSC organisations.

Questions/items marked with an asterisk* (Questions 1-3, 5, 8 and 12-15 and 18, as well as items throughout the appendices as applicable) must be completed prior to submission of the IRAS Form in all cases. Only if the localised Organisation Information Document is to be used as the Agreement between the parties should the Sponsor or authorised delegate check the relevant check-boxes at the top of each subsequent appendix and complete the authorisation section.

Items marked with a caret ^ are completed by the participating NHS / HSC organisation, after the Local Information Pack is shared and where relevant.

Remaining questions may be answered on the localised Organisation Information Document either by the Sponsor or authorised delegate prior to sharing the Local Information Pack, or by the participating NHS / HSC organisation (or collaboratively between the two) after the Local Information Pack is shared, as appropriate.

To provide an answer in the document, click in a box with the grey text (click here to enter text), or choose the relevant option if presented with a drop-down list.

A separate guidance document is provided and should be consulted prior to completion of this document. Please also read the question specific guidance where present.

We welcome your feedback on the use of the UK Local Information Pack. If you would like to provide feedback, please take the UK Local Information Pack Survey.

Study Information

1.* IRAS Project ID	**222335**
2.* Full Title of the Study	Nutritional supplementation of amino acids in patients with Primary Ciliary Dyskinesia: A feasibility study.
3.* Legal Name(s) of Sponsor/Co-Sponsors/Joint-Sponsors	University of Leeds

4. Contact details of person acting on behalf of Sponsor for questions relating to study set up. Please enter details of the person who is the Sponsor's main point of contact for all correspondence on setting up the study at this NHS / HSC organisation. This contact may be the Sponsor, a Study Manager, Clinical Research Scientist or Study Coordinator. Where a Contract Research Organisation (CRO) or Clinical Trials Unit (CTU) has been delegated to handle set up on behalf of the Sponsor, the contact at the CRO or CTU should be named here.

Name	**Linsey King**
Telephone Number	Enter telephone number
Email Address	**umlmk@leeds.ac.uk**

5.* Are all participating NHS / HSC organisations undertaking the same protocol activities?

Yes

If 'No' give details of the activities taking place at NHS / HSC organisations that you will use this outline Organisation Information Document with. Additional outline Organisation Information Documents may be required for NHS / HSC organisations undertaking different activities.

If no, give details

Participating NHS / HSC Organisation Information

6. Name of Participating NHS / HSC Organisation. If this Organisation Information Document is being used as an Agreement the name must be entered prior to agreement.

Leeds Teaching Hospitals Trust

7. Location/s*: Please provide detail below where it is planned to undertake the research only at specified locations with the participating NHS / HSC organisation (i.e. hospital(s), GP Practice(s) and/or Research Unit(s))*. It is not intended that the level of detail provided here captures individual departments within the participating NHS / HSC organisation.

Location (enter text below)	**Activity** (enter text below)
Seacroft Hospital, Leeds	**Completion of research**

8*. What is the role of the person responsible for research activities at the participating NHS / HSC organisation?

- Principal Investigators are expected to be in place at participating NHS / HSC organisations where locally employed staff take responsibility for research procedures. In this scenario Principal Investigator should be selected even for single centre studies where the Chief Investigator will also be the Principal Investigator.
- Where this is not the case, local collaborators are expected to be in place where central study staff will be present at the participating organisation to undertake research procedures (the role of the Local Collaborator is to facilitate the presence of Sponsor / CRO research staff).
- Where existing data is being provided for research purposes without additional research procedures and without the presence of central research team members at the participating NHS / HSC organisation, select Chief Investigator.

Principal Investigator

9. Contact details of person responsible for research activities at this participating NHS / HSC organisation as indicated in question 8 (if known). If known, please enter the details of the person you have spoken to about their role in this study at this participating NHS / HSC organisation. If unknown, please leave blank and that person can be identified and listed here during the setup of the study.

Name	Professor Daniel Peckham
Post / Job Title	Professor Respiratory Medicine/Honorary Consultant

Name of Employing Organisation	University of Leeds/Leeds Teaching Hospital NHS trust
Email Address	d.g.peckham@leeds.ac.uk
Telephone number	0113 2067170

Timescales

10. Predicted Start and End Dates of the Study at this Participating NHS / HSC Organisation The Sponsor or authorised delegate should propose a date on which it intends to start and complete research activity at this participating NHS / HSC organisation. Alternatively, this may be left blank when the Local Information Pack is shared, for agreement during study set up at the Participating NHS / HSC Organisation.	
Predicted Start Date (activities at this organisation)	**19/04/2021**
Predicted End Date (activities at this organisation)	**09/05/2022**
For many types of study the following dates are not applicable and this may be stated in answer. Where they are applicable, they should be provided by the Sponsor or authorised delegate before sharing the Local Information Pack, as indicative targets for agreement, or they may be negotiated between Sponsor or authorised delegate and participating NHS / HSC organisation after sharing the pack.	
Predicted Site Initiation Visit Date	**10/05/2021**
Predicted Start Date for participant recruitment	**10/05/2021**
Predicted End Date for participants recruitment (i.e. when the study moves into "follow up" activities.)	**09/05/2022**
Predicted End Date for all study activities (i.e. "last patient visit" completed and study is ready to be archived.)	**09/05/2022**

Participant Numbers

11. How many research participants are expected at this participating NHS / HSC organisation?

For studies not directly involving human participants, please indicate the number of samples or data-sets to be obtained. Please state if number of participants is per month, per year, overall, etc.
15-20

Study set up and delivery arrangements at Participating NHS / HSC Organisations

12*. The following are needed at the participating NHS / HSC organisation to deliver the study: *e.g. specific equipment, patient/participant groups, service support, nursing time, etc. Please detail any specific requirements for participating NHS / HSC organisations to deliver this study, including by clarifying any requirements on participating NHS / HSC organisations relating to monitoring / self-monitoring, e.g. requirements for staff signature and delegation logs to be returned to the Sponsor and/or any particular access requirements that the Sponsor may have that it wishes to bring to the attention of the participating NHS / HSC organisation, likelihood of staff not employed at the participating NHS / HSC organisation coming on site, etc.*
Access to the PCD clinic at Seacroft hospital all equipment required is available at the clinic and owned by the NHS **Identification of potential participants by direct care team staff and lead consultant** **Repeated routine care measures at an arranged 3 month appointment will include BMI, lung function, (FEV1 FVC, FEV1% FVC%), MRC score (medical research council dyspnoea scale, measure of breathlessness in terms of mobility), and blood measurement Vitamin D.**
13*. The following training will be provided by the Sponsor or authorised delegate for local research team members. Where only specific team members (e.g. the Principal Investigator) will receive this training, this should be specified.
Familiarise with SOP's created for clinic to ensure consistency

14*. The Sponsor expects that local research team members will have the following skills and where they do not have those skills that they will undertake the relevant training before undertaking the relevant study activities. It would not be usual for the Sponsor to expect study specific training additional to that which it will provide. This section does however allow Sponsors to state, for example, that when they expect **training in Good Clinical Practice** for appropriate team members where the study is a Clinical Trial of an Investigational Medicinal Product, they will accept UK nationally recognised GCP training, training recognised on the **Transcelerate mutual recognition scheme**, etc.
The research team are actively working within the NHS and conducting routine care. The primary researcher (CI) is a registered dietitian with the Professional regulatory body Health and Care Professions Council (HCPC) and has continually updated CPD skills in order to complete the additional measurements identified
15*. The following funding/resources/equipment, etc. is to be provided to this participating NHS / HSC organisation. The Sponsor should answer this question whether this Organisation Information Document is to be used as the Agreement with the participating NHS / HSC organisation or not. Where the document is intended as the Agreement, further detail should be provided in Appendix 2.
Payment is required for the repeated Vitamin D blood test. To be completed by LTHT Pathology department

18* Authorised on behalf of Sponsor by:	
Name	Claire E Skinner
Job Title	Head of research Integrity and Governance
Organisation Name	University of Leeds
Date	15 September 2020
16^ The Participating NHS / HSC Organisation confirms (by use of the drop-down box) that the Principal Investigator, where one is required, is aware of and has agreed to discharge their responsibilities in line with the UK Policy Framework for Research and Social Care..	
17^ The Participating NHS / HSC Organisation has considered and mitigated any conflict/s of interest declared by the principal investigator.	
If yes, please detail conflict of interest	

Appendices

(Contents)

Appendix 1: General Provisions

Appendix 2: Finance Provisions

Appendix 3: Material Transfer Provisions

Appendix 4: Data Processing Agreement

Appendix 5: Data Sharing Agreement

Appendix 6: Intellectual Property Rights

The sponsor or authorised delegate should answer the question at the top of Appendix 1 and, if it intends that this Organisation Information Document will be incorporated into an exchange of correspondence to form the Agreement ("Agreement") between itself and the participating NHS / HSC organisation, the questions that appear at the top of each subsequent appendix.

General Provisions

***Does the Sponsor intend that this Organisation Information Document forms the Agreement between itself and the participating NHS / HSC Organisation, or has a separate site agreement been provided?**	Organisation Information Document

It is recommended that the Organisation Information Document is used as the Agreement between Sponsor and participating NHS / HSC organisation for studies that are not clinical trials or investigations. The model Non-Commercial Agreement (mNCA) should be used for clinical trials or investigations.

Where the Organisation Information Document is to be used as the Agreement between the Sponsor and participating NHS organisation (hereafter singly "Party" or collectively the "Parties"), this document forms a formal legal contract between the Parties. In all cases where this document is the Agreement between the Parties, this Appendix 1 applies in full.

Additionally, the Sponsor or authorised delegate should use the questions at the top of each subsequent appendix to indicate whether or not that appendix also forms part of the Agreement.

Text highlighted in yellow is optional, including where alternative versions of the same clause may be used. The applicable option/s should be selected and text not to be used should be deleted prior to IRAS submission. No changes should be made to any text that does not appear in yellow highlight.

1. OBLIGATIONS OF THE PARTIES

1.1. The Parties agree to comply with all relevant laws, regulations and codes of practice applicable to this Agreement including to the performance of the study. The Parties agree to comply with the World Medical Association Declaration of Helsinki, titled "Ethical Principles for Medical Research Involving Human Subjects" (where applicable) and the UK Policy Framework for Health and Social Care Research. The Parties shall conduct the study in accordance with:

1.1.1. the Protocol, including appropriately made amendments thereto (which is/are hereby incorporated into this Agreement by reference);

1.1.2. the terms of all relevant permissions and approvals. These may include, but are not limited to the terms and conditions of the favourable opinion given by the relevant NHS Research Ethics Committee, where applicable.

1.2. The Parties shall carry out their respective responsibilities in accordance with this Agreement.

1.3. The Parties agree to comply with all applicable statutory requirements and mandatory codes of practice in respect of confidentiality (including medical confidentiality) in relation to participants and study personnel.

1.4. The Sponsor shall, on the giving of reasonable prior written notice to the Participating NHS / HSC Organisation, have the right to audit the Participating NHS / HSC Organisation's compliance with this Agreement. The Sponsor may appoint an auditor to carry out such an audit. Such right to audit shall include access, during normal working hours to the Participating NHS / HSC Organisation's premises and to all relevant documents and other information relating to the study.

1.5. The Participating NHS / HSC Organisation shall;

1.5.1. promptly notify the Sponsor should any responsible body conduct or give notice of intent to conduct any inspection at the Participating NHS / HSC Organisation in relation to the study;

1.5.2. allow the Sponsor to support the preparations for such inspection; and

1.5.3. following the inspection, provide the Sponsor with the results of the inspection relevant to the study. The Sponsor will be responsible for sharing such results with the funder if required.

1.6. In accordance with participant consent, the Participating NHS / HSC Organisation shall permit the Sponsor's appointed representatives and any appropriately appointed monitor access to all relevant data for monitoring and source data verification. The Parties agree that such access will be arranged at mutually convenient times and on reasonable notice. Such monitoring may take such form as the Sponsor reasonably thinks appropriate including the right to inspect any facility being used for the conduct of the study, reasonable access to relevant members of staff at the Participating NHS / HSC Organisation and the right to examine any procedures or records relating to the study, subject at all times to clause 6 of this appendix. The Sponsor will alert the Participating NHS / HSC Organisation promptly to significant issues (in the opinion of the Sponsor) relating to the conduct of the study.

2. LIABILITIES AND INDEMNITY

2.1. Nothing in this clause 2 shall operate so as to restrict or exclude the liability of a Party in relation to statutory or regulatory liability (including but not limited to breach of the data protection legislation), death or personal injury caused by the negligence or wilful misconduct of that Party or its agent(s), fraud or fraudulent misrepresentation or to restrict

or exclude any other liability of a Party which cannot be so restricted or excluded in law.

2.2. Where a Party is a non-NHS/HSC organisation, or an NHS/HSC organisation that is not a member of an NHS indemnity scheme, then that Party shall maintain all proper insurance or equivalent indemnity arrangements to cover liabilities arising from its participation in the study, in respect of any claims brought by or on behalf of a participant. Where the Party is an NHS/HSC organisation and is a member of an NHS indemnity scheme, it shall maintain its membership therein or otherwise ensure it has appropriate cover against claims arising as a result of clinical negligence by the Party and/or its agents brought by or on behalf of the participants. Each Party shall provide to the other such evidence of their insurance or equivalent indemnity cover maintained pursuant to clause 2.2 as the other Party shall from time to time reasonably request, such evidence might comprise confirmation that an NHS/HSC organisation is a member of one of the NHS indemnity schemes.

2.3. **[SINGLE SPONSOR]** Subject to clauses 2.4, 2.5, 2.6, 2.7 and 2.8, the Sponsor shall indemnify the Participating NHS / HSC Organisation and its agents, against any reasonable claims, proceedings and related costs, expenses, losses, damages and demands ("Claims") to the extent they arise or result from the negligent acts or omissions of, or the wilful misconduct of the Sponsor, and/or contracted third party, in its performance of this Agreement or in connection with the study.

2.4. Subject to clauses 2.3, 2.5, 2.6 and 2.8, the Participating NHS / HSC Organisation shall indemnify the Sponsor and its respective agents, against any reasonable claims, proceedings and related costs, expenses, losses, damages and demands to the extent they arise or result from the negligent acts or omissions of, or the wilful misconduct of the Participating NHS / HSC Organisation, or its agents, in its performance of this Agreement or in connection with the study.

2.5. An indemnity under clauses 2.3 or 2.4 shall only apply if the indemnified Party:

2.5.1. informs the Party providing the indemnity in writing as soon as reasonably practicable following receipt of notice of the claim or proceedings;

2.5.2. upon the indemnifying Party's request and at the indemnifying Party's cost gives the indemnifying Party full control of the claim or proceedings and provides all reasonable assistance; and

2.5.3. makes no admission in respect of such claim or proceedings other than with the prior written consent of the indemnifying Party.

2.6. Any indemnity under clauses 2.3 or 2.4 shall not apply to the extent any claims, proceedings and related costs, expenses, losses, damages or demands arise or result from the negligent acts or omissions or wilful misconduct or breach of statutory duty of the indemnified Party.

2.7. The indemnity under clause 2.3 shall not apply to the extent any claims, proceedings and related costs, expenses, losses, damages or demands arise or result from:

2.7.1. Participating NHS / HSC Organisation carrying out a treatment or procedure that would be routinely undertaken at or for that Participating NHS / HSC Organisation as part of National Health Service treatment; or

2.7.2. Participating NHS / HSC Organisation preparing, manufacturing or assembling any equipment which is not done in accordance

2.7.2.1. with the protocol; or

2.7.2.2. with written instructions of the manufacturer; or

2.7.2.3. (where such instructions differ from the instructions of the manufacturer) other written instructions of the Sponsor.

2.8. No Party shall be liable to another in contract, tort/delict, breach of statutory duty or otherwise for any loss of profits, revenue, reputation, business opportunity, contracts, or any indirect, consequential or economic loss arising directly or indirectly out of or in connection with this Agreement.

2.9. If a Party incurs any loss or damage (including costs and expenses) ("Loss") arising or resulting from this Agreement and:

2.9.1. All Parties are NHS bodies as defined in Section 9(4) of the National Health Service Act 2006 or Section 17 of the National Health Service (Scotland) Act 1978 or Section 7 (4) of the NHS (Wales) Act 2006 or Articles 16 and 26 of the Health and Personal Social Services (Northern Ireland) Order 1972, which established the Boards and Central Services Agency respectively and Article 10 of the Health and Personal Social Services (Northern Ireland) Order 1991: which established Trusts in Northern Ireland as appropriate; or

2.9.2. One or more Party is a NHS body and the other Party (ies) is a NHS Foundation Trust; or

2.9.3. All Parties are NHS Foundation Trusts;

Then clauses 2.10, 2.11 and 2.12 shall apply.

