The Impact of Frailty and Comorbidities on Lung Cancer Screening Invitation Response, Low-Dose CT Uptake, and Selection Strategies

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Intellectual Property and Publication Statements

I, Anas Almatrafi, confirm that the work submitted is my own, except where work which has formed part of jointly authored publications has been included. My contribution and that of the other authors of this work are explicitly indicated below. I confirm that appropriate credit has been given within the thesis where reference has been made to the work of others.

Study One (Chapter 2):

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Contributions of all authors to **Study One**:

I (AA) developed the search strategy, which was reviewed by MC, RJB, and RN. I (AA) initially screened all titles and abstracts, and then 20% were double-screened by another author (OT). Disagreements were resolved through consensus between two authors (AA, OT). Study data was extracted using Excel by one author (AA), and 20% of them were independently checked by another author (OT). I (AA) assessed the quality of all included studies. I (AA) conducted the meta-analysis and wrote the manuscript draft. All authors reviewed the final manuscript draft and provided comments and feedback before I (AA) submitted it to the Journal of Medical Screening. After submission, I (AA) addressed the reviewer's comments, and all authors reviewed the revised manuscript before re-submission.

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I (AA) developed the study's methodology with contributions from my supervisors (RJB, RG, RN, and MC). Two authors (AG and KEB) provided the SNOMED codes for calculating the electronic frailty index (eFI). One author (MB) uploaded all eFI SNOMED codes to SystmOne and developed the query to extract the data. I (AA) extracted the eFI data from 54 general practices with assistance from NH on the first few practices. MC mainly carried out communications with practices, and additional follow-ups were carried out by two authors (AA, NH). I (AA) transferred the data to the University of Leeds' Analytic Secure Environment for Research(LASER), where I cleaned, processed, and analysed the data. I (AA) wrote all STATA codes related to this study, and another author (SR) reviewed the STATA code used to calculate eFI. One author (HZT) facilitated the linkage of the extracted data with the existing data collected from participants in the YLST at baseline. I (AA) wrote the initial manuscript draft with contributions from my supervisor and an additional co-author (RJB, RG, RN, MC, and PAJC). All authors reviewed the manuscript before its submission to the journal.

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communications with practices, and additional follow-ups were carried out by two authors (AA, NH). I (AA) transferred the data to the University of Leeds' Analytic Secure Environment for Research(LASER), where I cleaned, processed, and analysed the data. I (AA) wrote all STATA codes related to this study, and another author (SR) reviewed the STATA code used to calculate eFI. One author (HZT) facilitated the linkage of the extracted data with the existing data collected from participants in the YLST at baseline. One author (DV) provided eligibility status by risk strategy for all study participants and contributed to the comparison between the risk strategies. I (AA) wrote the initial manuscript draft with contributions from my supervisor and an additional co-author (RJB, RG, RN, MC, and PAJC). All co-authors reviewed the final manuscript before its submission to the journal.

Conference abstracts

Study Two and Three are accepted for spoken presentations at the British Thoracic Society (BTS) Winter Meeting 2024.

Thesis structure

The thesis has been structured and submitted as an alternative style of doctoral thesis that includes published material. A total of three studies are included in the thesis. Study One has been published by a peer-reviewed journal. Study two has been submitted and received an invitation for revision and resubmission. Study three has been submitted to a peer-reviewed journal and is currently under publication consideration. All three studies have been included as submitted or published. There is an introduction chapter preceding the included studies and a discussion and conclusion chapter after the included studies to bind them into a coherent body of work. As per the guidance for an alternative style of doctoral thesis, each chapter contains its own list of references.

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Abstract

Lung cancer screening (LCS) using low-dose CT reduces lung cancer mortality among individuals at high risk of the disease. This high-risk population may have a higher incidence of frailty and multiple comorbidities, potentially due to the influence of age and smoking history, compared to those undergoing screening for other cancers. However, the incorporation of frailty and comorbidities into LCS has not been thoroughly studied. This thesis aimed to investigate the prevalence of frailty and comorbidities and their impact on LCS invitation response, low-dose CT uptake, and selection strategies within the Yorkshire Lung Screening Trial (YLST). **Study One** was a systematic review and meta-analysis that examined the prevalence of comorbidities in the lung cancer screening population. This study identified several prevalent comorbidities and highlighted the lack of frailty assessment among individuals undergoing LCS. **Study Two** was a retrospective case-control analysis that explored the prevalence of frailty and comorbidities, as well as the response to the YLST lung cancer risk assessment invitation and subsequent uptake of low-dose CT screening. The analysis revealed that frailty of any degree was present in 47.9% of eligible individuals offered low-dose CT appointments, including 16.2% with moderate to severe frailty. Interestingly, individuals without frailty or comorbidities were less likely to respond to the risk assessment invitation but showed higher participation in low-dose CT screening when deemed eligible. **Study Three** was a retrospective comparative analysis that evaluated frailty, comorbidities, and survival among populations eligible for LCS, identified by different selection strategies. The study found that the risk models currently used in the UK ($PLCO_{m2012}$ and LLP_{v2}) identified similar populations in terms of frailty and comorbidities, with both models showing higher prevalence than the $USPSTF_{2021}$ criteria. However, three-year overall survival appeared to be similar across all strategies. In conclusion, future LCS efforts should focus on increasing participation rates amongst fit individuals with fewer comorbidities (who appear less likely to take part currently) and comparing long-term outcomes across different levels of frailty and comorbidity.

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List of abbreviations

CCI: Charlson Comorbidity Index

CI: Confidence interval

CKD: Chronic kidney disease

COPD: Chronic obstructive pulmonary disease

CXR: Chest radiography

EMIS: Egton Medical Information Systems

GP: General practice

HER: Electronic health records

IHD: Ischaemic heart disease

IMD: Index of Multiple Deprivation

LC: Lung cancer

LCS: Lung cancer screening

LDCT: Low-dose computer tomography

LHC: Lung health check

LLP: Liverpool Lung Project

NESLON: Nederlands–Leuvens Longkanker Screenings Onderzoek trial

NLST: National Screening Trial

NSCLC: Non-small cell lung cancer

PLCO: The Prostate, Lung, Colorectal, and Ovarian cancer screening trial

PUD: Peptic ulcer disease

PVD: Peripheral vascular disease

RCT: Randomised controlled trial

SCLC: Small cell lung cancer

SNOMED CT: Systematized Nomenclature of Medicine Clinical Terms

TLHC: Targeted lung health check

UKLS: The UK Lung Cancer Screening trial

USPSTF: The US Preventive Services Task Force

YLST: Yorkshire Lung Screening Trial

Chapter 1 Introduction

1.1 Chapter overview

In this chapter, I provide an introduction to lung cancer and its screening, as well as the concepts of frailty and comorbidity. First, I introduce lung cancer and its epidemiology and discuss the existing literature related to lung cancer risk factors, screening studies, and screening criteria. Then, I discuss the concepts of frailty and comorbidity and the existing tools available for assessing their prevalence. In the final section of this chapter, I introduce the aims and objectives of the thesis with an overview of each included study.

1.2 Lung cancer

The main types of lung cancer are Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The NSCLC is the most common type and accounts for more than 80% of lung cancer cases (1). This type includes three main subtypes, which are squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. The SCLC is considered less common but more aggressive as it grows rapidly and spreads remotely outside the lung (2). In 2020, the estimated number of new lung cancer cases was over 2.4 million globally (3). Lung cancer was also the leading cause of cancer deaths in the world, with around 1.8 million deaths accounting for about 18% of all cancer deaths (3). Despite this, lung cancer incidence and mortality rates have been declining in many high and middle-income countries, especially in males, over the past 20 years (4).

In the UK, there are about 49,200 new lung cancer cases diagnosed every year, around half of them are diagnosed at a late stage, with high incidence rates observed among people aged 80 to 84 years (5) and people living in the most deprived areas. The NHS has an ambitious plan already in place to reduce high levels of late stage disease and increase the proportion of cancers diagnosed at stage I and II up to 75% by 2028 (6). Over the last decade, lung cancer incidence for males has decreased by more than 12%, while incidence in females has increased by 13% in the UK (5). This difference in lung cancer incidence rates between males and females mainly reflects historical variations in smoking prevalence, which peaked much earlier in males than in females (7). There are about 35,000 lung cancer deaths each year in the UK (5). People living in the most deprived areas tend to have a greater chance of dying from lung cancer in

the UK (8), which might be explained by the inequalities in the utilisation of both conventional (9, 10) and novel treatments (11) among patients with lower socioeconomic status. One- and five-year survival rates of lung cancer in the UK are less than 50% and 21%, respectively (12). When diagnosed early, 62.7% of people survive for five years or more, compared to only 4% when diagnosed at the latest stage (13). There are fewer lung cancer cases diagnosed at an early stage in the UK than in comparable countries (Australia, Canada, Denmark, Ireland, Norway), as reported by the International Cancer Benchmarking Partnership (ICBP) in 2021 (14). Higher age at diagnosis and pathological stage confirmation for patients with stage I/II disease in the UK might explain this observation (14).

1.2.1 Symptoms

Lung cancer is known to be widely asymptomatic in its early stages. Symptoms usually develop as the disease progresses, including a persistent cough, breathlessness, haemoptysis, ache or pain in the shoulder or chest, loss of appetite, fatigue, and weight loss. Other less common symptoms include joint pain and swelling and swollen fingers and nails (finger clubbing) (15).

1.2.2 Diagnosis and Staging

Accurate staging in lung cancer is essential for guiding treatment strategies and determining prognosis. The TNM staging system is used to classify lung cancer progression, with T representing the primary tumour size, N denoting the extent of regional lymph node involvement, and M indicating the presence of distant metastasis (16). Lung cancer is categorized into four stages (I-IV), with stage I indicating localized disease and stage IV signifying advanced metastatic spread. Diagnostic imaging, particularly computed tomography (CT), plays a central role in initial detection and staging. When malignancy is confirmed via CT, bronchoscopy, often combined with endobronchial ultrasound (EBUS), facilitates direct visualization of the bronchial tree and allows for real-time ultrasound assessment of the mediastinum and lymph nodes, enhancing the precision of tissue sampling and lymph node evaluation (16). More invasive tests involve a percutaneous lung biopsy or keyhole surgery to extract cell samples for pathological confirmation of lung cancer.

1.2.3 Risk factors

Lung cancer risk factors are identified mainly as either environmental or genetic factors. Tobacco smoking is considered the most dominant risk factor for lung cancer, and it is associated with 80% to 90% of lung cancer deaths (17). The causal relationship between smoking and lung cancer was first described in the early 1950s by two large epidemiologic studies (18, 19). The strength of the relationship between lung cancer and tobacco smoking was explored in a relatively recent meta-analysis, demonstrating an increased risk among smokers (RR: 8.96, 95%CI 6.73 – 12.1) and former smokers (RR: 3.85 95%CI 2.77-5.34) with never smokers as the referent category (20). Smoking cessation, especially before middle age, can reduce the risk of lung cancer significantly. Peto and colleagues reported, in two large case-control studies in the UK, decreased cumulative lung cancer risk at the age of 75 years by 9.9%, 6%, 3%, and 1.7% among men who stopped smoking at 60, 50, 40, and 30 years of age respectively (21). The cumulative risk was much higher (15.9%) for men aged 75 years who continued to smoke; a similar pattern was observed among women, which highlights the important role that smoking duration plays as a risk factor for lung cancer (21).

Occupational and environmental exposures to lung carcinogens are also among the known risk factors that play an important role in lung cancer. The International Agency for Research on Cancer (IARC) has classified 16 agents as occupational lung carcinogens and another 8 agents as potential environmental and occupational lung carcinogens (22). These include sources of ionising radiation (e.g. exposures from medical procedures or radon), silica dust, asbestos, diesel engine exhaust, arsenic compounds, and agents present in paint.

Lung cancer risk is also increased in people with pre-existing lung diseases, including pneumonia, chronic obstructive pulmonary disease (COPD), and tuberculosis, independently of tobacco smoking. A large pooled analysis from the International Lung Cancer Consortium found a significant increase in lung cancer risk for chronic bronchitis (relative risk= 1.47 95% CI 1.29-1.68), tuberculosis (relative risk=1.48 95% CI 1.17-1.87), and pneumonia (relative risk= 1.57 95% CI 1.22-2.01) (23). In addition, some individuals have an increased risk of developing lung cancer if they have a family member diagnosed with lung cancer, especially at a younger age (24).

1.2.4 Primary prevention of lung cancer

Primary prevention of lung cancer occurs mainly by increasing smoking cessation and reducing smoking intake. The prevalence of cigarette smoking among adults in the UK has largely declined over the last few decades, reaching 12.9% in 2022 (25). This sharp reduction in smoking habits was followed by a lagged reduction in lung cancer mortality (5). Smoking cessation not only reduces the risk of developing lung cancer but is also associated with improved outcomes for lung cancer patients. These improved outcomes include reduced risk of recurrence of early-stage lung cancers (26), better survival (27, 28), and fewer postoperative pulmonary complications (29). In the UK, The National Centre for Smoking Cessation and Training (NCSCT) provides training for practitioners on tobacco control and smoking cessation interventions (30). The NCSCT works with local stop-smoking services to provide behavioural support and advice on stop-smoking interventions. There are also policies and strategies in place in the UK to reduce the uptake of smoking, including restrictions on advertising, marketing and cigarette packaging. The increased taxation on tobacco products is also implemented in the UK and can act as a financial barrier for smokers to quit or reduce their uptake.

1.3 Lung cancer screening

1.3.1 Sputum cytology and chest radiography

Studies on using sputum cytology (SC) and chest radiography (CXR) for early detection of lung cancer were first carried out in the 1960s. Various studies have assessed their effectiveness, often with mixed results. In 1968, a large randomised controlled trial from the Northwest London Mass Radiography Service concluded that mortality from lung cancer was not statistically different between biannual CXR for three years compared to participants who received baseline and end-of-study CXR only (31). During the 1970s, The National Cancer Institute’s Cooperative Early Lung Cancer Detection Program sponsored three large trials (Johns Hopkins, Memorial Sloan-Kettering, and Mayo Clinic) to evaluate the effectiveness of SC and CXR in detecting lung cancer early (32, 33). The Johns Hopkins and Memorial Sloan-Kettering studies each randomised over 10,000 subjects to receive either annual CXR alone or annual CXR with sputum cytology and were followed for five years. No mortality benefits were found between the two groups (32, 34, 35). The Mayo Clinic trial compared CXR and SC every four months or usual care of annual CXR (36). The Mayo Clinic trial did

not find any lung cancer mortality difference between the groups (37). A similar finding was also reported from Czechoslovakia in Europe (now Czech Republic and Slovakia) (38, 39). At this point, none of the above studies have addressed the use of CXR alone, as all examined SC in conjunction with CXR. The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial was conducted during the 1990s to study four different cancers. The lung cancer screening part of the PLCO trial recruited 154,901 participants who were randomly assigned to receive either annual CXR for four years or no CXR (usual care) (40). Unlike earlier observational studies and trials, the PLCO trial tried to address several limitations in previous studies by including large sample size, usual care comparison group (no CXR), women and never-smokers. The PLCO trial showed that screening with annual CXR compared to no screening was not associated with any mortality benefit after 13 years of follow-up (41).

1.3.2 Low-dose computer tomography(LDCT)

Considering the negative findings from the above-mentioned studies regarding the use of CXR in LCS, research has shifted towards low-dose helical computed tomography (LDCT) as a potential screening tool. Several single-arm studies during the 1990s and early 2000s demonstrated enhanced identification of lung cancer nodules using LDCT compared to CXR (42-48). Following these studies, the Early Lung Cancer Action Project (ELCAP) was one of the first studies in the U.S. to show the feasibility of LDCT versus chest X-ray to detect early-stage resectable cancers in high-risk asymptomatic individuals (49). The ELCAP study enrolled 1,000 participants and found that LDCT identified more lung cancers (2.7% vs 0.7%) and at an earlier stage (85% vs 17%) compared to CXR. An international expansion to the ELCAP study (I-ELCAP) enrolled more than 30,000 participants, confirmed the ELCAP findings, and provided additional evidence of a 10-year survival rate of 92% for those with stage I cancer who underwent surgical resection (50).

The Lung Screening Study (LSS) (51) further confirmed that LDCT could early detect more lung cancer compared to CXR and led to the larger US National Lung Screening Trial (NLST) (51). The lung cancer positivity rate for the year one screen in LSS was 25.8% for LDCT and 8.7% for CXR stage I cancers, accounting for about half (48%) of the cases in the LDCT group and 40% in the CXR control group. The NLST was the first and largest RCT that established the

mortality benefit from LDCT over CXR screening. The NLST enrolled 26,722 participants to undergo three annual LDCT screenings compared to 26,732 participants who underwent CXR screening between 2002 and 2004, with a median follow-up of 6.5 years. The NLST showed a significant reduction in lung cancer death by 20% (95%CI: 6.8 to 26.7, P=0.004). This benefit in lung cancer-specific mortality was later observed in the Dutch–Belgian lung cancer screening trial (Nederlands–Leuvens Longkanker Screenings Onderzoek [NELSON]), which showed a 24% lung cancer mortality reduction in the LDCT arm (2.50 deaths per 1000 person-years) compared with no screening arm (3.30 deaths per 1000 person-years) after a median ten years of follow-up (52). Other screening trials from different countries were concluded in the last few years without showing lung cancer mortality benefits, largely due to insufficient power and limited follow-up time (Table 1.1). However, the evidence synthesized from nine trials included in a recent meta-analysis (53) indicates a significant reduction in lung cancer mortality, consistent with the findings from the NLST and NELSON trials.

1.3.3 Lung cancer screening in the UK

Following the findings of the NLST, Lung cancer screening in the UK has evolved significantly over the past decade, driven by a series of pilot studies and targeted initiatives aimed at early detection. The UK Lung Cancer Screening Trial (UKLS) (54), conducted between 2011 and 2014, was the first large randomized controlled trial in the country. Of the 1994 participants who underwent LDCT scanning in the UKLS, 42 (2.1%) were diagnosed with lung cancer. Among the detected lung cancer cases, 85.7% were diagnosed as stage 1 or 2 with the majority (83.3%) undertaking surgical resection. Following the UKLS pilot trial, several other successful pilot studies were conducted in England including the Liverpool Healthy Lung Programme (55), the Manchester Lung Health Check Pilot (56, 57), the Nottingham Lung Health MOT Pilot (58), the West London Lung Screening Pilot Trial (59) and the Lung Screen Uptake Trial (60). These pilots collectively highlighted the importance of reducing barriers to participation and tailoring outreach efforts to diverse populations including those living in most deprived areas. These UK-based projects showed a higher uptake of LCS, ranging from 27% in Nottingham to 52% in LSUT, compared to the implementation of LCS in the USA (56, 59-62). This higher LCS uptake is mainly

attributed to the targeted screening invitations, which were tailored to high-risk populations, including those living in the most deprived areas.

Alongside these trials, the Targeted Lung Health Check (TLHC) Programme was introduced in 2019 as a national initiative with a £70 million budget to offer LDCT screening to individuals aged 55–74 with a significant smoking history across ten pilot areas (63). So far, the TLHC Programme has conducted more than 1 million risk assessments and has diagnosed more than 5,500 people with lung cancer (75% were found at an early stage 1 or 2) (64). In July 2023, the UK government announced the national rollout of lung cancer screening with the aim of 100% coverage among the eligible population by 2030, informed by insights from the TLHC Programme and previous LCS initiatives. The TLHC Programme has recently been renamed to the "NHS Lung Cancer Screening Programme" to provide more clarity on the programme and its purpose (64).

Establishing a national screening programme requires a multi-faceted approach involving pilots, policy changes, advocacy, and financing. Pilot studies like those conducted in the UK provide critical evidence on feasibility, cost-effectiveness, and public health impact, which can inform policy decisions. Political advocacy is also essential to secure government support and funding for scaling up successful LSC programmes. Financing mechanisms must also be established to ensure sustainable implementation, including investments in infrastructure such as mobile screening units and trained personnel. Public engagement campaigns are also crucial to raise awareness and encourage participation, particularly among high-risk groups. By integrating these elements into a cohesive strategy, countries can develop effective national screening programmes that address both clinical outcomes and health inequalities.

1.3.4 The strengths and limitations of published lung cancer screening trials

Lung cancer screening trials have provided valuable insights into the benefits and limitations of various screening methods, particularly LDCT. These trials, including NLST (65), NELSON (52), and others such as UKLS (54), DANTE (66), DLCST (67), ITALUNG (68), LUSI (69), and MILD (70), demonstrate both strengths and weaknesses in their design and findings. One major strength across these trials is the documented reduction in lung cancer-specific mortality with LDCT screening. For example, the NLST reported a 20% reduction in lung

cancer mortality compared to CXR, while the NELSON trial showed a 24% reduction for men and an even greater 33% reduction for women. The meta-analyses of nine trials further confirm a significant relative reduction of lung cancer mortality by 17%-20% with LDCT screening (71, 72). Additionally, LDCT consistently increased the detection of early-stage cancers and resectable tumors, which are associated with better prognosis (71). These findings underscore the efficacy of LDCT in identifying lung cancer at treatable stages.

However, these trials also had important limitations. Gender representation is a notable issue; for instance, the NELSON trial included only 19% of women, which limits the generalizability of its results to female populations (52). Furthermore, while LDCT reduces lung cancer-specific mortality, its impact on all-cause mortality is less clear. Almost all trials, except for the NLST, failed to demonstrate significant reductions in all-cause mortality—an endpoint that requires unrealistically large sample sizes and longer follow-up periods. Even pooled analyses of multiple RCTs showed no significant reduction in all-cause mortality with LDCT screening, as demonstrated by two different meta-analyses (71, 73). Another critical limitation is the high rate of false positives and overdiagnosis associated with LDCT. Overdiagnosis rates in some studies ranged from 10% to as high as 38%, leading to unnecessary invasive procedures and patient anxiety (71, 74). Finally, variability in trial designs—such as differences in enrollment age, smoking history thresholds, follow-up durations, and definitions of positive findings—complicates direct comparisons and generalization of results (72). In conclusion, while LDCT screening demonstrates clear benefits in reducing lung cancer-specific mortality and detecting early-stage disease, its limitations—such as gender imbalances, overdiagnosis risks, and inconsistent effects on all-cause mortality—highlight areas for improvement in future trials.

1.3.5 Cancer stage at diagnosis as a surrogate endpoint for LCS

Cancer-specific mortality remains the gold-standard endpoint for cancer screening trials. Using lung cancer mortality as a trial outcome offers the clear advantage of providing an unambiguous and clinically meaningful measure of benefit that directly reflects reductions in mortality attributable to lung cancer (75). However, relying solely on lung cancer mortality requires long follow-up periods and large sample sizes to achieve adequate statistical power, which can considerably delay the evaluation of screening efficacy (76). Thus, while lung

cancer mortality remains the gold standard for capturing ultimate clinical benefit, its operational limitations may hinder the timely assessment of screening interventions.

An attractive alternative is to incorporate a surrogate endpoint—most notably, cancer stage at diagnosis—as they can be measured much earlier in the trial timeline and may serve as proxies for long-term survival benefit (77). A stage shift toward earlier diagnosis is premised on the expectation that detecting lung cancer at a less advanced stage will improve treatment outcomes and ultimately reduce mortality, providing a more immediate signal of screening effectiveness. Recent meta-regression evidence from randomised trials (78) has demonstrated a strong linear association between reductions in late-stage lung cancer incidence and corresponding decreases in lung cancer mortality, thereby validating the potential of surrogate endpoints such as stage shift. Similar findings were also observed in a recent meta-analysis (79) which reported that among the 12 lung cancer screening trials analysed, there was a very high correlation (Pearson $\rho = 0.92$, 95% CI, 0.72–0.98) between reductions in the incidence of advanced lung cancers (stage III-IV) and decreases in deaths from lung cancer. This indicates that declines in late-stage lung cancer incidence are associated with substantial mortality benefits, providing further empirical support for using stage shift as a surrogate endpoint in lung cancer screening trials.

Nevertheless, surrogate endpoints like the stage at diagnosis are susceptible to pitfalls such as lead time bias and overdiagnosis, meaning that an apparent shift toward earlier stages does not always translate into a true mortality benefit (75). Furthermore, variability in staging practices and differential treatment effects across lung cancer subtypes necessitate careful validation to ensure that early-stage detection reliably translates into long-term survival benefits (78). Another limitation of the stage at diagnosis as a surrogate endpoint includes variability in its predictive power across trials. For example, in the NLST, the same stage shift in lung cancer underestimated the observed mortality reduction (10% expected vs. 20% actual), suggesting biological heterogeneity. In summary, while lung cancer mortality remains the definitive outcome for assessing screening impact, its practical challenges have prompted interest in surrogate endpoints like cancer stage at diagnosis that could facilitate more timely evaluations (75).

1.3.6 The Yorkshire Lung Screening Trial (YLST)

The YLST is an ongoing randomised controlled trial evaluating targeted invitations to community-based Lung Health Checks (LHCs), which involve LDCT screening, in individuals aged 55-80 years identified as having a smoking history through their GP records (80). The trial is being conducted in Leeds, UK, and contains a usual care comparison group (no invitation). The main objectives of the YLST are to measure LCS participation rates, compare the performance of three LCS selection strategies, and assess the outcomes of invitations to community based LDCT screening for lung cancer versus usual care. The design of YLST incorporated three novel features, including permission from the UK Health Research Authority to analyse data from people who do not respond to LHC invitations, using telephone triage to assess screening eligibility, and utilising mobile units to deliver the screening in convenient community areas. Results of telephone triage risk assessment invitations, LCS eligibility, and LHC uptake have been previously reported (81). Overall, 50.8% of 44,943 individuals invited have responded to the LHC invitation and underwent telephone risk assessment. The YLST found that current smoking status was associated with a lower response rate (adjusted OR 0.44, 95% CI 0.42–0.46) and lower LHC uptake (adjusted OR 0.73, 95% CI 0.62–0.87). Socioeconomic deprivation was also found to be associated with lower LHC uptake (adjusted OR 0.78, 95% CI 0.62–0.98).

Table 1.1 Summary of completed lung cancer screening trials

Trial	Country	Screening method	Age range	Inclusion criteria	n	lung cancer mortality	All-cause mortality
NLST (65)	US	LDCT vs CXR	55-74	≥30 Pack-year, ≤15 years since quitting for former smokers	53454	247 (LDCT), 309 (CXR): **20% relative reduction**	1877 (LDCT), 2000(CXR): 6.7% reduction
NELSON (52)	Netherlands & Belgium	LDCT vs no screening	50-74	+15 cigarettes a day for +25 years, or +10 cigarettes a day for +30 years. Include former smokers who had quit in less than 10 years	15792	24% reduction in LC mortality	not powered to show a possible favourable difference
UKLS (54)	UK	LDCT vs no screening	50-75	≥5% 5-year lung cancer risk based on the LLPv2 model	4055	not powered for a long-term mortality	
MILD (70)	Italy	LDCT vs no screening	49-75	smokers or former smokers who consume more than 20 pack-years	4099	No mortality reduction at 5- and 7-year intervals. A significant 39% LC mortality reduction was observed after 10 years of follow-up	20% non-significant reduction after 10 years
DLCST (82)	Denmark	LDCT vs no screening	50-70	smokers or former smokers who consume more than 20 pack-years	4104	No statistically significant mortality benefit	

DANTE (66)	Italy	LDCT vs usual care	60-74	smokers or former smokers who consume ≥ 20 pack-years	2450	No statistically significant mortality benefit	
ITALUNG (68)	Italy	LDCT vs no screening	55-69	smokers or former smokers who consume ≥ 20 pack-years in the past 10 years	3206	non-significant 30% reduction in lung cancer mortality	non-significant 17% overall mortality reduction
LUSI (69)	Germany	LDCT vs no screening	50-69	+15 cigarettes a day for ≥25 years, or +10 cigarettes a day for ≥30 years. Including former who had quit in less than 10 years	4052	non-significant 26% reduction in lung cancer mortality	no significant impact on all-cause mortality

1.3.7 Participation

Participation in lung cancer screening (LCS) programmes varies significantly across different populations and is influenced by several demographic and socioeconomic factors. Previous studies have shown that individuals from socioeconomically deprived backgrounds, current smokers and older people are less likely to participate in LCS despite being at higher risk for lung cancer (60, 81, 83-85). In the US, participation rates in LCS have been low despite the early recommendation of LCS by the United States Preventive Services Task Force (USPSTF) in 2013. Following the observed cancer-specific mortality benefit in the NLST, the USPSTF recommended annual LDCT screening for adults aged 55-80 with a history of smoking. A recent analysis from the 2022 Behavioral Risk Factor Surveillance System (BRFSS) surveys showed that only 16.4% of the US LCS-eligible population reported screening using LDCT within the past year (86). In the UK, behavioural-science-informed approaches to screening invitation such as inviting people to “Lung Health Checks” or “M.O.Ts for the lung” have resulted in higher uptake. For example, 52.6% attended invitation to screening in the Lung Screen Uptake Trials (LSUT) (60). Similarly, the YLST reported a 50.8% response rate (n=22,815) to the telephone-based risk assessment invitation, with 29.9% (n=6819) attending their LHC appointment (81).It remains to be seen whether these higher participation rates will be maintained outside of trial settings in the coming years.

Barriers to participation in LCS are multifaceted. Practical barriers include the distance to screening centres, lack of transportation and time constraints (87). Psychological barriers, including fear of the imaging results, fatalistic attitudes towards lung cancer, and stigma associated with smoking, further prevent individuals from participating (88). The UKLS trial highlighted that many non-participants reported practical concerns such as travel distance, mean of transportation, and comorbidities as reasons for not attending, with additional emotional barriers like fear and avoidance of lung cancer information being prevalent among non-participants (89).

1.3.8 Potential harms

1.3.8.1 False-positive results

Despite the potential benefits that come with early detection of lung cancer, LDCT does have recognised harms. False-positive rates reported in the literature have different underlying definitions and vary across studies. A systematic review of lung cancer screening trials reported that more than 90% of screen-detected nodules were benign (90). This rate decreases with repeat screening rounds that ignore nodules detected in previous rounds. For instance, the benign nodule detection rate in the NLST was reduced from 24% at baseline to 16% in the third round (90). A higher false-positive rate was found in NLST participants aged above 65 years compared to younger participants (27.7% vs. 22.0%; $P < 0.001$) (91).

Some trials, like the UKLS and NELSON, distinguished suspicious nodules that needed a referral to a multidisciplinary team (MDT) from those benign nodules that required further scans. Thus, the false-positive rate in UKLS and NELSON trials is calculated based on the referral of cases to the MDT or diagnostic workup. The false-positive rates for UKLS and NELSON trials were 3.6%, and the interval imaging rates (rate for those requiring further CT imaging) were 23.2% and 19.2%, respectively (54, 92, 93). It is crucial to monitor and report false-positive rates and indeterminate results in screening trials to avoid any potential physical or psychological harm associated with diagnostic procedures.

1.3.8.2 Overdiagnosis

In addition to the high false-positive rates of LDCT screening, overdiagnosis presents another challenge when cancers are detected that would not have presented symptomatically or caused harm during the patient's lifetime. Overdiagnosis occurs when cancers have an indolent growth rate or when the patient dies from another cause in the presence of cancer (94). The overdiagnosis rate from the NLST was originally estimated to be 18.5% (with 6.4 years median follow-up) (95) and decreased significantly to 3% with more than 11 years of extended follow-up (96). However, the NLST overdiagnosis rate might not accurately reflect the true rate of LDCT overdiagnosis, as the US trial included an active control group that was screened with CXR. In contrast, the NELSON trial estimated an overdiagnosis rate of 8.9% after 11 years of follow-up (52). Estimates of overdiagnosis from LDCT have varied across other trials, ranging from 10.9 to 25.8% (74). These variations might be attributed to the differences in screened populations, screening practices, professional thresholds

(radiological and pathological) and follow-up duration (97). Therefore, it has been suggested that the overdiagnosis rate can be better estimated using population modelling of screening trials (98).