2.10. If all Parties are NHS bodies / NHS Foundation Trusts in England, Wales or Northern Ireland and are indemnified by the same indemnity scheme (being one of the NHS Resolution's clinical negligence schemes or the Welsh Risk Pool or the Clinical Negligence Fund in Northern Ireland) and the Party incurring any loss can recover such loss under one of the indemnity schemes, then such Party shall rely on the cover provided by the indemnity scheme and not seek to recover the Loss from the other Party (ies). Where the other Party (ies) caused or contributed to the Loss, it undertakes to notify the relevant indemnity scheme(s) to take this into account in determining the future levies of all Parties in respect of the indemnity schemes.

2.11. If:

2.11.1. The Parties are members of the same indemnity scheme in England, Wales or Northern Ireland and the Party incurring the Loss is not indemnified for that Loss by its indemnity schemes; or

2.11.2. All Parties are NHS bodies in Scotland; or

2.11.3. The Parties are NHS bodies/Foundation Trusts established in different jurisdictions within the United Kingdom;

Then the Parties shall apportion such Loss between themselves according to their respective responsibility for such Loss.

2.12. If one or more Parties are NHS Foundation Trusts and the Party incurring the Loss is not responsible for all or part of the Loss and is not indemnified in respect of the Loss by one of the indemnity schemes then the Party incurring the Loss shall be entitled to recover the Loss from the other Party (ies) pursuant to the provisions of this Agreement.

2.13. **[SINGLE SPONSOR]** Subject to clause 2.1 and 2.7 the liability of the Participating NHS / HSC Organisation to the Sponsor and the liability of the Sponsor to the Participating NHS / HSC Organisation arising out of or in connection with any breach of this Agreement or any act or omission of either Party in connection with the performance of the study should be the greater of the amount of fees payable by the Sponsor to the Participating NHS / HSC Organisation under this Agreement or one hundred thousand (£100,000 GBP) pounds. For the avoidance of doubt, this cap applies also but not exclusively to the indemnities offered under clauses 2.3 and 2.4.

2.14. Notwithstanding clause 2.13, in the case of equipment loaned by or on behalf of the Sponsor to the Participating NHS / HSC Organisation for the purposes of the study, the Participating NHS / HSC Organisation's liability for damage to or loss of that equipment arising from its negligence shall exclude fair wear and tear and shall not exceed the replacement value of the equipment.

3. PUBLICITY

3.1. [Neither Party] shall use the name, logo or registered image of the other or the employees of such other Party in any publicity, advertising or press release without the prior written approval of an authorised representative of that Party.

3.2. The content and timing of any publicity, advertising or press release shall be agreed by Parties, such agreement not to be unreasonably withheld.

4. PUBLICATION

In accordance with all relevant laws, regulations and codes of practice, it is agreed that the Sponsor has an obligation to and shall publish the results of the full study and that the Participating NHS / HSC Organisation shall not publish any study data, including through presentation or submission of an abstract, without the prior permission in writing from the Sponsor (which shall not be unreasonably withheld or delayed).

5. FREEDOM OF INFORMATION

5.1. Parties to this Agreement which are subject to the Environmental Information Regulations 2004 (EIR) and the Freedom of Information Act 2000 (FOIA) or the Freedom of Information (Scotland) Act 2002 (FOI(S)A) and which receive a request under EIR, FOIA or FOI(S)A to disclose any information that belongs to another Party shall notify and consult that Party, as soon as reasonably practicable, and in any event, not later than seven (7) working days after receiving the request.

5.2. The Parties acknowledge and agree that the decision on whether any exemption applies to a request for disclosure of recorded information under EIR, FOIA or FOI(S)A is a decision solely for the Party responding to the request.

5.3. Where the Party responding to an EIR, FOIA or FOI(S)A request determines that it will disclose information it will notify the other Party in writing, giving at least four (4) working days' notice of its intended disclosure.

6. CONFIDENTIALITY

6.1. Subject to clause 5 above, the Participating NHS / HSC Organisation agrees to treat the results, excluding any clinical data of the study, as confidential information of the Sponsor and the Sponsor agrees to treat personal data and confidential patient information as confidential information.

6.2. The receiving Party agrees:

6.2.1. To take all reasonable steps to protect the confidentiality of the confidential information and to prevent it from being disclosed otherwise than in accordance with this Agreement

6.2.2. To ensure that any of its employees, students, researchers, consultants or sub-contractors who participate in the operation of the Study are made aware of, and abide by, the requirement of this clause 6.2.

6.2.3. To use confidential information solely in connection with the operation of the Agreement and not otherwise, except in the case where the confidential information is personal data and/or confidential patient information, where it may be used solely on the basis of maintaining the common law duty of confidentiality and in accordance with the requirements of the data protection legislation, including but not limited to an appropriate legal basis/special category condition, appropriate transparency information and that the purpose is not incompatible with the original purpose.

6.2.4. Not to disclose confidential information in whole or in part to any person without the disclosing Party's prior written consent or, where the confidential information is personal data and/or confidential patient information, without maintaining the common law duty of confidentiality and in accordance with the requirements of the data protection legislation, including but not limited to an appropriate legal basis/special category condition, appropriate transparency information and that the purpose is not incompatible with the original purpose.

6.3. The provision of clause 6.2 shall not apply to the whole or any part of the confidential information that is:

6.3.1. lawfully obtained by the receiving Party free of any duty of confidentiality;

6.3.2. already in the possession of the receiving Party and which the receiving Party can show from written records was already in its possession (other than as a result of a breach of clause 6.2.1 or 6.2.2);

6.3.3. in the public domain (other than as a result of a breach of clause 6.2.1 or 6.2.2);

6.3.4. independently discovered by employees of the receiving Party without access to or use of confidential information;

6.3.5. necessarily disclosed by the receiving Party pursuant to a statutory obligation;

6.3.6. disclosed with prior written consent of the disclosing Party;

6.3.7. necessarily disclosed by the receiving Party by virtue of its status as a public authority in terms of the FOIA or the FOI(S)A;

6.3.8. published in accordance with the provisions of clause 4.

6.4. The restrictions contained in clause 6.2 shall remain in force without limit in time in respect of personal data and any other information which relates to a patient, his or her treatment and/or medical records. Save as aforesaid and unless otherwise expressly set out in this Agreement, these clauses shall remain in force for a period of 10 years after the termination or expiry of this Agreement.

Finance Provisions

Where this Organisation Information Document is to be used as the Agreement between Sponsor and Participating NHS / HSC organisation, please select an option below.	
*Are there funds / resources / equipment, etc. being provided to this participating NHS / HSC organisation by the Sponsor? If no, this appendix should be left blank. If yes, this finance appendix forms part of the Agreement between the participating NHS / HSC organisation and the Sponsor.	Yes

A. Financial Arrangements

The overall, study-wide recruitment for this study is competitive with a maximum figure of [20] Participants. Once this target has been reached, the Sponsor will notify the Participating NHS / HSC Organisation. No additional per participant payments will be made by the Sponsor to the Participating NHS / HSC Organisation for participants consented after such notification becomes effective.

	*Area of Cost	*Payment (£ Sterling)
1*	Blood Test Pathology lab	Approx. £542.40

If VAT is payable, then the Sponsor shall pay the VAT in addition to the payment of the agreed costs on presentation of a VAT invoice in which the VAT is stated as a separate item. Such invoices should quote the Participating NHS / HSC Organisation's VAT registration number. If VAT is not payable, then the Sponsor shall issue a VAT exemption certificate.

Schedule of payments and details of payment arrangements

*Invoices to be submitted to:

Dr Helen White

Subject group Head, Nutrition and Dietetics group

Leeds Beckett University

Leeds

LS1 3HE

B. Supplies Arrangements

Any equipment, materials, consumables, software or other items being provided by the Sponsor or procured by the participating organisation for use in the study shall be specified below.

Note 1: Parties should complete the table below. If the Participating NHS / HSC Organisation is to procure any items and is to be reimbursed by

the Sponsor this should be specified in this appendix. Similarly if the Participating NHS / HSC Organisation is to pay the Sponsor for any items provided to the Participating NHS / HSC Organisation by or on behalf of the Sponsor this should be specified in this appendix.

Note 2: Parties should specify in this appendix, as appropriate, arrangements for:

- Ownership of items
- Insurance
- Storage instructions
- Instructions for use, return and/or destruction
- Any training to be provided
- Maintenance of equipment

Item	**Quantity**	**Frequency of supply**	**Responsibility to supply/procure** **(either Sponsor or Participating NHS / HSC Organisation only)**
Click here to enter text	Click here to enter text	Click here to enter text	Click here to enter text
Click here to enter text	Click here to enter text	Click here to enter text	Click here to enter text
Click here to enter text	Click here to enter text	Click here to enter text	Click here to enter text
Click here to enter text	Click here to enter text	Click here to enter text	Click here to enter text
Click here to enter text	Click here to enter text	Click here to enter text	Click here to enter text

Material Transfer Provisions

Where this Organisation Information Document is to be used as the Agreement between Sponsor and Participating NHS / HSC organisation, please select an option below.	
*Does this study involve the transfer of human biological material from this participating NHS / HSC organisation to the Sponsor or its agents? If no, this appendix does not form part of this Agreement. If yes, these provisions form part of the Agreement between the Sponsor and this participating NHS / HSC organisation.	No

Data Processing Agreement

Where this Organisation Information Document is to be used as the Agreement between Sponsor and Participating NHS / HSC organisation, please select an option below.	
*Does this study involve any processing of personal data by this participating NHS / HSC organisation on behalf of the Sponsor. If no, this appendix does not form part of this Agreement. If yes, these provisions form part of the Agreement between the Sponsor and this participating NHS / HSC organisation. For the avoidance of doubt, when used, these provisions are intended to form a legally binding contractual obligation for the purposes of compliance with the GDPR, specifically GDPR Article 28 (3).	Yes

1. For the purposes of the data protection legislation, the Sponsor is the controller and the Participating NHS / HSC Organisation is the Sponsor's processor in relation to all processing of personal data that is processed for the purpose of this study and for any future research use under the controllership of the Sponsor, that would not have taken place but for this Agreement regardless where that processing takes place.
2. The Parties acknowledge that whereas the Sponsor is the controller in accordance with Clause 1 of this appendix, the Participating NHS / HSC Organisation is the controller of the personal data collected for the purpose of providing clinical care to the participants. This personal data may be the same personal data, collected transparently and processed for research and

for care purposes under the separate controllerships of the Sponsor and Participating NHS / HSC Organisation.

3. Where the Participating NHS / HSC Organisation is the Sponsor's processor and thus where the processing is undertaken by the Participating NHS / HSC Organisation for the purposes of the study, Clauses 5.a. to 5.j below will apply. For the avoidance of doubt, such Clauses do not apply where the Participating NHS / HSC Organisation is processing the participant personal data as a controller.
4. The Participating NHS / HSC Organisation agrees only to process personal data for and on behalf of the Sponsor in accordance with the instructions of the Sponsor and for the purpose of the study and to ensure the Sponsor's compliance with the data protection legislation;
5. The Participating NHS / HSC Organisation agrees to comply with the obligations applicable to processors described by Article 28 GDPR including, but not limited to, the following:
    a. to implement and maintain appropriate technical and organisational security measures sufficient to comply at least with the obligations imposed on the controller by Article 28(1);
    b. to not engage another processor without the prior written authorisation of the Sponsor (Article 28(2))
    c. to process the personal data only on documented instructions from the Sponsor unless required to do otherwise by legislation, in which case the Participating NHS / HSC Organisation shall notify the Sponsor before processing, or as soon as possible after processing if legislation requires that the processing occurs immediately, unless legislation prohibits such notification on important grounds of public interest (Article 28(3a)).;
    d. to ensure that personnel authorised to process personal data are under confidentiality obligations (Article 28(3b));
    e. to take all measures required by Article 32 GDPR in relation to the security of processing (Article 28(3c));
    f. to respect the conditions described in Article 28(2) and (4) for engaging another processor (Article 28(3d));
    g. to, taking into account the nature of the processing, assist the Sponsor, by appropriate technical and organisational measures, insofar as this is possible, to respond to requests for exercising data subjects' rights (Article 28(3e));
    h. to assist the controller, to ensure compliance with the obligations pursuant to Articles 32 to 36 GDPR taking into account the nature of the processing and the information available to the Participating NHS / HSC Organisation (Article 28(3f));
    i. to, at the choice of the Sponsor, destroy or return all personal data to the Sponsor at the expiry or early termination of the Agreement, unless storage is legally required (Article 28(3g)) or where that personal data is held by the Participating NHS / HSC Organisation as controller for the purpose of clinical care or other legal purposes; and

j. to maintain a record of processing activities as required by Article 30(2) GDPR.

6. The Participating NHS / HSC Organisation shall ensure that:
    a. its agents do not process personal data except in accordance with this Agreement (and in particular the protocol);
    b. it takes all reasonable steps to ensure the reliability and integrity of any of its agents who have access to the personal data and ensure they:
        i. are aware and comply with the Participating NHS / HSC Organisation 's duties under this clause;
        ii. are subject to mandatory training in their information governance responsibilities and have appropriate contracts including sanctions, including for breach of confidence or misuse of data; and
        iii. are informed of the confidential nature of the personal data and understand the responsibilities for information governance, including their obligation to process personal data securely and to only disseminate or disclose for lawful and appropriate purposes.
7. The Participating NHS / HSC Organisation agrees to:
    a. allow the Sponsor(s) or another auditor appointed by the Sponsor(s) to audit the Participating NHS / HSC Organisation's compliance with the obligations described by this Appendix, data protection legislation in general and Article 28 GDPR in particular, on reasonable notice subject to the Sponsor complying with all relevant health and safety and security policies of the participating site and/or to provide the Sponsor with evidence of its compliance with the obligations set out in this Agreement; and
    b. obtain prior agreement of the Sponsor to store or process personal data outside the European Economic Area.
8. Where the Participating NHS / HSC Organisation stores or otherwise processes personal data outside of the European Economic Area as the Sponsor's processor, it warrants that it does so in compliance with the Data Protection Legislation.

Data Sharing Agreement

Where this Organisation Information Document is to be used as the Agreement between Sponsor and Participating NHS/HSC organisation, please select an option below.	
*Does this study involve the transfer of personal data from this participating NHS / HSC organisation to the Sponsor or its agents, or transfer of confidential information between the Parties? If no, this appendix does not form part of this Agreement. If yes, these provisions	Yes

form part of the Agreement between the Sponsor and this participating NHS / HSC organisation.	

1. Personal data shall not be disclosed to the Sponsor by the participating NHS / HSC organisation, save where this is required directly or indirectly to satisfy the requirements of the protocol, or for the purpose of monitoring or reporting adverse events, or in relation to a claim or proceeding brought by a participant in connection with the study.
2. The Sponsor agrees to use personal data solely in connection with the operation of the Agreement, or otherwise for purposes not incompatible with this original purpose (Article 5, 1 (b) GDPR), and not otherwise. In particular,
    2.1. Not to disclose personal data to any person except in accordance with applicable legal requirements and codes of practice.
3. The Sponsor agrees to comply with the obligations placed on a controller by the data protection legislation. This is not limited to, but includes, being responsible for and able to demonstrate compliance with the principles relating to processing of personal data (Article 5 GDPR)
4. The Sponsor agrees to ensure persons processing personal data under this Agreement are equipped to do so respectfully and safely. In particular:
    4.1. To ensure any persons (excluding employees, honorary employees, students, researchers, consultants and subcontractors of the participating NHS / HSC organisation) processing personal data understand the responsibilities for information governance, including their obligation to process personal data securely and to only disseminate or disclose for lawful and appropriate purposes.
    4.2. To ensure any persons (excluding employees, honorary employees, students, researchers, consultants and subcontractors of the Participating NHS / HSC Organisation) have appropriate contracts providing for personal accountability and sanctions for breach of confidence or misuse of data including deliberate or avoidable data breaches.
5. The Sponsor agrees to proactively prevent data security breaches and to respond appropriately to incidents or near misses. In particular,
    5.1. To ensure that personal data are only accessible to persons who need it for the purposes of the study and to remove access as soon as reasonably possible once it is no longer needed.
    5.2. To ensure all access to personal data on IT systems processed for study purposes can be attributed to individuals.
    5.3. To identify, review and improve processes which have caused breaches or near misses, or which force persons processing personal data to use workarounds which compromise data security.
    5.4. To adopt measures to identify and resist cyber-attacks against services and to respond to relevant external security advice.
    5.5. To take action immediately following a data breach or near miss.
6. The Sponsor agrees to ensure personal data are processed using secure and up to date technology. In particular,
    6.1. To ensure no unsupported operating systems, software or internet browsers are used to support the processing of personal data for the purposes of the study.