1.3.8.3 Radiation exposure

The use of LDCT for LCS has been associated with relatively low effective doses (<2 millisieverts (mSv)) that are considered lower than the individual annual dose from natural background sources (3-5 mSv) (99). However, cumulative exposure from repeated LDCT screenings over a prolonged period might contribute to the risk of developing radiation-induced cancers. Rampinelli et al. reported that the median cumulative effective dose is 9.3 mSv for men and 13.0 for women after ten annual LDCT screenings in the Continuing Observation of Smoking Subjects (COSMOS) study (100). Age at first screening significantly impacts the lifetime attributable risk (LAR) of developing cancer from radiation exposure. For instance, starting annual LDCT screenings from age 50 is associated with higher LAR than starting at age 60 or 70 (100). Overall, the benefits of using LDCT for lung cancer screening outweigh the risks associated with radiation exposure (100). Nevertheless, LCS programmes should aim to minimise radiation exposure through advanced imaging technologies and adequately communicate the potential risks from radiation to LCS candidates.

1.3.9 Strategies for identifying LCS candidates

1.3.9.1 Factor-based strategies

United States Preventive Services Task Force (USPSTF) criteria

Following the results of the NLST, the USPSTF in 2013 recommended annual lung cancer screening using LDCT for asymptomatic adults aged 55-80 who have a 30-pack-year smoking history and are current smokers or who have quit in the past 15 years (101). The USPSTF recommendation was updated in 2021 to include people between the ages of 50 and 55, and reduced the smoking intensity to a 20 pack-year (102). The USPSFT strategy is considered simple and easy to implement, but concerns have been raised that this strategy might miss people who do not meet the age or pack-year criteria but who might be at high risk of developing lung cancer (103).

1.3.9.2 Model-based strategies

The PLCO model is a lung cancer risk prediction model that incorporates several lung cancer risk factors. It was developed according to data collected in the prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial (104). The model contains four smoking risk factors (smoking status, smoking intensity, smoking duration (years), and quit time for former smokers) and seven non-smoking risk factors (age, race, education level, body mass index (BMI), personal history of cancer, COPD, and family history of lung cancer) (104). The original PLCO model was later revised and updated to the $PLCO_{m2012}$ model to align with the NLST criteria (105). When compared with the NLST selection criteria, the $PLCO_{m2012}$ model showed higher sensitivity (83.0% vs. 71.1%, P<0.001), higher positive predictive value (4.0% vs. 3.4%, P=0.01), similar specificity (62.9% and. 62.7%, respectively; P=0.54) and 41.3% fewer missed lung cancers (115 vs.196). The $PLCO_{m2012}$ risk ≥1.51% was found to be more efficient than the USPSTF criteria as it resulted in a smaller number of eligible individuals and identified more lung cancers with fewer false positives (106, 107). Another version of the PLCO model ($PLCO_{all2014}$) was also developed to evaluate the lung cancer risk in never-smokers (106).

The Liverpool Lung Project risk model (LLP) is another model-based LCS strategy that was developed from a case-control cohort in Liverpool and presented an individual lung cancer risk score over five years. Multivariate conditional logistic regression was used to model the risk of developing lung cancer. Age, sex, family history of lung cancer, length of smoking, personal history of pneumonia, and occupational exposure to asbestos were included in the original model (108). The LLP model is applicable to smokers and never-smokers. LLP was used in the setting of the UKLS trial and following observations from the UKLS, the LLP model was amended (LLP_{V2}) to include previous diagnoses of other lung diseases (COPD, tuberculosis, bronchitis and emphysema) and other forms of smoking (cigar and pipe smoking) (109). The LLPv2 risk threshold of ≥5% was used in the UKLS and YLST trials, but some concerns were raised that this threshold was high (110). The use of a risk threshold of ≥2.5% for LLPv2 is now in use in the current NHS protocol for targeted screening for lung cancer (63). An updated LLP_{V3} model was published recently adjusted to the whole of England and to more updated lung cancer incidence figures (111).

There are other models that were developed to predict the risk of lung cancer but have not been widely used or validated as the $PLCO_{m2012}$ and LLP_{v2} models. The Bach Model, developed in 2003, estimates an individual's risk of developing lung cancer and the competing risk of dying without a lung cancer diagnosis over ten years The Etzel model (95) was developed using logistic regression (112). It was developed for ever-smokers aged 45-69 with a minimum 30 pack-year smoking history, excluding non-smokers and non-heavy smokers, thus limiting its utility. The Spitz model (113) predicts a one-year absolute risk of lung cancer using logistic regression and is applicable to individuals aged 20 and above, including smokers and never-smokers. The Etzel model (114) was developed to predict lung cancer risk among Black-Americans. The Hoggart Model (115) is a Weibull regression model developed from a cohort of 169,035 ever-smokers, designed to predict a one-year absolute risk of lung cancer based on age and smoking history. The model's simplicity, using only two variables, may allow its generalizability across different settings but could limit its accuracy in identifying higher-risk populations. The Lung Cancer Risk Assessment Tool (LCRAT) (116) is another model that was developed in the US using data from the PLCO and the NLST trials, as well as the National Health Interview Survey (NHIS).

While the above selection strategies might identify eligible individuals for LCS, they do not guarantee the maximum benefits from screening, as those selected may have a higher burden of comorbidities, potentially undermining the benefits of screening. A selection approach based on noncancer mortality might help improve the identification of LCS candidates by accounting for competing causes of deaths other than lung cancer (117). In this regard, a life-years gained from screening-CT (LYFS-CT) model (118) was developed by US researchers to incorporate the potential gain in life expectancy from LCS rather than focusing solely on the risk of developing lung cancer. This strategy could maximize the benefits of LCS by selecting individuals at high risk but with greater life expectancy and fewer comorbidities. However, its implementation and patient acceptance present challenges (118). Another consideration to enhance LCS selection is assessing candidates' fitness before screening and excluding those who are not fit to tolerate the screening and any subsequent procedures. Fitness assessments in LCS trials and programs have been inconsistent, often relying on metrics like self-rated health, ability to lie flat, tolerate treatment, or climb stairs

(119). Frailty assessment, though not currently utilised in LCS (120), could also be valuable in identifying candidates who are fit enough for screening.

1.4 Comorbidities

1.4.1 Comorbidity and Multimorbidity

Feinstein described comorbidity in 1970 as "any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study" (121). Different diseases might be found in the same individual by chance, surveillance bias or causal association (122). Very common conditions tend to coexist by chance, such as diabetes and hypertension. Surveillance bias might contribute to the diagnosis of comorbidities in patients who are under the radar from frequent health follow-ups. Also, a causal association might be established when an index condition is recognised to be a risk factor for a subsequent disease. Multimorbidity is widely defined as the coexistence of two or more medical conditions in the same person (123), with a prevalence ranging between 55-98% of the older population (124). Individuals with multimorbidity have a higher risk for functional impairment, worse quality of life, greater healthcare utilisation and higher mortality (125). The UK National Institute for Health and Care Excellence (NICE) has published a guideline on the clinical assessment and management of multimorbidity (126). The NICE guidelines highlighted the importance of multimorbidity in certain groups who may benefit from a tailored approach to care.

There is a recognisable overlap between multimorbidity and frailty. The accumulation of multiple health conditions is a common feature between frailty and multimorbidity, and the two may share similar pathophysiological mechanisms (127). The NICE guideline recognised the overlap between multimorbidity and frailty and suggests that the identification of people with frailty is one of the means to identify those with multimorbidity (126). This relationship was confirmed by a systematic review that found that most frail people have multimorbidity but a smaller proportion of multimorbid people present with frailty (128). The review found that the prevalence of multimorbidity among frail participants was 72%, and the prevalence of frailty in multimorbid participants was 16%. Ageing is another factor that is highly correlated with multimorbidity. A study conducted in England using a random sample of 403,985 adults found that

the prevalence of multimorbidity was 27.2% (95% CI: 27.1-27.3) and was significantly higher with increased age reaching more than 60% in those above the age of 65 (129). This increased prevalence of multimorbidity was also observed in the USA and Canada. Among adults aged more than 65 years, one study from the USA reported a prevalence of multimorbidity at 91.8% (counting obesity as one condition) (130), another US study reported a prevalence of 77.3% (131), and a study from Canada reported a prevalence of 73% (132).

1.4.2 Comorbidity and lung cancer screening

As the eligibility criteria for LCS are largely dependent on older age and smoking history, it is likely that this population will present with a high burden of comorbidities, especially diagnoses that are associated with smoking. Evidence from the NLST showed that conditions like heart disease, diabetes, and stroke were prevalent (12.7%, 9.7%, and 2.8%, respectively) among all NLST participants (52). These figures were estimated to be much higher among high-risk eligible individuals outside the controlled trial settings (133, 134). Compared to the breast cancer screening population, populations eligible for LCS are expected to have a 2-5 folds prevalence of comorbid conditions, including chronic lung disease, heart disease, and diabetes (135). Therefore, the presence of comorbidities and multimorbidity among the LCS population might undermine the benefit of early detection in this population. For example, a study found that the risk of complications after diagnostic evaluation was high in LCS-eligible patients who are older and have COPD or a history of myocardial infarction (136). In another simulation study, researchers quantified the life-years (LY) gained from screening a population with comorbidities who are eligible for LCS and found that the presence of comorbidities decreased LY and QALY compared with a population with no comorbidities (137). The concept of life gained from screening was previously suggested as a selection strategy for LCS to maximize the benefits of screening, ensuring the selection of healthier high-risk candidates with fewer comorbidities and higher life expectancy (118). Comorbidities are also prevalent among lung cancer patients as data from 331,655 cancer patients from the England National Cancer Registry revealed that about 27% of lung cancer patients aged 75–90 had one comorbidity, and about 50% had multimorbidity (138). In 2017, the American Thoracic Society gathered a multidisciplinary group of international clinicians and researchers to identify gaps and future

recommendations regarding comorbidities in lung cancer screening settings. The panel concluded that competing causes of death are highly prevalent in eligible individuals for LCS and might undermine the benefits of screening (139).

1.4.3 Tools available to assess comorbidity

The most widely used tool is the Charlson Comorbidity Index (CCI). This tool was developed in 1987 by Charlson et al. using 19 predefined comorbidities with a weighted score to predict postoperative outcomes (140). The comorbidities included in the CCI are as follows: diabetes with diabetic complications, renal disease, chronic pulmonary disease, congestive heart failure, mild and severe liver disease, hemiplegia, peripheral vascular disease, lymphoma, leukaemia, metastatic tumor, and acquired immunodeficiency syndrome (AIDS). The CCI was validated in a cohort of 604 patients who were treated for primary breast cancer. However, the CCI has not been widely used in LCS settings and there are some concerns about its scoring method as it allocates higher score for conditions like AIDS which do not reflect the recent medical advances for this condition (139).

The Elixhauser comorbidity index (ECI) is another tool that was developed by Anne Elixhauser in 1998 to handle large administrative inpatient records (141). Using 30 conditions, the ECI can be used to categorise patients based on comorbidity profile by the presence or absence of single conditions or by converting comorbidity data into a score for handling multiple comorbidities. The final list of 30 comorbidities was selected using inpatient data of 1,779,167 patients obtained from 438 hospitals to assess the length of stay, hospital charges, and in-hospital death as outcome measures (141). The comorbidities included in the ECI are AIDS/HIV, alcohol abuse, blood loss anaemia, cardiac arrhythmias, chronic pulmonary disease, coagulopathy, congestive heart failure, deficiency anaemia, diabetes (uncomplicated), diabetes(complicated), drug abuse, fluid and electrolyte disorders, hypertension (complicated), hypertension (uncomplicated), hypothyroidism, liver disease, lymphoma, metastatic cancer, neurodegenerative disorders, obesity, paralysis, peptic ulcer disease, peripheral vascular disorders, psychosis and depression., pulmonary circulation disorders, renal failure, rheumatoid arthritis/collagen, solid tumour without metastasis, valvular disease and weight loss (141). Similar to the CCI, the ECI has not been actively utilised in LCS research.

Another way of quantifying comorbidity is by reporting comorbidity count, which has been widely used in the medical literature and simply involves counting the number of certain conditions of a patient. Usually, the list of counted conditions is carefully selected based on the prevalence of these conditions or their importance to the research context using medical records or self-reports.

1.5 Frailty

The term frailty is often used in medical practice to describe the weakest and most vulnerable subset of patients (142). There are many definitions of frailty in the literature, with a combination of disease-specific and non-disease-specific definitions. However, frailty is often conceptually defined as a clinically identifiable state in older people with increased vulnerability as a result of age-associated declines in physiological reserve and function in multiple organ systems, which affect the ability to cope with everyday or acute stressors (143). Frailty has also been described as a dynamic process that has frequent transitions between frailty states. A study of community-living populations over the age of 70 in the USA reported that almost 60% of participants had had at least one transition (to greater or lesser frailty) during 54 months of follow-up (144). This highlights the dynamic nature of frailty and supports the continuous monitoring of frailty in older people.

The global picture of the incidence and prevalence of frailty has not been fully established, mainly because of the lack of standardisation in frailty definitions and assessments across countries. A recent systematic review and meta-analysis included data from 28 countries involving 120,000 over 60 years adults, estimated the incidence of frailty and prefrailty to be 43.4 and 150.6 new cases per 1000 person-years, respectively (145). The review also found that frailty and prefrailty incidence rates were higher in women compared to men, and this difference might be due to biological and socioeconomic factors (145).

In a meta-analysis of 21 studies in 61,500 older community-dwelling, the weighted prevalence of frailty was estimated to be 10.7% (95% CI:10.5–10.9). However, this review finds that frailty prevalence in the community varied largely across studies (range 4.0-59.1%) because of the differences in frailty definitions and assessment tools across studies. Despite these discrepancies, many studies have concluded that frailty is higher in women than men, and it generally increases with age (146-148). In addition, frailty prevalence tends to be higher in people with lower socioeconomic status and those living in the most deprived

areas (146, 149-151). Those who live (or move to) deprived areas tend to have less wealth, poorer health, and limited resources compared to those in the least deprived areas. In England, the prevalence of frailty in 2020 was estimated to be 8.1% among adults aged 50+ years, with females having a higher frailty prevalence than males (9.1% versus 6.8%) (152).

1.5.1 Frailty assessment

There are three widely utilised and validated instruments for assessing frailty: the Clinical Frailty Scale, the phenotype model, and the cumulative deficit model (153).

Clinical Frailty Scale

The Clinical Frailty Scale (CFS), developed as part of the Canadian Study of Health and Aging (CSHA), is a 9-point scale designed to measure frailty based on clinical judgment (154). It categorizes individuals from 1 (very fit) to 9 (terminally ill) by assessing factors like physical fitness, comorbidities, functional dependence, and cognitive impairment. The CFS shows strong predictive validity for mortality and the need for institutional care, performing comparably to the Frailty Index, which counts clinical deficits. The scale is easy to use in clinical settings, offering a practical tool for stratifying older adults by their vulnerability and planning appropriate care.

Phenotype model

The frailty phenotype model defines frailty as a clinical syndrome in which three or more patients' phenotypic characteristics are present (Table 1.2) (155). The model was developed using data (5,317 participants) from the Cardiovascular Health Study, a population-based observational study of coronary heart disease and stroke in adults aged 65 years and older (156). Individuals were considered frail if they had three or more frailty characteristics, intermediate (prefrail) if they had one or two characteristics, or not frail if they didn't have any criteria. About 7%, 47%, and 46% of the study participants have been identified as frail, pre-frail, and not frail, respectively (155). Frail individuals had higher rates of comorbidity and disability, had lower income, less education, and were more likely to be females than those who were not considered frail or were in the prefrail group ($P<0.5$) (155).

Table 1.2. Components of the phenotype frailty model adopted from the work of Fried et al. (155)

Characteristics of Frailty	Measurement
Weight loss	Baseline: >10 lbs lost unintentionally in the prior year
Weakness	Grip strength: lowest 20% (by gender, body mass index)
Poor endurance; Exhaustion	"Exhaustion" (self-report)
Slowness	Walking time/15 feet: slowest 20% (by gender, height)
Low activity	Kcals/week: lowest 20% **Males**: 383 Kcals/week. **Females**: 270 Kcals/week

Cumulative deficit model

In cumulative deficit models, deficits are referred to as abnormal signs, symptoms, laboratory values, disease states, and disabilities (157). When these deficits are identified, they can be calculated as a proportion of the total known deficits to produce a frailty index. The original frailty index used 70 parameters from the Canadian Study of Health and Ageing (158). These 70 variables were further reduced to 36 deficits (159).

1.5.2 Identifying frailty using routinely collected data

Some tools were designed to identify frailty using routinely collected data. These tools are considered more efficient as they can be performed without requiring additional effort or time from healthcare providers and are suitable for large-scale screening (160, 161). However, EHR-based frailty assessment tools rely heavily on the quality and completeness of routinely collected data. Missing or inaccurate data, such as unrecorded comorbidities or deficits, may lead to underestimating or overestimating a patient's frailty. In addition, these frailty tools are often used as risk stratification for patients living with frailty and require clinical judgment to confirm patients' frailty diagnosis.

Electronic Frailty Index (eFI)

The eFI is a simple and easy-to-calculate score using electronic health record (EHR) data that is collected routinely within primary care. It was developed by

Clegg et al. using data from 931,541 patients aged 65–95 years (207,814 development cohort; 207,720 internal validation cohort; 516,007 external validation cohort) extracted from ResearchOne primary care database and externally validated using cohort from the Health Improvement Network (THIN) database (162). The eFI was based on the cumulative deficit model, and it used 36 deficits (Table 1.3) obtained from 2,171 Clinical Terms Version 3 (CTV3) read codes. The calculation of the eFI depends on the number of deficits a patient has in relation to a total of 36 deficits (e.g. if a patient has ten deficits, eFI score=10/36=0.28). Based on the eFI score, patients are identified as fit (eFI=0–0.12), having mild frailty (>0.12–0.24), moderate frailty (>0.24–0.36), or severe frailty (>0.36) (162). The eFI is now readily available for GPs to calculate through SystmOne and EMIS Web GP EHRs and has been supported by NICE (126).

Table 1.3. List of the 36 deficits included in the eFI adopted from Clegg et al. (150)

Disease state	**Disability**
Arthritis	Activity limitation
Atrial fibrillation	Hearing impairment
Cerebrovascular disease	Housebound
Chronic kidney disease	Mobility and transfer problems
Diabetes	Requirement for care
Foot problems	Social vulnerability
Fragility fracture	Visual impairment
Heart failure	**Abnormal laboratory values**
Heart valve disease	Anaemia and haematinic deficiency
Hypertension	**Signs/Symptoms**
Hypotension/syncope	Dizziness
Ischaemic heart disease	Dyspnoea
Osteoporosis	Falls
Parkinsonism and tremor	Memory and cognitive problems
Peptic ulcer	Polypharmacy
Peripheral vascular disease	Sleep disturbance
Respiratory disease	Urinary incontinence
Skin ulcer	Weight loss and anorexia
Thyroid disease	
Urinary system disease	

Hospital Frailty Risk Score (HFRS)

Hospital Frailty Risk Score was developed in a cohort of patients (22,139) over 75 years who had been discharged from the hospital, using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) diagnostic codes (160). The authors first used cluster analysis to identify patients admitted to the hospital with similar frailty characteristics from their ICD-10 codes. The HFRS score was then calculated from the overrepresented ICD-10 codes in the study cohort, and three risk groups were identified: low-risk (less than five scores), intermediate-risk (5-15), and high-risk (>15). When compared to the low-risk group, patients with the highest HFRS scores had 71% higher adjusted odds of 30-day mortality (OR: 1.71, 95% CI:1.68–1.75), six times higher risk of extended hospital stay (6.03, 5 .92–6.10), and 48% higher day readmission (1.48, 146–1.50) (160).

Dr Forster global frailty score (FGFS)

The FGFS tool was developed and utilised 1.4 million patient records from the Dr Foster Global Comparators (GC) international database, a collaboration of 34 hospitals across nine countries across Europe, the USA, and the UK (163). The FGFS was calculated by using seven weighted frailty syndrome groups to predict long hospital stays, 30-day non-elective readmission, and in-hospital mortality. The FGFS was significantly associated with all three outcomes ($p>0.05$). External validation was carried out in the same study using the Hospital Episodes Statistics data set from England (163). The main concern about this score is its limited generalizability due to the observed variability in the frequency of frailty coding across countries.

1.5.3 Frailty and cancer

Older people with cancer are often underrepresented in clinical trials and have poorer prognosis and survival than younger cancer patients (164-166). These differences in cancer outcomes are not solely explained by chronological age. Frailty, comorbidity and disability could co-exist in older patients with cancer and might explain poorer prognosis rather than age alone. Previous research showed that frailty is significantly associated with increased postoperative deaths, complications, lengthy hospital stays, and adverse discharge dispositions (167). This highlights the importance of frailty as a key factor in prognostication and the

need for personalized perioperative care in older adults with cancer. Effective frailty assessment can help ensure that fit older patients are not undertreated based on age alone and allow frail patients to avoid aggressive treatments. Frailty level and individual vulnerabilities could also change over time due to the introduction of new stressors into patients' lives (i.e. diagnosis of cancer) (168).

Research has estimated the prevalence of frailty in cancer patients. A systematic review assessing the prevalence of frailty among cancer patients estimated that 43% of older cancer patients were considered frail and had a higher risk of mortality, postoperative complications, and chemotherapy intolerance (169). The prevalence of frailty ranged from 43-68% for cancer studies reported using two or more deficits to identify frailty and 22-56% for studies using three or more deficits. The review included only studies that reported the mean age of participants above 70 years. Previous research has also examined the prevalence of frailty and its association with mortality among lung cancer patients. One systematic review that included meta-analysis has estimated the prevalence of frailty from 16 included studies among 4,183 lung cancer patients to be approximately 45% (95% CI, 28-61) (170). The same study reported that the presence of frailty was also associated with increased risk for mortality in patients with lung cancer (hazard ratio: 3.01; 95% CI: 1.77-5.10; $P < .001$) (170). Assessment of frailty among lung cancer patients could help identify patients with a higher risk of death from non-cancer causes and can guide treatment selection. Surgical resection in early-stage NSCLC is considered the standard treatment for fit patients who can undergo surgery, while patients with frailty might benefit from Stereotactic Ablative Body Radiotherapy (SABR) as a less invasive treatment. In a study of 139 early-stage NSCLC patients (101 frail patients) treated with SABR, frailty was significantly associated with a lower three-year overall survival (37.3% vs 74.7%;$p = 0.003$) and three-year cumulative incidence of non-cancer mortality (36.7% vs. 12.5%; $p = 0.02$) (171).

Recent RCTs have demonstrated the importance of geriatric assessment as a frailty assessment for older cancer patients (168, 172, 173). The use of geriatric assessment in these RCTs has resulted in enhanced management of vulnerabilities, which has reduced the risk of toxicity and the premature discontinuation of systemic cancer treatment. Given the importance of frailty assessment among the lung cancer population, assessing frailty as part of LCS

programmes could also inform the screening decision between patients and their providers. However, there is a lack of utilisation of frailty assessment tools among individuals selected for LCS. It is common for LCS trials and programs to assess participants' fitness and overall health through non-frailty metrics such as the ability to climb stairs (52, 174), the ability to lie flat (54, 60), life expectancy (174-176), and self-reported health status (52). The YLST study is the only LCS trial that aimed to use an established frailty assessment tool, eFI, to exclude individuals with severe frailty. However, this exclusion criterion was not applied as it was intended to be and will be discussed more in section 5.3.2.2.

1.6 Chapter summary

I have highlighted the pivotal role of LDCT in lung cancer screening and discussed its emerging history and proven effectiveness in reducing lung cancer mortality, as demonstrated by landmark trials such as the NLST and NELSON. Despite the potential benefits, I brought into attention the significant challenges related to the harms associated with screening and participation barriers. The eligibility to determine candidates for screening was also introduced, including the USPSTF as a factor-based strategy and model-based risk strategies such as the PLCO, LLP and others. Then, I explored the complexities introduced by frailty, comorbidity, and multimorbidity, which are common in older populations who are typically eligible for screening. These factors might increase the risk of complications from diagnostic procedures and may diminish the overall benefit of screening by reducing life expectancy and quality of life. These health conditions must be carefully assessed when considering individuals for LCS, as the goal is to select those who will most benefit from early detection while avoiding unnecessary harm. In this thesis, I will explore the role of frailty and comorbidities among the LCS population and investigate these concepts across three screening strategies.

1.7 Aims and objectives

In this thesis, I will address several unanswered research questions regarding frailty and comorbidities in the context of lung cancer screening (LCS). I will examine the prevalence of frailty and comorbidities among populations selected for LCS and critically evaluate the current guidelines and recommendations for screening individuals with these conditions. Additionally, I will investigate the impact of frailty and comorbidities on the response to LHC invitations and the

uptake of screening in the YLST. Finally, I will compare frailty, comorbidities, and overall survival among populations selected for LCS under the $USPSTF_{2021}$, $PLCO_{m2012}$, and LLP_{v2} eligibility strategies.

Five objectives were identified for the thesis as follows:

1) To synthesise the evidence on the participation (prevalence) of comorbid and frail individuals enrolled in lung cancer screening programs.
2) To understand the current LCS recommendations and guidelines regarding screening individuals with frailty and comorbidity.
3) To estimate the prevalence of frailty and comorbidities in the population invited for risk assessment and lung health check as part of the YLST.
4) To examine the associations of frailty and comorbidity with response to telephone lung cancer risk assessment invitation and subsequent uptake of LDCT screening amongst those people found to be eligible.
5) To compare frailty, comorbidity and 3-year overall survival rates among individuals who would have been eligible for LCS based on three strategies: $USPSTF_{2021}$, $PLCO_{m2012} \geq 1.51\%$ and $LLP_{v2} \geq 2.5\%$.

The thesis aims to answer the following research questions:

1) What is the population prevalence of frailty and comorbidities among high-risk individuals selected for LCS?
2) How do current LCS guidelines address the screening of individuals with frailty and comorbidities?
3) What is the prevalence of frailty and comorbidities among the YLST population?
4) What is the impact of frailty and comorbidities on the initial response to the LHC invitation and LDCT uptake in the YLST population?
5) How do different LCS eligibility strategies compare in terms of selecting individuals with frailty and comorbidities?
6) To what extent do three-year overall survival rates differ between populations identified by different LCS eligibility strategies?

1.8 Thesis overview

First, a review of the literature was needed to explore the prevalence of frailty and comorbidities in the context of lung cancer screening. **Chapter Two** of the thesis presents a systematic review and meta-analysis study (Study One) that aimed to

estimate the prevalence of frailty and comorbidities among populations eligible for LCS and to summarise the current guidelines and recommendations regarding screening individuals with frailty and comorbidities. Given the gap in this area of research, it was important for the thesis to establish the current burden of frailty and comorbidities among the LCS population. **Chapter Three** presents a retrospective case-control study (Study Two) that investigated the prevalence of frailty and comorbidities among a subcohort from YLST and examined the impact of frailty and comorbidities on the response to telephone-based lung cancer risk assessment invitation and on LDCT uptake. This study shows unique insights on the association between frailty and participation in LCS. **Chapter Four** presents a retrospective cohort study (Study Three) that compared frailty, comorbidities, and three-year overall survival between populations identified as eligible for LCS by $USPSTF_{2021}$, $PLCO_{m2012}$, and LLPv2 eligibility strategies. The unique design of YLST allowed this study to explore the three strategies under one setting to inform future LCS programmes. Finally, **Chapter Five** discusses the findings from all included studies and provides a final conclusion and suggestions for future research.

1.9 Data acquisition and management

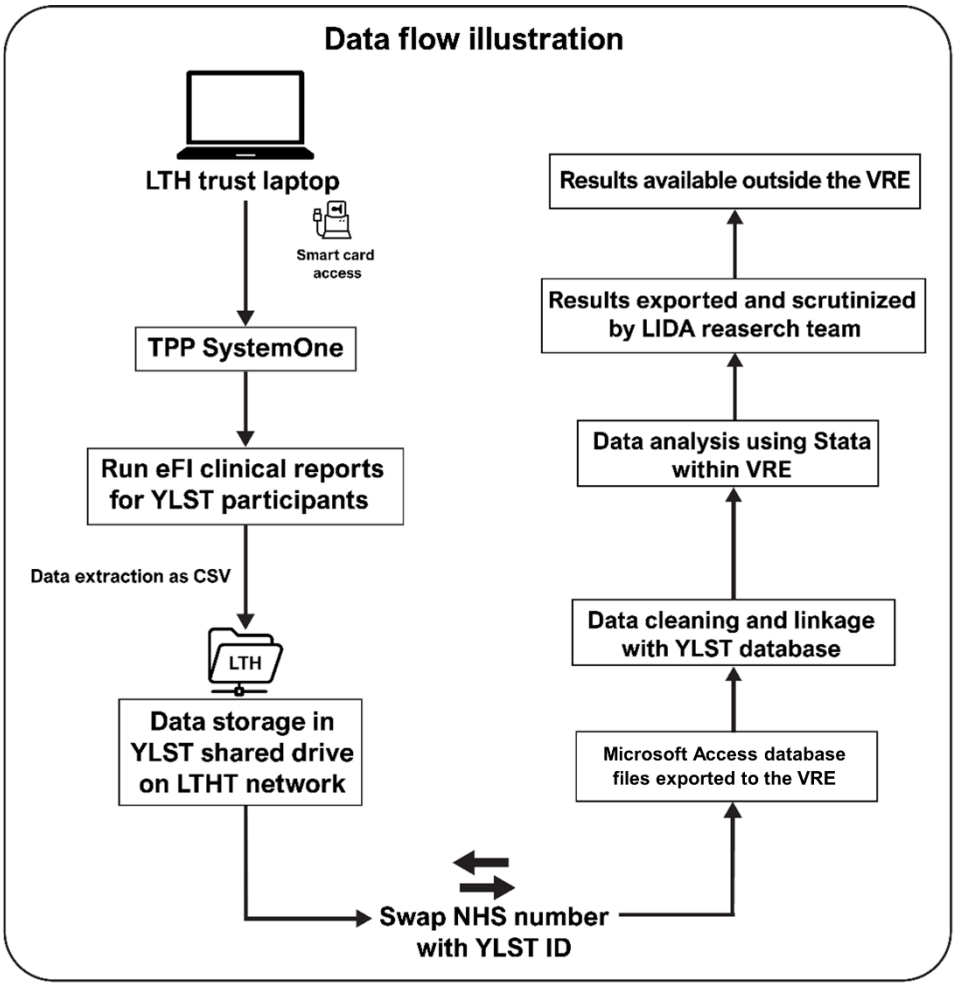
For the studies presented in chapters three and four, data was collected from participants in the intervention arm of the ongoing Yorkshire Lung Screening Trial (YLST). The SNOMED codes (n=8675) that were used to calculate eFI and derive comorbidity data were provided by Professor Andrew Clegg (Professor of Geriatric Medicine at the University of Leeds and principal investigator of the eFI project) and his team. A team from the Office of Data Analytics within the NHS West Yorkshire Integrated Care Board (ICB) then assisted in uploading the SNOMED codes to TPP SystmOne, where they designed a search algorithm to search for these codes within each participant's EHR. I primarily collected and extracted the frailty and comorbidity data for this thesis from 54 participating general practices. All data were extracted from the beginning of each patient's HER up until the date of extraction, which originally took place between August 2022 and February 2023 for all 54 practices. While conducting study three (Chapter Four), an issue in the extracted data was discovered after examining survival rates for the analytic sample. The initial survival findings appeared anomalous as individuals who were classified with moderate and severe frailty

were living much longer than their counterparts who were fit or with mild frailty, which was not medically plausible. At this point, I checked several aspects of the extracted data, and survival analysis was repeated by Professor Rhian Gabe (Professor of Biostatistics and Clinical Trials at Queen Mary University of London and external co-supervisor), reaching the same conclusion. Eventually, I discovered an issue in the algorithm that was used to search for SNOMED codes within SystmOne GPs' modules. The original algorithm was accidentally designed not to conduct any SNOMED searches for deceased participants (n=1459), which resulted in initially mislabelling them as fit individuals having few or no deficits. Those participants were alive when the YLST started and died during the trial follow-up time. The issue was discovered in December 2023 and was corrected by the ICB team in January 2024, when frailty and comorbidity data were re-extracted for the 1459 deceased participants and analyses for studies Two and Three were repeated using the corrected datasets prior to submission for publication.

All analyses were conducted up to the date of randomisation for each participant. Cohorts were extracted from a cluster of closely located General Practices each month over the first two years of the study, with the first cohort randomised on 26 September 2018 and the last cohort randomised on 9 December 2020. The included studies in Chapters Three and Four also utilised secondary data that was originally collected by the YLST and was linked to participants whose frailty and comorbidity data were primarily collected for this thesis. The variables provided by the YLST team included age, gender, Index of Multiple Deprivation (IMD) rank and quintile, ethnicity, smoking status, pack years, and LCS eligibility status. Ethnicity and smoking status were initially derived by the YLST statisticians for all invited subjects and, at a later stage, were self-reported by those who responded to the telephone risk assessment invitation.

Frailty and comorbidity data was obtained from primary care EHR using a Leeds Teaching Hospitals Trust (LTHT) laptop and stored directly on the YLST drive on the LTHT network. All data was stored, cleaned, and analysed in a secure Virtual Research Environment (VRE) within the Leeds Analytics Secure Environment for Research (LASER), which is a secure cloud-based platform hosted by the Leeds Institute for Data Analytics (LIDA). The extracted data was transferred from the

LTHT network to the VRE using a secure file-sharing service, Biscom, by the LIDA service team. This process is outlined in Figure 1.1 below.



Abbreviations
LTH: Leeds Teaching Hospitals, LIDA: Leeds Institute for Data Analytics, VRE: Virtual Research Environment, CSV: Comma-Separated Values, YLST: Yorkshire Lung Screening Trial, TPP: The Phoenix Partnership

Figure 1.1 Frailty and comorbidity data flow

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Chapter 2 : The prevalence of comorbidity in the lung cancer screening population: A systematic review and meta-analysis

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Study One

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2.1 Abstract

Objective Comorbidity is associated with adverse outcomes for all lung cancer patients, but its burden is less understood in the context of screening. This review synthesises the prevalence of comorbidities among lung cancer screening (LCS) candidates and summarises the clinical recommendations for screening comorbid individuals.

Methods We searched MEDLINE, EMBASE, EBM Reviews, and CINAHL databases from January 1990 to February 2021. We included LCS studies that reported a prevalence of comorbidity, as a prevalence of a particular condition, or as a summary score. We also summarised LCS clinical guidelines that addressed comorbidity or frailty for LCS as a secondary objective for this review. Meta-analysis was used with inverse-variance weights obtained from a random-effects model to estimate the prevalence of selected comorbidities.

Results We included 69 studies in the review: seven reported comorbidity summary scores, two reported performance status, 48 reported individual comorbidities, and 12 were clinical guideline papers. The meta-analysis of individual comorbidities resulted in an estimated prevalence of 35.2% for hypertension, 23.5% for history of chronic obstructive pulmonary disease (COPD) (10.7% for severe COPD), 16.6% for ischaemic heart disease (IHD), 13.1% for peripheral vascular disease (PVD), 12.9% for asthma, 12.5% for diabetes, 4.5% for bronchiectasis, 2.2% for stroke, and 0.5% for pulmonary fibrosis.

Conclusions Comorbidities were highly prevalent in LCS populations and likely to be more prevalent than in other cancer screening programmes. Further research on the burden of comorbid disease and its impact on screening uptake and outcomes is needed. Identifying individuals with frailty and comorbidities who might not benefit from screening should become a priority in LCS research.

2.2 Introduction

Lung cancer remains the leading cause of cancer deaths globally, with 1.8 million estimated deaths in 2020.[1] The five-year survival rate for lung cancer is 16–22% in high-income countries.[2] Patients with localised lung cancers have better five-year survival rates (above 50%) compared to most advanced distant stages (less than 10%).[3,4] This large disparity highlights the crucial role of early detection in maximising the survival benefit for high-risk individuals. The National Lung Screening Trial (NLST) was the first large-scale randomised study that reported a mortality benefit, with an estimated 20% reduction in lung cancer mortality using pulmonary low-dose computed tomography (LDCT) compared to X-ray.[5] In addition, the Dutch-Belgian Randomised Lung Cancer Screening Trial (NELSON) demonstrated a 24% reduction in male lung cancer mortality.[6] Following the NLST results, the US Preventive Services Task Force (USPSTF) issued its recommendations in 2013 for the annual screening of lung cancer with LDCT for current or former smokers aged 55 to 80 years. However, participation in lung cancer screening (LCS) among eligible smokers in the United States (US) has been limited to 6.6% on average in 2019 and remained the same in 2020.[7] When looking at the US state-level LCS uptake rates, nine states reported to have more than 10% participation rate.[7] In contrast, population-based LCS programmes in several Chinese provinces showed high uptake rates of 34%-52%.[8–10] The high uptake in China is believed to be owing mainly to the accessibility and affordability of LDCT scans across many provinces.[11] While LCS in the UK is not yet implemented on the national level, data from population-based targeted screening in Liverpool and Manchester showed high participation rates of 40% and 26%, respectively.[12,13] The presence of chronic diseases may positively impact participation in screening programmes because comorbid individuals might have direct contact with healthcare systems and services, leading to more opportunities for referral to or engagement with screening services, primarily when LCS is widely implemented, such as in the US.[14] However, the presence of comorbidities might limit management options for screen-detected lung cancer (mainly surgical resection), thereby impacting the effectiveness of treatments and patient outcomes.[15] Also, reduced life expectancy related to comorbidity would limit the life years gained through early detection by screening, especially in people with advanced or life-threatening illnesses.[16] The burden of comorbidity in LCS candidates has not previously been estimated. We systematically

reviewed the literature and utilised meta-analysis to obtain an overall estimate of the prevalence of comorbidities among high-risk populations who were selected for LCS. Additionally, LCS guidelines and recommendations were identified and summarised with respect to how they addressed comorbidities and frailty.

2.3 Methods

2.3.1 Search strategy and inclusion criteria

A systematic search was conducted in February 2021 to identify evidence regarding the comorbidity and frailty status of LCS (or screen-eligible) participants. The review protocol is registered on the PROSPERO database (Registration number CRD42021237040) and is available from https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=237040. The search was conducted using MEDLINE (OVID), EMBASE (OVID), EBM reviews- Cochrane Database of Systematic Reviews (OVID) and CINAHL (EBSCO) databases. The timeframe was from 1 January 1990 to 8 February 2021 with no language restriction, using a strategy of subject headings and free text words (Appendix 1, see online supplementary files). The timeframe of 1990 was used as a starting point to adequately capture studies investigating the utilisation of LDCT for LCS. We excluded case reports, case series, modelling studies, qualitative studies, conference abstracts, reviews, commentary, and editor letters. Titles and abstracts were screened for eligibility using Rayyan software.[17] Studies were considered for inclusion if they were 1) conducted in an LCS setting that included screened or high-risk eligible participants, and 2) reported comorbidity or frailty status, either as a prevalence of a specific condition, proportion, or a summary score (e.g. the Charlson Comorbidity Index (CCI)).[18,19] A 20% sample of the total identified titles and abstracts was double-screened by a second reviewer (OT), and disagreements were resolved through consensus. We have also considered and included clinical guidelines and recommendations that addressed comorbidity or frailty in the context of LCS as a supplementary goal of the review. No specific keywords were added to identify clinical guidelines, as we relied on our main keyword strategy to include these articles.

2.3.2 Data extraction and quality assessment

Data were extracted using a standardised data extraction form by one author (AA), and a 20% sample of extracted data was independently checked by another author (OT). Comorbidity prevalence was calculated as the number of people with the condition (numerator) divided by the total sample size (denominator). When studies reported only a proportion of a particular comorbidity, the numerator was converted to absolute numbers. Individual comorbidities were chosen based on their 1) clinical relevance to lung cancer (chronic obstructive pulmonary disease (COPD), chronic bronchitis, bronchiectasis, asthma, and pulmonary fibrosis), 2) competing nature in elevating the risk of death (stroke, peripheral vascular disease (PVD), and ischaemic heart disease (IHD)), or 3) frequent reporting in the included studies (type 2 diabetes and hypertension). We utilised the Cochrane risk of bias tool (RoB 2) to assess the quality of randomised control trials.[20] For observational studies (cohort and case-control studies), the Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias.[21] A modified version of NOS was used for the quality assessment of cross-sectional studies.[22]

2.3.3 Meta-analysis

The meta-analysis was conducted by using the *metaprop* command in STATA (version 16.1) to provide an overall pooled estimate (proportion) with inverse-variance weights obtained from a random-effects model. Confidence intervals were computed using the score method,[23] and heterogeneity across studies was evaluated using I^2 statistic.[24]

2.4 Results

The initial search identified a total of 5439 records. After removing duplicates, screening titles and abstracts, and excluding not retrieved studies, 335 were included for full-text screening. Two hundred and sixty-six studies were further excluded after the full-text screening, leaving 69 studies that met our inclusion criteria and were considered for final qualitative and quantitative synthesis (Figure 1). Of the 69 included studies, seven reported comorbidity using summary measure scores (Table 1), two reported performance status (Table 1), 48 reported individual comorbidities (Table 2), and 12 publications highlighted the recommendations of undergoing LCS for comorbid or frail individuals (Table 3).

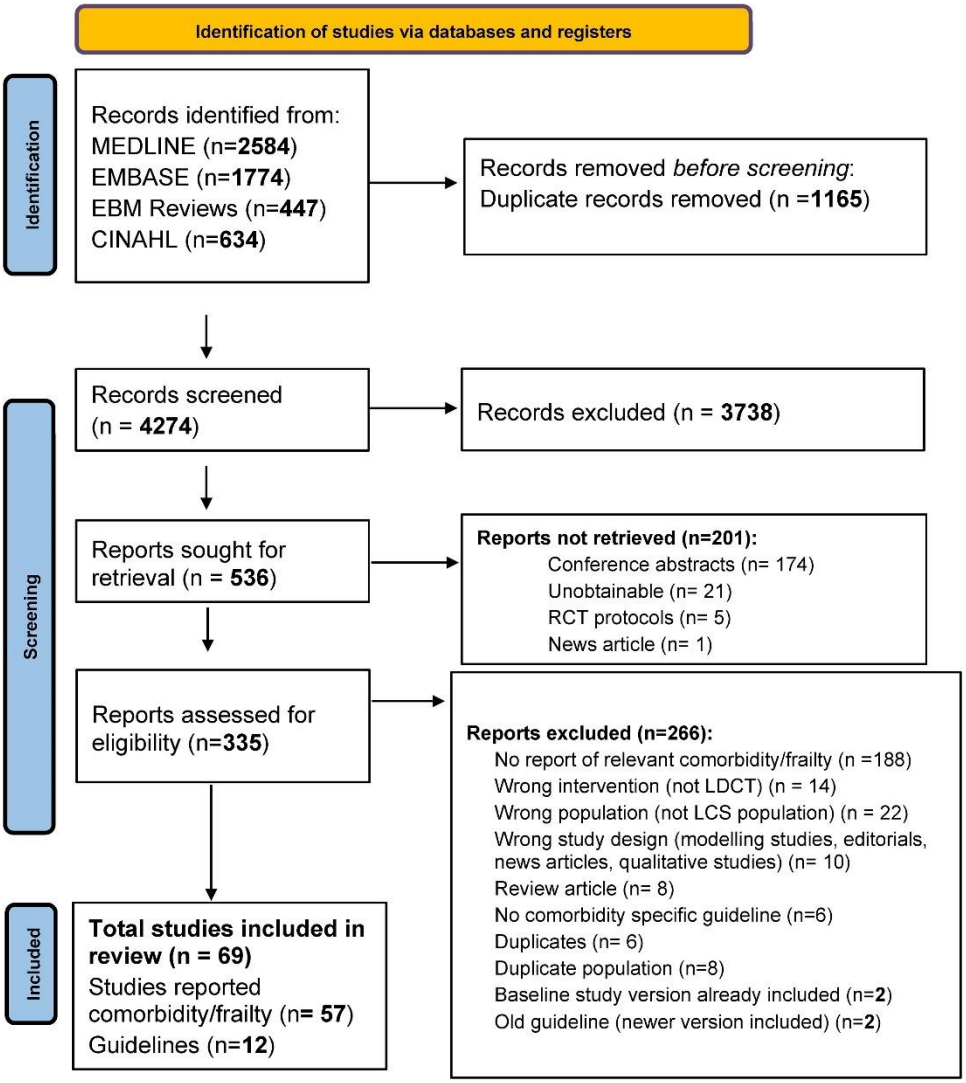

Figure 2.1. Flow diagram of the selection process according to the PRISMA 2020 statement. *Adapted from:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

Table 2.1. Studies reported comorbidity/frailty measure score

1st Author, Year	Design	Setting	Screening status	Country	Participants	Comorbidity/frailty measure	Cases	Total	Percentage	Risk of Bias
Iaccarino, 2018.[26]	CS	Academic safety-net hospital	Screened	USA	1203	**Charlson Comorbidity Index (CCI):**				8/10*
						0 (good health)	362	1203	30.1%	
						1–3 (average health)	640	1203	53.2%	
						>4 (poor health)	201	1203	16.7%	
Rasmussen, 2015.[27]	RCT	Danish randomised controlled lung cancer screening trial (DLCST)	Screened	Denmark	2052	**CCI:**				Low
						0	1697	2052	82.7%	
						1	196	2052	9.6%	
						≥2	159	2052	7.7%	
Li, 2018.[28]	RC	Primary care providers	Eligible	USA	12801	**CCI:**				7/9
						No major comorbidity (CCI =0)	3911	12801	30.6%	
						Mild (CCI =1–2)	5076	12801	39.7%	
						Moderate (CCI =3–4)	2179	12801	17.0%	
						Severe (CCI ≥5)	1635	12801	12.8%	
Carroll, 2020.[29]	RC	Non-profit integrated healthcare system	Screened	USA	3375	**CCI:**				6/9
						0 (good health)	1130	3375	33.5%	
						1–3 (average health)	1820	3375	53.9%	
						4 or more (poor health)	425	3375	12.6%	
Nishi, 2019.[30]	CS	Claims data of Medicare beneficiaries	Screened	USA	3673046	**Elixhauser comorbidity score**				9/10*
						0	1308685	3673046	35.6%	
						1	795487	3673046	21.7%	
						2	637809	3673046	17.4%	
						3	380835	3673046	10.4%	
						4+	550229	3673046	15.0%	
Nishi, 2020.[31]	CS	Commercial health insurance database	Screened	USA	11520	**Elixhauser comorbidity score:**				7/10*
						0	2424	11520	21.0%	
						1	2788	11520	24.2%	
						2	2245	11520	19.5%	

						3	1509	11520	13.1%	
						4+	2554	11520	22.2%	
						Number of Comorbidities:				
Tammemägi, 2014.[32]	RCT	Data from the National Lung Screening Trial	Screened	USA	14661	0	6661	14661	45.4%	9/10*
						1	5014	14661	34.2%	
						2	2098	14661	14.3%	
						≥3	888	14661	6.1%	
						WHO Performance Status:				
Ruparel, 2020.[41]	RCT	Lung Screen Uptake Trial (LSUT)	Screened	UK	732	0 - asymptomatic	891	996	89.5%	Low
						1 - completely ambulatory	95	996	9.5%	
						2 - <50% of day in chair/ bed	9	996	0.9%	
						3 - >50% of day in chair/ bed	1	996	0.1%	
						Performance status:				
Crosbie, 2019.[14]	PC	Community-based mobile CT scanners	Screened	UK	1429	0	768	1429	53.7%	9/9
						1	481	1429	33.7%	
						2	152	1429	10.6%	
						3	28	1429	2.0%	

PC= Prospective cohort study, RC= Retrospective cohort study, CS= Cross-sectional study, RCT= Randomized controlled trial. Risk of bias scores: very high risk of bias (0 to 3), high risk of bias (4 to 6), and low risk of bias (7 to 9) according to the Newcastle-Ottawa Scale (NOS). *A modified version of NOS was used to assess the risk of bias for cross-sectional studies.

Table 2.2. Studies reported individual comorbidities

1st Author, Year	Design	Setting	Screening status	Country	Participants	Risk of Bias
Lebrett, 2020. [42]	PC	Community- based screening	Screened	UK	1410	9/9
De Jong, 2014. [43]	RCT	University medical centre	Screened	Netherlands	1140	Low
Wilson, 2008. [44]	RC	Community-based study	Screened	USA	3638	8/9
Aberle, 2010. [45]	RCT	33 medical institutions	Screened	USA	26723	Low
Park, 2020. [46]	CS	Survey data	Eligible	Korea	4763098	7/10*
Goffin, 2020. [47]	PC	The Pan-Canadian Early Detection of Lung Cancer (PanCan)	Screened	Canada	2514	7/9
Marquette, 2020. [48]	PC	21 French university centres	Screened	France	614	7/9
Zhu, 2020. [49]	PC	The LDCT screening for lung cancer in New York State	Screened	USA	8618	5/9
Balkan, 2016. [50]	CS	community-based	Screened	USA	3183	6/10
Jacobs, 2012. [51]	Case-cohort study	RCT	Screened	Netherlands	958	8/9
Leigh, 2017. [52]	PC	Multi-Ethnic Study of Atherosclerosis (MESA)	Eligible	USA	481	8/9
Henschke, 2015. [53]	PC	The International Early Lung Cancer Action Program (I-ELCAP)	Screened	Multinational	62124	6/9

Sekine, 2014.[54]	CS	community-based	Screened	Japan	185	7/10*
Welch, 2019.[55]	CS	construction trades workers	Screened and eligible non- participants	USA	4399	7/10*
Li, 2011.[56]	CC	Mayo clinic	screened	USA	450	7/9
Wilshire, 2020.[57]	CS	Electronic Medical Record Review	Referrals	USA	2843	5/10*
Omori, 2006.[58]	CS	Kumamoto Red Cross Hospital	Screened	Japan	615	5/10
Guo, 2020.[59]	CS	Tertiary-level hospitals	Screened	China	22260	7/10*
Ruparel, 2019.[60]	CS	The Lung Screen Uptake Trial (LSUT)	Screened	UK	770	7/10*
Salvatore, 2016.[61]	CS	Lung cancer screening program	Screened	USA	951	5/10*
Anna, 2018.[62]	PC	Single centre	Screened	Hungary	739	7/9
Bons, 2020.[63]	RCT	DLCST	Screened	Denmark	1987	Low
Fu, 2018.[64]	CS	Spanish National Interview Health Survey (ENSE)	Eligible	Spain	1034	8/10*
Regan, 2019.[65]	CS	21 clinical centres	Screened	USA	4078	9/10*
Sanchez-Salcedo, 2015.[66]	PC	P-IELCAP & PLuSS	Screened	Spain & USA	P-IELCAP (n = 3,061), PLuSS (n = 3,638)	6/9
Sim, 2010.[67]	CS	University hospital	Screened	Korea	191	7/10*
Ahmed, 2018.[68]	RC	Academic medical centre	Screened	USA	272	6/9

Infante, 2008.[69]	RCT	DANTE trial	Screened	Italy	1276	Low
Raju, 2020.[70]	CC	Medical centre	Screened and Eligible controls	USA	542 (participants) vs 276 (LDCT eligible controls)	7/9
Sanchez-Salcedo, 2015.[71]	PC	Pamplona International Early Lung Cancer Detection Program (P-IELCAP)	Screened	Spain	2989	6/9
Ostrowski, 2019.[72]	PC	Open-access lung cancer screening program	Screened	Poland	8637	6/9
Calabro, 2010.[73]	CS	Secondary analysis of an RCT	Screened	Italy	3749	7/10*
Lewis, 2020.[74]	RC	Veterans based study	Screened	USA	80819	6/9
Aggarwal, 2019.[75]	PC	Princess Margaret Cancer Centre	Screened	Canada	359	7/9
Tammemagi, 2017.[76]	PC	8 centres	Screened	Canada	2537	8/9
Guichet, 2018.[77]	RC	Community clinics	Screened	USA	275	5/9
Wang, 2001.[78]	CS	Voluntary screening program	Screened	Japan	7847	7/10*
Ruparel, 2020.[79]	CS	Lung Screen Uptake Trial	Screened	UK	986	7/10*
Barros, 2018.[80]	RC	Tertiary hospital	Screened	Brazil	172	5/9
Hopkins, 2017.[81]	CS	NLST-ACRIN	Screened	USA	18714	8/10*
Sverzellati, 2012.[82]	CS	Multicentric Italian Lung Detection (MILD)	Screened	Italy	1159	6/10*
Rasmussen, 2013.[83]	CS	The Danish Lung Cancer Screening Trial	Screened	Denmark	1535	6/10*

Wille, 2016. [84]	RCT	The Danish Lung Cancer Screening Trial	Screened	Denmark	2052	Low
Perez-Warnisher, 2019. [85]	PC	The Sleep Apnea In Lung Cancer Screening (SAILS) study	Screened	Spain	236	6/9
Balata, 2020. [86]	CS	Community- based lung cancer screening programme	Screened	UK	2541	8/10*
Sekine, 2014. [87]	CS	Community-based lung cancer screening	Screened	Japan	7067	9/10*
Balata, 2018. [88]	CS	Community- based lung cancer screening programme	Screened	UK	958	7/10*
Mets, 2012. [89]	CS	NELSON trial	Screened	Netherlands	266	6/10*

PC= Prospective cohort study, RC= Retrospective cohort study, CS= Cross-sectional study, RCT= Randomized controlled trial. Risk of bias scores: very high risk of bias (0 to 3), high risk of bias (4 to 6), and low risk of bias (7 to 9) according to the Newcastle-Ottawa Scale (NOS). *A modified version of NOS was used to assess the risk of bias for cross-sectional studies.

Table 2.3. Clinical guidelines that address the issue of comorbidity among LCS candidates

Guideline Title	1st Author, Year	Recommendation
The American Association for Thoracic Surgery guidelines for LCS	Jaklitsch, 2012. [33]	"Individuals for whom adequate treatment cannot be offered because of comorbidity or functional status, regardless of age, should not undergo screening."
Screening for lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines	Detterbeck, 2013. [35]	"For individuals with severe comorbidities that would preclude potentially curative treatment and/or limit life expectancy, we suggest that CT screening should not be performed (Grade 2C)."
The International Association Study Lung Cancer (IASLC) Strategic Screening Advisory Committee (SSAC) Response to the USPSTF Recommendations	Field, 2014. [40]	"It is reasonable to assess fitness before entry to a screening program and at key intervals thereafter to ensure that (1) screenees are able to undergo, with tolerable risks, both the investigations indicated to evaluate suspicious nodules and the subsequent treatment of suspicious nodules or proven lung cancers, and (2) their life expectancy because of comorbid disease(s) will not prematurely limit their life expectancy relative to the treatment of a documented lung cancer."
Low-dose computed-tomography lung cancer screening: the first European recommendations from the European Society of Radiology and European Respiratory Society	Adamek, 2015. [90]	"Exclusion criteria: comorbidities precluding curative treatment or lack of consent to undergo radical therapy"
China national lung cancer screening guideline with low-dose computed tomography (2015 version)	Zhou, 2015. [39]	"Individuals who have a cancer history within the last five years (except or non-melanoma skin cancer, cervical carcinoma in situ, or localised prostate cancer), cannot tolerate possible lung cancer resection, or have a life-threatening disease, are not recommended for screening."
Choosing wisely: The Canadian Thoracic Society's list of six things that physicians and patients should question	Gupta, 2017. [37]	"Screening also leads to unnecessary anxiety and invasive procedures, which carry their own complications. Accordingly, it should not be used in patients who do not meet these strict criteria nor in patients with a health problem that substantially limits life expectancy or the ability or willingness to have curative therapy."
Screening for Lung Cancer CHEST Guideline and Expert Panel Report	Mazzone, 2018. [91]	"For individuals with comorbidities that adversely influence their ability to tolerate the evaluation of screen-detected findings, or tolerate treatment of an early-stage screen-detected lung cancer, or that substantially limit their life expectancy, we recommend that low-dose CT screening should not be performed. (Strong recommendation, low-quality evidence)."

Consensus statement on a screening programme for the detection of early lung cancer in Poland	Rzyman, 2018. [36]	"The decision to join a screening programme should be a shared decision made by the physician and a patient and should be individually discussed, particularly in patients with comorbidities."
The National Comprehensive Cancer Network (NCCN) Lung Cancer Screening, Version 3.2018	Wood, 2018. [34]	"Screening can be considered for individuals older than 74 years if they have good functional status, do not have serious comorbidities that would impede curative treatment, and are willing to undergo treatment" & "Patients with several comorbid conditions may be at greater risk than those with few or none."
Incorporating coexisting chronic illness into decisions about patient selection for lung cancer screening. An official American thoracic society research statement	Rivera, 2018. [16]	"There is controversy and confusion regarding who should be offered screening, and future research is needed with the aim of incorporating the balance of risk of LCD, competing causes of death, morbidity, mortality, and efficacy of treatment approaches in the face of comorbidities."
Recommendations for Implementing Lung Cancer Screening with Low-Dose Computed Tomography in Europe	Veronesi, 2020. [92]	"As comorbidities (coronary artery disease, heart failure, cardiac arrhythmias, hypertension, hypercholesterolemia, osteoporosis, diabetes) are frequent, they may benefit from treatment, but with a considerable reduction in quality-adjusted life years (QALY). Moreover, the ability to deliver effective treatments should be considered"
Screening for Lung Cancer, US Preventive Services Task Force Recommendation Statement	Krist, 2021. [38]	"The USPSTF recommends discontinuing screening if a person develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery"

When reporting comorbidity using summary measure scores, four studies used the CCI,[25–28] two used the Elixhauser Comorbidity Index,[29,30] and one study used a simple comorbidity count.[31] We could not perform a meta-analysis of the four studies that utilised CCI as two studies used different sub-categories. The search results did not retrieve any study that directly utilised an established frailty measure, although two studies reported performance status.

2.4.1 Studies that reported individual comorbidities

Most studies were conducted in North America (42%) and Europe (42%), with only seven studies (12%) conducted in Asia, one in Brazil, and one was multinational. The review included studies varied in design with 26 cross-sectional studies, 22 cohort studies, seven randomised controlled trials (RCTs), and two case-control studies. All RCTs were found to have a low risk of bias. The majority of non-randomised studies (32 studies) were rated as having a low risk of bias (scored between 7 and 10) based on the NOS system, and 18 studies were rated as having a high risk of bias (scored 5 and 6).

Pooled estimations of the prevalence of individual comorbidities among LCS populations are presented in forest plots and included in the supplementary files (Appendix 2). The results show that the estimated prevalence of individual comorbidities sequentially ordered by proportion was: hypertension (35.2%, number of reported cases (c) = 1,498,429, total screening population (n) = 4,812,180), history of COPD (23.5%, c = 9868, n = 67,662), chronic bronchitis (17.2%, c = 31,329; n = 92,102), IHD (16.6%, c = 22,236, n = 94,379), PVD (13.1%, c = 327, n = 2648), asthma (12.9%, c = 4043, n = 36,134), diabetes (12.5%, c = 93,6813, n = 4,822,167), advanced COPD (stage 3 and 4) (10.7%, c = 3747, n = 35,778), bronchiectasis (4.5%, c = 13,221, n = 86,530), stroke (2.2%, c = 1068, n = 42,004), and pulmonary fibrosis (0.55%, c = 102, n = 33,072).

2.4.2 Findings from clinical guidelines

Findings regarding recommendations for screening comorbid individuals set by clinical guidelines are summarised and presented in Table 3. The American Association for Thoracic Surgery (AATS)[32] and The National Comprehensive Cancer Network (NCCN)[33] guidelines do not endorse LCS in individuals with limited functional status or comorbidity that might affect potential curative treatment. Other guidelines such as the American College of Chest Physicians

(CHEST),[34] the European Society of Radiology (ESR) and European Respiratory Society (ERS),[35] and the Canadian Thoracic Society (CTS)[36] guidelines condition the screening of comorbid people on their ability to undergo curative treatment without considering functional status or frailty. The USPSTF[37] and the Chinese national[38] LCS guidelines specify the ability to undergo lung surgery as a criterion for screening individuals with comorbidity or serious health illness. In addition, a consensus statement from Poland recommends that the decision to undergo LCS should be a shared one between the physician and patients with comorbidities,[37] Unlike other guidelines, the International Association Study Lung Cancer (IASLC) guideline was the only one that recommended performing fitness assessments for high-risk individuals before their enrolment in LCS programmes.[39] Finally, the AATS organised a multidisciplinary panel in 2017 that emphasised the need for future research on incorporating comorbidities and functional status in selecting candidates for LCS.[15]

2.5 Discussion

This systematic review is the first to estimate the prevalence of comorbidities among LCS populations, evaluating 57 studies and 12 clinical guidelines. Most of the included studies (84%) were from western countries (Europe and North America), and only 12% were conducted in Asia. The total number of included studies in our review is fewer than the total number of LCS studies available in the literature because we find that not all LCS programmes report comorbidity or frailty data. Despite using a comprehensive search strategy, we found only a small fraction of included studies (10%) used validated comorbidity indices, and none utilised a pre-screening validated frailty assessment tool. However, two studies (24, 25) utilised performance status, which might be a proxy for frailty. These findings highlight the underutilisation of comorbidity and frailty measures among LCS population.

Even though only seven studies used comorbidity summary scores, we found that proportions of people without comorbidity (CCI = 0) were higher in clinical trial settings (83% and 45%)[26,31] compared to population-based screening settings (range: 30%-33%),[25,27,28] indicating a potential role of healthy volunteer effect in LCS trials.[40] The same observation applies to studies that utilised WHO performance status; one RCT[41] reported asymptomatic performance status

(score 0) in about 90% of participants compared to 54% from a community-based LDCT screening programme.[13]

The comorbidity profile of LCS participants differs from those reported in breast and colorectal cancer screening programmes. The proportion of individuals without comorbidity (CCI = 0) reported previously in large breast cancer (56%,[42] 76%,[43] 84%,[44] and 93%[45]) and colorectal cancer (65%,[46] 52%[47]) screening studies is much higher than what we observed in LCS studies included in our review (30%-33%).[25,27,28] A possible explanation is that breast and colorectal screening programmes sample from the entire community with age as the primary risk factor. In contrast, lung cancer screening relies more on smoking as the leading risk factor, which is associated with comorbidities. This observation highlights the need for more research and innovations to deliver LCS to those with greater life expectancy, considering the presence of comorbidities.