6.2. To put in place a strategy for protecting relevant IT systems from cyber threats which is based on a proven cyber security framework such as Cyber Essentials.
6.3. To ensure IT suppliers are held accountable via contracts for protecting personal data they Process and for meetings all relevant information governance requirements.

Where this Organisation Information Document is to be used as the Agreement between Participating NHS / HSC organisation, please select an option below.	
*Does this study require the protection of background intellectual property rights, or is there potential for the generation of new intellectual property? If no, this appendix does not form part of this Agreement. If yes, these provisions form part of the Agreement between the Sponsor and this participating NHS / HSC organisation.	No

1. All background intellectual property rights (including licences) and know how and their improvements used in connection with the Study shall remain the property of the Party introducing the same and the exercise of such rights for purposes of the Study shall not knowingly infringe any third party's rights.
2. All intellectual property rights and know how in the Protocol, and in the study data, excluding clinical procedures developed or used by the Participating NHS / HSC Organisation independently of the Study, shall belong to the Sponsor. The Participating NHS / HSC Organisation hereby assigns all such intellectual property rights, and undertakes to disclose all such know how, to the Sponsor.
3. Subject to clauses 1 and 2, all intellectual property rights deriving or arising from the Material or any derivations of the Material provided to the Sponsor by the Participating NHS / HSC Organisation shall belong to the Sponsor.
4. At any time within the duration of the Study, the Participating NHS / HSC Organisation shall at the request and expense of the Sponsor execute all such documents and do all acts necessary to fully vest the intellectual property rights in the Sponsor. To give effect to this clause 4, the Participating NHS / HSC Organisation shall ensure that its agents involved in the Study assign such intellectual property rights falling within clauses 2 and 3 and disclose such know how to the Participating NHS / HSC Organisation.
5. Subject to this Clause 5 and Clause 6, nothing in this Appendix shall be construed so as to prevent or hinder the Participating NHS / HSC Organisation from using its own know how or clinical data gained during the performance of the Study, at its own risk, in the furtherance of its normal activities of providing clinical care to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of the Sponsor, or their funder. This clause 5 does not permit the disclosure of any of the study data, all of which remain

confidential until publication of the results. Any study data not so published remains the confidential information of the Sponsor, or their funder.

6. The Participating NHS / HSC Organisation may, with the prior written permission of the Sponsor (such permission not to be unreasonably withheld), use study data gained during the performance of the Study, at its own risk, in the furtherance of its normal activities of commissioning clinical services, teaching and research to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of the Sponsor or their funder. This clause 6 does not permit the disclosure of any of the study data, all of which remain confidential until publication of the results of the Study.

Authorisation When Using This Organisation Information Document as An Agreement

(when used as an Agreement, the Participating NHS Organisation is a "Party" to the Agreement and the Sponsor is a "Party" to the Agreement – collectively the "Parties").

Authorisation on behalf of Participating NHS / HSC Organisation It is not intended that this confirmation requires wet-ink signatures, or a passing of hard copies between the Sponsor and participating NHS / HSC organisation. Instead, Sponsors are expected to accept confirmation by email from an individual empowered by the Participating NHS / HSC Organisation to agree to the commencement of research (including any budgetary responsibility, where the study involves the transfer of funds).	
^ Authorised on behalf of Participating NHS / HSC Organisation by:	
Name	Rebecca Savage
Job Title	Research & Innovation Manager
Organisation Name	Leeds Teaching Hospitals
Date	27 April 2021

From: Jean Uniacke <J.M.Uniacke@leeds.ac.uk>
Sent: Friday, August 28, 2020 10:56 AM
To: Linsey King <umlmk@leeds.ac.uk>
Subject: 222335 confirmation of sponsorship

Dear Linsey,

We can now confirm University of Leeds sponsorship in principle for this study, 'Feasibility of consumption of nutritional supplements in PCD' (IRAS 222335).
We will therefore proceed with electronic authorisation via IRAS. Please use the governance-ethics@leeds.ac.uk address for this.
A copy of the University Indemnity certificate is attached to this email.

As a condition of sponsorship, a full set of the HRA approved documents for this study are to be kept by the Chief Investigator in the Site file and made available to the sponsor for audit or monitoring purposes when requested.

In addition, once HRA approval has been granted please send copies of all of the final HRA approved documents attached to an email to governance-ethics@leeds.ac.uk.

Please note, when you receive HRA Approval for your study you will need to obtain confirmation of their capacity and capability to undertake the research from the relevant NHS organisations R&D departments (where applicable as per the HRA Approval letter) before you commence recruitment to the study. The sponsor delegates the responsibility to the Chief Investigator to supply the R&D offices and the local research teams with the relevant HRA approved documents for their study (local document pack). You cannot commence recruitment at an NHS site until you have received confirmation of capacity and capability that they can undertake the study from the R&D department at that site.

Role of the Research Sponsor under the UK policy framework for health and social care research (2017 v3.3) and the Medicines for Human Use (Clinical Trials) Regulations 2004

I hereby confirm that the University of Leeds would be prepared to accept the role of research sponsor as currently defined in the UK policy framework for health and social care research version 3.3 and the *Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031)*, in relation to the study:

'Feasibility of consumption of nutritional supplements in PCD' (IRAS 222335).

I have been informed that this study will be led by, Ms Linsey King, a PhD student at the University of Leeds under the supervision of Professor Daniel Peckham and Dr Helen white of the University of Leeds and Dr Theocharis Ispoglou of Leeds Beckett University.

Sponsorship is conditional upon review and approval of the research by appropriate ethics, NHS and regulatory bodies.

To enable the sponsor to meet their responsibilities as listed in section 9.10 of the UK policy framework for health and social care research, Chief Investigators are required to adhere to their responsibilities as outlined in section 9.2 of the Framework, https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/

In line with this requirement Ms King must ensure that all involved in the research project understand and discharge their responsibilities in accordance with the agreed protocol and any relevant management, ethical and regulatory approvals.

If you have any queries about sponsorship of this project then please address them to Mrs Clare Skinner, at governance-ethics@leeds.ac.uk or 0113 343 4897.

Yours,

Jean Uniacke

J.3 Retrospective handgrip study - Chapter 6

NHS
The Leeds Teaching Hospitals
NHS Trust

Enquiries to: Information Governance Team
Date: 27th October 2022
Our Ref: HGS

Professor Daniel Peckham
Professor of Respiratory Medicine and Cystic Fibrosis
Centre for respiratory medicine
St James' Hospital
Beckett Street
Leeds
LS9 7TF

Trust Headquarters
St James's University Hospital
Beckett Street
Leeds
LS9 7TF
Direct Line: (0113) 2066433
Email: leedsth-tr.informationgovernance@nhs.net
www.leedsth.nhs.uk

Re: A retrospective longitudinal analysis of Hand Grip Strength (HGS) measures in Bronchiectasis and Primary Ciliary Dyskinesia (PCD) regional clinic populations

Dear Prof Peckham

Thank you for your application for Leeds Teaching Hospitals NHS Trust (LTHTrust) regarding A retrospective longitudinal analysis of Hand Grip Strength (HGS) measures in Bronchiectasis and Primary Ciliary Dyskinesia (PCD) regional clinic populations project.

Exploring the use of HGS as a standard care measure and evaluating measures collected against standard assessment parameters as part of routine care, will aid in understanding further muscle strength and its relationship with clinical outcomes for the Bronchiectasis and PCD population. It will also help identify impaired handgrip which responds more quickly to nutritional status and will enable identification of clinically relevant needs that inform intervention in areas of nutrition and muscle functionality to improve outcomes.

This study is being undertaken by Linsey King, PhD Student as part of their research at the Trust. The study aims to explore HGS in a Bronchiectasis and PCD population establishing normative values and associations with other standard care outcomes.

The primary objectives are:

- To explore retrospective values recorded as routine care of muscle functionality measured by Handgrip strength (HGS) in clinical populations of Bronchiectasis and PCD against standard normative values for age and sex,
- To explore retrospective HGS measures at individual collection points over time for a period of 1 year.

The secondary objectives are:

- To explore any associations of mean HGS to aetiology, lung function, BMI, Number of infections, co morbidities and physiotherapy input.

- To explore any associations with HGS over time to aetiology, lung function, BMI, Number of infections, co morbidities and physiotherapy input.

All patients who attended the Leeds regional PCD clinic or bronchiectasis clinic will be eligible to be included in this study. Data will be collected by a member of the direct care team, pseudonymised and stored on a secure, password protected drive at the University of Leeds by Linsey King.

The data from this study will be analysed, and a final study report prepared as part of Linsey King's PhD thesis. The data will be stored for the duration of the undertaking of the educational aspect linked to this research, which is up to 3 years.

As no new or additional data is being collected patient consent will not be required.

Prof Peckham has demonstrated a clear understanding of the Data Protection legislation and Caldicott guidelines, understanding his duties to comply fully with the legislation during the collection and processing of Trust data/other organisations data.

I am happy to express my support for the HGS project and wish Prof Peckham well with his project.

Yours sincerely

Dr John McElwaine
Deputy Caldicott Guardian
Leeds Teaching Hospitals NHS

The Leeds Teaching Hospitals NHS Trust

UNIVERSITY OF LEEDS

Full Title: A retrospective longitudinal analysis of Hand Grip Strength (HGS) measures in Bronchiectasis and Primary Ciliary Dyskinesia (PCD) regional clinic populations.

Short Title: Handgrip strength measures in Bronchiectasis and PCD

PROTOCOL VERSION NUMBER: 1.0

PROTOCOL DATE VERSION DATE: 17/09/2021

SPONSOR

Claire E Skinner, Head of research Integrity and Governance , Faculty of Medicine and Health Research Office, Room 9.29, Level 9, Worsley Building, University of Leeds, Clarendon Way, Leeds, LS2 9NL

Governance-ethics@leeds.ac.uk 01133434897

This protocol will be completed as part of a PhD project for Linsey King (Chief Investigator/study coordinator).

Declaration

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date: ...../...../.....

.....

.....

Name: University of Leeds

.....

.....

Position:

.....

.....

Chief Investigator:

Signature: ..... Date: ...../...../.....

Name: Mrs Linsey King

.....

KEY STUDY CONTACTS

Director of Studies	Professor Daniel Peckham, Professor of Respiratory Medicine and Cystic Fibrosis, Leeds Teaching hospitals NHS trust, Centre for respiratory medicine, St James' University Hospital, Beckett Street, Leeds LS9 7TF 01132433144 Daniel.peckham@nhs.net d.g.peckham@leeds.ac.uk
Chief Investigator and Study Co-ordinator	Linsey King PhD Student Clinical Sciences Building University of Leeds St James' University hospital, Beckett Street, Leeds, LS9 7TF umlmk@leeds.ac.uk
Sponsor	Claire E Skinner Head of Research Integrity and governance, Faculty of Medicine and Health Research Office, Room 9.29, Level 9, Worsley Building, Clarendon Way, Leeds, LS2 9NL Governance-ethics@leeds.ac.uk 01133434897
Key Contributors	Professor Daniel Peckham Professor of Respiratory Medicine and Cystic Fibrosis

	Leeds Teaching hospitals NHS trust Centre for respiratory medicine St James' University Hospital Beckett Street Leeds LS9 7TF Daniel.peckham@nhs.net D.G.Peckham@leeds.ac.uk 01132433144

Study Title	A retrospective longitudinal analysis of hand grip strength measures in Bronchiectasis and Primary Ciliary Dyskinesia (PCD) regional clinic populations.
Internal ref. no. (or short title)	Handgrip Strength in Bronchiectasis and Primary Ciliary Dyskinesia
Study Design	This retrospective study aims to report on Hand Grip Strength measures in a population of those diagnosed with Bronchiectasis and those with Primary Ciliary Dyskinesia in their scheduled regional clinics. Following an initial characterisation study, conducted in 2017 and published in 2021 Handgrip strength was shown to be impaired in 70% of the Bronchiectasis population recruited. As a result, this practical and quick assessment was introduced as a standard measure of care alongside the measurement of height and weight in both the regional Bronchiectasis and Primary Ciliary Dyskinesia clinics from October 2021. This Study will look at the HGS measures over a period of 1 year retrospectively and explore any associations with sex, age, BMI, aetiology, infective episodes and physiotherapy
Study Participants	Those diagnosed with Primary Ciliary Dyskinesia (PCD) Those diagnosed with Bronchiectasis
Planned Size of Sample (if applicable)	Total planned sample is whole population of Bronchiectasis and Primary Ciliary Dyskinesia patients in the regional clinics seen in the year of data collection October 2021 – October 2022 Sample size needed is 186 considering clinical populations
Follow up duration (if applicable)	NA
Planned Study Period	Data will be drawn from medical records for the period of 1 year following initiation of the HGS measurement.

Research Question/Aim(s)	**Objectives** 1. To explore HGS measures in both populations against standard normative values for age and sex. Muscle functionality measured by Handgrip strength (HGS)	**Outcomes** 1. Measurement of populations HGS against standardised indicators of impairment or sufficiency.
Secondary Outcomes	2. To explore relationship of HGS to aetiology, ethnicity, lung function, BMI, No. of infections and physiotherapy input.	2. Comparison of values against other parameters observed as part of routine care as part of the usual experience of disease progression and management. 1. Underlying aetiology 2. Ethnicity 3. Lung Function (FEV1%) 4. BMI 5. Number of infections within duration of data collected 6. Predominant infections 7. Co morbidities e.g. Diabetes 8. Physiotherapy input during study period 9. Self-declared physiotherapy

ROLE OF STUDY SPONSOR

The sponsor has no role in design, analysis, interpretation, or manuscript writing. The sponsor is responsible for overseeing the conduct of the study. The funder may be involved in dissemination and publication of results and will be regularly updated on study progress, as per funding requirement.

STUDY PROTOCOL

A retrospective longitudinal analysis of Hand Grip Strength (HGS) measures in Bronchiectasis and Primary Ciliary Dyskinesia (PCD) regional clinic populations to explore if parameters such as lung function have any associations with other standard measures of care deemed clinically

BACKGROUND

Bronchiectasis is a debilitating respiratory condition, which can be acquired or congenital. The aetiology of Non Cystic Fibrosis Bronchiectasis (NCFB) is

unknown in up to 50% of cases but is associated with many underlying diseases e.g., rheumatoid arthritis, aspiration, environmental exposure, immunodeficiency, Cystic Fibrosis and Primary Ciliary dyskinesia (PCD) (Hill et al., 2019) Resulting chronic inflammation and repeated immune stimulation can influence effective utilisation and attainment of nutrition leading to increased gluconeogenesis and compromised nutritional status (Brill et al., 2015, Boyton and Altmann, 2016). PCD is a rare autosomal recessive genetic disorder which presents as a specific phenotype. This condition results in uncoordinated or absent cilia within the respiratory system which reduces the lungs' ability to effectively clear sputum leading to repeated infections. As a result PCD patients can develop bronchiectasis, developing cyclical infective episodes requiring repeated intravenous antibiotics and intensive physiotherapy (Kuehni and Lucas, 2017)

Recent published research within a regional clinic population (King et al, 2021), has identified this group has having statistically significant impaired handgrip strength (HGS), (57.76 %, ±15.56 p= 0.004), despite mean BMI within the normal range (23.20 Kg/m^2, ±3.49). HGS as a marker of muscle functionality has been shown to respond more quickly to deficiency or repletion than overall muscle mass assessed through BMI. (Norman et al., 2011). In addition, the diverse NCFB population also showed impaired (<85%) HGS when compared with normative values for age and sex, despite seemingly adequate nutritional intakes, identifying a need for the introduction of routine hand grip measures to be conducted alongside other standard anthropometrics such as height.

RATIONALE

Exploring the use of HGS as a standard care measure and evaluating measures collected against standard assessment parameters as part of routine care will aid in understanding further muscle strength and its relationship with clinical outcomes for this patient group. It will also aid in identifying impaired handgrip which responds more quickly to nutritional status and will enable identification of clinically relevant needs that inform intervention in areas of nutrition and muscle functionality to improve outcomes.

RESEARCH QUESTION/AIM(S)

The retrospective study aims to explore HGS in a Bronchiectasis and PCD population establishing normative values and associations with other standard care outcomes.

Primary Objectives

1. To explore retrospective values recorded as routine care of muscle functionality measured by Handgrip strength (HGS) in clinical populations of Bronchiectasis and PCD against standard normative values for age and sex.
2. To explore retrospective HGS measures at individual collection points over time for a period of 1 year.

Secondary Objectives

1. To explore any associations of mean HGS to aetiology, lung function, BMI, No of infections, co morbidities and physiotherapy input.
2. To explore any associations with HGS over time to aetiology, lung function, BMI, No of infections, co morbidities and physiotherapy input.