The prevalence of history of COPD was also considered for meta-analysis, resulting in a pooled estimate of 23.5% (95% CI: 16.5, 31.4) from 11 studies. The sub-group analysis by data collection method indicated significant heterogeneity ($p < 0.001$). The estimated prevalence from studies that utilised health records to identify the history of COPD was 38.7% (95% CI: 31.5, 46.2, $I^2 = 95.6\%$, $p < 0.001$) compared to 16.9% (95% CI: 10.5, 24.5, $I^2 = 99.7\%$, $p < 0.001$) pooled from studies that relied on self-reporting. This finding suggests that relying on self-reporting of COPD may underestimate the true burden of COPD in a LCS population, potentially misclassifying participants having low risk when using lung cancer risk-prediction methods that incorporate COPD (i.e. $PLCO_{M2012}$).[48,49] We also estimated the prevalence of advanced COPD, stages 3 and 4, to be 10.7% (95% CI: 6.1, 16.4), as reported in 12 studies using the Global initiative for chronic Obstructive Lung Disease (GOLD) criteria (www.GOLD.org). Most studies reported a prevalence of advanced COPD of less than 10%, while four reported a prevalence of advanced COPD above 20% (range: 20.3%-31.0%).[50–53] Screening individuals with advanced COPD remains controversial as they may not benefit from screening due to inoperability and an increased risk of respiratory and other competing causes of death.[54,55] The utilisation of functional assessment tools, such as the BODE index,[56] is suggested to be a better way of assessing the severity and fitness of patients with advanced COPD by

incorporating not only the degree of airflow obstruction but also functional dyspnea, body-mass index, and exercise capacity.[15,56]

We also estimated the prevalence of four lung diseases: chronic bronchitis, asthma, bronchiectasis, and pulmonary fibrosis. The pooled estimate for chronic bronchitis was 17.2% (95% CI: 5.5, 33.0) among the LCS population and considered higher than what is usually found in the general population, which is around 3%.[57,58] The increasing age and smoking habits could explain the higher prevalence of chronic bronchitis in the LCS population.[59] Estimate of asthma prevalence was 12.9% (95% CI: 8.3, 18.3), which is more than what is normally observed in the general population.[60,61] A similar observation was reported by Zahnd et al.[62] when they found that individuals with asthma tend to utilise LCS more than those without asthma (22.9% vs. 12.9%, $p = 0.006$). Bronchiectasis and pulmonary fibrosis were less prevalent with pooled estimates of 4.5% (95% CI: 0.4, 12.4) and 0.55% (95% CI: 0.18, 1.10), respectively. Previous studies, not captured by our search as we did not include bronchiectasis in our search strategy, reported a prevalence of bronchiectasis ranging from 0.2% to 16%.[63–66] The higher presence of bronchiectasis in the LCS population is suggested to be associated with a higher incidence of new nodules and false-positive results on both baseline and subsequent screening rounds.[67]

In addition to respiratory comorbidities, we estimated the prevalence of ischemic heart disease (IHD), PVD, and strokes as conditions that may have a competing cause of death in the LCS population. We found that IHD was prevalent in 16.6% (95% CI: 11.0, 23.0) of screened candidates across eight studies (9 estimates). The estimated prevalence of IHD in our review is more than twice the prevalence of IHD found in the general population of the United States[68] and the UK.[69] Smoking habits and age might explain the elevated IHD prevalence in the LCS population compared to the general population.

The second part of this systematic review is related to the inclusion of comorbidity and frailty in LCS guidelines. Overall, clinical guidelines were generally vague and did not fully address comorbidity or frailty in their LCS recommendations. The ability to tolerate curative treatment before undertaking LCS was agreed upon as an inclusion criterion among most included guidelines. Only the USPSTF[37] and the Chinese[38] guidelines recommended LCS for people who could withstand lung surgery. The ability to tolerate treatment or withstand surgery is not well defined

across clinical guidelines, with little information about how physicians should communicate the benefits and harms of LCS to their patients who have frailty or severe comorbidity. The American Thoracic Society issued a research statement in 2018 acknowledging this dilemma, and outlined future research directions to incorporate the severity of comorbidities and functional status into the selection process.[15]

Our review highlighted the current scarcity of pre-screening frailty or functional assessment tools in LCS programmes. Previous studies have demonstrated the association of frailty with poor cancer screening consequences,[70] postoperative complications,[71,72] and higher mortality of non-cancer causes.[73,74] In addition, the prevalence of frailty among lung cancer patients of different stages was recently estimated to be 45%, with a significant adverse impact on survival.[75] Future LCS programmes and research should invest in this area by examining the feasibility and usefulness of incorporating a pre-screening assessment of frailty and comorbidity severity.

To the best of our knowledge, this study is the first to estimate the burden of comorbidity among LCS candidates to inform researchers and policymakers about the magnitude of this public health problem. The strengths of this review include utilising a comprehensive search strategy and including a large number of studies. The variability of the methods used to report single comorbidities is a potential limitation of this review, as most studies relied on self-reporting of comorbidities, with only a few studies utilising medical records and administrative databases. As a result, the pooled prevalence estimates should be interpreted with caution. Another limitation is the observed high heterogeneity between studies, and accounting for different study locations and designs didn't explain this observation. In addition, there might be other clinical guidelines not covered by our review as we didn't incorporate guidelines-specific keywords in our search strategy.

Conclusion

In this study, we reviewed 57 studies and 12 clinical guidelines to estimate the prevalence of comorbidities in LCS populations and summarise the clinical recommendations for screening comorbid individuals. Detailed prevalence of selected comorbidities was reported. LCS is an essential element of early detection and cancer control and will likely become more available to high-risk

individuals in the coming years. Before widely implementing LCS, identifying subpopulations with a high burden of comorbidities and frailty who would be less likely to benefit from screening should become a priority. To optimise the benefits of screening and increase its cost-effectiveness, future LCS research needs to incorporate existing comorbidity and frailty measures and develop new approaches for personalising the selection process.

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Chapter 3 : Impact of Frailty and Comorbidity on Initial Response to Lung Cancer Screening Invitation and Low-Dose CT Screening Uptake: Findings from the Yorkshire Lung Screening Trial

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Study Two

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3.1 Abstract

Background: Low-dose CT screening reduces lung cancer-specific mortality in high-risk individuals. Lung cancer risk factors overlap with comorbid diseases, highlighting the significance of frailty and comorbidities for lung cancer screening (LCS). Here, we describe the prevalence of frailty and comorbidity in those invited for LCS and evaluate their associations with response to telephone risk assessment invitation and subsequent uptake of LCS.

Methods: Analysis was based on the intervention arm of the Yorkshire Lung Screening Trial, where ever-smoked individuals aged 55-80 were invited to telephone risk assessment followed by community-based LCS if at higher risk. The electronic frailty index (eFI) was used to compute individual frailty scores (categorised as fit, mild, moderate and severe) and derive comorbidity data.

Results: Of 27,761 individuals invited, 24.1% (n=6,702), 8.5% (n=2,353) and 1.7% (n=459) had mild, moderate and severe frailty, respectively. Over half responded to the invitation to telephone risk assessment (n=14,523, 52.5%) with frailty associated with a higher response rate compared to fit individuals (ORadj 1.34 95%CI 1.26-1.42 for mild frailty, ORadj1.28 95%CI 1.16-1.40 for moderate frailty, and ORadj 1.32 95%CI 1.08-1.61 for severe frailty). Similar patterns were seen with comorbidity counts. After assessment, moderate (ORadj 0.75 95%CI 0.59-0.96) and severe (ORadj 0.67 95%CI 0.43-1.04) frailty were associated with reduced screening uptake.

Conclusion: The presence of frailty was associated with increased response to LCS invitation. Given the strong association between frailty and reduced life expectancy, these results suggest that people with potentially more life years to be gained from LCS may be less inclined to take part. Further research is needed to explore the interactions between frailty and LCS decision-making to inform future invitation strategies.

Highlights

- Frailty and comorbidity are critical considerations in lung cancer screening, but the prevalence of frailty among LCS candidates is unknown, and its association with response to invitation for lung cancer risk assessment and subsequent LDCT uptake in eligible people has not been evaluated.

- Using the electronic Frailty Index (eFI), the prevalence of frailty among those invited for LCS in the Yorkshire Lung Screening Trial was 24%, 9% and 2% for mild, moderate, and severe frailty, respectively.

- Compared to fit people, those with mild, moderate, and severe frailty were more likely to respond to an invitation to undergo lung cancer risk assessment, with similar patterns seen for comorbidity counts. However, among individuals deemed to be high-risk and eligible for LDCT, frailty was associated with reduced screening uptake.

3.2 Introduction

Lung cancer is the leading cause of cancer-specific mortality in the UK (1) and globally (2), with low survival rates reflecting the fact that most patients presenting symptomatically have late-stage disease at diagnosis, which is less responsive to treatment. Early diagnosis of lung cancer significantly improves survival rates, hence the importance of screening for early detection, especially in high-risk groups. The National Lung Screening Trial (NLST) in the US and the Nederlands–Leuvens Longkanker Screenings Onderzoek (NELSON) in Europe have shown that lung cancer screening (LCS) with low-dose CT (LDCT) reduces lung cancer mortality by 20% and 24% respectively (3, 4). In the UK, following the recommendation from the National Screening Committee, the UK government announced in June 2023 the rollout of targeted LCS for individuals between the ages of 55 and 74 who were recognised as having a higher risk of developing lung cancer, largely based on smoking history (5).

However, in individuals with significant frailty or comorbidities, competing causes of death may limit the life years gained by LCS, and this may be more apparent in real-world studies compared to that observed in the original randomised trials due to the healthy volunteer effect. Data on smoking history and frailty are potentially available from General Practice (GP) electronic patient records. Frailty is defined as the loss of biological reserves across several organ systems and vulnerability to physiological decompensation following a stressor event (6). There is relatively little published research assessing frailty in the context of LCS (7). Most LCS guidelines highlight the need to assess candidates' fitness and ability to tolerate screening and subsequent curative treatment (7). Yet, the ability of LCS programs to identify and exclude candidates who might not benefit from screening is still a challenging area that needs further research, as recognised by the American Thoracic Society (8). Given the relationship between frailty and comorbidity with adverse outcomes in patients with lung cancer (8-10), it is critical to establish the prevalence of frailty and comorbidity among potential screenees

and examine their association with LCS invitation response, uptake and outcomes from screening

The objective of this study was to describe the prevalence of frailty and comorbidities in a subcohort of the population invited for LCS as part of the Yorkshire Lung Screening Trial (YLST), as well as examine the associations of frailty and comorbidity with response to invitation for telephone lung cancer risk assessment and uptake of LDCT screening amongst those people found to be eligible (framed as part of a lung health check (LHC)).

3.3 Methods

We conducted a retrospective case-control analysis using data extracted from the intervention arm of the ongoing Yorkshire Lung Screening Trial (YLST), where frailty was the primary exposure of interest and case-control status was defined by response/non-response to an invitation to telephone-based lung cancer risk assessment to determine eligibility for LDCT screening. In addition, screening uptake was defined based on the attendance at a mobile CT scanning unit for those people found to be eligible for screening based on any one of three criteria (the USPSTF $_{2013}$ criteria, a $PLCO_{M2012}$ risk of ≥1.51% over six years, or an LLP_{v2} risk of ≥5% over five years). Details of the YLST design and participation in the baseline screening round have been published previously (11, 12). Briefly, the YLST is a randomised controlled trial evaluating invitations to community-based Lung Health Checks (involving LDCT screening) in people aged 55-80 years with a GP record indicating a smoking history. The trial is being conducted in Leeds, UK and includes a usual care (no invitation) comparison group.

For this study, 66 participating practices that used the Phoenix Partnership (TPP) SystmOne (13) electronic patient records were approached for permission to extract additional participant information. Participant data was extracted under a Section 251 amendment approved by the HRA Confidentiality Advisory Group (further details below). Frailty was investigated using the electronic Frailty Index eFI (14), which can be applied to electronic GP records through an algorithm that uses READ/Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) codes. The eFI consists of 36 equally weighted deficits with no time constraints to individual deficits except for polypharmacy. Frailty was investigated by categorising the frailty scores into a 4-level variable (fit, mild, moderate, severe) according to pre-defined cutoffs of (0-0.12 was defined as fit; >0.12-0.24

as mild frailty; >0.24-0.36 as moderate frailty and >0.36 as severe frailty) (14). YLST included a coded diagnosis of severe frailty in the electronic GP record as an exclusion criterion. GP electronic health records are configured to automatically calculate the eFI (15), but frailty codes are only added to the patient record following clinical review and confirmation. Thus, people with sufficient deficits to be categorised as having severe frailty, but in whom this had not been clinically verified, were invited for screening and are included in the analysis presented here.

In addition, 12 physical health comorbidities were selected for analysis including Cancer, Stroke, chronic obstructive pulmonary disease(COPD), Heart failure, Peripheral vascular disease(PVD), Inflammatory arthritis, Liver problems, Mono/hemiparesis, Peptic ulcer disease(PUD), Chronic kidney disease(CKD), Diabetes and Ischaemic heart disease(IHD). These comorbidities were selected based on their inclusion in the Charlson Comorbidity Index (CCI) (16) and were analysed separately from the eFI. Polypharmacy is one of the eFI deficits, defined originally based on the presence of ≥5 prescribed medications, using chapters 1-15 of the British National Formulary. Unfortunately, it was not possible to extract comprehensive medication data to calculate the polypharmacy deficit for all included participants. Therefore, for each frailty category, the presence/absence of polypharmacy for participants was inferred using the observed frailty-specific prevalence of polypharmacy in the eFI development cohort used by the eFI authors (14). We conducted several sensitivity analyses that examined the effect of using different polypharmacy prevalences on calculating eFI scores. An Excel file containing all eFI SNOMED CT codes was provided by the eFI development team and uploaded to TPP SystmOne by the NHS West Yorkshire Integrated Care Board (ICB) Office of Data Analytics team. Data for all participants were extracted between August 2022 and February 2023, and all analyses were conducted using SNOMED CT codes entered into the GP record up to the date of randomisation. Ethnicity and smoking status were derived by the YLST statisticians using general practice codes for all invitees, as reported previously (12). YLST invited participants aged up to 80 at the time of data extraction from primary care records, whereas the current NHS England Targeted Lung Health Check programme only includes participants up to 74 years. Frailty descriptors and comorbidity counts are therefore shown for participants aged <75 and ≥75 years.

The univariable relationships between response to invitation (telephone assessment), attendance and baseline factors, including frailty and comorbidities, were investigated using logistic regression. Multivariable logistic regression was used to investigate the relationship between response to telephone eligibility assessment and the exposure of interest, adjusting for factors previously identified as significantly associated with response (including age, Index of Multiple Deprivation (IMD) quintile, smoking status, sex and ethnicity) (12). These analyses were conducted for exposures of interest, including eFI and physical health comorbidities of interest. The analyses were repeated for attendance status in those eligible and invited to the LHC. Odds ratios are presented with 95% confidence intervals, and statistical tests were two-sided. Analyses were conducted using Stata version 17.0.

The Health Research Authority approved the YLST following a review by the Research Advisory Group (18/NW/0012) and the Confidentiality Advisory Group (CAG) (18/CAG/0038). The approval covers using eFI to explore the link between frailty/comorbidity and response to the invitation for an eligibility check and LHC screening attendance.

3.4 Results

Among all individuals randomised to the intervention arm of the YLST (n=44,943), we accessed 27,761 participants' records (61.8%) from 54 general practices in Leeds; 12 practices did not respond to requests for data access, and an additional 18 practices used a different software system (EMIS) from which we were unable to access data. A comparison of demographic and clinical characteristics according to whether people responded to a written invitation for telephone risk assessment for the 61.8% of YLST individuals randomised to the intervention arm for whom frailty/comorbidity data was available is shown in Table 1. Baseline demographics in the frailty/comorbidity subcohort (shown in Table 1) were comparable to those reported in the YLST intervention arm (12), indicating that the data presented here is representative of the YLST intervention cohort. Overall, the mean age of people invited for a risk assessment was 66, 14.4% were ≥75 years, 52.2% were male, and 29.3% resided in areas associated with the most deprived IMD quintile. Based on primary care record codes, 30.3% of the cohort were currently smoking, and 68.5% had previously smoked but now quit. The prevalence of individual deficits that make up the eFI is presented in

supplementary data (Table S1). In line with the findings observed during the development of the eFI (14), we found an inverse correlation between the eFI and IMD – i.e. people from more deprived populations were more frail (Supplementary data Figure S1). The eFI identified 24.1% of participants as having mild frailty, 8.5% with moderate frailty and 1.7% with severe frailty. Of the selected 12 comorbidities, 46.4% of participants had zero comorbidities, 26.2% had one comorbidity, 14.1% had two comorbidities, 7.5% had three comorbidities and 5.8% had four or more comorbidities. Invitees aged ≥75 years had higher levels of frailty and comorbidity (Figure

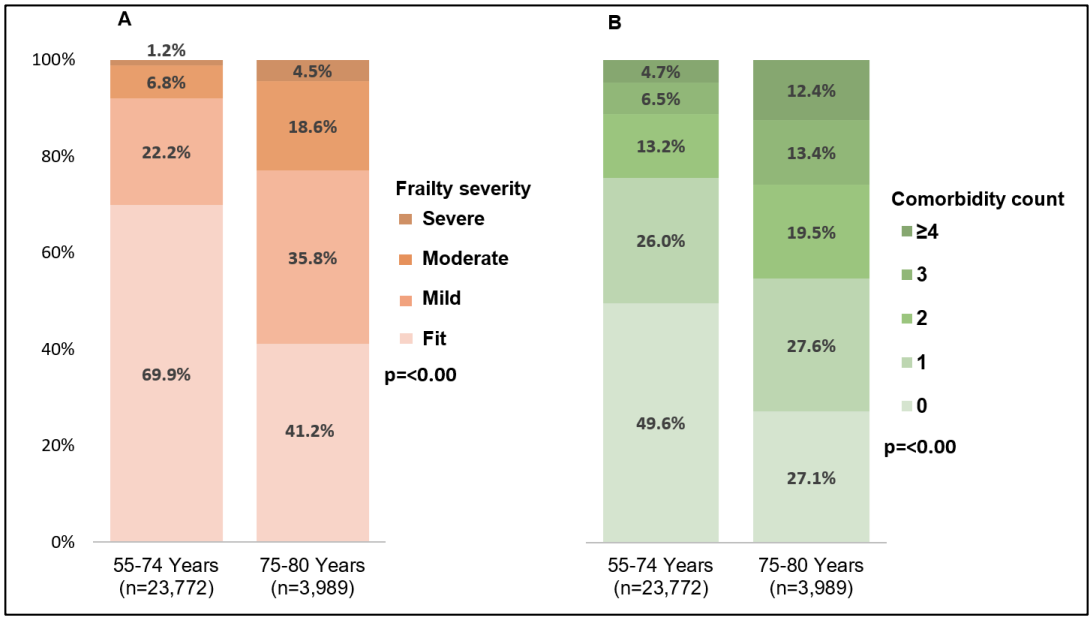
Table 3.1: Baseline factors by the response to the invitation to telephone eligibility assessment

	Intervention subcohort (n=27761), n (%)	Nonresponders (n=13238), n (%)	Responders (n=14523), n (%)	p-value*	Univariate OR (95% CI)	OR p-value
Age, years	66.1±7.2	64.7±7.1	67.3±7.1			
Age group, years				<0.001		
<60	7360 (26.5)	4425 (33.4)	2935 (20.2)		1 (reference)	
60-64	6061 (21.8)	3166 (23.9)	2895 (19.9)		**1.38 (1.29-1.48)**	**<0.001**
65-69	5319 (19.2)	2214 (16.7)	3105 (21.4)		**2.11 (1.97-2.27)**	**<0.001**
70-74	5032 (18.1)	1973 (14.9)	3059 (21.1)		**2.33 (2.17-2.51)**	**<0.001**
≥75	3989 (14.4)	1460 (11.0)	2529 (17.4)		**2.61 (2.41-2.82)**	**<0.001**
Gender				<0.001		
Female	13283 (47.8)	5918 (44.7)	7365 (50.7)		1 (reference)	
Male	14477 (52.2)	7319 (55.3)	7158 (49.3)		**0.78 (0.75-0.82)**	**<0.001**
Indetermine	1 (<0.1)	1 (<0.1)	0			
IMD rank (IQR)	14412	10206	17192	<0.001		
	(4092-22753)	(3086 -21414)	(6813-23464)			
IMD quintile				<0.001		
1 (most deprived)	8127 (29.3)	4755 (35.9)	3372 (23.2)		**0.47 (0.43-0.51)**	**<0.001**
2	5161 (18.6)	2553 (19.3)	2608 (18.0)		**0.68 (0.62-0.74)**	**<0.001**
3	4260 (15.3)	1874 (14.1)	2386 (16.4)		**0.84 (0.77-0.93)**	**<0.001**
4	6620 (23.9)	2618 (19.8)	4002 (27.6)		1.02 (0.93-1.10)	0.664
5 (least deprived)	3566 (12.8)	1426 (10.8)	2140 (14.7)		1 (reference)	
Missing	27 (0.1)	12 (0.1)	15 (0.1)			
Ethnicity (derived)[1]				<0.001		
White	14336 (51.6)	6420 (48.5)	7616 (52.4)		1 (reference)	
Black or Black British	411 (1.5)	248 (1.9)	463 (3.2)		**0.53 (0.44-0.65)**	**<0.001**
Asian or Asian British	696 (2.5)	396 (3.0)	300 (2.1)		**0.61 (0.53-0.71)**	**<0.001**
Mixed	10857 (39.1)	5312 (40.1)	5545 (38.2)		**0.85 (0.81-0.89)**	**<0.001**
Other	297 (1.1)	177 (1.3)	120 (0.8)		**0.55 (0.43-0.69)**	**<0.001**
Unclear	147 (0.5)	72 (0.5)	75 (0.5)		0.85 (0.61-1.17)	0.309
Not stated	1017 (3.7)	613 (4.6)	404 (2.8)		**0.53 (0.47-0.61)**	**<0.001**
Smoking status (derived)[1]				<0.001		
Previously smoked	19029 (68.5)	7679 (58.0)	11350 (78.2)		1 (reference)	
Currently smoking	8418 (30.3)	5430 (41.0)	2988 (20.6)		**0.37 (0.35-0.39)**	**<0.001**
Never smoked	12 (<0.1)	5 (<0.1)	7 (<0.1)		0.95 (0.30-2.98)	0.926
Noninformative code	302 (1.1)	124 (0.9)	178 (1.2)		0.97 (0.77-1.22)	0.804
eFI score: mean (SD)	0.11 (0.09)	0.10 (0.09)	0.12 (0.09)			
eFI category				<0.001		
Fit	18247 (65.7)	9329 (70.5)	8918 (61.4)		1 (reference)	
Mild	6702 (24.1)	2749 (20.8)	3953 (27.2)		**1.50 (1.42-1.59)**	**<0.001**
Moderate	2353 (8.5)	973 (7.3)	1380 (9.5)		**1.48 (1.36-1.62)**	**<0.001**
Severe	459 (1.7)	187 (1.4)	272 (1.9)		**1.52 (1.26-1.84)**	**<0.001**
Comorbidity count						
0	12876 (46.4)	6605 (49.9)	6271 (43.2)	<0.001	1 (reference)	

1	7278 (26.2)	3253 (24.6)	4025 (27.7)	**1.30 (1.23-1.38)**	**<0.001**
2	3922 (14.1)	1758 (13.3)	2164 (14.9)	**1.29 (1.21-1.39)**	**<0.001**
3	2072 (7.5)	939 (7.1)	1133 (7.8)	**1.27 (1.16-1.39)**	**<0.001**
≥4	1613 (5.8)	683 (5.1)	930 (6.4)	**1.43 (1.29-1.59)**	**<0.001**
Physical health comorbidity					
Cancer	2878 (10.4)	1068 (8.1)	1810 (12.5)	**1.62 (1.50-1.76)**	**<0.001**
Stroke	1385 (5.0)	652 (4.9)	733 (5.1)	1.03 (0.92-1.14)	0.641
COPD	3253 (11.7)	1530 (11.6)	1723 (11.9)	1.03 (0.96-1.11)	0.428
Heart failure	937 (3.4)	439 (3.3)	498 (3.4)	1.03 (0.91-1.18)	0.603
PVD	1753 (6.3)	858 (6.5)	895 (6.1)	0.95 (0.86-1.04)	0.276
Inflammatory arthritis	4442 (16.0)	1784 (13.5)	2658 (18.3)	**1.44 (1.35-1.53)**	**<0.001**
Liver problems	330 (1.1)	162 (1.2)	168 (1.1)	0.94 (0.76-1.17)	0.607
Mono/hemiparesis	264 (0.9)	123 (0.9)	141 (0.9)	1.04 (.82-1.33)	0.72
PUD[2]	148 (0.5)	59 (0.4)	89 (0.6)	**1.38 (0.99-1.91)**	**0.057**
CKD	5369 (19.3)	2460 (18.6)	2909 (20.0)	**1.10 (1.03-1.16)**	**0.002**
Diabetes	4387 (15.8)	2024 (15.3)	2363 (16.3)	**1.07 (1.01-1.15)**	**0.025**
IHD	3493 (12.6)	1530 (11.6)	1963 (13.5)	**1.19 (1.11-1.28)**	**<0.001**

Data are presented as n (%), mean±SD or median (interquartile range). *Groups were compared using Chi-squared test or Fisher exact test for categorical variables and using two-sample t test or Mann-Whitney U test for continuous variables. IMD: Index of Multiple Deprivation. eFI: electronic frailty index. COPD: chronic obstructive pulmonary disease, PVD: peripheral vascular disease, PUD: peptic ulcer disease, CKD: chronic kidney disease, IHD: ischaemic heart disease. [1]: General practice electronic record codes used to derive ethnicity and smoking status. [2]: Up to 5 years before the randomisation date.

Figure 3.1: Distribution of frailty and comorbidity count by age group based on the current LCS UK recommendation cutoff age of 74 years; A: eFI; B: comorbidity count.



Response to the invitation for telephone lung cancer risk assessment

Over half of the invitees (n=14523, 52.5%) responded to the invitation for lung cancer risk assessment by making telephone contact. As reported previously (12), age, sex, deprivation, ethnicity, and smoking status were significantly different between responders and nonresponders (Table 1). Considering the novel frailty and comorbidity data presented here, a higher proportion of those responding were classified as having moderate (9.5%) or severe (1.9%) frailty compared to those who did not respond (7.3% and 1.4%, respectively) using eFI. There was a higher proportion of responders with three or more comorbidities (14.2%) than nonresponders (12.2%). Unadjusted and adjusted analysis of the effect of frailty and comorbidities on the response to the invitation is shown in Tables 1 and 2. Overall, individuals with mild, moderate, and severe frailty were more likely to respond to invitation compared to fit individuals based on the eFI (adjusted OR 1.34 95% CI 1.26-1.42, 1.28 95% CI 1.16-1.40, 1.32 95% CI 1.08-1.61, respectively). The sensitivity analysis of different polypharmacy prevalences showed similar results.

People with 1, 2, 3 and 4 or more comorbidities were more likely to respond to the invitation compared to people without any comorbidities based on the comorbidity count of the 12 selected comorbidities (Table 2). Individuals with

primary care records of comorbidities including cancer (OR_{adj} 1.34 95% CI 1.23-1.45), COPD (OR_{adj} 1.15 95% CI 1.06-1.25), inflammatory arthritis (OR_{adj} 1.27 95% CI 1.19-1.36), and ischaemic heart disease(OR_{adj} 1.10 95% CI 1.02-1.19) were more likely to respond to invitation compared with those without these conditions.

Table 3.2 Relationship of frailty and comorbidities with response in multivariable analyses

	N	OR_{adj}[1] (95% CI)	p-value
eFI category	27761		
Fit		1 (reference)	
Mild		**1.34 (1.26-1.42)**	**<0.001**
Moderate		**1.28 (1.16-1.40)**	**<0.001**
Severe		**1.32 (1.08-1.61)**	**0.006**
Comorbidity count			
0	12,876	1 (reference)	
1	7,278	**1.21 (1.14-1.29)**	**<0.001**
2	3,922	**1.18 (1.10-1.27)**	**<0.001**
3	2,072	**1.15 (1.04-1.27)**	**0.007**
≥4	1,613	**1.26 (1.13-1.41)**	**<0.001**
Physical health comorbidity			
Cancer	2878	**1.34 (1.23-1.45)**	**<0.001**
Stroke	1385	0.91 (0.81-1.02)	0.115
COPD	3253	**1.15 (1.06-1.25)**	**<0.001**
Heart failure	937	0.97 (0.85-1.11)	0.693
Peripheral vascular disease	1753	0.93 (0.84-1.03)	0.164
Inflammatory arthritis	4442	**1.27 (1.19-1.36)**	**<0.001**
Liver problems	330	1.01 (0.80-1.27)	0.926
Mono/hemiparesis	264	1.10 (0.85-1.42)	0.454
Peptic ulcer disease[2]	148	1.41 (0.99-1.98)	0.052
Chronic kidney disease	5369	0.98 (0.91-1.04)	0.47
Diabetes	4387	1.03 (0.97-1.11)	0.313
Ischaemic heart disease	3493	**1.10 (1.02-1.19)**	**0.012**

[1]Adjusted for Age, IMD quintile, derived smoking status, Sex and Ethnicity. COPD: chronic obstructive pulmonary disease, PVD: peripheral vascular disease, PUD: peptic ulcer disease, CKD: chronic kidney disease, IHD: ischaemic heart disease; eFI: electronic frailty index. [2]Up to 5 years before the randomisation date.

Uptake of LDCT screening in eligible responders

Of the 14,523 participants undergoing telephone risk assessment for whom data was available to calculate eFI, 5,041 were eligible for screening according to one of the three risk criteria, and were invited for LDCT screening for lung cancer (representing 64.2% of all eligible invitees for LDCT screening in the whole YLST intervention cohort). Of the 5,041 invited, 4383 (86.9%) attended their appointment. As reported previously (12), age, sex, deprivation, and smoking status were all significantly different between those who attended their LHC

appointment and those who did not. Following univariate analysis, both moderate and severe frailty were associated with lower attendance for LDCT screening, but there was no impact of mild frailty nor of comorbidity counts (Table 3). Adjusted analyses of the effect of frailty and comorbidities on the uptake of the LHC are presented in Table 4. The presence of moderate frailty was negatively associated with attendance for LDCT (OR_{adj} 0.75 95% CI 0.59-0.96, p=0.024), and there was a trend to lower attendance with severe frailty (OR_{adj} 0.67 95% CI 0.43-1.04, p=0.072) albeit the number of severely frail participants was much smaller than the other groups (146 = 2.9% of total eligible cohort). The sensitivity analysis estimating different polypharmacy prevalences showed similar results.

All five levels of comorbidity count were not significantly associated with LDCT uptake (Table 4). However, Individuals with cancer and inflammatory arthritis were more likely to attend the LHC appointment than those without these comorbidities (cancer OR_{adj} 1.42 95% CI 1.12-1.82, inflammatory arthritis OR_{adj} 1.37 95% CI 1.09-1.72). Conversely, individuals with COPD, PVD and CKD were less likely to attend the LHC appointment than those without these conditions (COPD OR_{adj} 0.78 95% CI 0.65-0.94, PVD OR_{adj} 0.72 95% CI 0.56-0.92, CKD OR_{adj} 0.79 95% CI 0.66-0.95).

Table 3.3 Baseline factors by attendance to lung health check appointment

	Total invited (n=5041), n (%)	Attended (n=4383), n (%)	Declined/ did not attend (n=658), n (%)	p-value*	Univariate OR (95% CI)	OR p-value
Age, years	68.7 ±7.0	68.7 ±7.0	69.9 ±6.9			
Age group, years				<0.001		
<60	737 (14.6)	666 (15.2)	71 (10.8)		1 (reference)	
60-64	843 (16.7)	751 (17.1)	92 (14.0)		0.87 (0.63-1.21)	0.404
65-69	1103 (21.9)	966 (22.0)	137 (20.8)		0.75 (0.55-1.02)	0.065
70-74	1198 23.8)	1034 (23.6)	164 (24.9)		**0.67 (0.50-0.90)**	**0.008**
≥75	1160 (23)	966 (22.0)	194 (29.5)		**0.53 (0.39-0.71)**	**<0.001**
Gender				<0.001		
Female	2347 (46.6)	1992 (45.4)	355 (53.6)		v	
Male	2694 (53.4)	2391 (54.6)	303 (46.0)		**1.41 (1.19-1.66)**	**<0.001**
IMD rank (IQR)	12170	12065	12413	0.433		
	(3790-21613)	(3845-21681)	(3342-21414)			
IMD quintile				0.004		
1 (most deprived)	1571 (31.2)	1343 (30.6)	228 (34.7)		0.94 (0.70-1.25)	0.662
2	1040 (20.6)	938 (21.4)	102 (15.5)		**1.46 (1.0 6-2.02)**	**0.02**
3	816 (16.2)	697 (15.9)	119 (18.1)		0.93 (0.68-1.28)	0.667
4	1087 21.6)	951 (21.7)	136 (20.7)		1.11 (0.82-1.51)	0.491
5 (least deprived)	524 (10.4)	452 (10.3)	72 (10.9)		1 (reference)	
Missing	3 (0.1)	2 (0.05)	1 (0.1)			
Ethnicity (self-reported)				0.506		
White	4859 (96.4)	4229 (96.5)	630 (95.7)		1 (reference)	
Black	34 (0.7)	29 (0.7)	5 (0.8)		0.86 (0.33-2.24)	0.764
Hispanic	1 (<0.1)	1 (<0.1)	0		*	
Asian	66 (1.3)	58 (1.3)	8 (1.2)		1.08 (0.51-2.27)	0.839
Other	47 (0.9)	40 (0.9)	7 (1.1)		0.85 (0.38-1.91)	0.696
Prefer not to say	34 (0.7)	26 (0.6)	8 (1.2)		**0.48 (0.22-1.07)**	**0.074**
Smoking status (self-reported)				<0.001		
Previously smoked	3367 (66.8)	2973 (67.8)	394 (40.1)		1 (reference)	
Currently smoking	1674 (33.2)	1410 (32.2)	264 (59.9)		**0.70 (0.60-0.84)**	**<0.001**
Pack-years	35 (25.5-45)	35.2 (26-45)	34 (24.5-45)	0.358		
Quit time (previously smoked)	11 (4-21)	12 (5-21)	13 (6-21)	0.935		
eFI score: mean (SD)	0.14 (0.09)	0.14 (0.09)	0.15 (0.10)			
eFI category				0.001		
Fit	2628 (52.1)	2321 (53.0)	307 (46.7)		1 (reference)	
Mild	1599 (31.7)	1386 (31.6)	213 (32.4)		0.86 (0.71-1.04)	0.116
Moderate	668 (13.3)	558 (12.7)	110 (16.7)		**0.67 (0.53-0.85)**	**0.001**
Severe	146 (2.9)	118 (2.7)	28 (4.2)		**0.56 (0.36-0.86)**	**0.008**
Comorbidity count						
0	1553 (30.8)	1370 (31.3)	183 (27.8)	0.239	1 (reference)	
1	1496 (29.6)	1294 (29.5)	202 (30.7)		0.85 (0.69-1.06)	0.153
2	886 (17.6)	762 (17.4)	124 (18.8tab)		0.82 (0.64-1.05)	0.114

3	556 (11.2)	498 (11.3)	68 (10.3)	0.98 (0.72-1.32)	0.884
≥4	540 (10.7)	459 (10.5)	81 (12.3)	0.76 (0.57-1.00)	0.053
Physical health comorbidity					
Cancer	828 (16.4)	741 (16.9)	87 (13.2)	**1.33 (1.05-1.69)**	**0.018**
Stroke	354 (7.0)	305 (6.7)	49 (7.4)	0.93 (0.68-1.27)	0.648
COPD	1322 (26.2)	1112 (25.4)	210 (31.9)	**0.75 (0.61-0.87)**	**<0.001**
Heart failure	242 (4.8)	209 (4.8)	33 (5.0)	0.95 (0.65-1.38)	0.782
PVD	524(10.4)	435 (9.9)	89 (13.5)	**0.70 (0.55-0.90)**	**0.005**
Inflammatory arthritis	968 (19.2)	866 (19.8)	102 (15.5)	**1.34 (1.07-1.68)**	**0.01**
Liver problems	69 (1.4)	57 (1.3)	12 (1.8)	0.71 (0.38-1.33)	0.284
Mono/hemiparesis	59 (1.1)	51 (1.1)	8 (1.2)	0.96 (0.45-2.02)	0.908
PUD[1]	31 (0.6)	27 (0.6)	4 (0.6)	1.01 (0.35-2.90)	0.98
CKD	1179 (23.4)	1000 (22.8)	179 (27.2)	**0.79 (0.66-0.95)**	**0.013**
Diabetes	949 (18.8)	818 (18.6)	131 (19.9)	0.92 (0.75-1.13)	0.446
IHD	900 (17.8)	779 (17.8)	121 (18.4)	0.96 (0.78-1.18)	0.701

Data are presented as n (%), mean±SD or median (interquartile range). * Groups were compared using Chi-squared test or Fisher exact test for categorical variables and using two-sample t test or Mann-Whitney U test for continuous variables. IMD: Index of Multiple Deprivation. eFI: electronic frailty index. COPD: chronic obstructive pulmonary disease, PVD: peripheral vascular disease, PUD: peptic ulcer disease, CKD: chronic kidney disease, IHD: ischaemic heart disease. [1]: Up to 5 years before the randomisation date.

Table 3.4 Relationship of frailty and comorbidities with lung health check appointment uptake in multivariable analyses

	N	OR_{adj}[1] (95% CI)	p-value
eFI category	5041		
Fit		1 (reference)	
Mild		0.92 (0.76-1.12)	0.408
Moderate		**0.75 (0.59-0.96)**	**0.024**
Severe		0.67 (0.43-1.04)	0.072
Comorbidity count			
0	1,553	1 (reference)	
1	1,496	0.89 (0.72-1.08)	0.299
2	886	0.88 (0.68-1.13)	0.316
3	566	1.04 (0.77-1.41)	0.794
≥4	540	0.79 (0.59-1.06)	0.589
Physical health comorbidity			
Cancer	828	**1.42 (1.12-1.82**)	**0.004**
Stroke	354	0.95 (0.69-1.30)	0.739
COPD	1322	**0.78 (0.65-0.94)**	**0.009**
Heart failure	242	0.95 (0.65-1.39)	0.785
PVD	524	**0.72 (0.56-0.92**)	**0.010**
Inflammatory arthritis	968	**1.37 (1.09-1.72)**	**0.006**
Liver problems	69	0.59 (0.31-1.12)	0.106
Mono hemiparesis	59	0.97 (0.46-2.08)	0.947
PUD[2]	31	0.98 (0.34-2.85)	0.974
CKD	1179	0.83 (0.68-1.01)	0.055
Diabetes	949	0.91 (0.74-1.12)	0.388
IHD	900	0.96 (0.77-1.19)	0.703

[1]Adjusted for Age, IMD quintile, self-reported smoking status, Sex and Ethnicity. COPD: chronic obstructive pulmonary disease, PVD: peripheral vascular disease, PUD: peptic ulcer disease, CKD: chronic kidney disease, IHD: ischaemic heart disease; eFI: electronic frailty index. [2]Up to 5 years before the randomisation date.

3.5 Discussion

The current study measured the prevalence of frailty and selected comorbidities and their effects on response to the invitation for telephone lung cancer risk assessment and LDCT screening appointment uptake within the YLST. Our results indicate that mild, moderate and severe frailty, as defined by eFI, were prevalent in 24.1%, 8.5% and 1.7% of the invited population, respectively. We found an increase in response to telephone triage invitations based on the eFI frailty category whereby compared to fit people, the odds of responding were 34%, 28%, and 32% increased in those with mild, moderate and severe frailty, respectively, after adjustment. Similar effects were seen with overall comorbidity

counts (i.e. higher odds of response to invitation in people with comorbidities versus no comorbidities). The presence of cancer, COPD, inflammatory arthritis, and ischaemic heart disease were also associated with an increased response to telephone triage invitations. Considering LDCT uptake in eligible responders, the odds of attending for screening were 25% and 33% lower in those with moderate and severe frailty, respectively, compared to fit people. There were no differences in uptake by comorbidity count. The presence of cancer and inflammatory arthritis were associated with increased odds of uptake, whereas a diagnosis of COPD reduced the odds of uptake.

To our knowledge, this is the first study that measures the prevalence of frailty severity and its impact on LCS invitation and uptake using an established frailty assessment tool, the eFI (14). Previous LCS trials and studies relied on other metrics for determining the fitness and overall health of candidates, including self-reported health status (3), the ability to climb stairs (3, 17), the ability to lie flat (18, 19) and life expectancy (17, 20, 21). While these metrics might be practical and the only feasible options in many settings, they only capture part of the spectrum of frailty compared to a comprehensive frailty measure such as the eFI. In the UK, the eFI is currently integrated into primary care systems for all GPs in England (15) and Scotland (22), making it a readily available option for assessing the severity of frailty when delivering LCS at the national level. In the context of LCS, incorporating well-established frailty models for frailty assessment remains a significantly underexplored avenue. Notably, a limited body of research has addressed the subject of frailty within the breast (23) and colon (24) cancer screening contexts. This underutilisation of frailty assessment in cancer screening might be due to the emerging nature of frailty as a concept and the challenges of assessing frailty through established frailty models in many settings.

Several studies have reported frailty in patients with lung cancer. One UK study reported that 31% of patients presenting with symptomatic lung cancer had some degree of frailty, as measured by the eFI (25), and a recent meta-analysis reported the prevalence of frailty in patients with lung cancer to be around 45% (95% CI, 28-61) (26). The results presented here show that 47.9% of those offered an LDCT screening appointment had some degree of frailty and are therefore consistent with these estimates.

Qualitative research is needed to explore the relationship between frailty and response to LCS invitation and subsequent uptake of screening in order to understand the basis for the findings reported here. One possible explanation for the difference in the initial response to an invitation is that people with frailty may be more used to engaging with or requiring health services in general and, therefore, more accepting of an invitation to participate in a new service such as LDCT screening when offered. Conversely, fitter people with less interaction with healthcare may perceive themselves as lower risk and may ignore the invitation as a result (27).

The prevalence of individual physical comorbidities in our cohort is in line with what has been observed in LCS settings (7) and is comparable to what has been reported among the eFI development cohort (14). In our cohort, individuals with several comorbidities (e.g. cancer, COPD, inflammatory arthritis and ischaemic heart disease) were more likely to be contacted for telephone risk assessment following postal invitation and the presence of cancer and inflammatory arthritis was additionally associated with an increased likelihood of attending the screening appointment in those eligible following a risk assessment. Previous malignancy might encourage attendance due to greater awareness of the importance of early detection. Findings regarding COPD were somewhat conflicting, with the presence of COPD increasing the likelihood of undergoing telephone risk assessment but reducing the likelihood of attending screening in those fulfilling eligibility criteria. Evidence from the US has shown increased LCS participation overall among candidates with self-reported COPD (28). The benefit of LCS relates to the life years gained by participants in whom a lung cancer death is prevented through early diagnosis and treatment. Given that increasing frailty is strongly linked to reduced life expectancy, the fact that fit people are less likely to respond to an initial invitation to participate in screening is concerning. Qualitative research is required to better understand the impact of frailty and fitness on decision-making around screening participation. In addition, determining the impact of frailty and comorbidity on LCS outcomes is of great interest and will be the subject of a future paper.

Strengths and limitations

The current study gives a unique insight into the target population for LCS and has several strengths, including a large sample size, being representative of the

whole YLST screening arm, the novel investigation of an established, widely appliable frailty tool in the context of UK LCS and the ability to investigate non-response to the screening invitation. A possible limitation is the inability to collect polypharmacy data from all participants due to logistical challenges. To overcome this, we conducted a series of sensitivity analyses, which indicated that our results were robust. An additional consideration is that the age range for the population invited to participate in YLST was from 55 to 80 years at the time of data extraction, whereas other screening programmes, such as the Targeted Lung Health Check programme in England, only screen up to 74 years. The prevalence of frailty has been shown to be higher in those invitees over 75 years, and this will influence the generalisability of our findings to screening programmes accordingly. Finally, responses to LCS invites within a trial context may differ from LCS offered outside research settings. YLST was designed as an implementation study for LCS, and as such, the initial written invitation and telephone call did not mention any research. While the research study was fully discussed with participants at the time they attended the mobile unit for screening (prior to obtaining written consent), the timing of response and uptake predated the discussion about research.

Conclusion

The key finding from this study is that frailty is associated with a higher likelihood of people undergoing telephone risk assessment for lung cancer following postal invitation as part of a community-based LCS programme. Conversely, amongst those eligible for screening and offered an appointment for LDCT, there was some evidence of reduced uptake associated with frailty. By focusing efforts on encouraging initial engagement from the fit population who potentially have more life years to be gained, LCS programmes may be able to maximise the clinical efficacy of the intervention.

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Data sharing arrangements: Researchers wishing to use the data will need to complete a request for data sharing form describing a methodologically sound proposal. The form will need to include the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release

definition in the contract and participant informed consent, etc. A data sharing agreement from the sponsor may be required.

Conflict of interest: P.A.J. Crosbie reports stock options from Everest Detection, and lecture honoraria from Bayer, outside the submitted work. R.J. Beeken reports fellowship and grant funding from Yorkshire Cancer Research and grant funding from Roy Castle Lung Cancer Foundation, outside the submitted work. A. Clegg has received consultancy fees from the Geras Centre for Aging Research, received meeting/travel support from the Australian and New Zealand Society of Geriatric Medicine, and is a chair of the global Ageing Research Trialists collaborative.

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Chapter 4 Frailty, comorbidity, and survival comparisons between populations eligible for screening according to risk factor versus risk score criteria: results from the Yorkshire Lung Screening Trial

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Study Three

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4.1 Abstract

Background Lung cancer screening is effective for people at higher risk of the disease, but there is no international consensus on eligibility criteria. Some programmes use risk factors; others use multivariable risk scores, which might target an older, more comorbid population and thus limit life years gained. Here, we compare frailty, comorbidities and overall survival between different eligible populations.

Methods Participants aged 55-74yrs undergoing lung cancer risk assessment in the Yorkshire Lung Screening Trial were analysed, comparing those who met the $USPSTF_{2021}$ criteria against risk score criteria currently in use in the UK ($PLCO_{m2012}$≥1.51% and LLP_{v2}≥2.5%). In addition, risk score thresholds were set to select equivalent numbers of people screened compared to $USPSTF_{2021}$. Data recorded in primary care prior to randomisation were retrospectively extracted to allow calculation of the electronic frailty index (eFI) and an overall comorbidity count. Frailty, comorbidity counts, and three-year overall survival were compared between these various populations.

Results Of 11,994 individuals aged 55-74 undergoing risk assessment, 3,521 were eligible by $USPSTF_{2021}$, 3,163 by $PLCO_{m2012}$≥1.51% and 3,992 by LLP_{v2}≥2.5%. The proportion of individuals with moderate/severe frailty was significantly lower for the $USPSTF_{2021}$ population (10.7%) compared to $PLCO_{m2012}$≥1.51% (13.2%, p=0.024) and LLP_{v2}≥2.5% (13.5%, p=0.009). Similar patterns were seen for the proportion with ≥2 comorbidities (30.7%, 36.2% and 37.4%, respectively). When compared in equivalent populations, the LLP_{v2} ≥2.96% population had a higher proportion of people with moderate/severe frailty than $USPSTF_{2021,}$ but there was no significant difference between $PLCO_{m2012}$ ≥1.32% population and $USPSTF_{2021}$. There were no apparent differences in 3-year overall survival between any of the eligible populations.

Conclusion These data suggest that currently used risk models identify populations with a small increase in moderate/severe frailty and multimorbidity compared to the $USPSTF_{2021}$ criteria but there is no evidence to suggest that this results in differences in three-year overall survival.

What is already known on this topic

The risk-factor selection strategy for lung cancer screening is thought to select healthier individuals with fewer comorbidities compared to risk-score strategies. However, the magnitude of the difference in frailty and comorbidities between populations selected using these strategies has not been adequately quantified before.

What this study adds

The study examined frailty, comorbidities, and survival of populations eligible for lung cancer screening by three different eligibility criteria under the Yorkshire Lung Screening Trial. The study shows that the currently used lung cancer screening risk models in the UK ($PLCO_{m2012}$ and LLP_{v2}) identify populations with slightly more frailty and comorbidities than the $USPSTF_{2021}$ risk-factor criteria. However, there are no apparent differences in 3-year survival between populations identified by the risk models versus the risk-factor strategies.

How this study might affect research, practice or policy

The study findings suggest that the differences between risk-factor and risk-score strategies may be less significant than previously believed. Further evidence is needed to understand the long-term survival differences between populations identified by these eligibility strategies.

4.2 Introduction

Lung cancer remains a leading cause of cancer-related mortality worldwide for both men and women(1). Treatment advances have improved the 5-year survival rates over the last two decades but remain poor compared to other cancer types(2). This poor survival is mainly associated with delayed detection, as early-stage lung cancers have mild or no apparent symptoms. Large randomised controlled trials (RCTs) have demonstrated that lung cancer screening (LCS) using low-dose computed tomography (LDCT) can reduce lung cancer mortality by at least 20% in high-risk individuals(3-5). Identifying optimal criteria to select these high-risk individuals for screening is a challenging task, but it is crucial for maximising LCS benefits while reducing potential harms and costs.

The original randomised trials demonstrating screening efficacy used risk factors to determine eligibility for screening (e.g. pack years smoked, time since quit smoking), and these informed the US Preventive Services Task Force (USPSTF)(6) with $USPSTF_{2021}$ criteria being age 55-80 years, ≥ 20 pack-years

smoking exposure and smoking quit time of within 15 years for those who have stopped smoking(7). Multi-variable risk models have been suggested as an alternative way to define eligibility with evidence of increased cancer-detection within the eligible population(8). Two examples of risk prediction models are the Prostate Lung Colorectal and Ovarian Cancer Screening Trial model ($PLCO_{m2012}$)(9) and the Liverpool Lung Project model (LLP)(10) which predict the likelihood of developing lung cancer within the next 6 or 5 years respectively. Lung cancer screening implementation programmes in Canada are currently using the $PLCO_{m2012}$ model, and the English Targeted Lung Health Check programme uses both the $PLCO_{m2012}$ and LLP_{v2} risk models concurrently with risk thresholds of ≥1.51% and ≥2.5%, respectively, to select candidates for LCS(11).Lung cancer screening implementation programmes in Canada are currently using the $PLCO_{m2012}$ model(12, 13), and the English Targeted Lung Health Check programme uses both the $PLCO_{m2012}$ and LLP_{v2} risk models concurrently with risk thresholds of ≥1.51% and ≥2.5%, respectively, to select candidates for LCS(11).

Previous studies have assessed various lung cancer screening selection strategies, comparing risk prediction models, such as the $PLCO_{m2012}$ and LLP_{v2} models, against the $USPSTF_{2021}$ risk criteria. These analyses evaluated different factors, including the size of eligible population, lung cancer detection rates, averted deaths, and potential racial or sex disparities(8, 9, 14-21). One concern about using risk models is that they may identify an older, more comorbid population for screening, and thus limit the life-years gained by the programme due to competing causes of death. Therefore frailty, comorbidity and overall survival are key considerations in determining the optimal population for lung cancer screening programmes.

The Yorkshire Lung Screening Trial (YLST)(22) offered community-based LDCT screening for high-risk ever smokers who met one of three eligibility criteria: the $USPSTF_{2013}$ (age 55-80 years, ≥30 pack-years, smoked within 15 years), the $PLCO_{m2012}$ 6-year risk of ≥1.51% or the LLP_{v2} 5-year risk of ≥5%. In this study, we compared frailty, comorbidity and 3-year overall survival rates among individuals who would have been eligible for LCS based on the updated version of USPSTF criteria ($USPSTF_{2021}$) and the risk criteria currently used in the

English Targeted Lung Health Check (TLHC) programme ($PLCO_{m2012}$≥1.51% and LLP_{v2} ≥2.5%).

4.3 Methods

This comparative study used data prospectively collected from the intervention arm of the Yorkshire Lung Screening Trial (YLST), alongside retrospectively collected data on frailty and comorbidities from primary care. The YLST design and results of invitation response, screening eligibility and uptake of community-based LDCT screening have been previously described(22, 23). Briefly, the YLST is a randomised controlled trial assessing invitations to community-based Lung Health Checks (which involve LDCT screening) for individuals aged 55-80 years with a smoking history documented in their GP records. For this study, frailty and comorbidity data were retrospectively extracted from 54 participating practices that use the Phoenix Partnership (TPP) SystmOne electronic patient records. This represents 64% (54/84) of the practices participating in the YLST, with 12 practices not responding to requests for data and 18 practices using a different software system (EMIS) from which we were unable to access data. Frailty was investigated using the electronic Frailty Index (eFI)(24), which contains 36 equally weighted deficits identified from a set of Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) codes.

The eFI score can be categorised into a 4-level variable (fit, mild, moderate, severe) according to pre-defined cutoffs (0-0.12, >0.12-0.24, >0.24-0.36, >0.36, respectively). Comorbidities were investigated using comorbidity count (0, 1, 2, 3, and ≥4) summed from 12 selected comorbidities derived from the extracted eFI SNOMED codes and based on inclusion in the Charlson Comorbidity Index (CCI) (25) including cancer, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), diabetes, heart failure, inflammatory arthritis, ischaemic heart disease (IHD), liver problems, mono/hemiparesis, peripheral vascular disease (PVD), peptic ulcer disease (PUD) and stroke. Proportions of individual comorbidities were calculated by dividing the number of people with a comorbidity by the total number of people eligible for LCS at a given risk score threshold ($PLCO_{m2012}$ or LLP_{v2}) or criteria ($USPSTF_{2021}$). Comorbidity and frailty data were extracted between August 2022 and February 2023, and analyses were performed using SNOMED CT codes that had been in the GP record before the YLST randomisation date. Socio-demographic variables were collected at

baseline, with ethnicity and smoking status being self-reported by all participants(22).

Screening eligibility

Individuals were included in this study if they had primary care records indicating a smoking history, were aged 55-80, randomised to the intervention arm of YLST, responded to the baseline lung cancer risk assessment invitation(22) and were identified as having a high risk of lung cancer determined by either the $USPSTF_{2021}$ criteria (≥20 pack-year smoking history and ≤15 quit-years), a $PLCO_{m2012}$ risk threshold of ≥1.51% at six years, or an LLP_{v2} risk threshold of ≥2.5% at five years. The original YLST design used the $USPSTF_{2013}$ age criteria of 55-80 years and did not invite individuals 50-55 years who are additionally included in $USPSTF_{2021}$.

Here, we present data for people aged 55-74 years, matching the current NHS protocol for lung cancer screening(11). Additional results for those aged 55-80 years are provided as supplementary data (Tables S1-S4 and Figure S1).Here, we present data for people aged 55-74 years, matching the current NHS protocol for lung cancer screening(11). Additional results for those aged 55-80 years are provided as supplementary data (Tables S1-S4 and Figure S1).

Statistical analysis

Descriptive statistics were calculated for socio-demographic, frailty and comorbidity measures for each risk strategy. In addition, we conducted comparative analyses of USPSFT with the risk models using risk score thresholds that would define equivalent sized populations. The proportions of people with moderate/severe frailty and ≥2 comorbidities were compared between risk strategies by dividing the number of individuals at each frailty/comorbidity level by the total number of eligible individuals for each eligibility strategy. The $USPSTF_{2021}$ was selected as a reference group, while $PLCO_{m2012}$ and LLP_{v2} were two comparison groups. We constructed 95% confidence intervals for these proportions, and non-overlapping confidence intervals were considered to indicate any differences, i.e. if the upper limit of the confidence interval for the reference group ($USPSTF_{2021}$) was less than the lower limit for the comparison group ($PLCO_{m2012}$ or LLP_{v2}). The exact p-values were calculated using the standard normal distribution to quantify the statistical significance of the difference between frailty/comorbidity proportions.

We derived 3-year overall survival (and 95% CIs) from the date of randomisation until the date of death due to any cause with a censoring date of January 26th, 2024. The date of death was obtained from PPM+ (Patient Pathway Manager), the electronic health record of Leeds Teaching Hospitals linked to the central NHS records(Spine Portal). The proportion of people with moderate/severe frailty, ≥2 comorbidities, and deaths from any cause within three years was plotted separately against the number of people eligible by different risk scores (for $PLCO_{m2012}$ and LLP_{v2}) or risk factor ($USPSTF_{2021}$).

Ethical Approval

The Health Research Authority approved the YLST following a review by the Research Advisory Group (18/NW/0012) and the Confidentiality Advisory Group (CAG) (18/CAG/0038). The approval covers using eFI codes to explore the link between frailty/comorbidity and screening outcomes.

4.4 Results

Of the 11,994 YLST participants aged 55-74 who underwent lung cancer risk assessment, 3521 individuals met the $USPSTF_{2021}$ criteria, 3163 met the $PLCO_{m2012}$ ≥1.51% threshold, and 3992 met the LLP_{v2} ≥2.5% risk threshold. The risk score thresholds that identified a similar number of individuals as the $USPSTF_{m2012}$ criteria were 1.32% for $PLCO_{m2012}$ (n=3515) and 2.96% for LLP_{v2} (n=3518). Demographic characteristics, frailty and comorbidity are summarised by risk strategy in Table 1. Overall, the mean age by risk strategy was between 64.2 ($USPSTF_{2021}$) and 67.7 ($LLP_{v2\ \geq 2.96\%}$), with a higher proportion of younger individuals (<60 years) selected by the $USPSTF_{2021}$ criteria (28.9%) compared to other models. Females were similarly represented under the $USPSTF_{2021}$ risk criteria (51.5%) and $PLCO_{m2012}$ thresholds (50.8%) compared to LLP_{v2} risk thresholds (43.0%).

When investigating frailty (Table 1), small but statistically significant differences were observed, with the population eligible by the $USPSTF_{2021}$ having fewer individuals with moderate/severe frailty (10.7%) compared to $PLCO_{m2012}$≥1.51% (13.2%, p=0.024 vs $USPSTF_{2021}$) and LLP_{v2}≥2.5% (13.5%, p=0.009 vs $USPSTF_{2021}$). There was no statistically significant difference between populations eligible by the two pre-defined $PLCO_{m2012}$ and LLP_{v2} thresholds (p=0.841). When moderate/severe frailty was compared in equivalent

populations, there was no statistically significant difference between individuals eligible by $USPSTF_{m2012m2012}$ (10.7%) and individuals with a $PLCO_{m2012m2012}$ risk≥1.32% (12.7%, p=0.071 vs $USPSTF_{2021}$), but the observation of a statistically significant difference with more frail eligible individuals with a LLP_{v2} risk ≥2.96% remained (13.5%, p=0.009 vs $USPSTF_{2021}$). Considering comorbidity, the $USPSTF_{2021}$ eligible population (30.7%) had a lower proportion of individuals ≥2 comorbidities than $PLCO_{m2012}$≥1.51% (36.2%, p<0.001 vs $USPSTF_{2021}$) and LLP_{v2}≥2.5% (37.4%, p<0.001 vs $USPSTF_{2021}$) with no difference between the two risk score thresholds ($PLCO_{m2012}$≥1.32% vs LLP_{v2}≥2.5%, p=0.468). Again, when compared in equivalent populations, the proportion with ≥2 comorbidities was higher in individuals with a $PLCO_{m2012}$ risk of ≥1.32% than those eligible by the $USPSTF_{2021}$ criteria (35.2% vs 30.7% respectively, p=0.005). The population eligible by an LLP_{v2} risk of ≥2.96% also had a higher proportion with ≥2 comorbidities (38.7%) than either $USPSTF_{2021}$ (p<0.001) or $PLCO_{m2012}$≥1.32% (p=0.03). Similar patterns were seen overall when analyses included individuals up to 80 years old (Tables S1 and S2).

The mean follow-up time was 49.9 months (SD ±9.9) for the whole analytic sample in this study(55-74 years population), with at least three years of follow-up time from the latest date of randomisation. Table 3 shows the 3-year survival stratified by frailty and comorbidity levels in individuals aged 55-74 years who were eligible for LCS according to different risk strategies studied. Within the frailty categories, the 3-year survival decreased from 97.8% to 98.2% in those deemed fit to 81.3% to 83.7% in those with severe frailty. Similarly, 3-year survival declined with increasing comorbidity count as people with no comorbidities have the highest survival (98.0%-98.5%), whereas those with ≥4 comorbidities have the lowest survival (86.3%-87.8%). Overall, there were no apparent differences (overlapping 95% CIs across all comparisons) between the LCS eligibility strategies ($USPSTF_{2021}$, $PLCO_{m2012}$, LLP_{v2}) in terms of 3-year survival (Table 3).

Figure 1 illustrates how frailty, comorbidity and overall survival vary with lung cancer risk threshold. Both risk scores show a progressive reduction in the proportion of patients with moderate/severe frailty, ≥2 comorbidities, and all-cause 3-year mortality as the lung cancer risk threshold falls and the size of the eligible population rises. The proportion of 12 individual comorbidities according to different $PLCO_{m2012}$ and LLP_{v2} risk scores and the $USPSTF_{2021}$ risk criteria is

shown in Figure 2 (and supplementary Table S4). COPD was the most prevalent comorbidity, occurring in 23.9% of the $USPSTF_{2021}$ group, 27.3% of the $PLCO_{m2012}$ ≥1.32% group, and 28.1% of the LLP_{v2} ≥2.96% group; COPD prevalence increased with lung cancer risk. Other comorbidities, including CKD, IHD, cancer, PVD and stroke, showed similar increases in burden among the highest-risk groups compared to the lowest-risk (Figure 2).