Hypothesis

Hand grip strength measures in patients with Bronchiectasis and Primary Ciliary Dyskinesia reflect normal values adjusted for age and sex and do not change over time nor have any associations with standard of care outcomes within clinic populations

Null Hypothesis

Hand grip strength measures in patients with Bronchiectasis and Primary Ciliary Dyskinesia do not reflect normal values adjusted for age and sex and do not change over time and have negative or positive associations with standard of care outcomes within clinic populations

Outcomes

Primary

c. Use retrospective HGS data to calculate mean HGS measures for all who attended the Leeds regional bronchiectasis and PCD clinics for a period of 1 year.
d. Use retrospective HGS data to explore changes in HGS over time at routine clinical appointments

Secondary

a. Retrieve retrospective routine data on aetiology, lung function (FEV1%), BMI, No. of infections requiring antibiotic therapy, co morbidities, age, gender and physiotherapy for statistical analysis of any associations

STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

Retrospective study exploring new standard measures of care (HGS) values and their association with other longer established routine care measures

Study Setting

This is a single site study taking place with the Leeds Adult Primary Ciliary Dyskinesia and Bronchiectasis services

Study Group

Patients with Bronchiectasis or Primary Ciliary Dyskinesia that attend the Leeds regional clinics

Sampling/Study size

based on estimated of 350 sample size of 186 is required (see below)

Recruitment

Inclusion criteria

- All patients who attend the Leeds regional Primary ciliary dyskinesia clinic or bronchiectasis clinic

Exclusion criteria

- Those not diagnosed with PCD or Bronchiectasis

Consent

All participants have consented to their standard care outcomes to be used in research or audit and evaluation. Therefore, further consent is not required.

Study Procedures

All participants will have had routine care measures taken including the following

Recording of infections

Established as part of clinical conversation

Type and cause of infection identified as part of treatment pathway

Height and Weight to determine BMI

- These measurements are taken routinely for every patient at every clinic appointment and are required for accuracy of data analysis.

Lung Function (FEV_1, FVC, FEV_1%, FVC %)

Participants will perform spirometry (test to measure lung function) using their normal technique this usually includes:

- Sitting upright or standing.
- They are instructed to take a big breath in and then breathe out as hard and fast as possible into the spirometer that is connected to a computer.
- The measurements are usually repeated until 3 acceptable and repeatable ones have been obtained.

Handgrip strength measure (HGS)

- Hand grip measure is used in many clinical areas and used as a measure of health outcomes. It has been shown to be a strong predictor of outcomes in other respiratory diseases such as COPD. Participants will be required to take the dynamometer and using the non-dominant arm squeeze for 5 seconds and then the measure is recorded.

Physiotherapy interventions

- Frequency of physiotherapy undertaken
- Physiotherapy recommendations

Withdrawal criteria

As this is retrospective and all have agreed to their outcomes being used as part of research there is no withdrawal criteria.

Statistics and data analysis

Sampling/Study size

The total population of PCD and Bronchiectasis clinic patients is 350 with a 5% margin of error and 95% confidence level would result in a sample size of 184 to be able to determine any statistical significances in associations explored.

Statistical analysis

Data collected as part of this study will be tabulated and checked for anomalies or missing data points. Descriptive statistics will be used for population characteristics. Variables reviewed will include handgrip strength as a mean value and individual measures over time, which is determined dependent on clinical need.

Continuous outcomes

Weight
BMI
Lung function

Binary Outcomes

Sex
Ethnicity
Physiotherapy intervention
Number of infections

Primary outcome measures

- Mean Handgrip strength recorded as part of routine care
- Individual Handgrip measures recorded at all clinic appointments over time

Secondary outcome measures

- All retrospective measures collected as part of routine care will be explored to determine any associations with HGS. To determine these associations and any changes between start and end of identified year, and subsequent measures will be explored using inferential statistics to determine relationships.

ETHICAL AND REGULATORY CONSIDERATIONS

Assessment and management of risk

As this is a retrospective evaluation of routinely collected data there is no risk to the Bronchiectasis or PCD population

Regulatory Review & Compliance

Research Ethics (REC) approval

Local Research and Innovation department approval will be required to review retrospective data as part of routinely collected measures. This research will measure HGS against standards adjusted for age and sex.

Peer review

This protocol has been reviewed by the director of studies and other members of the supervisory team.

Data protection and patient confidentiality

All data will be allocated individual number to enable comparisons to be made over time.

Data collection Spreadsheet

The full study data spreadsheet will hold data of all clinical outcome data identified above using only their individual participant number as the identifier. Results will be collated and analysed from this form. The full study data form will be stored on a password-protected University drive, secure and encrypted.

The data custodian is the Director of studies, Professor Daniel Peckham

Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

Indemnity

University of Leeds insurance will apply to meet the potential legal liability of the sponsor for harm to participants arising from the management of the research.

University of Leeds insurance will apply to meet the potential legal liability of the sponsor or employer for harm to participants arising from the design of the research.

NHS indemnity apply to meet the potential legal liability of investigators arising from harm to participants in the conduct of the research.

Access to the final study dataset

The study coordinator (CI) will have access to the full dataset. Once the study is completed then only the Study Coordinator (CI) and custodian of the data, Professor Daniel Peckham will have access, as the data is stored.

DISSEMINIATION POLICY

Dissemination policy

The Study Coordinator (CI) will own the data arising from the study. On completion of the study, the data will be analysed and tabulated, and a Final study Report prepared as part of a PhD thesis. The full study report will be accessed from the University of Leeds password protected computers. Only the Study Coordinator (CI) and director of studies will coordinate publication of data.

Authorship eligibility guidelines and any intended use of professional writers

The study team will have authorship on the final report. Criteria for individually named authors will be met.

REFERENCES

BOYTON, R. J. & ALTMANN, D. M. 2016. Bronchiectasis: Current Concepts in Pathogenesis, Immunology, and Microbiology. *Annu Rev Pathol,* 11**,** 523-54.

BRILL, S. E., PATEL, A. R., SINGH, R., MACKAY, A. J., BROWN, J. S. & HURST, J. R. 2015. Lung function, symptoms and inflammation during exacerbations of non-cystic fibrosis bronchiectasis: a prospective observational cohort study. *Respir Res,* 16**,** 16.

HILL, A. T., SULLIVAN, A. L., CHALMERS, J. D., DE SOYZA, A., ELBORN, S. J., FLOTO, A. R., GRILLO, L., GRUFFYDD-JONES, K., HARVEY, A., HAWORTH, C. S., HISCOCKS, E., HURST, J. R., JOHNSON, C., KELLEHER, P. W., BEDI, P., PAYNE, K., SALEH, H., SCREATON, N. J., SMITH, M., TUNNEY, M., WHITTERS, D., WILSON, R. & LOEBINGER, M. R. 2019. British Thoracic Society Guideline for bronchiectasis in adults. *Thorax,* 74**,** 1-69.

KING, L., WHITE, H., CLIFTON, I. SOPLETINI, G., ISPOGLOU, H., and PECKHAM, D. P., 2021, Nutritional status and intake in patients with non-cystic fibrosis bronchiectasis (NCFB) – a cross sectional study. *Clin Nutr* 40, 5162 -5168.

KUEHNI, C.E. and LUCAS, J.S., 2017, Diagnosis of primary ciliary dyskinesia: summary of the ERS Task Force report, Breathe, 13: 166-178

NORMAN, K., STOBAUS, N., GONZALEZ, M. C., SCHULZKE, J. D. & PIRLICH, M. 2011. Hand grip strength: outcome predictor and marker of nutritional status. *Clin Nutr,* 30**,** 135-42.

Appendix K Participant information sheets and consent forms

K.1 Participant information sheet - Chapter 4 and 5

The Leeds Teaching Hospitals NHS Trust

UNIVERSITY OF LEEDS

Participant Information Sheet **IRAS 216351**

Characterisation of Bronchiectasis patients including dietary and functional assessment.

My name is Linsey King. I am a student studying for my PhD at University of Leeds and I am conducting a research study as part of this. I am looking for patients who have been diagnosed with Bronchiectasis who attend the Leeds Regional Bronchiectasis clinic at Seacroft Hospital. You have been invited to participate in this study because you are a patient with Bronchiectasis attending the clinic at Leeds Teaching Hospitals trust and are able to contribute to this research.

What will be involved?

The study will involve using the data that is routinely collected as part of your pathway of care. In addition, you will be asked about your dietary intake for the previous day e.g. what you have eaten and drunk throughout yesterday. We will also assess a functional measure of your handgrip strength and a measurement of your muscle mass using callipers and a tape measure. This will take place in addition to your usual appointment with the Clinical team. The handgrip measure and muscle mass assessment should take 5 minutes each and the dietary recall will take about 10 minutes and will be carried out by the researcher. You will also be asked to be contacted at 2 other points at your convenience to collect 2 further dietary recalls over the telephone. You will be asked again about the previous day's dietary and fluid intake. It is hoped this will be over the telephone and will be agreed with you at the time of the first data collection. The normal data collected is that which is usually undertaken at your clinic appointment by the nurses and the consultant. This would include your lung function, blood results and recent infections. Once collected in full the data will be extracted from your patient record and anonymised so that it cannot be traced back to you as an individual.

What are the possible benefits of taking part?

None, but the data you provide will help in the understanding of the relationship between your dietary intake, muscle strength and mass and the clinical disease measures that are usually taken when you attend clinic. This is to identify if there is any relationship between what you eat and how strong you are with how your body copes with Bronchiectasis. It is hoped that this will also inform future research.

What are the possible risks of taking part?

Being asked to recall your dietary intake relies on memory and may cause you frustration if you struggle with this. Assessing handgrip strength will also require you to hold and grip a piece of equipment (3 times) which if not done correctly may cause discomfort. The last assessment requires a measurement of the upper arm and so access to this is required which may result in

moving of clothes. All other data is routinely collected and therefore should not involve further risk.

Do I have to take part in the study?

Your participation in this project is voluntary which means you do not have to take part. You will be given time to consider your involvement and if you require more time, you will be approached again at your next clinic appointment. If you do decide to take part in this project, I will ask you

to complete and sign a consent form indicating that you agree to participate. At any point throughout the taking of the dietary recall and measurements, you have the right to stop the without giving a reason. You can withdraw any information you do provide at any point up to the point when handgrip, muscle mass measure and all the dietary recall, has been completed. Once this is complete the information will be anonymised and therefore analysis and summarising of the information will have begun, and it will not be possible to identify the information which came from you.

Confidentiality

All information which is provided to the study by you will be kept strictly confidential. All completed consent forms will be kept in a locked filing cabinet within the clinic setting only accessible by the direct research team. No names will be used in this study. All data will be stored in a secure manner on an encrypted computer that is password protected. All information provided to the researcher at the clinic appointment will remain confidential.

However, please note: any information shared within the interview relating to anything that may be considered harmful to you or others will be disclosed to the appropriate authorities**.**

What will happen to my information?

With your consent, the information you and the other participants provide from routine data and the dietary recall, measurements and functional ability, will be analysed to establish similarities or difference. Only my supervisors and I will have access to these data. The results will be summarised and written up in a report (PhD thesis) and is likely to be presented at some point, as part of my PhD and may also be suitable for publication in a research paper. No names or other identifying material will be used in the report to protect your anonymity. The data will be kept for five years and will be destroyed after this period. A short fact sheet of the main findings will be made available to you after the study is complete however, if you would like to have a more detailed copy of the findings, please let me know during the study or get in touch using the details overleaf.

Ethical approval

The study has been given ethical approval by NHS Ethics

Thank you for reading this information sheet. Please contact me or my supervisor if you have any further queries.

Researcher details:
Mrs Linsey King
Email: umlmk@leeds.ac.uk

Supervisor details:
Professor Daniel Peckham
Respiratory Consultant

If you wish to contact someone about the study who is not directly involved in the study then please contact

Dr Helen White
Email: h.white@leeedsbeckett.ac.uk

If you wish to make a complaint about the study then please contact
Patient advice and Liaison services (PALS)
St James's University Hospital
Beckett Street
Leeds
West Yorkshire
LS9 7TF
Tel: 01132067168
Email: patientexperience.leedsth@nhs.net

K.2 Participant consent form – Chapter 4

The Leeds Teaching Hospitals NHS Trust

UNIVERSITY OF LEEDS

IRAS 216351 **Participant Consent Form**

Characterisation of Bronchiectasis patients in a Regional Clinic

Please initial the boxes if you agree with the statements

1. I confirm that I have read and understood the information sheet (V4 23/03/17) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical or legal rights being affected[1]. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers. ☐

5. I agree to take part in the study and to complete 24 hour recall, handgrip and tricep skinfold measurements. ☐

6. I agree that the research results can be included in a report, presentation and research paper and that all personal identifying details will be removed. ☐

If you wish to take part, please write and sign your name below

Name of participant	**Signature**	**Date**

Name of person taking consent	**Signature**	**Date**

[1]Participants can withdraw from the study at any point without giving a reason. However, to maintain anonymity and confidentiality we will not ask you for your name or any other information which will identify you once extra assessments (24hr recall, handgrip dynamometry) over and above your standard appointment are completed. If you wish to withdraw from the study, it will not be possible to identify your response in order to remove it.

K.3 Participant information Sheet – Chapter 7

The Leeds Teaching Hospitals NHS Trust

UNIVERSITY OF LEEDS

Participant Information Sheet **IRAS 222335**

Feasibility study exploring supplementation of nutritional protein gels in Primary Ciliary Dyskinesia

We would like to invite you to take part in our research study because you have Primary Ciliary Dyskinesia. Before you decide, we would like you to understand why the research is being done and what it would involve.
Please take time to read this information and feel free to ask us any questions or raise any concerns. The research is very safe and will help us to better understand if specific nutrition supplements can be taken easily and in people with Primary Ciliary Dyskinesia. The first part of the study is looking at the information that is usually collected at your usual appointments with the doctors along with some additional assessments. As part of the study you will be in contact with the researcher on a monthly basis until the final appointment which will repeat measures taken in the initial appointment.

Purpose of the study
In previous research we have identified people with Primary Ciliary Dyskinesia may require additional nutrition support. In this study we will look at the acceptability of an additional nutritional supplement and other measures such as a walking test and percentage body fat to determine if these are manageable for patients to complete as part of their care. We hope that this study will inform future research to establish if specific nutrition is needed as part of routine care and to help in improving symptoms associated with the condition and overall quality of life.

Why have I been chosen?
You have been chosen because you have been diagnosed with Primary Ciliary Dyskinesia and you attend the regional clinic as well as meeting the inclusion criteria

Do I have to take part?
You do not have to take part in this study. If you do not wish to take part, your decision will not affect your usual clinical care. You can withdraw from the study at any point if you change your mind after consenting. You can also consent to some, but not all of the tests if you would rather.

What will happen if I decide to take part?
If you agree to participate, you will be given further information by one of the study team
We will arrange with you at your next routine appointment for the additional assessments to take place.
You will be given a unique study number so that your data remains anonymous to anyone else**.**
Your name and study number will be recorded and locked in a filing cabinet in a locked office

which only the research team have access to. This is so that we can remove you from the study at a later point should you not wish to continue.

What will be involved?

The study will involve collecting routine information as part of your usual care. This would include your lung function, blood tests and recent infections. Once collected in full, the data will be extracted from your patient record and your unique study number applied. This means there will be a link to you and your corresponding study number, but this will not be used as part of viewing the data, only to remove you from the study should you not wish to continue. As well as this, further measures will be completed at this first appointment with some being repeated at specific time points in the following 3 months.

Part 1 - Additional baseline assessments

You would be asked to complete additional assessments these have been listed below along with the time each test should take.

- **Taste test of the nutritional gel and completion of taste questionnaires – (5 mins)** – this will help us to see if you are able to take the gel and record how it tastes to you. If you are unable to or do not like the gel you will not be asked to continue to take them and you will continue with your routine care. If you are able to continue to take the gels you will be asked to take 2 each day for a period of 3 months.
- **Specific Health Related quality of life Questionnaire (5 mins)** – this asks questions about your daily life and the impact of your condition upon it at that time of completion.
- **Generic Health Related quality of life questionnaire (5mins)** – this is similar to the previous questionnaire but is not directly linked to your lung condition. This helps us to understand the impact on your daily life of your condition when compared with different clinical diseases.
- **Dietary intake (10 minutes) –** this will be a short conversation with the dietitian, who will ask about what you had to eat and drink the previous day. This will help us to understand any changes to your eating and drinking during the study. This record of your dietary intake will occur 4 times over a 3-month period. Once at the initial appointment, a further 2 over the telephone and the last at your return appointment at 3 months.
- **Measurement of handgrip strength and skinfolds (7 mins)** – using a small handgrip device we will ask you to squeeze this 3 times and record the results. This measure tells us about the functionality of the muscles in your arm and is a very useful indicator of wellness. In addition to understand a little more about your body e.g. percentage body fat we would also like to take measurements of your skinfolds and will require access to your upper arm. This will be carried out by a qualified dietitian.
- **Walking test (10 minutes)** – this test is to understand your ability to walk for a period of time and assess the impact of this on your breathing it can tell us a lot about how well you may be at the time of the assessment. You may become breathless during this test; how much will be dependent on your current lung function and wellness. You will need to wear comfortable clothes and walk for a total time of 6 minutes. Throughout this test you will be asked to rate your level of breathlessness using an identified scale. If you use

walking aids you should still use them during the test. You will be instructed to walk at your own pace between two points until you are asked to stop or until you feel you cannot continue.