Table 4.1. Baseline factors by risk strategy among screen-eligible participants aged 55-74 years

	$USPSTF_{2021}$	$PLCO_{m2012}$ ≥1.32%*	LLP_{v2} ≥2.96%*	$PLCO_{m2012}$ ≥1.51%	LLP_{v2} ≥2.5%
eligible participants	n=3521	n= 3515	n= 3518	n= 3163	n= 3992
Age, years	64.2 ±5.5	66.3 ±5.4	67.7 ±4.9	66.5 ±5.3	67.5 ±5.0
Age group					
<60	1,019 (28.9%)	572 (16.3%)	318 (9.0%)	480 (15.2%)	390 (9.8%)
60-64	919 (26.1%)	789 (22.4%)	638 (18.1%)	701 (22.2%)	825 (20.7%)
65-69	918 (26.1%)	1,058 (30.1%)	1,197 (34.0%)	979 (31.0%)	1,257 (31.5%)
70-74	665 (18.9%)	1,096 (31.2%)	1,365 (38.8%)	1,003 (31.7%)	1,520 (38.1%)
Gender					
Female	1,812 (51.5%)	1,787 (50.8%)	1,514 (43.0%)	1,619 (51.2%)	1,703 (42.7%)
Male	1,709 (48.5%)	1,728 (49.2%)	2,004 (57.0%)	1,544 (48.8%)	2,289 (57.3%)
IMD rank: median, (IQR)	10103 (3,174-20,503)	10125 (3,208-21,180)	11973 (3,758-21,681)	10120 (3,208-20,733)	11974 (3,790-21,681)
IMD quintile					
1 (most deprived)	1,222 (34.7%)	1,205 (34.3%)	1,113 (31.6%)	1,096 (34.7%)	1,248 (31.3%)
2	778 (22.1%)	775 (22.1%)	751 (21.4%)	697 (22.0%)	859 (21.5%)
3	548 (15.6%)	533 (15.2%)	549 (15.6%)	483 (15.3%)	628 (15.7%)
4	654 (18.6%)	672 (19.1%)	749 (21.3%)	600 (19.0%)	844 (21.1%)
5 (least deprived)	317 (9.0%)	329 (9.4%)	355 (10.1%)	286 (9.0%)	412 (10.3%)
missing	2 (0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Ethnicity (self-reported)					
White	3,354 (95.3%)	3,389 (96.4%)	3,375 (95.9%)	3,061 (96.8%)	3,823 (95.8%)
Black	27 (0.8%)	33 (0.9%)	31 (0.9%)	26 (0.8%)	38 (1.0%)
Hispanic	4 (0.1%)	-	2 (0.1%)	-	2 (0.1%)
Asian	64 (1.8%)	34 (1.0%)	60 (1.7%)	28 (0.9%)	67 (1.7%)
Other	51 (1.4%)	39 (1.1%)	30 (0.9%)	32 (1.0%)	38 (1.0%)
Prefer not to say	21 (0.6%)	20 (0.6%)	20 (0.6%)	16 (0.5%)	24 (0.6%)
Smoking status (self-reported)					
Previously smoked	2,024 (57.5%)	2,065 (58.7%)	2,230 (63.4%)	1,795 (56.7%)	2,579 (64.6%)
Currently smoking	1,497 (42.5%)	1,450 (41.3%)	1,288 (36.6%)	1,368 (43.3%)	1,413 (35.4%)
Pack-years	36 (28.5-45.0)	37.5 (29.2-46.7)	32.5 (20.5-44)	38.2 (30.5-48)	31.5 (19.5-43.2)

Quit time (previously smoked)	7 (4-11)	10 (5-17)	12 (5-25)	10 (5-16)	13 (5-27)
eFI score: mean ±SD	0.12 ±0.09	0.13 ±0.09	0.13 ±0.09	0.13 ±0.09	0.13 ±0.09
eFI category (eFI range)					
Fit (0 -0.12)	2,187 (62.1%)	2,008 (57.1%)	1,922 (54.6%)	1,770 (56.0%)	2,223 (55.7%)
Mild (>0.12 -0.24)	957 (27.2%)	1,062 (30.2%)	1,099 (31.2%)	974 (30.8%)	1,231 (30.8%)
Moderate (>0.24 -0.36)	323 (9.2%)	375 (10.7%)	416 (11.8%)	355 (11.2%)	452 (11.3%)
Severe (>0.36)	54 (1.5%)	70 (2.0%)	81 (2.3%)	64 (2.0%)	86 (2.2%)
Comorbidity count					
0	1,392 (39.5%)	1,176 (33.5%)	1,063 (30.2%)	1,017 (32.2%)	1,260 (31.6%)
1	1,049 (29.8%)	1,103 (31.4%)	1,094 (31.1%)	1,001 (31.6%)	1,240 (31.1%)
2	542 (15.4%)	602 (17.1%)	659 (18.7%)	553 (17.5%)	728 (18.2%)
3	284 (8.1%)	339 (9.6%)	367 (10.4%)	314 (9.9%)	400 (10.0%)
≥4	254 (7.2%)	295 (8.4%)	335 (9.5%)	278 (8.8%)	364 (9.1%)

* $USPSTF_{2021}$ equivalent size eligible population

Table 4.2. Frailty and comorbidity in those aged 55-74 years selected for lung cancer screening by $USPSTF_{2021}$ versus $PLCO_{m2012}$ and LLP_{v2} at different risk thresholds

	$USPSTF_{2021}$	**$PLCO_{m2012}$ ≥1.32%***	**LLP_{v2} ≥2.96%***	**$PLCO_{m2012}$ ≥1.51%**	**LLP_{v2} ≥2.5%**
eFI category					
Moderate/severe	377/3521 (10.7% [9.7-11.7])	445/3515 (12.7% [11.6-13.8])	497/3518 (14.1% [13.0-15.3])	419/3163 (13.2% [12.1-14.4])	538/3992 (13.5% [12.4-14.5])
p-value**	-	0.071 (0.201)‡	**0.002**	**0.024** (0.841)$	**0.009**
Comorbidity count					
≥2 comorbidities	1080/3521 (30.7% [29.1-32.2])	1236/3515 (35.2% [33.6-36.7])	1361/3518 (38.7% [37.1-40.3])	1145/3163 (36.2% [34.5-37.9])	1492/3992 (37.4% [35.9-38.9])
p-value**	-	**0.005 (0.03)**‡	**<0.001**	**<0.001** (0.468)$	**<0.001**

Data presented as n/N (% [95% CI]), *= $USPSTF_{2021}$ equivalent size eligible population ** =p-value for the difference between $USPSTF_{2021}$ as a reference group and $PLCO_{m2012}$ or LLP_{v2} thresholds. ‡=p-value between parentheses is for the difference between $PLCO_{m2012}$ ≥1.32% and LLP_{v2} ≥2.96%. $=p-value between parentheses is for the difference between $PLCO_{m2012}$ ≥1.51% and LLP_{v2} ≥2.5%.

Table 4.3. 3-year survival at each frailty/comorbidity level by risk strategy for those aged 55-74 years

	$USPSTF_{2021}$			$PLCOm_{2012}$ >=1.32%*			LLP_{v2} >=2.96%*			$PLCO_{m2012}$ >=1.51%			LLP_{v2} >=2.5%		
	N	3-year survival rate (%)	95% CI	N	3-year survival rate (%)	95% CI	N	3-year survival rate (%)	95% CI	N	3-year survival rate (%)	95% CI	N	3-year survival rate (%)	95% CI
Eligible participants	3521	96.1	95.4 - 96.7	3515	95.7	95.0 - 96.3	3518	95.6	94.8 - 96.2	3163	95.3	94.53 - 96.0	3992	95.9	95.2 - 96.5
Frailty category															
Fit	2187	98.2	97.5 - 98.7	2008	98.0	97.2 - 98.5	1,922	98.0	97.2 - 98.5	1770	97.8	97.0 - 98.4	2223	98.1	97.4 - 98.6
Mild	957	94.8	93.2 - 96.0	1062	94.9	93.4 - 96.1	1099	95.0	93.5 - 96.1	974	94.6	92.9 - 95.8	1231	95.3	94.0 - 96.3
Moderate	323	87.9	83.9 - 91.0	375	88.3	84.6 - 91.1	416	88.5	85.0 - 91.2	355	87.6	83.7 - 90.6	452	89.2	85.9 - 91.7
Severe	54	81.5	68.3 - 89.6	70	82.9	71.8 - 89.9	81	82.7	72.6 - 89.4	64	81.3	69.4 - 88.9	86	83.7	74.1 - 90.0
Comorbidity count															
0	1,392	98.4	97.5 - 98.9	1176	98.1	97.17 - 98.8	1063	98.5	98 - 99.1	1017	98.0	96.97 - 98.7	1260	98.3	97.46 - 99
1	1,049	97.5	96.4 - 98.3	1103	97.6	96.56 - 98.4	1094	97.4	96 - 98.2	1001	97.4	96.21 - 98.2	1240	97.7	96.65 - 98
2	542	93.9	91.5 - 95.6	602	94.2	92 - 95.8	659	94.2	92 - 95.8	553	93.9	91.5 - 95.6	728	94.8	92.9 - 96
3	284	90.9	86.9 - 93.7	339	91.2	87.59 - 93.7	367	92.4	89 - 94.7	314	90.5	86.62 - 93.2	400	92.8	89.73 - 95
≥4	254	87.8	83.1 - 91.3	295	87.1	82.73 - 90.5	335	86.6	82 - 89.8	278	86.3	81.7 - 89.9	364	87.1	83.19 - 90

*$USPSTF_{2021}$ equivalent size eligible population

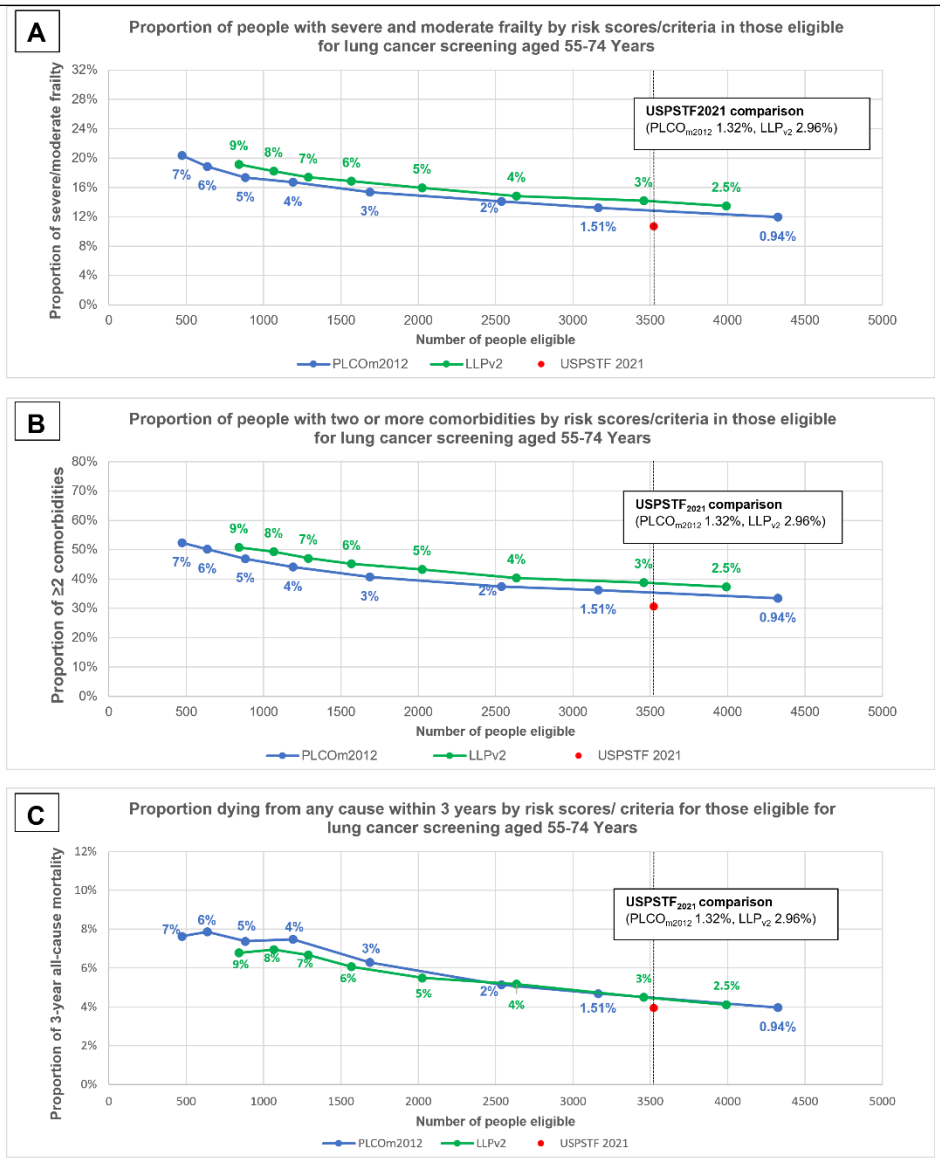

Figure 4.1. The proportion (%) of **A**) severe/moderate frailty, **B**) ≥2 comorbidities, and **C**) dying from any cause within 3 years in those eligible for lung cancer screening by different risk scores ($PLCO_{m2012}$ and LLP_{v2}) vs risk criteria ($USPSTF_{2021}$) in individuals aged 55-74 years. Dotted line to compare % between the three selection strategies when selecting the same number

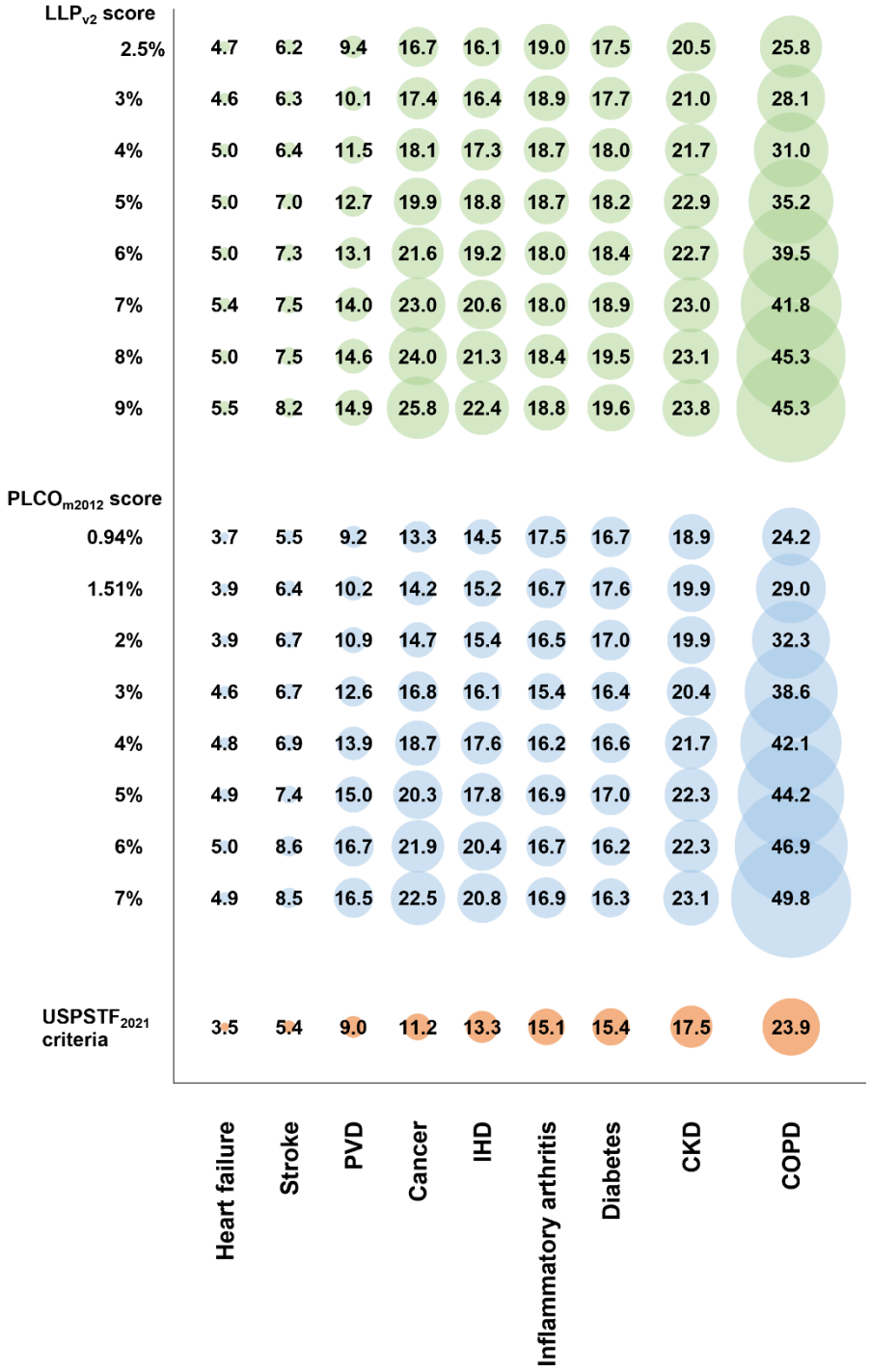

Figure 4.2. Proportion (%) of individual comorbidities by different lung cancer risk scores (LLP_{v2}, $PLCO_{m2012}$) and LCS eligibilty criteria ($USPSTF_{2021}$) in individuals aged 55-74 years. Data for Liver problems, Mono/hemiparesis and peptic ulcer disease was not vizualised in this figure as thier proportions were <2%.

4.5 Discussion

This study, to our knowledge, is the first to report frailty using a validated index in individuals undergoing lung cancer risk assessment for screening. Within this YLST cohort, we observed that the $USPSTF_{2021}$ criteria identified fewer LCS candidates with severe or moderate frailty (10.7%) than the risk score thresholds currently used by the NHS LCS programme(13.2% for $PLCO_{m2012}$ ≥1.51% and 13.5% for LLP_{v2} ≥2.5%). A similar pattern was observed for those with two or more comorbidities.

Frailty and comorbidity increased with lung cancer risk. Given that the lung cancer risk models are predominantly driven by age and smoking history, this is to be expected and has been shown in previous studies(19). This demonstrates how selecting a lower risk threshold would have the effect of reducing the proportion of comorbid and frail individuals within the eligible population. Using equivalent thresholds for comparison, the population identified by $PLCO_{m2012}$≥1.32% had a higher proportion of comorbid individuals, but there was no difference in those with moderate/severe frailty compared to $USPSTF_{2021}$. The population identified by LLP_{v2}≥2.96% had a higher proportion both of comorbid individuals and people with moderate/severe frailty compared to $USPSTF_{2021}$. When comparing the two equivalent risk score thresholds, there was no difference in frailty, but the proportion with ≥2 comorbidities was higher for LLP_{v2}.

The finding that the risk scores generally select more comorbid individuals than the USPSTF criteria matches results from other studies(8, 15, 26, 27). Furthermore, our study shows that both risk thresholds used in the current NHS TLHC programme identify a greater proportion of people with moderate/severe frailty compared to $USPSTF_{2021}$. However, when used in equivalent populations, only LLP_{v2} showed a difference in frailty compared to the $USPSTF_{2021}$ population, with no difference seen between $PLCO_{m2012}$ and $USPSTF_{2021}$ populations.

Comparison of survival rates of all-cause mortality by criteria revealed similar findings with no observed differences between all criteria, as 3-year survival rates were between 95.3% and 96.6% for each risk strategy with overlapping confidence intervals. These survival rates align with what has been reported among LCS-eligible individuals in the US(28) and Poland(29).

As would be expected, our analysis showed that the lowest survival rates were among individuals with severe frailty (81.5% to 83.7%) and individuals with four or more comorbidities (86.3% to 87.8%) across all risk strategies. There was a notable 14.5% to 16.5% decrease in survival rates between those who were fit and those who were classified with severe frailty. Mean life expectancy is expected to be lower for those with increased frailty(24), and those with a higher burden of comorbidities are at higher risk of dying from competing causes than people without comorbidities (30). Our study confirms this relationship in an LCS-eligible population and the potential usefulness of measuring frailty and comorbidities in future lung cancer screening research. It seems likely therefore that the differences in frailty and comorbidity demonstrated between these various eligible populations, whilst mostly statistically significant, are not of sufficient magnitude to translate into a survival difference at three years in the cohort analysed here.

There are two broad considerations in selecting eligibility criteria for screening. The first is the efficiency of the criteria – specifically the cancer yield in the eligible population identified for screening. Lung cancer screening saves lives by detecting early-stage lung cancers, so the more cancers detected potentially, the more lung cancer deaths are prevented, and thus, more lives are saved. The second consideration is the clinical characteristics of the population identified for screening – specifically related to the life-years that might be gained by preventing lung cancer deaths in people within the eligible population. Individuals who are younger, fitter, and less comorbid will be expected to live longer following successful treatment of their screen-detected cancers, and thus contribute to more life-years gained by the screening programme overall.

The evidence to date has suggested that, when comparing risk factor versus risk score-based eligibility criteria, these considerations have opposite effects – i.e. that the risk score-based criteria identify a population with a higher cancer incidence but who are older and more co-morbid, thus with potentially shorter life expectancy. The data presented here therefore help inform discussions about the potential trade-off between these competing effects. Overall, the risk score criteria do appear to select older, more comorbid, and frailer participants, but the differences in these parameters between equivalent populations identified for screening are relatively small and may not translate into measurable differences

in life expectancy. This potential downside of using risk scores is perhaps less significant than previously thought. However, further research is required to understand the relative merit of these different approaches and how they might impact the efficiency of the screening programmes.

Strengths and limitations

Strengths of this study include the prospective calculation of lung cancer risk using data collected directly from individuals during telephone triage consultations. Another strength of this study is that using eFI as an established frailty assessment tool and collecting comorbidities from participants' primary care records allowed us to quantify frailty and comorbidities comprehensively and reliably. Limitations include the fact that our study only recruited people aged 55 and above (and so was unable to fully evaluate the $USPSTF_{2021}$ criteria, which includes people between the ages of 50 and 80). In addition, we only have complete follow-up data for three years to date. It is possible, therefore, that clinically important differences in survival become apparent with longer follow-up. Finally, these results are from a single centre, so these analyses need to be reproduced elsewhere to determine generalisability.

In conclusion, $PLCO_{m2012}$ and LLP_{v2} risk-based models selected slightly higher proportions of eligible individuals with frailty and comorbidities than the $USPSTF_{2021}$ risk criteria. When all strategies were set to select similar numbers, LLP_{v2} selected higher proportions of individuals with two or more comorbidities than $PLCO_{m2012}$ and $USPSTF_{2021}$. Despite these differences, individuals selected by all examined LCS strategies had similar 3-year survival rates. Future research should compare frailty and comorbidities with cancer outcomes and treatment choices across different risk strategies and examine differences in long-term survival.

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Data sharing arrangements: Researchers wishing to use the data will need to complete a request for data sharing form describing a methodologically sound proposal. The form will need to include the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release

definition in the contract and participant informed consent, etc. A data sharing agreement from the sponsor may be required.

Conflict of interest: P.A.J. Crosbie reports stock options from Everest Detection, and lecture honoraria from Bayer, outside the submitted work. R.J. Beeken reports fellowship and grant funding from Yorkshire Cancer Research and grant funding from Roy Castle Lung Cancer Foundation, outside the submitted work. A. Clegg has received consultancy fees from the Geras Centre for Aging Research, received meeting/travel support from the Australian and New Zealand Society of Geriatric Medicine, and is a chair of the global Ageing Research Trialists collaborative.

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Chapter 5 : Discussion and conclusions

5.1 Chapter Summary

In this chapter, I summarise the findings of the three included studies in the thesis. First, I present and discuss the main findings from the systematic review and meta-analysis (Study One) and highlight the gap in the existing literature that the subsequent study aimed to address. For Study Two, I discuss the estimated prevalence of frailty and comorbidities in the YLST population and their impact on response to telephone risk assessment invitation and LDCT uptake. The findings from Study Three are also discussed. Finally, I review the strengths and limitations of all three studies and discuss the implications of findings on current practices and future research.

5.2 Discussion of the included studies

In this thesis, I investigated frailty and comorbidities in the context of lung cancer screening, examining their association with response to risk assessment invitation, subsequent LDCT uptake, and different lung cancer screening eligibility criteria. Following the NLST findings, screening for lung cancer using LDCT has been recommended in many settings for individuals at high risk of the disease. However, prior to this thesis, there was a lack of utilisation of the frailty concept in LCS settings. Also, little was known about the impact of comorbidities on LCS participation in UK-based settings and how these comorbidities vary across different LCS eligibility criteria. In this thesis, I conducted three studies to address the existing gaps related to frailty and comorbidities in the LCS literature.

In Study One, I conducted a systematic review and meta-analysis to estimate the prevalence of frailty and comorbidities among high-risk populations who were screened or eligible for LCS. Additionally, I summarised the current guidelines and recommendations regarding screening individuals with frailty or comorbidities. Using a comprehensive search strategy across four major databases, the systematic review included 69 publications, comprising 57 research studies and 12 clinical guidelines. Frailty was not assessed by any of the included studies, nor was it addressed by any of the included clinical guidelines. Among populations selected for LCS, the pooled analysis of the proportions of individual comorbidities resulted in an estimated prevalence of 35.2% for hypertension, 23.5% for history of chronic obstructive pulmonary

disease (COPD) (10.7% for severe COPD), 16.6% for ischaemic heart disease (IHD), 13.1% for peripheral vascular disease(PVD), 12.9% for asthma, 12.5% for diabetes, 4.5% for bronchiectasis, 2.2% for stroke, and 0.5% for pulmonary fibrosis. Seven studies reported comorbidities using summary measure indices or scores (CCI, ECI, comorbidity count) and showed that the proportions of people without comorbidity were higher in clinical trials than in non-trial LCS settings. Although no study assessed frailty, two UK-based studies reported the WHO performance status (PS), showing a significantly higher proportion of participants classified as PS 0 in one RCT setting compared to a community-based study. The review also summarised guidelines from major clinical bodies, which generally recommend against screening individuals with severe comorbidities that might preclude curative treatment. However, the guidelines varied in specificity and detail regarding how to assess and incorporate these conditions in the context of LCS.

The systematic review identified important gaps in the literature. Few studies examined the presence of comorbidities and their association with LCS screening participation in the UK. Also, none of the included studies assessed frailty among individuals eligible for LCS. The review confirmed a need to better understand the prevalence of frailty and comorbidities among the LCS population and examine their association with LCS initial participation (response to risk assessment invitation) and LDCT uptake in a UK-based setting.

In Study Two, I conducted a retrospective analysis of individuals invited to the YLST study aged 55 to 80, where I utilised data from EHRs to identify their frailty and comorbidity prevalence stratified by their initial participation status (response to telephone-based risk assessment invitation) and LDCT uptake status (attendance at a mobile CT scanning unit). I also examined the associations of different frailty levels, comorbidity count, and individual comorbidities with initial participation status and LDCT uptake. One of the main findings from this study was the estimated prevalence of frailty in two populations: a population of all individuals invited to participate in a telephone-based lung cancer risk assessment (n=27,761) and another population including those who were deemed to be at high-risk and invited to LDCT screening appointment (n=5,041). Using the eFI for the first population identified 24.1% of participants with mild frailty, 8.5% with moderate frailty and 1.7% with severe frailty. For those invited

to the LDCT screening, the eFI identified 31.7% of participants with mild frailty, 13.3% with moderate frailty and 2.9% with severe frailty. In addition, the study identified the prevalence of 12 individual comorbidities and reported comorbidity counts for the two populations. The presence of any level of frailty and comorbidity counts of one or more were associated with a higher response rate but lower LDCT screening uptake compared with individuals without frailty and comorbidity.

For Study Three, I carried out a comparative analysis of the frailty and comorbidity data identified in Study Two between populations eligible for LCS according to risk factors versus risk score criteria. The study aimed to compare individuals who responded to the baseline YLST lung cancer risk assessment invitation and were deemed to be eligible for LCS by the $USPSTF_{2021}$ risk factor criteria (aged 50-80 years with ≥20 pack-year smoking history and ≤15 quit-years), a $PLCO_{m2012}$ risk threshold of ≥1.51% at six years, or an LLP_{v2} risk threshold of ≥2.5% at five years. I also examined the three-year overall survival among the eligible populations. This study identified 3,521, 3,163, and 3,992 participants to be eligible for LCS according to the $USPSTF_{2021}$, $PLCO_{m2012}$ ≥1.51%, and LLP_{v2} ≥2.5% risk strategies, respectively. The main finding from this study is that risk models ($PLCO_{m2012}$ and LLP_{v2}) identify populations with slightly more moderate/severe frailty and comorbidities than the $USPSTF_{2021}$ risk factor criteria. However, this did not result in short-term survival differences between all examined strategies.

5.2.1 Frailty and comorbidities in lung cancer screening – Studies One and Two

5.2.1.1 Prevalence of frailty and comorbidities

In Study One, I conducted a systematic review and meta-analysis to estimate the prevalence of frailty and comorbidities among high-risk populations who were screened or eligible for LCS. Additionally, I summarised the current guidelines and recommendations regarding screening individuals with frailty or comorbidities. Using a comprehensive search strategy across four major databases, the review included 69 publications, comprising 57 research studies and 12 clinical guidelines. In this study, I observed that the majority of LCS studies that reported comorbidities were conducted in Europe and North America

(50/57with), with fewer studies conducted in Asia (7/57). Several factors might explain why LCS studies in Asia lag behind Western countries, including limited healthcare infrastructure, financial constraints, access to screening, and the lack of specific government programmes (1). I did not find any study that used an established frailty assessment tool to identify frail subjects among the LCS population. Although no study assessed frailty, two UK-based studies reported the WHO performance status (PS), showing a significantly higher proportion of participants classified as PS 0 in one RCT setting compared to a community-based study. In Study Two, I have estimated the prevalence of frailty and comorbidities in two populations: a population of all individuals invited to participate in a telephone-based lung cancer risk assessment (n=27,761) and another population including those who were deemed to be at high-risk and invited to LDCT screening appointment (n=5,041). I assessed frailty severity using eFI for all individuals invited to the YLST telephone risk assessment, and I have identified 24.1% of participants with mild frailty, 8.5% with moderate frailty, and 1.7% with severe frailty. The frailty prevalence was higher among those found to be eligible and offered LDCT appointments, with 31.7%, 13.3% and 2.9% of them having mild, moderate and severe frailty, respectively.

In Study One, I have found that most included studies tend to report individual comorbidity proportions rather than utilising comorbidity indices or reporting the sum of comorbidities, which are useful measures in identifying individuals with multiple comorbidities. For example, only seven studies (out of 57) reported comorbidities using comorbidity summary score/index, including CCI, ECI, and comorbidity count. Reporting and assessing multiple comorbidities in LCS are crucial as it can identify patients who might be at higher risk of screening complications or subsequent management strategies which might affect the overall life-years gained from the screening programme.

Another important finding of this study is the documentation of the effect of healthy volunteers on LCS trials compared to non-trial settings. This effect was observed when comparing the reported comorbidities across the two settings. For instance, the DLCST and NLST RCTs reported proportions of participants without any comorbidity to be 82.7% (2) and 45.4% (3), respectively, while this proportion ranged from 21% to 35.6% in non-trial studies included in the review. Although YLST is an RCT by design, findings from Study Two indicated that the

proportion of screen-eligible participants without comorbidities more closely resembled those reported in non-trial settings in Study One(30.8%). This observation may reflect the fact that YLST was designed as a targeted, community-based LCS programme that included high-risk individuals identified using risk scores. In contrast, the DLCST and NLST recruited volunteers for clinic-based LDCT screenings using only risk-factor eligibility criteria, which is known to select individuals with fewer comorbidities than the risk-scores selection strategy (4).

The same observation also extends to specific comorbidities reported in Study One, where conditions like asthma, chronic bronchitis, diabetes, history of COPD, IHD, pulmonary fibrosis, and PVD appear to be less prevalent in trial settings. In addition, the prevalence of diabetes (18.8%), IHD (17.8%), and stroke (7.0%) was higher among the screen-eligible YLST population in Study Two compared to NLST data (9.7%, 12.7%, and 2.8%, respectively) (5), and compared to the pooled prevalence estimates from Study One (12.5% for diabetes and 2.2% for stroke). This finding suggests that when implementing LCS in real-world community settings, screening programs are likely to encounter a population with a higher burden of comorbidities compared to trial participants (6-8). This difference might pose significant challenges in replicating the positive outcomes observed in controlled trial environments.