- **Measuring Body composition with Bio Electrical Impedance machine (10 mins) –** this is a machine that you will be required to stand on, it measures in more detail what your body is made up of e.g. percentage body fat and is used to compare with the skinfold measures also taken. It can tell us if any changes have happened from the beginning of the 3 months and starting to have the additional nutritional supplements and the end.
- **Recording of gels consumed and sachets saved –** we will ask you to take 2 gels each day 1 at breakfast and 1 at lunch. We will also ask you to save all the sachets from the gels you have eaten and return them at the 3 month appointment.

What do I need to do before the additional tests?

Before you come to the next routine care appointment and if you have expressed interest in taking part in the study there are some things you will be asked to do before you attend the appointment. These will be sent to you with this information and they are the following

- Wear loose comfortable clothes for the walking test and to help gain access to your arm for the skinfold measures
- Avoid any vigorous activity 8 hours before the Bioelectrical Impedance Analysis (BIA) and to not eat or drink within 4 hours of taking the measurement (where possible)
- Avoid any vigorous activity 2 hours before the walking test

It is important that you feel you can prepare for this and so please contact the research team via the contact information below should you have any queries

You will be asked about the pre test guidelines and if you have been able to undertake them and your response recorded. This will affect what aspect of the study you will be involved in.

Part 2 and Part 3 (Measures at end of month 1 and month 2)

An appropriate time will be arranged with you to contact you via telephone at 1 month after the initial assessments. You will be asked to repeat the following over the telephone.

- **Dietary intake (10 minutes) –** this will be a short conversation with the dietitian who will ask about what you had to eat and drink the previous day. This will help us to understand any changes to your eating and drinking during the study. This record of your dietary intake will occur 4 times over a 3-month period. Once at the initial appointment, a further 2 over the telephone and the last at your return appointment at 3 months.
- **Taste test of the nutritional gel and completion of taste questionnaires – (5 mins)** – this will help us to see if you are still able to take the gel and record how it tastes to you. If you are unable to or do not like the gel anymore you will not be asked to continue to take them. If you are able to continue to take the nutritional gels you will be asked to take 2 each day for the following 2 months.

Part 4 final measures at end of month 3

All measures outlined in **Part 1** will be repeated at this appointment that will have been arranged for you at the start of the research this includes a repeat of the measures you would normally have taken as part of your routine care. At this appointment you will also be asked to have an additional blood test. This test is to measure the vitamin D level in your blood. This blood test would usually only be carried out once a year and so we are asking you to have another test done at the end of the 3 months.

The amount of blood taken will be approx. 8.5ml and this will be sent to the lab for measuring the vitamin D level in your blood. The blood will then be discarded.

What are the possible benefits of taking part?

This study will help us learn if these supplements can be tolerated for a period of time and any impacts on you as a patient with Primary Ciliary Dyskinesia.

What are the possible risks of taking part?

This is a safe study, but some parts may feel more difficult to do and these are listed below

- Being asked to recall your dietary intake relies on memory and may cause you frustration if you struggle with this.
- Being asked to complete questionnaires may also cause frustration and survey fatigue
- Completing a six-minute walking test requires you to walk for a continued period of 6 minutes and you may feel tired afterwards and experience breathlessness that may force you to stop. How breathless you become will be measured but you may feel uncomfortable during this test.
- Assessing handgrip strength will also require you to hold and grip a piece of equipment (3 times) which if not done correctly may cause discomfort.
- The measurement of the upper arm requires access and so will result in moving of clothes.

Whilst all the measures above may cause some difficulty you can at any point stop any of the measures if you choose not to continue. This will not affect the delivery of your routine care which will continue as usual.

Confidentiality

All information which is provided to the study by you will be kept strictly confidential. People who do not need to know who you are will not be able to see your name or contact details. Once the study is completed, we will keep your data to check some of the results and the reports will be written so nothing can be linked back to you as an individual. The only linked data will be the original name and allocated study number along with consent this will be stored in a locked filing cabinet and locked office at the research site and only accessible by the research team.

What will happen to my information?

University of Leeds is the sponsor for this study and following your consent, the information you and the other participants provide will be used as part of a written of educational report (PhD thesis). These are also likely to be presented and possibly published as research

Data Storage

Consent forms will be kept at your local hospital site. This will then be stored in a locked cabinet in local hospital site building and allow access for the main study coordinator (also Chief Investigator). These will have the unique study number and participant identifiable data. Only the unique study number will be entered onto the computer database for the assessments and storage of results. Assessment data will be stored on secure, encrypted NHS computer drive and University of Leeds password protected servers. Assessment data will be anonymized with only individual study number and will be stored for 4 years. We would like to be able to identify data we have collected for participants. Only the study team Chief Investigator and coordinator will have access to the stored data after study completion.
Further information can be found here
https://dataprotection.leeds.ac.uk/wp-content/uploads/sites/48/2019/02/Research-Privacy-Notice.pdf. https://dataprotection.leeds.ac.uk/wp-content/uploads/sites/48/2019/09/HRA-transparency-wording.pdf.

Ethical approval
The study has been given ethical approval by NHS Ethics

Can I see the results?
We will not be routinely sending results to individuals however if you specifically request your results this can be arranged by informing the chief investigator (see below) as your data will be link anonymised.

What if I have a problem with the study?
If you have a problem or any concern about any aspect of this study, please do contact a member of the research team using the details below as we may be able to answer the query for you.

Concerns and contact details
If you have any concerns with regard to the way your personal data is being processed or have a query with regard to this Notice, please contact our Data Protection Officer at dpo@leeds.ac.uk Our data controller registration number provided by the Information Commissioner's Office is Z553814X

Researcher details:
Mrs Linsey King is the Chief Investigator and study coordinator and a registered dietitian DT 08004
Email: umlmk@leeds.ac.uk

Supervisor details:
Professor Daniel Peckham, Director of Studies
Respiratory Consultant
Contact number (0113) 2065282

If you wish to make a complaint about the study then please contact
Patient advice and Liaison services (PALS)/Complaints
St James's University Hospital
Beckett Street
Leeds
West Yorkshire
LS9 7TF
Tel: 01132067168

Email: patientexperience.leedsth@nhs.net

Thank you for reading this information sheet. Please speak to any of the research team detailed above if you have any further questions.

University of Leeds is the sponsor for this study based in the United Kingdom.
We will need to use information from your medical records for this research project.

This information will include your name and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.
We will keep all information about you safe and secure.
Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.
What are your choices about how your information is used?
You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.
Where can you find out more about how your information is used?
You can find out more about how we use your information by contacting one of the research team

K.4 Participant consent form - Chapter 7

The Leeds Teaching Hospitals NHS Trust

UNIVERSITY OF LEEDS

IRAS ID: 222335

Participant Identification Number for this research:

CONSENT FORM

Title of Project: Feasibility of consumption of nutritional supplementation in Primary Ciliary Dyskinesia (PCD)

Name of Researcher: Linsey King

Please initial box

1. I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. (If appropriate) I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers. ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

Appendix L Oral supplement gel formula

VITRITION UK LTD

PRODUCT SPECIFICATION	**QD27 V8.2 25.04.2017**	**APPROVED: T CAINE**
PRODUCT CODE	1223 (D603/2)	
DESCRIPTION	OVER 50S GEL WITH VITAMIN D	
CUSTOMER	LEEDS BECKETT UNIVERSITY	

Version 1 15/09/2020 **IRAS 222335**

17.2 PRODUCT PRESENTATION

PHYSICAL APPEARANCE	Off white opaque gel
FLAVOUR/TASTE	Orange
TEXTURE/AROMA	Gel

SUGGESTED SERVING SIZE/DOSAGE
1 sachet – 65g

DIRECTIONS FOR USE
Consume directly from sachet

STATUTORY CATEGORY AND LABEL DESCRIPTION
17.2 Supplements in a liquid form

OTHER LABELLING CONSIDERATIONS

APPENDIX K LABEL CLAIMS

INGREDIENTS BY RANKING	**CODE**	**E No**	**Mg/65g**	**COMMENT**
Water	9999		29,745	Excipient
Glucose liquid	3553		24,290	Sweetener
L Leucine	6006		3000	Active
Sucrose	3088		2000	Sweetener
L Lysine	3059		900	Active
L Valine	6003		900	Active
Citric acid	3000		840	Flavour enhancer
L Isoleucine	6006		830	Active
L Threonine	1606		830	Active
DL phenylalanine	102		530	Active

L Hystidine hcl			380	Active
Xanthan gum	3017		300	Thickener
Flavours (orange/passion fruit)	3429		250	Flavours
DL methionine	3079		150	Active
Potassium sorbate	3062		50	Preservative
Cholecalciferol	6031		5	Active

NUTRITIONAL DATA

Energy KJ				
Kcal	**113.65**			
Protein				
Carbohydrates	**21.936**			
of which sugars	**13.36**			
Fat	**0**			
of which saturates				
Fibre				
Salt	**0.026**			

ACTIVE INGREDIENTS

INGREDIENT	Mg per 65g	+ over %	Per 65g serving	Assay %	Mg per 65g	As
L Leucine	3000		3000	100.0	3000	L Leucine
L Lysine hcl	900		900	100.0	900	L Lysine hcl
L Valine	900		900		900	L Valine
L Isoleucine	830		830		830	L Isoleucine
L Threonine	830		830		830	L Threonine
DL phenylalanine	530		530		530	DL phenylalanine
L Hystidine hcl	380		380		380	L Hystidine hcl
DL methionine	150		150	100.0	150	DL methionine
Cholecalciferol	5		5	0.25%	12.5mcg	Vitamin D

ANALYTICAL STANDARDS

	UNIT	**MIN**	**MAX**	**TYPICAL**	**FREQUENCY**
MICROBIOLOGICAL					
TVC	**cfu/g**		100		Every batch
Enterobacteriaceae	**cfu/1g**		10		Every batch
Salmonella	**cfu/10g**		ND		Every batch

Yeasts	**cfu/g**		100		Every batch
Moulds	**cfu/g**		100		Every batch
PHYSICAL					
p.H.				3.1	Every batch
Colour				Against standard	Every batch
FUNCTIONAL					
At customer's request					

To the best of our knowledge and from information provided from our suppliers the product is considered to be of the following:

ASSESSMENT	**Y/N**	**COMMENTS**
Free from additives	N	
Free from artificial colours	Y	
Free from benzoates	Y	
Free from BHA/BHT	Y	
Free from egg/egg derivatives	Y	
Free from cheese/cheese derivatives	Y	
Free from milk/milk derivatives	Y	
Free from shell/fish derivatives	Y	
Free from sulphur dioxide	Y	
Free from nuts/seeds	Y	
Free from peanut oil	Y	
Free from sources of celery	Y	
Free from sources of Mustard	Y	
Free from sources of lupins	Y	
Free from Soya/soya derivatives	Y	
Free from Gluten	Y	
Free from glutamates	Y	
Free from genetic modification	Y	
Free from wheat/wheat derivatives	Y	
Free from artificial sweeteners	Y	
Free from irradiated ingredients	Y	
Free from sulphur dioxide <=10mg/kg as SO2	Y	
Free from alcohol	Y	
Free from treatment with gas	Y	
Suitable for Phenylketonurics	Y	
Suitable for Halal diet		Not certified
Suitable for Kosher diet		Not certified

Suitable for vegetarians	Y	
Suitable for Vegans	N	Cholecalciferol from sheeps wool
Suitable for Diabetics		Seek medical advice
Suitable for lactose intolerants	Y	
Suitable for allergy to fruit/fruit extracts	N	Natural fruit flavours

DESCRIPTION OF PRIMARY PACKAGING

Plain four sided foil sachet 12/9/75 measuring 75mm wide x 150mm long. Batch number stamped on.

DETAILS OF PRIMARY PACKAGING LABEL AND CODING

SHELF LIFE/EXPIRY	BATCH EXPIRES (BBE)
DATE OF MANUFACTURE PLUS	

PRIMARY TARGET WEIGHT	65g
PRIMARY TARKET VOLUME	
PRIMARY PACKAGE WEIGHT	Negligible
No of units per secondary packaging	

DESCRIPTION OF SECONDARY PACKAGING

INCLUSIONS WITH SECONDARY PACKAGING

TOTAL GROSS KG OF FINISHED UNIT	65g

FURTHER COLLATION/SHIPPERS	Packed to shippers measuring 372 x 315 x 155mm
UNITS PER TRAY/SHIPPER	150 sachets per shipper

DESCRIPTION OF PALLET CONFIGURATION/LABELLING
To be determined

STORAGE REQUIREMENTS
Store in a cool dry place. Keep away from children

HANDLING PRECAUTIONS, HEALTH & SAFETY CONSIDERATIONS

ENVIRONMENTAL PACKAGING WASTE DETAILS

	ITEM	MATERIAL	RECYCLABLE ?
APPENDIX K PRIMARY:	Sachet	Foil	Yes
APPENDIX L SECONDARY	Shipper	Cardboard	Yes
APPENDIX K			
TERTIARY			

Appendix I – List of Associated Legislation for product compliance
The Food Safety Act 1990

The Food Hygiene (England) Regulations 2005, 2006, 2014.

Weights & Measures Act 1985

The Weights and Measures (Packaged Goods) Regulations 2006

Food Labelling Regulations 1996

Food Information Regulations 2014

Food (Miscellaneous Amendment and Revocation) (England) Regulations 2013

General Food Regulations 2004

Food Supplements Regulations 2003

Nutrition & Health Claims Regulations 2007

Miscellaneous Food Additive Regulations 1995
(and amendment Regulations 1999, 2001, 2005,)

Sweeteners in Food Regulations 1995
(and amendment Regulations 1997, 1999, 2001, 2002,2003)

Fish Oils and Hygiene Legislation EC 1664/2006

EC Food Supplements Directive 2002/46 (1925/2006) addition of vitamins & minerals and certain other substances to foods. (amended by EC 1170/2009)

The Food Labelling (Declaration of Allergens) (England) Regulations 2007, 2008, 2011.

The Colours in Food Regulations 1995

The Foods Intended for Use in Energy Restricted Diets for Weight Reduction Regulations 1997

The Foods for Particular Nutritional Uses (Addition of Substances for Specific Nutritional Purposes)(England) Regulations 2002, 2006, 2009.

Contaminants in Foods Regulations 2007, 2010, 2013
(and EC1881/2006 as amended by EC 629/2008)

Genetically Modified Food Regulations 2004

Food Irradiation Provisions Regulations 2000

Food Irradiation (England) Regulations 2009

Materials and Articles in Contact with Food Regulations 2005, 2012.
The Food Additives (England) Regulations 2009

Official Feed and Food Controls (England) Regulations 2009

Specified Products from China (Restriction on First Placing on the Market) (England) Regulations 2008, 2012, 2013.

Food Additives, Flavourings, Enzymes and Extraction Solvents (England) Regulations 2013.

The Food Safety and Hygiene (England) Regulations 2013.

Food for Particular Nutritional Uses (Addition of Substances for Specific Nutritional Purposes) Legislation.

Food for Particular Nutritional Uses (Miscellaneous Amendments) Legislation.

Appendix M Calculated protein and energy requirements

Energy requirements FFM x 30 kcal x PAL

Protein requirements 1.0 – 1.5g/actual body weight/d

Adjusted for BMI >30 kg/m^2 75% of requirements.

Participant	Energy calculation	Energy requirement (kcal)	Protein calculation	Protein requirement	Adjusted 75%
1 Baseline	44.3 x 30 x 1.3	1727	77.9 x 1.0 X 1.5	78 – 117g	59-88g
1 3 month	42.7 x 30 x 1.3	1665	75 x 1.0 X 1.5	75-113g	56-85g
3 Baseline	46.2 x 30 x 1.4	1940	89.8 x 1.0 X 1.5	90-135g	68 – 101g
3 3 month	46.6 x 30 x 1.4	1957	84.4 x 1.0 X 1.5	85-127g	64 – 95g
6 Baseline	63.4 x 30 x 1.4	2663	94.4 x 1.0 X 1.5	95-143g	71 – 107g
6 3 month	63.9 x 30 x 1.4	2683	98 x 1.0 X 1.5	98 – 147g	74 – 110g
7 Baseline	62.1 x 30 x 1.3	2422	83 x 1.0 X 1.5	83 – 125g	NA
7 3 month	61.3 x 30 x 1.3	2391	83.5 x 1.0 X 1.5	84 – 126g	NA
8 Baseline	62.6 x 30 x 1.3	2441	86 x 1.0 X 1.5	86 – 129g	NA
8 3 month	61.6 x 30 x 1.3	2402	86.3 x 1.0 X 1.5	86 – 129g	NA
10 Baseline	49.1 x 30 x 1.4	2062	63.5 x 1.0 X 1.5	64-96g	NA
10 3 month	48.1 x 30 x 1.4	2020	62 x 1.0 X 1.5	62-93g	NA
11 Baseline	52.8 x 30 x 1.3	2059	76.2 x 1.0 X 1.5	76-114g	NA
11 3 month	53.0 x 30 x 1.3	2067	80.1 x 1.0 X 1.5	80-120g	NA
13 Baseline	53.8 x 30 x 1.5	2421	68.9 x 1.0 X 1.5	69-104g	NA
13 3 month	54.1 x 30 x 1.5	2435	71 x 1.0 X 1.5	71 – 107g	NA
14 Baseline	27.8 x 30 x 1.4	1168	42.8 x 1.0 X 1.5	43-65g	NA
14 3 month	27.8 x 30 x 1.4	1168	42 x 1.0 X 1.5	42-63g	NA
15 Baseline	42.1 x 30 x 1.4	1768	57.5 x 1.0 X 1.5	58-87g	NA
15 3 month	44.3 x 30 x 1.4	1861	58 x 1.0 X 1.5	58-87g	NA

Appendix N Physical Activity Levels (PAL) and Habitual Activity estimation Scales (HAES) equivalence

HAES score	PAL value
Inactive	1.1
Somewhat Inactive	1.2
Somewhat active	1.4
Active	1.5

Appendix O Published paper

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Original article

Nutritional status and intake in patients with non-cystic fibrosis bronchiectasis (NCFB) - a cross sectional study

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SUMMARY

Background & aims: Bronchiectasis is a heterogeneous, chronic respiratory condition, in which the role of nutrition remains unclear and nutritional guidance is lacking. Few studies have explored the role of nutrition in disease management, and little is known about nutritional requirements during periods of stability or metabolic stress. The aim of this study was to characterise nutritional status and intakes in a cohort of patients and identify potential associations with body composition and functional capacity.
Methods: A prospective observational cohort study was undertaken in an adult population (>17 years). Bronchiectasis was confirmed by high-resolution computerised tomography (HRCT). Anthropometric (weight, height, Body Mass Index (BMI), triceps skinfold thickness (TSF), mid upper-arm circumference (MUAC) and mid arm muscle circumference (MAMC)] lung function and nutritional intakes were measured. Results were analysed as a whole and by disease aetiology [primary ciliary dyskinesia (PCD), Idiopathic cause (IC), bronchiectasis in association with asthma and other] and associations tested.
Results: In total, 128 participants (65.5% female) completed the study. Median handgrip strength (HGS) in the total sample was only 66.5% (IQR 60.5–89.8) of reference population norms and was low for those with PCD [58.0% (IQR 43.5–70.0))]. Univariate regression indicated that BMI was a statistically significant predictor of lung function in the whole population with HGS and weight identified as statistically significant predictors of lung function in PCD. The total population and each sub-group failed to meet estimated average requirements for energy but exceeded the Reference nutrient intake (RNI) for protein. Vitamin D was consistently <35% of the RNI.
Conclusion: BMI lay within normal to overweight ranges within the whole population and sub-groups, but masked important functional, body composition and nutritional deficits. This was particularly so within a younger sub-group with PCD, who had impaired muscle function, when compared to other causal and associative diseases.

Bronchiectasis is a chronic debilitating respiratory condition which may be either congenital or acquired [1,2]. It is associated with many underlying diseases, including pneumonia, tuberculosis, cystic fibrosis (CF), primary ciliary dyskinesia (PCD), immunodeficiency, rheumatoid arthritis [3,4], and environmental exposure. Bronchiectasis is characterised by thickening and dilatation of the bronchial walls, abnormal muco-ciliary clearance, airway inflammation and a predisposition to infection. Neutrophil infiltration and raised pro-inflammatory cytokines driven by a cycle of repeated bacterial and viral infections can result in a milieu of infection and inflammation which further impairs lung function, health status and recovery from infective episodes [5,6]. Its increasing prevalence [7,8] and heterogeneous nature highlights the importance of characterising disease sub-populations as treatment may well differ between the various phenotypes.

While studies support the concept that nutrition is important in determining outcomes in bronchiectasis [9–11], evidence is still emerging. Unlike other respiratory diseases such as CF and chronic obstructive pulmonary disease (COPD) where nutritional

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0261-5614/

intervention has a distinct role in disease stabilisation or functional status [12,13], the wide spectrum of clinical phenotype associated with bronchiectasis has created challenge in assessing new therapies and interventions such as nutrition. As a result, few studies have explored its role in disease management, and little is known about nutritional requirements during periods of either stability or metabolic stress [6]. Nutritional guidance is lacking and instead treatments have focused on antibiotic therapy [14] and physiotherapy [15] to enable clearance and management of infection.

Most nutritional studies have focused on micronutrient status, in particular Vitamin D. In a study by Ferri et al. [16], 64% of subjects were found to be deficient in Vitamin D and reduced levels were associated with an increase in bacterial lung colonisation [17]. Vitamin D supplementation may also contribute towards reduced frequency of exacerbations and suppression of the inflammatory response [18].

Less is known about macronutrient intakes, the nutritional status of this population, and whether there is any correlation with body composition and functional capacity. Emerging evidence suggests that the measurement and understanding of body composition is important to support effective medical and nutritional management of chronic conditions, recognising the impact of reduced lean tissue mass (LTM) and fat mass and its proinflammatory impact on chronic lung disease. Whilst initial case control studies in small populations have identified reductions in peripheral muscle endurance [19] and fat free mass [20] compared to healthy individuals, an understanding of the relationship between nutritional status, dietary intake and body composition is lacking. Within current guidance for the management of Non-Cystic Fibrosis bronchiectasis (NCFB), the need for further research into nutritional supplementation has been acknowledged [21].

The aim of this study was therefore to characterise nutritional status and dietary intakes in a cohort of patients with NCFB and identify potential associations with body composition and functional capacity.

1. Methodology

1.1. Study design

This was a prospective observational study. Patients attending a Regional NCFB clinic from July 2017 to July 2018 were consecutively recruited at their routine clinic appointments as part of annual review during a period of clinical stability. All participants had confirmed bronchiectasis, diagnosed by high-resolution computerised tomography (HRCT) and were ≥17 yrs. Patients who were pregnant, had a cancer diagnosis or were aged less than 17 yrs were excluded. The frequency of chest physiotherapy was recorded for each participant.

1.2. Measures

Baseline data recorded as part of routine care were retrieved for each participant. The recording of each parameter was undertaken following a standardised operating procedure at each clinic visit.

Anthropometry Weight (kg) and height (m) were collected using calibrated SECA weighing scales (SECA 956 Class III, SECA, Birmingham. UK) and Leicester Height measure (MK II, SECA, Birmingham, UK). Body mass index (BMI) was calculated for each participant (Weight/Height^2). Participants were classified according to the following BMI ranges; <18.5 kg/m^2 (Underweight), 18.6–24.9 kg/m^2 (normal range), 25–29.9 kg/m^2 (overweight), 30–39.9 kg/m^2 (obese), 40–49.9 kg/m^2 (morbidly obese) [22].

Pulmonary function was assessed by means of standard spirometry using a Vitalograph Compact II Spirometer (Vitalograph Ltd, UK). FEV_1 and FVC were compared with reference values and reported as the percentage of the predicted normal value. The number of infective episodes over the previous year was recorded.

Peripheral muscle strength was evaluated by Hand Grip Strength (HGS), using a Takei 5401 Handgrip dynamometer (Takei Scientific Instruments Co., Ltd, Tokyo, Japan). This was performed with the participants in standing position, arm by their side with full elbow extension. Measurements were repeated 3 times for the non-dominant side. Values were expressed as a mean of all three measures. Measures were then compared to consolidated grip strength values adjusted for age and sex with values less than 85% of standard mean considered as impaired muscle function [23].

Triceps skinfold thickness (TSF) was measured using Harpenden skinfold calipers (Baty International, Burgess Hill, West Sussex, UK). The midpoint was determined from the acromium to the olecronan process and a skinfold measure was taken at the midpoint, with a mean determined from three repeated measures. Mid Upper Arm Circumference (MUAC) was recorded at this midpoint using a tape measure. Mid arm muscle circumference (MAMC), an established measure of muscle protein mass, was calculated from MAC and TSF using a standard formula: MAMC = MAC - (3.1415 × TSF). The MAMC and TSF results were expressed as a percentage of the expected reference values, adjusted for sex and age [24]. Values were then dichotomised into those >50th centile and those <50th centile according to reference norms.

Nutritional Intake A 24-h dietary recall (using a multiple pass technique) was undertaken for each participant at 3 time points (baseline recruitment and each subsequent week for 2 weeks, until a total of 3 were retrieved) by a registered dietitian. Dietary recall interviews were undertaken face to face at the clinic appointment and then by telephone interview. Each dietary recall was coded, and energy, protein, carbohydrate, fat, vitamin D, iron and Calcium intakes were calculated. A mean of all seven nutrients for each individual patient was then recorded. Food records were analysed by the same dietitian using MyFood24© [25] and intakes compared to the EAR (energy) and RNI (protein, calcium, vitamin D) [26,27]. Macronutrient values were also presented as a proportion of total energy intake.

1.2.1. Disease aetiology

All participants were characterised by disease aetiology defined as primary ciliary dyskinesia (PCD), Idiopathic cause, bronchiectasis in association with asthma and other (inclusive of Immunoglobulin, Post Infective, Auto −immune, other genetic cause).

1.2.2. Microbiology

All participants were also characterised by their predominant microbiological status throughout the study period.

1.2.3. Comorbidity

Presence of diabetes was also recorded for all participants.

1.2.4. Statistical analysis

Data was analysed using IBM SPSS statistics version 24 (IBM Corp, Armonk, N.Y. USA) by whole population and then grouped by aetiology. Data was checked for normality using the Shapiro Wilk test. Data variables were varied in their distribution. Data was therefore presented in a standard way as median and interquartile range (IQR). Pearson's (r) or Spearman's (rho) correlations were used to explore associations of lung function (FEV_1%) with anthropometric measures (MAMC, HGS, TSF, BMI, Weight) and

nutrient intake (energy, protein, carbohydrate, fat, vitamin D, iron and calcium). Kruskal–Wallis was used to determine differences between the medians of values within aetiological groups. Linear regression analysis was used to identify predictors of lung function outcome. Statistical significance was set at a p-value less than 0.05 ($p < 0.05$).

1.3. Ethics

Health Research Authority granted ethical approval, by proportionate review at South Central Hampshire B Research Ethics Committee (IRAS 216351).

2. Results

2.1. Participants

In total, 129 participants were recruited to the study. Of this number, one was lost to incorrect diagnosis of NCFB (n = 128) and 125 completed nutritional recall interviews. The total population was predominantly female (65.6%), with the majority of participants lying just within the overweight range [mean BMI 25.1 (±5.4) kg/m^2]. Participant characteristics are presented in Table 1.

Analysis by disease aetiology indicated that idiopathic disease was the most predominant (38.5%). Significant difference was noted in median age between aetiological groups; those with PCD [23.0 years (IQR 19.0–27.0)] more than 4 decades younger than those presenting with idiopathic disease [70.0 years (IQR 59.0–75.0)], bronchiectasis in association with asthma [67.0 years (IQR 59.0–71.0)]or 'other' aetiologies [70.0 years ([IQR 54.0–75.0)], $p < 0.001$.

2.2. Anthropometry

Mean handgrip strength in the total sample was only 66.5% (IQR 60.5–89.8) of reference population norms. Significant differences were noted between aetiological sub-groups. Participants with PCD and Bronchiectasis associated with asthma had a lower percentage of normative values than all other aetiologies, [58.0% (IQR 43.5–70.0)] [56.0% (IQR 37.5–74.5)]. In contrast there were no differences noted in MAMC (an estimate of somatic protein reserve) or triceps skinfold thickness between groups (Table 1). Mean MAMC adjusted for age and gender reflected 46% of the total population having adequate measurements based on calculations of <90% of 50th centile being inadequate and >90% of 50th centile being adequate compared to normative values with similar results in all other aetiologies. TSF, a measure of predicted fat mass, did reflect higher numbers less than 50th centile cut offs.

When the total population was stratified by lung function (FEV_1 (%) quartile) no differences were observed between participants (Table 2). In contrast, significant differences were observed across all strength parameters in the total population when classified by BMI into categories of underweight, normal weight, overweight and obese. Those classified as underweight had lower handgrip strength, handgrip as a percentage of the norm, mid upper arm circumference, triceps skinfold thickness and mid arm muscle circumference (Table 2).

There was a significant association between weight and lung function (FEV_1%) within the total population [r (126) = 0.18, $p = 0.036$ and BMI and FEV_1%) [r (126) = 0.18, $p = 0.043$.

In those with PCD there was a significant association between handgrip strength and lung function r (23) = 0.41 $p = 0.042$, which was not seen in other aetiologies.

2.3. Nutritional intake

Mean total energy intakes for the whole population (n = 125) were below estimated requirements [27] as were energy intakes for each sub-group (Table 3). Protein intakes exceeded the RNI for protein for the whole population and all sub-groups with Vitamin D consistently <20% of the RNI (Table 3). Whilst none reached statistical significance between groups, those with PCD had the lowest mean intakes of protein, iron, calcium and vitamin D (see Table 3).

2.4. Predictors of lung function

Univariate regression indicated that weight ($\beta = .185$, $p = 0.036$), and BMI ($\beta = 0.179$ $p < 0.043$) were statistically significant predictors of lung function in the whole population with HGS and weight identified as statistically significant predictors of lung function in PCD ($\beta = .431$, $p = 0.03$, $\beta = 0.409$ $p = 0.04$) (Table 4) Vitamin D intake was a significant predictor of lung function for 'other' aetiologies, but not for any other category.

3. Discussion

This is the first study to report dietary intake, body composition and functional capacity (as measured by handgrip strength), in a population with bronchiectasis. Our results show that whilst BMI lay within normal to overweight ranges within the whole population and sub-groups, important functional, body composition and nutritional deficits exist. This is particularly so within a younger sub-group with PCD, who had impaired muscle function, when compared to other causal and associative diseases.

3.1. Anthropometry

Anthropometric measures of body composition including tricep skinfold thickness (TSF), mid upper arm circumference (MUAC) and mid arm muscle circumference (MAMC) (a measure of somatic protein reserves) were comparable to normative values with no statistically significant differences between groups. This was reflected in BMI which remained in the normal or overweight range for the whole population and aetiological sub-groups. In contrast peripheral muscle strength, measured by handgrip strength, was impaired within the total population suggesting functional deficits are present. Previous studies have also shown a significant reduction in peripheral muscle strength [19,28] and exercise capacity [19] in bronchiectasis. It suggests peripheral muscle strength, measured by simple handgrip measures may have potential as an outcome measure for use in routine monitoring, pulmonary rehabilitation and risk stratification in clinical practice.

Similar findings have been reported in other respiratory diseases. In COPD, HGS is associated with CT-based markers of body composition, but not BMI [29] and more recently in those with interstitial lung disease, severity is associated with upper limb muscle dysfunction and worse physical performance, independent of muscle mass [30]. The presence of impaired muscle functionality, independent of muscle mass and BMI, aligns with the revised European consensus on definition and diagnosis of sarcopaenia [31]. Here the definition of sarcopaenia was extended, adding muscle function to previous classifications that relied on low muscle mass alone, recognising that strength is better than mass in predicting adverse outcomes. Our own findings support this, with approximately half (46%) of the total population having functional muscle impairment in the presence of adequate somatic protein reserve.

Although a reduction in peripheral muscle strength (functionality) was reflected across all aetiologies, it was significant in those with PCD where 96% of individuals failed to achieve normative

Table 1
Baseline characteristics of patients with bronchiectasis [in total and by disease aetiology].