In contrast to breast and colorectal screening studies, the review found that populations eligible for LCS seem to have a higher comorbidity burden. For example, previous population-based breast cancer screening studies have reported proportions of women without comorbidities ranging from 54%-93% (9-12), compared to the 21%-35% range reported in the review from population-based LCS studies (13-16). Similar findings were observed from colorectal cancer screening studies, with proportions of individuals without comorbidities ranging between 53% (17) and 65% (18). This disparity between the LCS population and breast and colorectal cancer screenings is largely attributed to smoking as a major risk factor for lung cancer, which is often associated with the presence of comorbidities.

The review also highlighted the issue of self-reporting comorbidities with a particular focus on COPD. It was clear from the included studies in the review

that COPD prevalence was higher among studies that derived COPD diagnosis from health records (38.8%) compared to studies that relied on self-reporting (17.0%). The global prevalence of COPD among people aged above 55 years was previously estimated to be 17.9% in 2019 (19). Given that people who are eligible for LCS are expected to have a higher burden of COPD than the general population, the pooled prevalence of self-reported COPD in Study One of this thesis might underestimate the extent of COPD in this population. This underestimation could be attributed to recall bias associated with self-reporting or undiagnosed COPD among this population. The prevalence of undiagnosed symptomatic COPD has been reported in previous LCS studies between 10% and 20% (20-23) among individuals who attended lung cancer screening. Given the strong association between COPD and the risk of developing lung cancer, incorporating spirometry into LCS has been considered by several LCS studies (20, 23, 24), primarily to manage this condition. Misclassifying individuals with COPD might have a direct implication on the accuracy of their estimated lung cancer risk using risk-based models that include COPD as a risk factor, such as $PLCO_{m2012}$ and LLP_{v2} models (25, 26). However, it should be noted that the inclusion of spirometry in LCS programs has not been pursued for the early detection of COPD itself, as there is ongoing controversy regarding the benefits of such early detection.

The prevalence of advanced COPD (stages 3 and 4) among the LCS population was estimated in Study One to be 10.7%, using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (27). While the risk of lung cancer is higher in smokers with COPD than those without COPD, the severe form of the disease may contribute to the harm of LCS and subsequent evaluation and treatment of screen-detected cancers (28). Individuals with advanced COPD may also not benefit from LCS as they are at greater risk of respiratory mortality and non-lung cancer mortality (29). The review also estimated individual comorbidities that are prevalent and commonly reported by LCS studies. These comorbidities include four respiratory diseases (chronic bronchitis, asthma, bronchiectasis, and pulmonary fibrosis) and five other comorbidities that may have a competing cause of death in the LCS population (diabetes, hypertension, IHD, PVD and strokes). Of particular interest was the estimated prevalence of IHD among the LCS population, which was 16.6% (19.5% when excluding a single RCT with a 2% prevalence). This finding is important as the prevalence of

IHD among the general population was estimated to be much lower. For example, the prevalence of IHD was estimated to be between 3.4% and 5.5% among adults in the UK (30), USA (31), and France (32). These findings underscore the significant burden of cardiovascular disease within the LCS population, which may have implications for clinical management and outcomes. The prevalence of other comorbidities among the LCS population was in line with what has been reported among the general population. For example, the review estimated the prevalence of diabetes, hypertension and stroke to be 12.5%, 35.2%, and 2.2%, respectively, which come close to the previous prevalence estimate of these conditions among the general public (33-35).

5.2.1.2 Screening individuals with frailty and comorbidities according to LCS guidelines

A secondary objective of Study One was to summarise the evidence regarding screening individuals with frailty and comorbidities from LCS guidelines. The guidelines for LCS consistently highlight the importance of considering comorbidities in deciding eligibility for screening. Across various professional organisations and expert panels, there is a clear agreement that individuals with severe comorbidities should not undergo LCS. This agreement is mainly because these individuals are less likely to benefit from early detection due to their limited ability to tolerate diagnostic procedures and subsequent curative treatments, and their overall life expectancy may be significantly affected by other health issues. However, it was evident that these recommendations were broad and lacked specific, detailed criteria for assessing comorbidities among potential screening candidates.

In summary, the systematic review identified important gaps in the literature. Few studies examined the presence of comorbidities and their association with LCS screening participation in the UK. Also, none of the included studies assessed frailty among individuals eligible for LCS. Conducting this review highlighted the need to establish the LCS population prevalence of frailty and comorbidities and to examine their association with LCS initial participation (response to risk assessment invitation) and LDCT uptake in a UK-based setting.

5.2.2 Response to risk assessment invitation and LDCT uptake - Study Two

The presence of any degree of frailty was associated with a higher response to the initial risk assessment invitation compared to fit individuals. This finding indicates that the fit population who might benefit the most from early detection did not engage to the same extent with the initial invitation to lung cancer risk assessment compared to frailer populations. This fit population represents the majority (70%) of those under 75 years in Study Two, and the fact that they showed reduced responses to the risk assessment invitation is concerning. There might be several factors that could explain the reduced response in this population. The low perceived risk of lung cancer might partially explain this finding, as fit and healthy individuals may select not to engage with such preventive measures if they believe it is unnecessary (36). Previous studies, including the NELSON trial, have shown that people with higher affective risk perception of developing lung cancer are more keen to participate in LCS (37-39). Further research is needed to understand this lower response rate among the fit population in order to increase their engagement and maximise the benefits of early detection.

On the other hand, Study Two found that when fit individuals responded to the risk assessment invitation and were found to be eligible, they were more likely to attend LDCT screening when offered one, compared to others with variable degrees of frailty. Although individuals with severe frailty showed a lower likelihood of LDCT screening appointment attendance compared to fit people, the result was not statistically significant. The small sample size of individuals with severe frailty (n=146, of which only 28 did not attend) might affect the reliability of this estimate in this group. Further research with a larger sample size, particularly in the severe frailty group, is warranted in order to confirm these findings.

In addition to frailty, comorbidities were examined in Study Two and reported using a comorbidity count summed from 12 comorbidities. Similar to the frailty findings, people without comorbidity seem less likely to respond to risk assessment invitations than people with one or more comorbidities. This reduced response to the risk assessment invitation is also of concern, given that almost 50% of participants under the age of 75 had no comorbidity (comorbidity count=0). However, there was no statistical difference in LDCT uptake at different levels of comorbidity count between those who attended the LDCT

screening appointment and those who did not. Study Two also highlighted that individual comorbidity, including cancer, inflammatory arthritis, COPD, and ischaemic heart disease, were associated with a higher likelihood of response to the risk assessment invitation. On the uptake level, I have found that individuals with cancer and inflammatory arthritis were more likely to attend the LDCT appointment, while individuals with COPD and PVD were less likely to attend. Personal history of cancer has been linked with increased utilisation of LDCT screening(38). Despite this finding, individuals with a cancer history are often excluded from LCS trials(39). Since individuals with a personal history of cancer in Study Two have shown greater response to risk assessment invitations and higher LDCT screening uptake, it is important that this population not be neglected in future LCS programmes.

5.2.3 Frailty, comorbidity and survival by LCS strategies - Study Three

In Study Three, the use of the dual risk model ($PLCO_{m2012}$ and LLP_{V2}) and risk factor (USPSTF) criteria in the YLST design allowed for novel comparisons between the three strategies under one setting. The YLST was designed to prospectively evaluate the selection of $PLCO_{m2012}$ ≥1.51% threshold, LLP_{v2} ≥5% threshold and the 2013 USPSTF strategy – i.e. only people fulfilling at least one of these criteria were invited for screening. Since 2017, when the YLST protocol was designed, further iterations have taken place to screen eligibility criteria nationally and internationally. In the UK, the NHS England Targeted Lung Health Check (TLHC) programme has selected an LLP_{v2} threshold of ≥2.5% for eligibility for screening (alongside ≥1.51% for PLCO). In addition, the USPSTF has revised its 2013 criteria, reducing the pack-year requirement from 30 to 20 and the age-to-start- screening from 55 to 50. As Study Three was designed to look at the characteristics of the whole eligible population, it did not require people to have attended the screening. As such, it was therefore possible to evaluate more contemporary eligibility criteria (i.e. $USPSTF_{2021}$, LLP_{v2} ≥2.5% as well as $PLCO_{m2012}$ ≥1.51%). To the best of my knowledge, this is the first time that the three selection strategies have been studied simultaneously under one setting. I have found that the proportion of individuals with moderate/severe frailty among populations identified using the $USPSTF_{2021}$ risk factor was lower than those who were identified using $PLCO_{m2012}$ and LLP_{V2} risk scores. The same pattern was observed for a comorbidity count of two or more. This finding aligns with previous

concerns that multivariable risk prediction models tend to select populations with more comorbidities than strategies that only rely on age and smoking factors (4, 40). It is also worth noting that risk scores, $PLCO_{m2012}$ in particular, tend to find more cancers than the USPSTF criteria (40).

Study Three investigated for the first time frailty levels and comorbidities between the currently used risk thresholds in the UK ($PLCO_{m2012}$≥1.51% and LLP_{V2}≥2.5%) and found no statistically significant differences between the two populations. However, the LLP_{v2} risk model seems to select a population with slightly more comorbidities than the $PLCO_{m2012}$ risk model when the two risk models were set to identify an equivalent number of eligible individuals. This comparison between the two risk models could inform future discussions on whether to use a single risk model instead of the current dual risk model for defining eligibility for LCS, especially with the anticipated wider rollout of LCS in the UK in the coming years.

Another important finding from Study Three is the sharp increase in the prevalence of severe/moderate frailty, two or more comorbidities, and some individual comorbidities among those with the highest risk of developing lung cancer determined by the $PLCO_{m2012}$ and LLP_{v2} risk models. For example, the proportion of individuals with COPD among the highest-risk group (49.8% for PLCOm2012≥7%) was more than double that of those at the lowest risk (24.2% for $PLCO_{m2012}$≥1.51%). A similar observation was reported from the Manchester LHC pilot (41) with respiratory and cardiovascular comorbidities. Thus, increasing the risk thresholds would generally reduce the number of eligible individuals, but it will result in selecting more frailer and comorbid individuals, as suggested by the data presented in Study Three.

Despite the observed differences between the three selection strategies in terms of frailty and comorbidities, this was not translated into any meaningful differences in three-year survival rates, even after stratifying by frailty and comorbidity levels. The main argument for not using risk scores in some countries is that it was believed to select high-risk individuals with more comorbid conditions and reduced life expectancy. While this is partly true, I did not find apparent differences in three-year survival, which may make previous concerns regarding risk scores less significant. The short-term comparison of survival could explain this lack of difference between the LCS selection strategies, and prolonged follow-up is needed to see if differences arise over longer follow-up.

5.3 Strengths and limitations of the methods

In this thesis, I used different methodological approaches to investigate the burden and impact of frailty and comorbidities in the context of lung cancer screening. First, I systematically reviewed the literature to understand the participation of individuals with frailty and comorbidities in LCS programs. Then, I conducted a case-control analysis to examine both the response to lung cancer risk assessment invitation and subsequent LDCT screening uptake for eligible responders. Finally, a retrospective comparative analysis of frailty and comorbidities was conducted for different populations who would have been eligible for LCS under three eligibility criteria. The strengths and limitations of the methods employed are summarised below.

5.3.1 The systematic review and meta-analysis

To my knowledge, this is the first systematic review to provide a pooled estimate of the prevalence of individual comorbidities in the lung cancer screening population. The review used a comprehensive search strategy and risk of bias assessment and included a large number of studies.

However, there was clear variability among study populations, including differences in demographics, healthcare systems, and criteria for LCS eligibility. This heterogeneity might limit the generalizability of the findings and complicate the interpretation of pooled prevalence estimates. Another limitation of Study One is the variations in comorbidity data sources, as the majority of studies relied on self-reporting of these conditions, with only a few studies utilising medical records. The reliance on self-reported data for comorbid conditions might introduce a risk of bias, as self-reported health conditions are often associated with recall bias, misinterpretation of medical terms, or intentional underreporting. In contrast, studies that utilised medical records to obtain comorbidity data are likely to provide more accurate and objective information. However, the small number of studies that did so limits the ability to generalize their findings. Additionally, the inclusion of reviewing medical guidelines was decided as a secondary objective, and the search strategy was not optimised specifically to search for LCS guidelines. Therefore, the review might have missed some LCS guidelines that did not appear in the search results or guidelines that did not get published.

5.3.2 The Dataset (Study Two and Three)

A key strength of this thesis, particularly in Studies Two and Three, is the primary collection of frailty and comorbidity data from 54 GPs in Leeds, along with the use of a comprehensive frailty assessment tool (eFI) for the first time within an LCS setting. Additionally, insights obtained from non-responders to the risk assessment invitation further strengthen these studies. Studies Two and Three specifically focus on frailty and comorbidities at the time of the screening invitation, with data excluding recent frailty deficits or comorbidities that may have arisen after or as a result of the screening, ensuring that only pre-existing conditions were analysed. Furthermore, the ability to compare different populations identified by three different LCS selection strategies under one setting is another strength of Study Three.

5.3.2.1 Data source and representativeness

Studies Two and Three collected frailty and comorbidity data from 54 GPs participating in the YLST who use SystmOne as their clinical computer system. This represents 62% of all GPs in Leeds (54/86) and 64% (54/84) of the total participating practices in YLST. I did not include any data from 18 GPs because they were using a different clinical system EMIS, nor from 12 GPs who did not respond to the repeated requests to access their clinical system. The decision to exclude practices using the EMIS clinical system was based on the fact that uploading the eFI SNOMED code list (n=8675) to the EMIS system requires manual entry of each individual code. This differs from SystmOne, which allows hundreds of SNOMED codes to be uploaded simultaneously. Despite not including data from all the 84 GPs participating in the YLST, participants' sociodemographic and smoking status variables reported from the 54 GPs were comparable and representative of the YLST screening arm population as a whole (42). Although the YLST is an RCT by design, recruitment based on primary care records from all practices in Leeds and the delivery of LDCT screening at convenient, community-based locations enable the generalisability of the findings to the wider community of Leeds. However, SystmOne's geographical coverage in the rest of England may not be similar to its coverage in Leeds, and other clinical systems might be in use, potentially limiting the representativeness of the findings from Studies Two and Three to areas where SystmOne is predominantly used. For example, an analysis of the clinical computer systems used in primary

care in England revealed that 56% of practices used EMIS, 34% used SystmOne, and 9% used Vision (43). The use of SystmOne was dominant only in three NHS regions, including Yorkshire and the Humber, Central Midlands, and the East region (43).

5.3.2.2 Exclusion of individuals with severe frailty in the YLST

When the YLST was designed in 2017, individuals with a GP-coded diagnosis of severe frailty or an eFI >0.36 were intended to be excluded from the trial. However, this exclusion criterion was not applied as effectively as intended. This issue was mainly due to the way the eFI functions within primary care records. As a risk stratification tool, the eFI allows GPs to screen and classify their patient population based on frailty severity, but this stratification process requires further clinical validation for a frailty diagnosis to be confirmed and coded in the patient's EHR. Consequently, patients with enough deficits to be classified as severely frail but whose eFI results were not clinically confirmed ended up being included in the trial and eventually in this thesis. The unintended inclusion of these individuals allowed me to calculate their eFI scores and evaluate their response to the risk assessment invitation and LDCT uptake.

5.3.2.3 Opt-out

YLST was given permission by the Health Research Authority's Confidentiality Advisory Group to use data on people who had not consented to participate in the study (using a Section 251 amendment). One of the conditions of this permission was that people should have the right to opt-out of their data being used in this way. This was achieved in two main ways: first, attempts were made to disseminate the way in which people's data was to be used amongst people in Leeds who might be involved in the study – through newspaper advertisements and text in screening invitations. Second, people with registered objections to data usage were excluded – at the study's outset, this was termed "Type 1 and type 2 objection to participation in the GP Extraction Service", and later in the study, this changed to the National Data Opt-Out.

Patients who choose to opt out of inclusion in research might have different characteristics from those who do not, potentially introducing some bias. However, the number of participants who have requested to opt out of sharing their information with YLST in studies Two and Three is relatively small

(231/27,992), and all were excluded from the analysis. Other opt-outs were automatically excluded by the data extraction algorithm within SystmOne, and their exact number was not known. However, the national opt-out rate in England is generally low, with only 2.4% of patients is currently registered to opt out of sharing their identifiable data outside of NHS Digital for purposes beyond direct care (44). This rate is unlikely to impact the findings of Studies Two and Three.

5.3.2.4 Informed presence bias

In conducting research using EHRs, informed presence bias could pose a significant challenge. This bias develops because the presence of individuals in EHR datasets is not random; rather, it is often correlated with the presence of illness, as individuals usually engage with healthcare services when they are unwell (45). Therefore, this can lead to a non-representative sample where the population under study appears systematically sicker than the general population. When using eFI to assess frailty from EHRs, informed presence bias can be particularly concerning. The eFI relies on data collected from medical records, including diagnoses, symptoms, medications, and healthcare interactions. However, the likelihood of being classified as frail might increase with the number of healthcare visits, not because of true frailty but due to more chances for frailty-related deficits to be recorded. This can result in an overestimation of frailty prevalence among the studied population compared to the general population. In this thesis, I did not employ specific mitigation strategies to address informed presence bias, which was not feasible within the thesis timeframe. Therefore, the observed associations of frailty and comorbidities reported in Studies Two and Three should be interpreted with the recognition that they may represent stronger associations than what truly exists in the general population.

5.3.2.5 Missing data

As studies Two and Three utilised data from participants in the YLST, baseline sociodemographic data were complete, with only 0.1% missing data for the IMD quintile. This missing data was not handled due to its small magnitude, which would be unlikely to impact the findings. Missing data in EHRs poses a significant challenge due to irregular recording practices that are inherent in clinical settings (46). It is possible that the absence of recording does not directly reflect the

absence of the event as a diagnosis outside the primary care might not have been entered into EHRs, entered as free-text clinical notes, or incorrectly recorded.

Polypharmacy data extracted from EHRs for Studies Two and Three were largely missing, with only 60 participants initially showing a documented coded record of polypharmacy. This rate did not capture the true prevalence of polypharmacy in the studied population, as the development cohort of eFI showed a much higher polypharmacy rate of 69% (47). The main reason for not capturing actual polypharmacy prevalence in EHRs is the underutilisation of recording polypharmacy using CTV3 or SNOMED codes. The polypharmacy deficit was included in the original eFI development cohort (47) by obtaining a list of all prescribed medications and was determined if more than or equal to five medications were present. Unfortunately, obtaining a list of all prescribed medications for participants in Studies Two and Three was not possible due to logistical and time constraints. Instead, the presence of polypharmacy was randomly imputed for all participants for each level of frailty based on the polypharmacy prevalences obtained from the eFI development team (through personal communication). This random imputation resulted in a polypharmacy prevalence of 42.9%, as reported in Study Two. I have conducted several sensitivity analyses (Appendix B.3) to examine if the risk assessment invitation response or LDCT uptake findings in Study Two would be changed if different polypharmacy prevalences (26%, 57%, and 100%) were accounted for when calculating eFI scores. The sensitivity analyses indicated that the imputed polypharmacy data did not change the overall conclusions of Study Two, where the prevalence of frailty was first established using eFI for all participants (n=27,761).

5.4 Implications of findings

5.4.1 Implications for practice

In Study Two, the finding that fit individuals and those without comorbidities are less responsive to lung cancer risk assessment invitations compared to frail individuals and those with comorbidities has significant implications for clinical practice, particularly if confirmed by future research in non-trial settings. These results suggest that the population most likely to benefit from lung cancer screening are not adequately participating in the initial risk assessment.

Consequently, there is a need to reconsider how lung cancer screening invitations are targeted and communicated to this population to ensure that these individuals are adequately engaged. This fit population could potentially benefit from further interventions, such as patient navigation (48) or what is referred to as Pathway Navigation (PN) under the current YLST nested study (49), in order to increase their LCS utilisation.

Studies Two and Three provided important insights on individuals aged 75 to 80, as the YLST enrolled participants up to the age of 80. Despite the fact that almost half (45%) of the people diagnosed with lung cancer in the UK are aged 75 and older (50), this age group is currently excluded from the NHS LHC screening recommendation in the UK (51). In this thesis, I have found that individuals aged 75 or older showed comparable rates of response to the risk assessment invitation and LDCT uptake compared to their counterparts aged 70-74 years. A sizable proportion of those aged above 75 were not frail or with mild frailty and had zero or one comorbidity. Identifying this fit population (not frail or with mild frailty) was feasible, as demonstrated in Study Two. Future LCS programmes might consider using eFI to identify and invite fit people beyond 75 years instead of depending on an upper age limit of 75 years as a blanket exclusion criterion.

In Study Three, I observed that the two risk score criteria currently in use in the UK ($PLCO_{m2012}$≥1.51% and LLPv2≥2.5%) selected similar populations in terms of their frailty and comorbidity profiles. However, given that LLP_{v2} ≥2.5% risk threshold identified a larger eligible population than $PLCO_{m2012}$ ≥1.51% risk threshold (n=3992 versus n=3163), an equivalent population size comparison showed that LLP_{v2} selected an eligible population with significantly higher comorbidities compared to the $PLCO_{m2012}$ model. There is a potential that the NHS LHC protocol for targeted LCS could be amended in the future to rely only on one model-based selection strategy instead of the dual model selection that is currently used ($PLCO_{m2012}$ and LLP_{V2}). The findings from Study Three provide valuable evidence comparing the two risk models and support the use of $PLCO_{m2012}$ as a single risk score selection strategy rather than incorporating LLP_{v2} as an additional selection method.

Finally, assessing frailty among the LCS population using routinely collected data within primary care electronic health records was feasible, as demonstrated in this thesis. However, some logistical and practical considerations are needed for

future LCS in the UK if a decision is made to exclude people with severe frailty based on the eFI. The current integration of eFI calculation within primary care clinical systems depends mainly on the validation of the calculated scores by a clinician in order for a frailty diagnosis to appear in patients' records. This is because the eFI was meant to be used as a population risk stratification tool rather than a clinical diagnostic one. Therefore, any attempts to universally identify people with severe frailty through primary care records would only identify a small proportion of patients who have had their frailty diagnosis confirmed by their GP, which could result in missing the majority of those with undiagnosed severe frailty.

5.4.2 Directions for future research

I have identified several gaps that have emerged during this thesis for future research to address. In Study One, the observation that the majority of LCS studies reporting comorbidities were conducted in Europe and North America suggests a geographical disparity in research between Western countries and Asia. This highlights the need for increased LCS research focus in Asian countries. The lack of studies using established frailty assessment tools to identify frail subjects among the eligible population is another critical gap. Future research should prioritise the use of existing frailty assessment tools or develop and validate new frailty tools specific to the LCS population. Incorporating these tools into the screening decision-making can help identify individuals who may not benefit from LCS due to their frailty while also helping in identifying fit candidates to ensure they take part in screening programs. This approach optimises the selection process for LCS candidates. The documented healthy volunteer effect in LCS trials suggests that real-world LCS programs will encounter populations with higher comorbidities. Future LCS trials should explore strategies to mitigate this effect to better reflect the general population's health status. YLST appears to have avoided the healthy volunteer effect to some extent by initially sampling based on primary care records and delivering LDCT screening at convenient, community-based locations. The difference in COPD prevalence based on self-reporting versus health records suggests that LCS studies that rely on self-reporting of COPD may underestimate its prevalence. Future research should incorporate objective measures like spirometry to accurately capture the burden of COPD in LCS candidates. This will ensure better risk stratification in LCS

programmes that employ model-based risk selection strategies. The review of LCS guidelines revealed a lack of specific criteria for assessing frailty and comorbidities. Future LCS guidelines should focus on incorporating the concept of frailty and provide clear recommendations for screening individuals with frailty, including which tools should be used for assessment, which degrees of frailty should lead to inclusion or exclusion, and who should make these decisions.

In Study Two, I have identified that fit individuals, who are likely to benefit most from early detection in terms of life-years gained from screening, showed lower response rates to lung cancer risk assessment invitation compared to those with some level of frailty. Understanding the perceptions and motivations of this fit population should be a priority in future LCS research, particularly in exploring interventions such as pathway navigation to increase their participation rates in screening programs. The study's findings on severe frailty were limited by the small sample size, which might affect the reliability of the estimate regarding LDCT uptake in this population. There is a clear need for larger studies focusing on individuals with severe frailty to obtain more robust conclusions. While screening outcomes were not the focus of this study, future research should explore the outcomes of patients with screen-detected cancers according to their frailty and comorbidity levels.

In Study Three, populations identified by the risk models ($PLCO_{m2012}$ and LLP_{v2}) exhibit a slightly higher prevalence of moderate/severe frailty and multiple comorbidities compared to the population identified by the $USPSTF_{2021}$ criteria, yet no significant differences in three-year overall survival were observed. Further research is warranted to explore the long-term survival and screening outcomes among populations identified by different LCS strategies. In addition, the replicability of the study findings in other settings and geographical locations is warranted to fully understand the differences between the LCS selection strategies.

5.5 Conclusions

In summary, this thesis contributes novel insights regarding frailty and comorbidities in the context of LCS. Throughout the thesis, frailty was assessed for the first time in an LCS population using the eFI, and it was prevalent with varying degrees. Individuals who were identified as fit were less responsive to the lung cancer risk assessment invitation but showed an increased LDCT uptake

when found eligible compared to individuals with some degree of frailty. People without comorbidities showed a similar pattern of decreased response when invited to the lung cancer risk assessment. Several individual comorbidities were identified to be prevalent among the YLST population, with multimorbidity also being present in about 40% of the YLST-eligible population. The two currently in use LCS risk models in the UK ($PLCO_{m2012}$ and LLP_{v2}) seem to identify similar populations in terms of frailty and comorbidities, but both identify more people with frailty and comorbidities when compared to the $USPSTF_{2021}$ selection criteria. Despite this, three-year survival rates seemed similar between all examined eligibility strategies. More research is needed to understand the barriers and facilitators for response to risk assessment invitations, especially for people who are fit without frailty or comorbidities. Additional insights are also warranted on the screening outcomes and the long-term survival of eligible individuals by varying degrees of frailty and comorbidities and across LCS selection strategies.

5.6 References

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Appendix A: Study One supplementary data

Appendix A.1: Systematic review search strategy

Database: Ovid MEDLINE(R) ALL <1946 to February 05, 2021>

1 comorbidity/ or Multimorbidity/ or Alzheimer disease/ or dementia/ or arthritis/ or asthma/ or cardiovascular diseases/ or stroke/ or chronic disease/ or terminally ill/ or pulmonary disease, chronic obstructive/ or cognition disorders/ or depression/ or renal dialysis/ or myocardial infarction/ or hypertension/ or life expectancy/ or liver diseases/ or mental disorders/ or lung diseases/ or Diabetes Mellitus/ or Atrial Fibrillation/ or Renal Insufficiency, Chronic/ or Myocardial Ischemia/ or Polypharmacy/ or Peripheral Vascular Diseases/ or Peptic Ulcer/ or Sarcopenia/ or cognition disorders/ (2040837)

2 (comorbid* or co-morbid* or multimorbid* or coexist* or Feinstein or Charlson index or Charlson score or CCI or Elixhauser Index or Elixhauser score or Elixhauser comorbidity measure or ECM or NCI Comorbidity Index or Adult Comorbidity Evaluation-27 or ACE-27 or Alzheimer disease or dementia or arthritis or asthma or cardiovascular diseases or stroke or chronic bronchitis or chronic disease or chronic hepatitis or renal insufficiency or chronic obstructive pulmonary disease or COPD or obstructive pulmonary disease or cognition disorder* or depression or depressive disorder* or renal dialysis or myocardial infarction or hypertension or liver disease* or mental disorder* or lung disease* or Hypotension or Atrial Fibrillation or Cerebrovascular Disorders or Myocardial Ischemia or Polypharmacy or Peripheral Vascular Disease* or Peptic Ulcer or Sarcopenia or mobility impairment or motor dysfunction or motor impairment or motor limitation or physical disability or physical disease or physical disease* or physical impairment or physical limitation or physical functioning or walking difficulty or cognitive defect* or cognitive impairment* or cognitive decline*).ti,ab,kw. (2365661)

3 frailty/ or Frail Elderly/ or aged/ or disabled persons/ or health status/ or activities of daily living/ or Hip Fractures/ or Geriatric Assessment/ or debility/ or life expectancy/ (3280670)

4 (health status or Frailty Syndrome or Frailties or Frailness or Frail Elderly or aged or disabled person* or cumulative deficit or Prefrailty or (Phenotype adj2 model) or Geriatric Assessment or comprehensive geriatric assessment or Modified Frailty Index or Frailty index or Frailty indicator or Gait speed or walking speed or grip strength or "Timed up and go test" or TUG Test or "get up

and go" or Karnofsky Performance Score or Karnofsky Performance Status or KPS score or Performance Status or daily life activity or functional status or functional disease or functional diseases or functional impairment or functional limitation or elderly population or Functional limitation* or broken hip or Frailty Phenotype or SHARE-FI or 3-item Frailty Trait Scale or FTS-3 or 5-item Frailty Trait Scale or FTS-5 or FRAIL or 35-item Frailty Index or FI-35 or Frailty Screening Tool or GFST or Clinical Frailty Scale or Robinson Frailty Score or Edmonton Frail Scale or G8 or cognitive frailty).ti,ab,kw. (769790)

5 1 or 2 or 3 or 4 (6213098)

6 exp Lung Neoplasms/ or Small Cell Lung Carcinoma/ or Carcinoma, Non-Small-Cell Lung/ (238424)

7 exp Early Detection of Cancer/ or exp Mass Chest X-Ray/ or Mass Screening/ or exp Tomography, X-Ray Computed/ or exp tomography/ (1069275)

8 (lung cancer or lung tumour*or lung tumor* or Lung Neoplasm or Early Detection of Cancer or Mass Chest X ray or Mass Screening or X-Ray Computed Tomography or tomography or detect* or chest x ray or identif* or LDCT or scan).ti,ab,kw. (5787408)

9 6 or 7 or 8 (6476166)

10 5 and 9 (1612729)

11 ((lung cancer or lung) adj6 screen*).ti,ab,kw. (6732)

12 10 and 11 (2679)

13 exp animals/ not humans.sh. (4785222)

14 12 not 13 (2668)

15 limit 14 to yr="1990 -Current" (2584)

Database: Embase Classic+Embase <1947 to 2021 February 05>

Search Strategy

1 Alzheimer disease/ or dementia/ or arthritis/ or asthma/ or cardiovascular diseases/ or stroke/ or bronchitis, chronic/ or chronic disease/ or terminally ill/ or hepatitis, chronic/ or renal insufficiency, chronic/ or kidney failure, chronic/ or pulmonary disease, chronic obstructive/ or cognition disorders/ or depression/ or depressive disorder/ or renal dialysis/ or myocardial infarction/ or hypertension/ or life ectancy/ or liver diseases/ or mental disorders/ or lung diseases/ or Diabetes Mellitus/ or Diabetes Mellitus, Type 1/ or Diabetes Mellitus, Type 2/ or Hypotension/ or Atrial Fibrillation/ or Cerebrovascular

Disorders/ or Renal Insufficiency, Chronic/ or Myocardial Ischemia/ or Polypharmacy/ or Peripheral Vascular Diseases/ or Peptic Ulcer/ or Sarcopenia/ or cognition disorders/ (3062122)

2 exp comorbidity/ or exp Charlson Comorbidity Index/ or exp comorbidity assessment/ or exp Elixhauser comorbidity index/ or exp multiple chronic conditions/ (312614)