	Total participants Proportion (%) or median (Interquartile range)	Aetiology				P value
		Primary ciliary dyskinesia (PCD) Proportion (%) or median (Interquartile range)	Idiopathic Proportion (%) or median (Interquartile range)	Bronchiectasis + asthma Proportion (%) or median (Interquartile range)	Other (Immunoglobulin Post Infective, Autoimmune, other genetic) Proportion (%) or median (Interquartile range)	
Number (%)	128	25 (19.5%)	49 (38.5%)	24 (18.6%)	30 (23.4%)	
Sex (M/F) %	44/84 (34.4% M).	8/17 (32.0% M)	17/32 (35.0% M)	7/17 (29.0% M)	12/18 (40.0% M)	p = 0.85
Age (Yrs)	65.5 (37.5–73)	23.0 (19.0–27.0)	70.0 (59.0–75.0)	67.0 (59.0–71.0)	70.0 (54.0–75.0)	p < 0.001
Weight (kg)	63.1 (55.0–77.6)	60.9 (51.7–68.3)	66.0 (56.1–83.5)	63.4 (57.9–75.6)	66.9 (51.8–83.8)	p = 0.48
BMI (Kg/m^2)	23.8 (21.4–28.1)	22.1 (20.6–25.4)	25.6 (21.6–30.1)	23.5 (22.1–30.1)	23.0 (20.5–26.6)	p = 0.15
FEV_1 (L)	1.5 (1.1–1.2)	1.6 (1.4–2.8)	1.6 (1.1–1.2)	1.4 (1.0–1.2)	1.6 (1.1–2.1)	p = 0.70
FEV_1 (%)	67.0 (52.3–80.8)	64.0 (50.5–75.5)	70.0 (55.0–83.0)	63.0 (53.0–80.0)	68.0 (50.0–84.0)	p = 0.20
FVC (L)	2.4 (1.9–3.1)	2.7 1.9–3.2)	2.5 (1.8–3.2)	2.3 (1.8–3.0)	2.5 (2.0–2.9)	p = 0.70
FVC (%)	80.5 (65.0–94.0)	73.0 64.0–86.5)	86.0 (68.0–86.5)	79.0 (71.5–100.5)	75.0 (63.0–100.0)	p = 0.10
Handgrip (Kgf)	15.4 (10.5–22.8)	15.6 (12.7–19.9)	16.8 (10.6–28.1)	13.4 (8.9–17.4)	15.8 (10.5–23.8)	p = 0.23
Handgrip (% norm)	66.5 (60.5–89.8)	58.0 (43.5–70.0)	78.0 (56.0–97)	56.0 (37.5–74.5)	77.0 (50.0–95.0)	p = 0.02
MUAC	29.3 (26.5–32.3)	29.0 (26.6–31.0)	29.5 (26.5–32.8)	29.5 (26.5–32.9)	29.4 (25.8–32.0)	p = 0.72
TSF (mm)	15.7 (12.2–18.5)	15.7 (12.4–18.1)	16.9 12.1–13.7)	16.1 (13.0–17.7)	14.3 (11.2–17.9)	p = 0.52
◦ TSF >50th percentile	31/128 (24%)	7/25 (28%)	14/49 (29%)	11/24 (46%)	7/30 (23%)	p = 0.47
MAMC (cm)	24.1 (22.1–26.9)	23.6 (21.5–26.2)	25.1 (21.8–26.9)	25.0 (22.6–27.9)	24.1 (21.8–± 4.1)	p = 0.66
◦ % MAMC >50th percentile	59/128 (46%)	12/25 (48%)	22/49 (44%)	12/24 (50%)	13/30 (43%)	p = 0.95
Infections (number previous year)	2.0 (1.0–4.0)	3.0 (0.5–5.5)	2.0 (1.0–3.0)	2.0 (1.0–5.0)	3.0 (1.0–5.0)	p = 0.49
Diabetes	4/128 (3.1%)	0/25 (0%)	1/49 (2%)	1/24 (4%)	2/30 (6.7%)	p = 0.99
Microbiology n (%)						
◦ None isolated	31 (24.2%)	2 (8.0%)	21 (42.9%)	4 (16%)	4 (13.8%)	p = 1.00
◦ Haemophilus	42 32.8%)	12 (48%)	10 (20.4%)	10 (40%)	10 (34.5%)	
◦ Pseudomonas	33 (25.8%)	9 (36%)	10 (20.4%)	7 (28%)	7 (24.1%)	
◦ Staph Aureus	7 (5.5%)	2 (8.0%)	1 (2.0%)	0 (0%)	4 (13.8%)	
◦ Aspergillus	6 (4.7%)	0	3 (6.1%)	1 (4%)	2 (6.9%	
◦ Other	9 (7.0)	0	4 (8.2%)	3 (12%)	2 (6.9%)	

FEV_1, forced expiratory volume in 1 s; FEV_1 (%) forced expiratory volume in 1 s (% predicted value); FVC, forced vital capacity; FVC (%) forced vital capacity (% predicted value); BMI, Body Mass Index; MAMC, midarm muscle circumference; TSF, triceps skinfold thickness.

Table 2
Nutritional and strength parameters [stratified by lung function and BMI category].

	Predicted FEV_1 (%) quartiles				P-value
	1st Quartile (<52%) Median (IQR)	2 d Quartile (53%–67%) Median (IQR)	3rd Quartile (68%–80%) Median (IQR)	4th Quartile (>81%) Median (IQR)	
Number (n)	32	33	33	30	
Weight (kg)	62.3 (50.9–70.4)	60.0 (52.2–71.5)	72.9 (58.5–83.6)	65.3 (53.4–86.8)	p = 0.10
BMI (Kg/m^2)	22.2 (20.6–26.9)	23.5 (21.2–27.5)	25.4 (21.8–30.4)	24.0 (21.5–29.3)	p = 0.16
Handgrip (Kgf)	15.7 (10.7–27.1)	14.0 (9.9–18.7)	17.8 (11.5–23.8)	15.4 (11.1–28.5)	p = 0.41
Handgrip (% norm)	65.5 (48.0–86.8)	65.0 (50.5–88.5)	68.0 (52.5–91.5)	70.0 (45.8–90.5)	p = 0.89
MUAC (cm)	28.8 (25.7–31.4)	28.4 (25.6–31.5)	31.0 (28.3–32.6)	29.7 (27.4–33.3)	p = 0.08
TSF (mm)	14.1 (10.8–17.4)	15.6 (13.5–20.5)	16.0 (11.5–18.2)	16.8 (13.2–19.2)	p = 0.09
MAMC (cm)	24.3 (21.2–26.5)	23.4 (20.5–26.7)	25.7 (24.0–27.8)	24.1 (22.5–28.3)	p = 0.08
	BMI Categories				P-value
	Underweight (BMI<18.5) Median (IQR)	Normal weight (BMI 18.5–24.9) Median (IQR)	Overweight (BMI 25.0–29.9) Median (IQR)	Obese (BMI >30) Median (IQR)	
Number (n)	5	71	28	24	
Handgrip (Kgf)	11.7 (9.1–14.5)	14.1 (9.9–18.2)	22.4 (16.3–29.8)	15.7 (13.2–27.2)	p = 0.003
Handgrip (% norm)	56.0 (33.6–69.0)	61.0 (47.0–79.0)	75.0 (66.0–99.5)	83.0 (54.5–95.5)	p = 0.01
MUAC (cm)	21.0 (20.8 22.6)	27.0 (25.7 29.0)	32.0 (31.0 34.0)	33.3 (31.7 38.8)	p < 0.001
TSF (mm)	13.6 (7.4–16.0)	14.9 (11.4–17.5)	16.2 (12.1–18.9)	19.3 (17.2–24.2)	p = 0.001
MAMC (cm)	17.9 (16.8–18.7)	22.9 (20.8–24.5)	26.8 (25.4–28.7)	28.3 (25.5–31.1)	p < 0.001

values (>85%) and only 8% remained free of respiratory pathogens during the study period The autosomal recessive nature of PCD, distinguishes it from other forms of bronchiectasis and in line with European registry data [32] PCD was characterised by earlier decline in lung function. These findings are supported by an earlier study in younger children with PCD who displayed deficits in exercise capacity and respiratory muscle strength as early as age 10 years [33]. Impaired muscle strength and function may predate adulthood by many years in PCD indicating a need for closer group monitoring.

A positive association between HGS and lung function in the PCD population was also observed, not shown in other aetiologies but has been noted in both healthy [34] and respiratory populations [35]. In respiratory conditions such as COPD and Cystic fibrosis, the loss of muscle mass in patients with poorer nutritional status has been hypothesized to contribute to worsening of

Table 3
Comparison of nutritional intake by whole population and according to aetiology.

	Whole population (125)	PCD	Idiopathic	Bronchiectasis + asthma	Other (Immunoglobulin Post Infective Auto − immune, other genetic)	p value
Energy intake (kcal)	1645 (1262–2019)	1615 (1161–2352)	1768 (1322–2003)	1496 (1236–2019)	1680 (1340–1843)	0.14
Energy intake (%EAR)	77.0 (62.3–94.8)	79.0 (66.0–95.5)	81.1 (±28.8)	71.0 (59.0–98.0)	79.0 (65.0–93.0)	0.5
Protein intake (g)	66.0 (52.0–81.0)	70.0 (52.0–84.0)	70.18 (±24.7)	62.0 (50.0–78.5)	62.0 (53.5–84.5)	0.34
Protein (% total energy)	16 13.0–18.5)	15.0 (13.0–19.0)	15.5 (13.8–18.0)	15.0 (13.0–17.5)	17.0 (13.3–18.8)	0.27
Protein (% RNI)	131.3 (93.9–168.8)	116.0 (88.2–170.4)	139.2 (98.8–173.2)	120.6 (95.9–169.1)	133.1 (110.9–160.8)	0.54
Protein (% 1 g/kg)	99.9 73.7–127.8)	90.6 (67.8–128.1)	104.7 (74.6–130.4))	90.5 (71.9–126.8)	100.0 (83.4–120.8)	0.65
Carbohydrate intake (g)	181.1 (141.3–216.0)	183.3 (153.3–227.3)	181.1 (134.9–218.8)	191.3 (140.7–240.2)	175.5 (134.5–194.0)	0.81
Carbohydrate (% total energy)	41.0 (36.4–46.7)	44.5 (37.0–49.1)	40.1 (±7.0)	45.5 (37.8–48.9)	40.4 (36.1–45.9)	0.12
Fat (g)	66.3 (48.4–82.9)	61.3 (44.2–82.8)	74.1 (54.6–90.3)	65.3 (48.5–89.3)	64.3 (46.6–75.2)	0.23
Fat (% total energy)	37.2 (31.9–41.0)	34 (30.2–38)	40.3 (35.3–43.1)	37.0 (30.9–39.8)	36.0 (30.4–38.7)	0.004
Fe (mg)	9.2 (7.0–11.9)	8.0 (6.2–9.5)	9.2 (7.3–11.1)	10.0 (8.0–13.5)	9.0 (7.0–11.9)	0.68
Fe (% RNI)	100.7 (68.9–126.4)	80.4 (57.4–113.2)	103.4 (80.4–126.4)	114.9 (78.7–155.1)	86.2 (68.9–136.7)	0.40
Ca (mg)	721 (570.5–954.5)	702.0 (468.5–916.5)	786.0 (593.0–1065.0)	705.0 (532.5–928.0)	713.5 (587.8–995.8)	0.72
Ca (% RNI)	103.0 79.8–134.3)	100.2 (66.9–124.0)	112.3 (82.7–112.1)	100.7 (76.1–132.6)	101.9 (84.0–142.3)	0.72
Vitamin D (μg)	2.0 (1.0–3.0)	1.0 (0.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–2.0)	0.81
Vitamin D (% RNI)	20.0 (10.0–30.0)	10.0 (0.0–30.0)	20.0 (10.0–30.0)	20.0 (10.0–30.0)	20.0 (10.0–20.0)	0.81

EAR, Estimated average requirement; RNI, Reference Nutrient intake.

Table 4
Univariate predictors of lung function by whole population and aetiology.

Predictors	All participants		PCD		Idiopathic		NCFB + Asthma		Other	
	P value	Confidence Intervals	P value	Confidence Intervals	P value	Confidence Intervals	P value	Confidence Intervals	P value	Confidence Intervals
Aetiology	0.082	− 4.84–0.29								
Sex	0.388	− 4.27, − 10.94	0.11	−26.03 − 2.85	0.25	− 0.46–17.61	0.19	− 6.32–30.89	0.61	− 15.43–25.60
Weight	0.036[a]	0.02–0.44	0.04[a]	0.02–1.15	0.90	− 0.31–0.27	0.51	− 0.38–0.75	0.05	− 0.09–1.07
BMI	0.043[a]	0.02–1.34	0.40	− 1.20–2.90	0.78	− 0.82–1.09	0.49	− 1.10–2.21	0.07	− 0.16–3.00
HGS	0.983	− 3.93–0.38	0.03[a]	0.12–2.32	0.06	− 0.10–0.02	0.76	− 0.97–1.31	0.68	− 0.77–116
TSF	0.061	− 0.030–1.36	0.38	−0.73 − 1.83	0.59	−0.77 − 1.34	0.82	− 1.95–2.43	0.09	−0.28 − 3.16
MAMC	0.141	− 0.23–1.61	0.88	− 2.08–2.42	0.49	−0.92 − 1.90	0.28	− 0.89–2.95	0.42	− 1.49–3.47
Energy	0.481	− 0.00–0.01	0.77	− 0.01–0.12	0.46	−0.01– 0.01	0.15	−0.00 − 0.01	0.96	− 0.025–0.02
Protein	0.548	− 0.07–0.13	0.69	− 0.28–0.19	0.32	−0.33 –0.11	0.10	− 0.02–0.24	0.78	−0.56 − 0.42
Vitamin D	0.246	− 0.24–0.61	0.40	− 2.32–5.58	0.26	− 2.78–0.77	0.35	− 1.82–4.87	0.01[a]	− 12.52 to −1.55

[a] Statistically significant results.

lung function as a result of increased metabolic demand from poor respiratory function [36,37]. Potentially, these mechanisms may also be present in underweight patients with PCD Within our own population, the lower strength parameters noted for those with low BMI (<18.5 kg/m^2) would suggest that interventions to improve BMI might have a positive impact on lung function. Further research to understand longitudinal trends of weight, muscle functionality and its association with lung function and repeated infections is warranted.

3.2. Nutritional intake

Muscle mass and function are both influenced by protein intake. All aetiologies met dietary protein reference values and the proportional intakes of energy by protein (15% of energy intake) recommended within national guidelines [26]. This was sufficient to maintain muscle mass within normal range but could not maintain optimal muscle function, which relies on both protein intake and resistance exercise [38]. This study did not assess physical activity levels which may have provided further insight into specific contributions of both factors. However, it suggests that adequate protein intakes were achieved when compared to reference nutrient intakes. Comparison of protein with adjusted requirements recommended by the PROTAGE study [39] of 1 g/kg/day show that targets of 1 g/kg were almost met in the total population but not for those with bronchiectasis and asthma and PCD compounding the limited muscle function, especially in this younger PCD group. Further work to assess and monitor nutritional intakes is needed to inform whether recommendations for other respiratory diseases such as COPD and Cystic Fibrosis [6,40] might also be required for PCD.

Vitamin D intakes were only 20% of dietary reference values for the whole population and similarly low for all aetiologies. The immunomodulatory role of Vitamin D within lung disease is well established [41]. From a mechanistic perspective Vitamin D is involved in the regulation of pathogen recognition receptors (PRRs) on the respiratory epithelial cells, which limit viral or bacterial spread and activation of the immune system, through the production of cytokines and anti-microbial peptides (AMPs). It is implicated in the enhancement of AMPs, reduction of antigen presenting capacity, suppression of T cell inflammation and reduction in B cell immunoglobulin production [41]. Our own findings align with previous studies in bronchiectasis showing high levels of deficiency (defined as <25 nmol/l) ranging from 50 to 64% [16,42] with a recent systematic review in COPD concluding, those with lowest levels of <25 nmol/l demonstrate the greatest benefits of supplementation in reducing chest exacerbations. Dietary intake therefore appears suboptimal and would suggest strategies to improve intake through supplementation are required. Of note our PCD subgroup had similar or greater infection rates (3 exacerbations per year) compared to all other aetiological groups, despite being 30 years younger in age. In bronchiectasis, three or more exacerbations per year at baseline have been shown to be associated with worse quality of life, greater likelihood of future

hospitalisation, increasing exacerbation frequency and mortality over a 5 year follow up period [43]. Together these are powerful drivers to investigate potential strategies such as Vitamin D supplementation and establish target levels that might address the greater risks associated with PCD. It would also suggest that routine annual monitoring is required which would align with guidance from other respiratory conditions [40].

The lowest intakes for iron and calcium were also within this PCD group, although only iron intakes were suboptimal in terms of meeting recommendations. Together it illustrates that those with PCD have greater nutritional vulnerability, apparent at a significantly younger age. Further exploration of nutritional intakes over time with appropriate nutritional needs and intervention is required to begin to address some of these identified deficiencies in nutritional status and their impact on health and quality of life.

The prospective nature of this study and large sample, reflected a true clinic population. The use of a single researcher, standard operating procedures for anthropometry and dietary recall helped to minimise error when measuring body composition and dietary intake. The high completion rate (98%) indicates strong adherence to the protocol adding rigour. Reliance on anthropometric data rather than DEXA measures might be considered limiting but enabled high completion rates.

4. Conclusion

In conclusion NCFB is a condition requiring repeated medical intervention to enable clinical stability. Patients have limitations within normal daily living, which can be influenced by their nutritional status. Whilst seventy percent of the whole participant group had impaired handgrip measures when compared to normative values for sex and age this was statistically significant in those with PCD, identifying a younger but more nutritionally vulnerable group. Further research to understand nutritional needs and associated improvement in functionality and its influence on clinical outcomes and quality of life is warranted.

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The research was conducted as part of a pathway of education.

Statement of authorship

Linsey King: Conceptualization, Methodology, data curation, project administration, formal analysis, writing- Original draft preparation.
Daniel Peckham.: Conceptualisation, resources, reviewing and editing.
Helen White: Visualization, reviewing and editing.
Ian Clifton: Conceptualisation, Reviewing.
Giulia Spoletini: Visualisation.
Theocharis Ispoglou: Reviewing.

Conflict of interest

The author declares they have no conflicts of interest.

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Appendix P BDA Abstract

Characterisation of Nutritional status in patients with non-cystic fibrosis bronchiectasis **(NCFB) A cross-sectional study and analysis across subgroups of the population.**

Background: Bronchiectasis is a condition resulting in recurrent pulmonary infections and lung inflammation. Specific guidance on nutritional assessment is lacking in non-cystic fibrosis bronchiectasis (NCFB)[1]. The aim of this study was to characterise nutritional status in a cohort of patients with NCFB and identify potential associations with lung function as a clinical indicator of progression.
Methods: Patients attending a regional NCFB clinic [July 2017-July 2018] were recruited at routine clinic appointments during clinical stability. Weight (kg); height (m); Body Mass Index (BMI Kg/m^2); Forced expiratory volume in 1s (FEV_1%); Forced vital capacity (FVC%); Hand Grip Strength (HGS) Triceps Skinfold thickness (TSF) and Mid arm Muscle Circumference (MAMC) were also recorded. Data was presented for the whole population and for each of 4 aetiologies (Idiopathic, Primary ciliary dyskinesia, asthma, other). Data was tested for normality, presented as mean (±SD) and ANOVA used to test differences across subgroups [p value <0.05 considered significant]. Linear regression explored potential predictors of lung function. Ethical approval was granted at South Central Hampshire B Research Ethics Committee (IRAS 216351)
Results: Of 129 patients recruited, 128 had clinical data for analysis. In the total population, mean age was 57(± 21.3) years, 70% had HGS measures < 85% of normative values. Differences in age and HGS were apparent across aetiology (Table 1). Univariate regression analysis identified HGS and weight as independently statistically significant predictors of lung function (FEV_1%) in subjects with Primary Ciliary Dyskinesia (PCD) (β = .431, p < 0.05, β = .409 p < 0.05).

Table 1. Demographic and anthropometric data by aetiology in a population with NCFB

Aetiology	PCD	Idiopathic	Asthma	Other	Significance
% Male	8/25 (32%)	17/49 (35%)	7/24 (29%)	12/30 (40%)	
Age	28.7 (±13.4)	63.4 (±18.2)	64.6 (±13.2)	61.7 (±18.4)	p <0.001**
FEV_1 (%)	63.24 (±16.86)	68.53 (± 18.49)	63.42 (±20.34)	68.97 (±26.52)	p = 0.565
FVC (%)	74.40 (±12.47)	83.84 (±17.85)	81.71 (± 23.61)	80.2 (±24.4)	p = 0.158
Number Infections	3.00 (± 3.25)	2.41 (± 2.42)	3.21 (±2.87)	3.30 (±2.72)	p = 0.442
Handgrip (kgf)	16.85 (± 5.95)	19.53 (±10.40)	15.01 (±7.85)	18.86 (±10.63)	p = 0.234
Handgrip (% norm)	57.76 (±15.56)	79.16 (±27.90)	60.75 (±25.95)	74.97 (± 27.25)	p = 0.004*
Handgrip strength < 85% norm	24/25 (96%)	29/49 (59%)	19/24 (79%)	18/30 (60%)	
TSF (mm)	15.94 (±5.58)	16.41 (±5.13)	15.52 (±4.10)	15.26 (±5.68)	p = 0.787
MAMC (cm)	24.02 (±3.23)	24.65 (±3.82)	25.55 (±4.55)	24.73 (±4.08)	p = 0.602
Weight (kg)	61.58 (±11.81)	69.44 (±18.89)	68.64 (±15.79)	68.48 (±17.75)	p = 0.385
BMI (kg/m^2)	23.20 (±3.49)	26.04 (±5.67)	25.08 (±5.38)	24.80 (±6.14)	p = 0.169

Data are presented as means ±SD or n [%] unless otherwise stated. **p value < 0.001 * p-value <* <0.05

Discussion: Despite BMI within the normal range for a population with NCFB, HGS is below the norm for 70% of this population. Nutritional status differs significantly according to aetiology. This is amplified in PCD, the youngest age group, where 96% fail to meet the normative range for handgrip strength. It suggests that exploration of use of HGS to more accurately predict nutritional status is warranted alongside interventions to improve/optimise lean tissue mass and associations with improvement in lung function and quality of life. Although not statistically significant in other grouped aetiologies a deterioration in muscle mass and functionality may be clinically relevant and warrants further investigation.

Conclusion: In this first study to characterise nutritional status in NCFB and by aetiology, muscle mass is low for a significant sector of the population and particularly for those with PCD. Further exploration of body composition and associated clinical and functional benefits of improving muscle mass is needed.

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Appendix Q Conference Poster SARCA

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Nutritional status in patients with non-cystic fibrosis bronchiectasis (NCFB)

Introduction:

- Bronchiectasis is a condition with diverse aetiology and variable phenotypic expression resulting in damaged lungs predisposed to recurrent pulmonary infections and lung inflammation.
- Little is known about nutritional status in this diverse population.
- Regular nutritional assessment and intervention is standard practice in other respiratory diseases such as chronic obstructive pulmonary disease and cystic fibrosis, but no such practice or guidance exists in non-cystic fibrosis bronchiectasis (NCFB).

Aim:

- Characterise nutritional status and dietary intakes in patients with NCFB
- Identify whether nutritional status is associated with clinical indicators of progression.

Method:

- Patients attending a Regional Bronchiectasis clinic from July 2017 to July 2018 were recruited at routine clinic appointments during a time of clinical stability and characterised according to the diagnosis of Primary Ciliary Dyskinesia (PCD), Idiopathic disease, Asthma and Other.
- Measures for each participant: weight (kg); height (m); Body Mass Index (BMI; Kg/m ^{2}); forced expiratory volume in 1s (FEV_1 %); forced vital capacity (FVC %) were recorded
- Additional measures: Hand Grip Strength (HGS) (Kgf) (Takei 5401 Handgrip dynamometer), Tricep Skinfold thickness (TSF) (mm) using Harpenden skinfold calipers, 24-hour dietary recall was undertaken 3 times (initial and subsequent weeks), analysed (Myfood24) then compared to the EAR (energy) and RNI (protein, vitamin D).

Statistical analysis: Data was tested for normality and presented as means (±SD). ANOVA was undertaken to test differences across groups. P value <0.05 considered statistically significant

Results:

Participant Characteristics

- 129 patients were recruited (1 lost to incorrect diagnosis and 3 incomplete dietary intake data) resulting in 128 for clinical data analysis and 126 dietary analyses.
- As a whole population, participants were predominantly Idiopathic in disease nature (38%), of female gender (66% female), with a mean age of 57 (± 21.3) yrs. and mean BMI of 25. 1 (± 5.4 Kg/m^2)), with 45% having a BMI within the normal range (25 -29.9kg/m2). Notably anthropometric means were [TSF 15.9 mm (± 5.2), (10th centile), MAMC 24.7mm (± 3.91) (75th centile)]. Mean HGS measure for the population was 18 (±9.36 Kgf), meaning that 70% had HGS < 85% of normative values.
- Participant characteristics are presented by aetiology in Table 1. Statistically significant differences were found between aetiology groups for age and % HGS compared to normative values
- Univariate regression showed weight and BMI were statistically significant predictors of lung function (Table 3). HGS and weight were identified as statistically significant predictors of lung function in PCD (Table 4).

Nutritional intakes

- Mean intakes of total energy, protein and vitamin D with estimated average requirement (EAR) and Reference nutrient intake (RNI) (calculated for age and gender) (SACN, 2011) are shown in Table 5.
- No statistically significant associations were found when looking at dietary intake and lung function.

Table 1: Demographic characteristics by disease aetiology

	PCD	Idiopathic	Asthma	Other (Immunoglobulin Post Infective, Auto–immune, other genetic)
Sex				
Male	8 (32%)	17 (35%)	7 (29%)	12 (40%)
Female	17(68%)	32 (65%)	17 (71%)	18 (60%)
Physio				
Yes	12 (48%)	24 (49%)	15 (63%)	15 (50%)
No	13 (52%)	25 (51%)	9 (37%)	15 (50%)
Age (yrs)				
17-29	18 (72%)	4 (8%)	0	5 (17%)
30-44	2 (8%)	4 (8%)	2 (8%)	0
45-59	4(16%)	5 (10%)	4 (16%)	4 (13%)
60-74	1 (4%)	24 (50%)	13 (55%)	13 (43%)
75-89	0	12 (24%)	5 (21%)	8 (27%)
>89	0	0	0	0
<85% of the norm	24 (96%)	29 (59%)	19 (79%)	18 (60%)
>85% of the norm	1 (4%)	20 (41%)	5 (21%)	12 (40%)
BMI Ranges				
<20	4 (16%)	7 (14%)	2 (8%)	6 (20%)
20-24.9	15 (60%)	17 (35%)	12 (50%)	13 (43%)
25-29.9	5 (20 %)	13 (27%)	4 (17%)	6 (20%)
30-39.9	1 (4%)	11 (22%)	5 (21%)	4 (13%)
40-49.9	0	1 (2%)	1 (4%)	1 (3%)

Table 2: Nutritional, anthropometric & lung function measures according to disease aetiology

	PCD Mean (SD)	Idiopathic Mean (SD)	Asthma Mean (SD)	Other (Immunoglobulin Post Infective, Auto – immune, other genetic) Mean (SD)	P value§
Age	28.7 (±13.4)	63.4 (±18.2)	64.6 (±13.2)	61.7 (±18.4)	<0.001*
FEV_1 (l)	2.07 (± 0.90)	1.66 (±0.68)	1.54 (±0.77)	1.74 (± 0.83)	0.143
FEV_1 (%)	63.24 (±16.86)	68.53 (± 18.49)	63.42 (±20.34)	68.97 (±26.52)	0.565
FVC (l)	2.77 (±0.99)	2.53 (±0.94)	2.48 (±1.17)	2.60 (±1.05)	0.687
FVC (%)	74.40 (±12.47)	83.84 (±17.85)	81.71 (± 23.61)	80.2 (±24.4)	0.158
Infections	3.00 (± 3.25)	2.41 (± 2.42)	3.21 (±2.87)	3.30 (±2.72)	0.442
Handgrip (kgf)	16.85 (± 5.95)	19.53 (±10.40)	15.01 (±7.85)	18.86 (±10.63)	0.234
Handgrip % of norm	57.76 (±15.56)	79.16 (±27.90)	60.75 (±25.95)	74.97 (± 27.25)	0.004*
TSF (mm)	15.94 (±5.58)	16.41 (±5.13)	15.52 (±4.10)	15.26 (±5.68)	0.787
MAMC (cm)	24.02 (±3.23)	24.65 (±3.82)	25.55 (±4.55)	24.73 (±4.08)	0.602
Weight (kg)	61.58 (±11.81)	69.44 (±18.89)	68.64 (±15.79)	68.48 (±17.75)	0.385
BMI (kg/m^2)	23.20 (±3.49)	26.04 (±5.67)	25.08 (±5.38)	24.80 (±6.14)	0.169

* p <0.05

Table 3: Univariate predictors of lung function (FEV1%) in the total population

Predictors	p value	Confidence Intervals (CI)
Sex	0.388	- 4.27 – 10.94
Aetiology	0.082	- 4.84 - 0.29
Weight (kg)	0.036*	0.015 - 0.44
BMI (kg/m^2)	0.043*	0.022 - 1.34
HGS	0.983	- 3.93 - 0.38
TSF	0.061	- 0.030 -1.36
MAMC	0.141	- 0.23 – 1.61
Energy	0.481	- 0.003 – 0.01
Protein	0.548	- 0.070 – 0.13
Vitamin D	0.246	- 0.235 – 0.61

*Table 4: **Univariate** predictors of lung function (FEV1%) according to disease aetiology*

	PCD		Idiopathic		NCFB Asthma		Other	
Predictors	P value	Confidence Intervals	P value	Confidence Intervals	P value	Confidence Intervals	P value	Confidence Intervals
Sex	0.11	-26.03 – 2.845	0.25	- 0.464 – 17.61	0.19	- 6.32 – 30.89	0.61	- 15.43 – 25.60
Weight	0.04*	0.02 - 1.15	0.90	- 0.31 – 0.269	0.51	- 0.38 – 0.75	0.054	- 0.09 – 1.072
BMI	0.40	- 1.204 – 2.90	0.78	- 0.82 – 1.09	0.49	- 1.10 – 2.21	0.07	- 0.163 – 2.99
HGS	0.03*	0.12 - 2.32	0.06	- 0.098 - 0.02	0.76	- 0.97 - 1.31	0.68	- 0.77 – 116
TSF	0.38	-0.73 – 1.83	0.59	-0.769 – 1.34	0.82	- 1.95 – 2.43	0.09	-0.278 – 3.16
MAMC	0.88	- 2.08 – 2.42	0.49	-0.92 – 1.90	0.28	- 0.89 – 2.95	0.42	- 1.49 – 3.47
Energy	0.77	- 0.009 – 0.12	0.46	-0.014 – 0.006	0.15	-0.002 – 0.013	0.96	- 0.025 – 0.024
Protein	0.69	- 0.280 – 0.189	0.32	-0.326 -0.109	0.10	- 0.024 – 0.235	0.78	-0.564 – 0.425
Vitamin D	0.40	- 2.32 – 5.58	0.26	- 2.78 – 0.767	0.35	- 1.82 – 4.87	0.01*	- 12.52 - -1.55

Table 5: Comparison of mean Energy, protein and Vitamin D intakes

	Energy intake (kcal)	% energy intake compared to EAR	Protein intake (g)	% Protein intake compared to RNI	Vitamin D (µg)	% Vitamin D intake compared to RNI
Total participants	1719 (± 705)	79.2 (± 30.2)	69.7 (± 36.6)	88.2 (±39.1)	2.1 (± 2.5)	20.8 (± 25.0)
Aetiologies						
PCD	1706.4 (± 733.2)	70.96 (± 28.91)	64.13 (± 32.36)	86.38 (± 48.89)	1.71(± 1.89)	17.08 (± 18.99)
Idiopathic	1708 (± 534.63)	81.14 (± 28.78)	70.18 (± 24.7)	89.04 (± 36.32)	2.16 (± 3.01)	21.63 (± 30.16)
Asthma	1802.08 (± 1141.56)	85.04 (± 43.15)	75.33 (± 65.38)	87.96 (± 46.05)	2.54 (± 2.63)	25.42 (± 26.37)
Other (Immunoglobulin Post Infective Auto – immune, other genetic)	1674.79 (± 450.85)	78.04 (± 17.73)	68.64 (± 22.16)	88.61(± 28.91)	1.86 (± 1.79)	18.57 (± 17.78)
p value	0.823	0.461	0.567	0.847	0.486	0.486

Conclusion

- In a population with NCFB, 70% had impaired HGS(<85% normative value) (Bohannon et al, 2006) despite mean BMI of 25.1 kg/m^2, reflecting limitations in using BMI alone in this clinic population.
- PCD participants were significantly younger, with lower FEV_1(%) and BMI (23.2 kg/m^2) and HGS (Kgf) with HGS (Kgf) and weight (Kg) as statistically significant predictors of lung function. Further evaluation into deterioration in muscle strength is needed.
- Further exploration is needed of body composition and associated clinical and functional benefits of improving muscle mass in PCD and NCFB populations.

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