3 (comorbid* or co-morbid* or co morbid* or multimorbid* or coexist* or Feinstein or Charlson index or Charlson score or CCI or Elixhauser Index or Elixhauser score or Elixhauser comorbidity measure or ECM or NCI Comorbidity Index or Adult Comorbidity Evaluation-27 or ACE-27 or Alzheimer disease or dementia or arthritis or asthma or cardiovascular diseases or stroke or chronic bronchitis or chronic disease or terminally ill or chronic hepatitis or renal insufficiency or chronic obstructive pulmonary disease or COPD or obstructive pulmonary disease or cognition disorder* or depression or depressive disorder* or renal dialysis or myocardial infarction or hypertension or life expectancy or liver disease* or mental disorder* or lung disease* or Hypotension or Atrial Fibrillation or Cerebrovascular Disorders or Myocardial Ischemia or Polypharmacy or Peripheral Vascular Disease* or Peptic Ulcer or Sarcopenia or mobility impairment or motor dysfunction or motor impairment or motor limitation or physical disability or physical disease or physical disease* or physical impairment or physical limitation or physical functioning or walking difficulty or cognitive defect* or cognitive impairment* or cognitive decline*).ti,ab,kw. (3672820)

4 exp Lung Neoplasms/ or exp Carcinoma, Bronchogenic/ or exp Lung cancer/ or exp Solitary Pulmonary Nodule/ or exp Carcinoma, Non-Small-Cell Lung/ or exp Small Cell Lung cancer/ or exp Carcinoma, Small Cell/ (434951)

5 (lung cancer or lung tumour or lung tumours or lung tumor or lung tumors or Pulmonary Cancer or Cancer of Lung or Cancer of the Lung or Pulmonary Neoplasm or Lung Neoplasm).ti,ab,kw. (277801)

6 exp Early Detection of Cancer/ or exp Cancer Screening/ or exp Mass Chest X ray/ or Mass Screening/ or exp Tomography, X-Ray Computed/ or radiography/ or exp Population Surveillance/ (898094)

7 (Early Detection of Cancer or Cancer Screening or Early Diagnosis of Cancer or Mass Chest X ray or Mass Screening or radiography or Population Surveillance or screening or chest x ray or identif* or LDCT).ti,ab,kw. (5156851)

8 ((exp frailty/ or exp Frail Elderly/ or exp aged/ or exp Middle Aged/ or exp aged, 80/) and over/) or exp disabled persons/ or exp health status/ or exp

activities of daily living/ or exp Hip Fractures/ or exp Geriatric Assessment/ or exp debility/ (451952)

9 (((((health status or Frailty Syndrome or Frailties or Frailness or Debility or Debilities or Frail Elderly or aged or disabled person* or cumulative deficit or Phenotype model or Prefrailty or Geriatric Assessment or comprehensive geriatric assessment or Modified Frailty Index or index or indicator or score or scale or tool or test or model or phenotype or Gait speed or walking speed or grip strength or Timed up) and go test) or TUG Test or get up) and go) or Karnofsky Performance Score or Karnofsky Performance Status or KPS score or daily life activity or functional disease or functional diseases or functional impairment or functional limitation or elderly population or Functional limitation* or broken hip or Performance Status or Frailty Phenotype or SHARE-FI or 3-item Frailty Trait Scale or FTS-3 or 5-item Frailty Trait Scale or FTS-5 or FRAIL or 35-item Frailty Index or FI-35 or Frailty Screening Tool or GFST or Clinical Frailty Scale or Robinson Frailty Score or Edmonton Frail Scale or G8 or cognitive frailty).ti,ab,kw. (137958)

10 1 or 2 or 3 or 8 or 9 (5566476)

11 4 or 5 or 6 or 7 (6163829)

12 10 and 11 (1120510)

13 (((Lung adj6 screening) or "Lung cancer") adj6 screening).ti,ab,kw. (9791)

14 12 and 13 (1877)

15 (exp animal/ or nonhuman/) not exp human/ (7341404)

16 14 not 15 (1845)

17 limit 16 to yr="1990 -Current" (1774)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 28, 2021>, EBM Reviews - ACP Journal Club <1991 to January 2021>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Cochrane Clinical Answers <January 2021>, EBM Reviews - Cochrane Central Register of Controlled Trials <December 2020>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>

Search Strategy

1 comorbidity/ or Multimorbidity/ or Alzheimer disease/ or dementia/ or arthritis/ or asthma/ or cardiovascular diseases/ or stroke/ or chronic disease/ or

terminally ill/ or pulmonary disease, chronic obstructive/ or cognition disorders/ or depression/ or renal dialysis/ or myocardial infarction/ or hypertension/ or life expectancy/ or liver diseases/ or mental disorders/ or lung diseases/ or Diabetes Mellitus/ or Atrial Fibrillation/ or Renal Insufficiency, Chronic/ or Myocardial Ischemia/ or Polypharmacy/ or Peripheral Vascular Diseases/ or Peptic Ulcer/ or Sarcopenia/ or cognition disorders/ (127465)

2 (comorbid* or co-morbid* or multimorbid* or coexist* or Feinstein or Charlson index or Charlson score or CCI or Elixhauser Index or Elixhauser score or Elixhauser comorbidity measure or ECM or NCI Comorbidity Index or Adult Comorbidity Evaluation-27 or ACE-27 or Alzheimer disease or dementia or arthritis or asthma or cardiovascular diseases or stroke or chronic bronchitis or chronic disease or chronic hepatitis or renal insufficiency or chronic obstructive pulmonary disease or COPD or obstructive pulmonary disease or cognition disorder* or depression or depressive disorder* or renal dialysis or myocardial infarction or hypertension or liver disease* or mental disorder* or lung disease* or Hypotension or Atrial Fibrillation or Cerebrovascular Disorders or Myocardial Ischemia or Polypharmacy or Peripheral Vascular Disease* or Peptic Ulcer or Sarcopenia or mobility impairment or motor dysfunction or motor impairment or motor limitation or physical disability or physical disease or physical disease* or physical impairment or physical limitation or physical functioning or walking difficulty or cognitive defect* or cognitive impairment* or cognitive decline*).ti,ab,kw. (381463)

3 frailty/ or Frail Elderly/ or aged/ or disabled persons/ or health status/ or activities of daily living/ or Hip Fractures/ or Geriatric Assessment/ or debility/ or life expectancy/ (221276)

4 (health status or Frailty Syndrome or Frailties or Frailness or Frail Elderly or aged or disabled person* or cumulative deficit or Prefrailty or (Phenotype adj2 model) or Geriatric Assessment or comprehensive geriatric assessment or Modified Frailty Index or Frailty index or Frailty indicator or Gait speed or walking speed or grip strength or "Timed up and go test" or TUG Test or "get up and go" or Karnofsky Performance Score or Karnofsky Performance Status or KPS score or Performance Status or daily life activity or functional status or functional disease or functional diseases or functional impairment or functional limitation or elderly population or Functional limitation* or broken hip or Frailty Phenotype or SHARE-FI or 3-item Frailty Trait Scale or FTS-3 or 5-item Frailty Trait Scale or FTS-5 or FRAIL or 35-item Frailty Index or FI-35 or Frailty Screening Tool or GFST or Clinical Frailty Scale or Robinson Frailty Score or Edmonton Frail Scale or G8 or cognitive frailty).ti,ab,kw. (274372)

5 1 or 2 or 3 or 4 (741703)

6 exp Lung Neoplasms/ or Small Cell Lung Carcinoma/ or Carcinoma, Non-Small-Cell Lung/ (8270)

7 exp Early Detection of Cancer/ or exp Mass Chest X-Ray/ or Mass Screening/ or exp Tomography, X-Ray Computed/ or exp tomography/ (23091)

8 (lung cancer or lung tumour*or lung tumor* or Lung Neoplasm or Early Detection of Cancer or Mass Chest X ray or Mass Screening or X-Ray Computed Tomography or tomography or detect* or chest x ray or identif* or LDCT or scan).ti,ab,kw. (277225)

9 6 or 7 or 8 (290674)

10 5 and 9 (133742)

11 ((lung cancer or lung) adj6 screen*).ti,ab,kw. (1371)

12 10 and 11 (651)

13 limit 12 to yr="1990 -Current" [Limit not valid in DARE; records were retained] (648)

14 limit 13 to humans [Limit not valid in CDSR,ACP Journal Club,DARE,CCA,CCTR,CLCMR; records were retained] (648)

15 (comorbid* or co-morbid* or multimorbid* or coexist* or Feinstein or Charlson index or Charlson score or CCI or Elixhauser Index or Elixhauser score or Elixhauser comorbidity measure or ECM or NCI Comorbidity Index or Adult Comorbidity Evaluation-27 or ACE-27 or Alzheimer disease or dementia or arthritis or asthma or cardiovascular diseases or stroke or chronic bronchitis or chronic disease or chronic hepatitis or renal insufficiency or chronic obstructive pulmonary disease or COPD or obstructive pulmonary disease or cognition disorder* or depression or depressive disorder* or renal dialysis or myocardial infarction or hypertension or liver disease* or mental disorder* or lung disease* or Hypotension or Atrial Fibrillation or Cerebrovascular Disorders or Myocardial Ischemia or Polypharmacy or Peripheral Vascular Disease* or Peptic Ulcer or Sarcopenia or mobility impairment or motor dysfunction or motor impairment or motor limitation or physical disability or physical disease or physical disease* or physical impairment or physical limitation or physical functioning or walking difficulty or cognitive defect* or cognitive impairment* or cognitive decline*).ti,ab,kw. (381463)

16 (health status or Frailty Syndrome or Frailties or Frailness or Frail Elderly or aged or disabled person* or cumulative deficit or Prefrailty or (Phenotype adj2 model) or Geriatric Assessment or comprehensive geriatric assessment or Modified Frailty Index or Frailty index or Frailty indicator or Gait speed or walking speed or grip strength or "Timed up and go test" or TUG Test or "get up

and go" or Karnofsky Performance Score or Karnofsky Performance Status or KPS score or Performance Status or daily life activity or functional status or functional disease or functional diseases or functional impairment or functional limitation or elderly population or Functional limitation* or broken hip or Frailty Phenotype or SHARE-FI or 3-item Frailty Trait Scale or FTS-3 or 5-item Frailty Trait Scale or FTS-5 or FRAIL or 35-item Frailty Index or FI-35 or Frailty Screening Tool or GFST or Clinical Frailty Scale or Robinson Frailty Score or Edmonton Frail Scale or G8 or cognitive frailty).ti,ab,kw. (274372)

17 15 or 16 (577696)

18 (lung cancer or lung tumour*or lung tumor* or Lung Neoplasm or Early Detection of Cancer or Mass Chest X ray or Mass Screening or X-Ray Computed Tomography or tomography or detect* or chest x ray or identif* or LDCT or scan).ti,ab,kw. (277225)

19 17 and 18 (102790)

20 ((lung cancer or lung) adj6 screen*).ti,ab,kw. (1371)

21 19 and 20 (449)

22 limit 21 to (humans and yr="1990 -Current") [Limit not valid in CDSR,ACP Journal Club,DARE,CCA,CCTR,CLCMR; records were retained] (447)

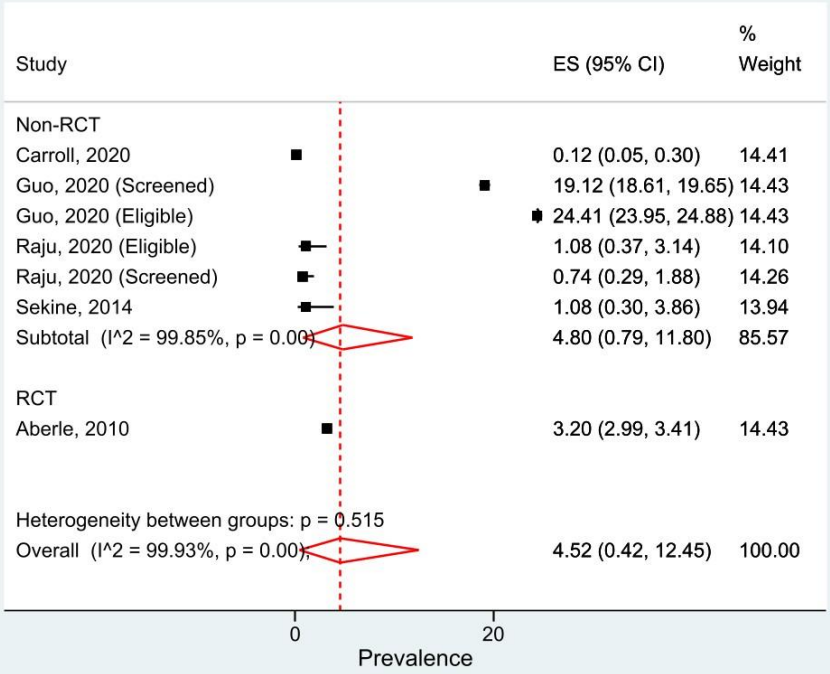
Database: EBSCO-CINAHL

#	Query
S11	S9 NOT S10
S10	(((MH "Animals+") OR (MH "Animal Studies") OR (TI "animal model*")) NOT (MH "human"))
S9	(lung cancer W7 screening or lung W7 screening) AND (S7 AND S8)
S8	lung cancer W7 screening or lung W7 screening
S7	((S2 OR S3) AND (S1 OR S4)) AND (S5 AND S6)
S6	(S2 OR S3) AND (S1 OR S4)
S5	S2 OR S3
S4	((MH "Health Services for the Aged") OR (MH "Aged+") OR (MH "Activities of Daily Living+") OR (MH "Age Factors") OR (MH "Geriatric Functional Assessment") OR (MH "Senior Centers") OR (MH "Aging+") OR (MH "Frail Elderly") OR (MH "Health Status+") OR (MH "Geriatric Assessment+") OR (MH "Functional Assessment+") OR (MH "Motor Activity+") OR (MH "Geriatrics)) OR (Frailty Syndrome or Frailties or Frailness or Debility or Debilities or Frail Elderly or aged or disabled person* or cumulative deficit or Phenotype model or Prefrailty or Geriatric Assessment or comprehensive geriatric assessment or Modified Frailty Index or index or indicator or score or scale or tool or test or model or phenotype or Gait speed or walking speed or grip strength or Timed up and go test or TUG Test or get up and go or Karnofsky Performance Score or Karnofsky Performance Status or KPS score or daily life activity or functional disease or functional diseases or functional impairment or functional limitation or elderly population or Functional limitation* or broken hip or Performance Status or Frailty Phenotype or SHARE-FI or 3-item Frailty Trait Scale or FTS-3 or 5-item Frailty Trait Scale or FTS-5 or FRAIL or 35-item Frailty Index or FI-35 or Frailty Screening Tool or GFST or Clinical Frailty Scale or Robinson Frailty Score or Edmonton Frail Scale or G8 or cognitive frailty)
S3	((MH "Early Detection of Cancer") OR (MH "Tomography, X-Ray Computed+") OR (MH "Tomography, X-Ray+") OR (MH "Radiography, Thoracic+") OR (MH "Cancer Screening")) OR (Early Detection of Cancer or Cancer Screening or Early Diagnosis of Cancer or Mass Chest X ray or Mass Screening or X-Ray Computed Tomography or tomography or radiography or Population Surveillance or screening or detect* or LCS or chest x ray or screen or diagnos* or identif* or LDCT or scan)
S2	((MH "Carcinoma, Non-Small-Cell Lung") OR (MH "Carcinoma, Small Cell") OR (MH "Lung Neoplasms+")) OR (lung cancer or lung tumour or lung tumours or lung tumor or lung tumors or Pulmonary Cancer or Cancer of Lung or Cancer of the Lung or Pulmonary Neoplasm or Lung Neoplasm)
S1	((MH "Comorbidity") OR (MH "Alzheimer's Disease") OR (MH "Dementia+") OR (MH "Arthritis+") OR (MH "Asthma+") OR (MH "Pulmonary Disease, Chronic Obstructive+") OR (MH "Lung Diseases, Obstructive+") OR (MH "Cardiovascular Diseases+") OR "cardiovascular diseases" OR (MH "Stroke+") OR "stroke" OR (MH "Bronchitis, Chronic") OR "bronchitis" OR (MH "Chronic Disease+") OR "chronic disease" OR (MH "Kidney Failure, Chronic+") OR (MH "Terminally Ill Patients+") OR "terminally ill" OR (MH "Hepatitis, Chronic+") OR (MH "Renal Insufficiency, Chronic+") OR "renal insufficiency" OR (MH "Cognition Disorders+") OR (MH "Depression+") OR "depression" OR (MH "Geriatric Depression Scale") OR (MH "Myocardial Infarction+") OR "myocardial infarction" OR (MH "Myocardial Ischemia+") OR (MH "Hypertension+") OR "hypertension" OR (MH "Hypotension+") OR "hypotension" OR (MH "Life Expectancy") OR "life expectancy" OR (MH "Liver Diseases+") OR "liver diseases" OR (MH "Mental Disorders+") OR "mental disorders" OR (MH "Lung Diseases+") OR "lung diseases" OR (MH "Diabetes Mellitus+") OR "Diabetes Mellitus" OR (MH "Atrial Fibrillation") OR "Atrial Fibrillation" OR (MH "Cerebrovascular Disorders+") OR "Cerebrovascular Disorders" OR (MH "Polypharmacy") OR "Polypharmacy" OR (MH "Peptic Ulcer+") OR "Peptic Ulcer" OR (MH "Sarcopenia") OR "Sarcopenia") OR (comorbid* or co-morbid* or co morbid* or multimorbid* or coexist* or Feinstein or Charlson index or Charlson score or CCI or Elixhauser Index or Elixhauser score or Elixhauser comorbidity measure or ECM or NCI Comorbidity Index or Adult Comorbidity Evaluation-27 or ACE-27 or Alzheimer disease or dementia or arthritis or asthma or cardiovascular diseases or stroke or chronic bronchitis or chronic disease or terminally ill or chronic hepatitis or renal insufficiency or chronic obstructive pulmonary disease or COPD or obstructive pulmonary disease or cognition disorder* or depression or depressive disorder* or renal dialysis or myocardial infarction or hypertension or life expectancy or liver disease* or mental disorder* or lung disease* or Hypotension or Atrial Fibrillation or Cerebrovascular Disorders or Myocardial Ischemia or Polypharmacy or Peripheral Vascular

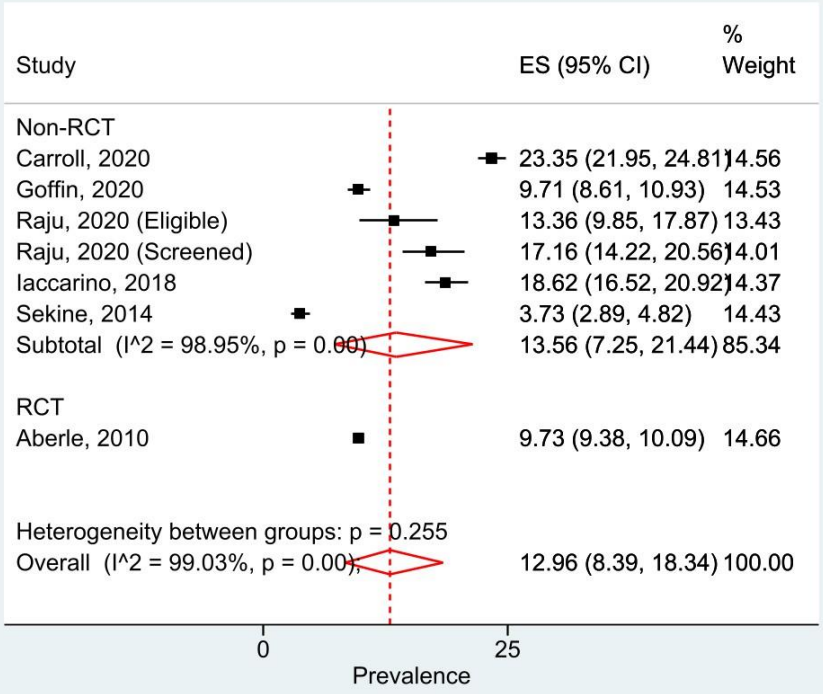
Appendix A.2: Forest plots

Meta-analysis of the prevalence of selected comorbidities in the lung cancer screening population is presented below as forest plots. Pooled prevalence was calculated with inverse-variance weights obtained from a random-effects model. The effect measure is represented by a proportion with a 95% confidence interval and the heterogeneity analysis carried by I2 statistic.

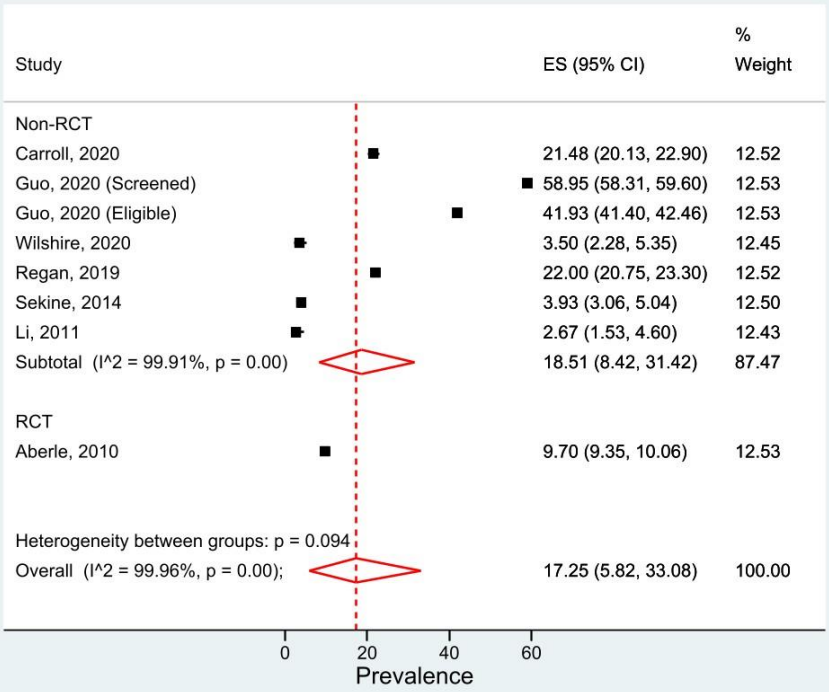
Bronchiectasis



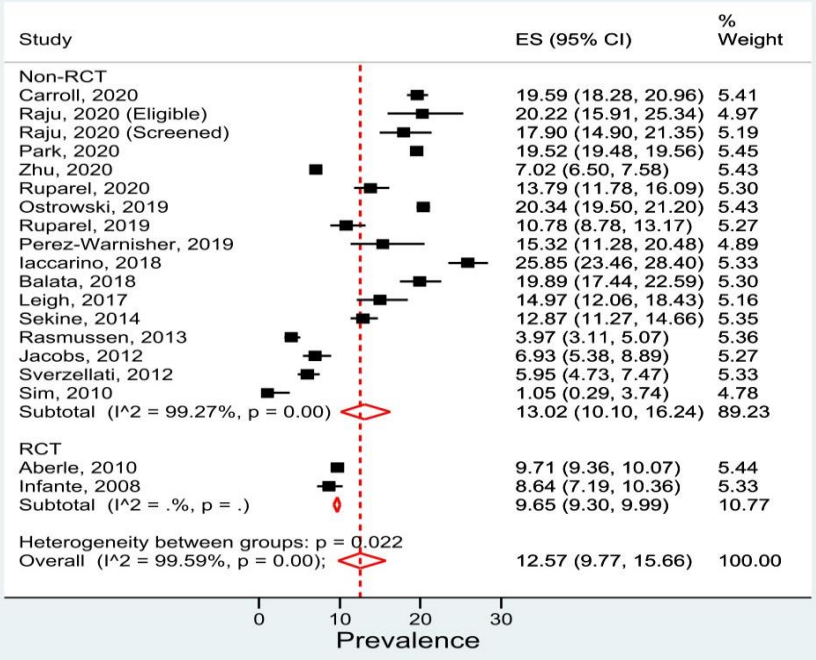
Asthma



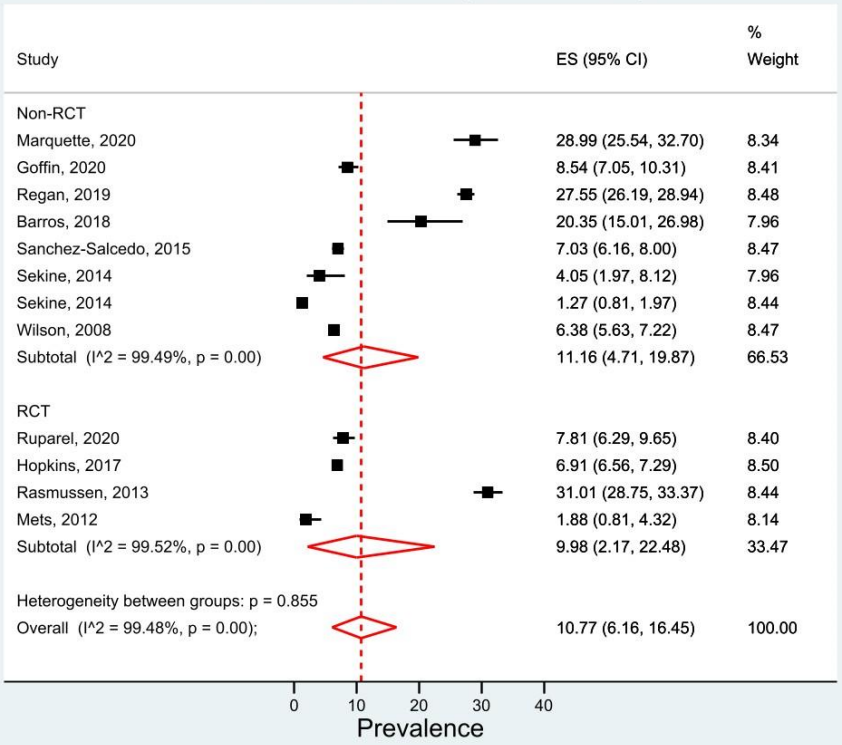
Chronic Bronchitis



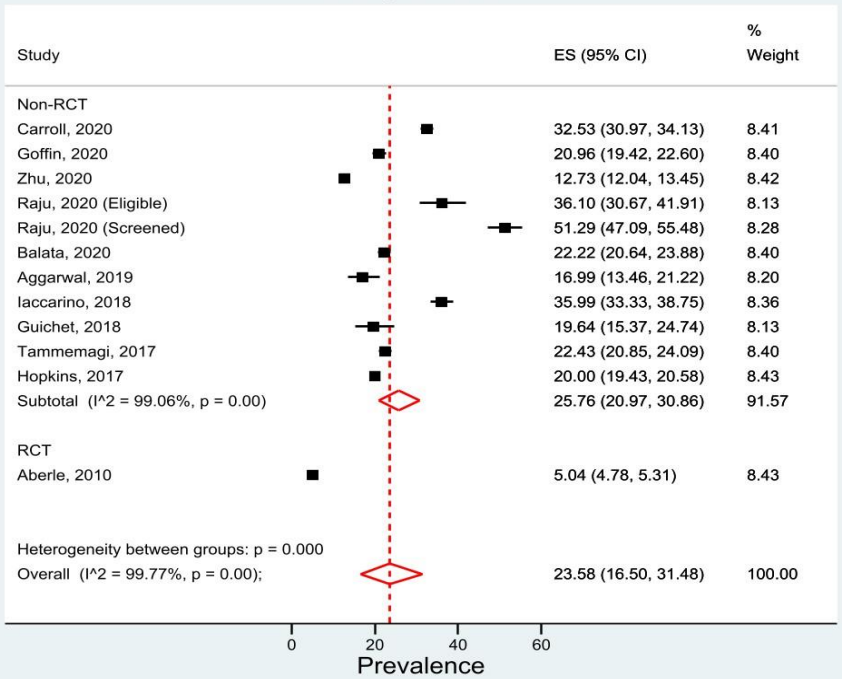
Diabetes



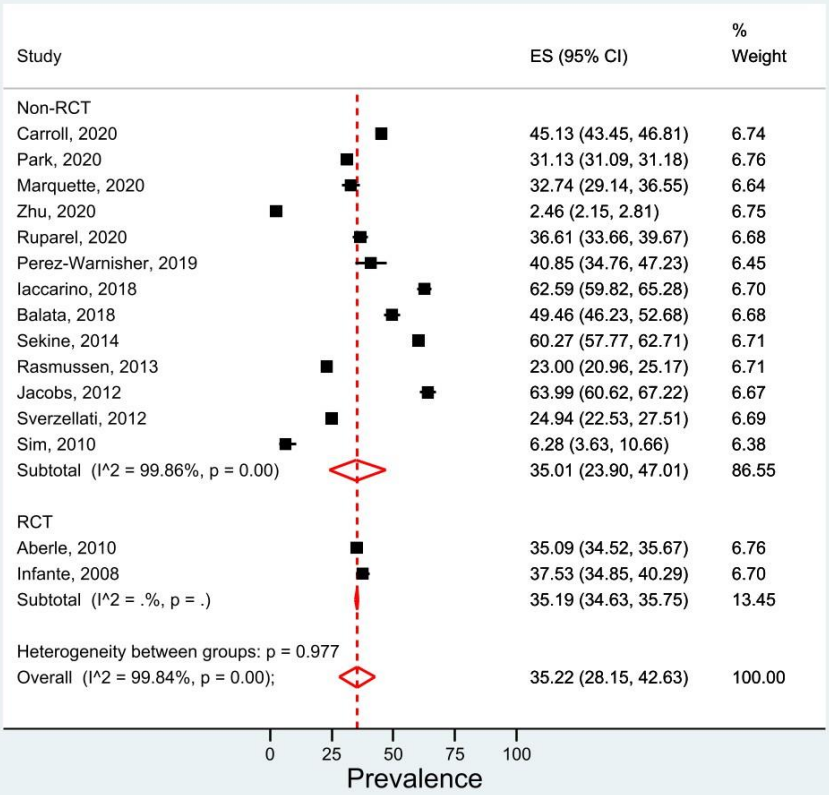
Advanced COPD (GOLD 3&4)



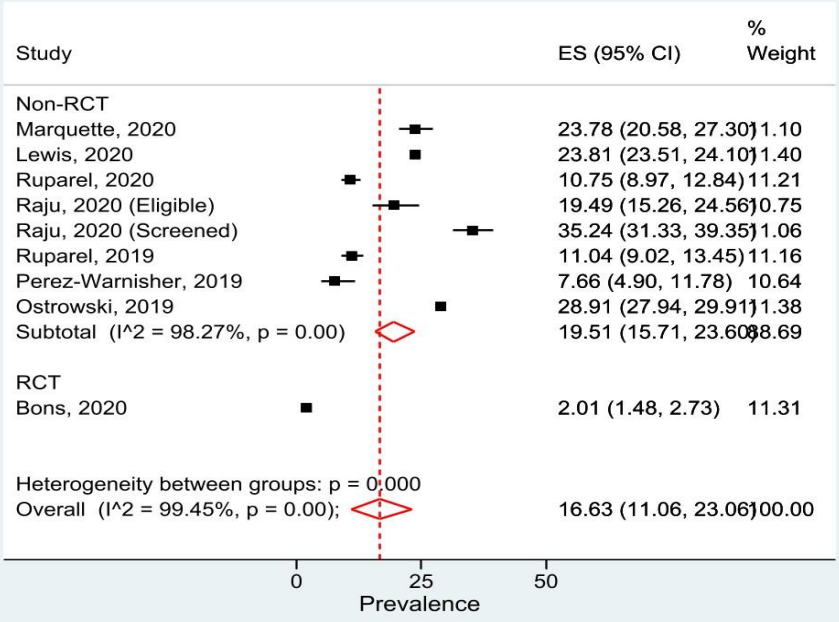
History of COPD



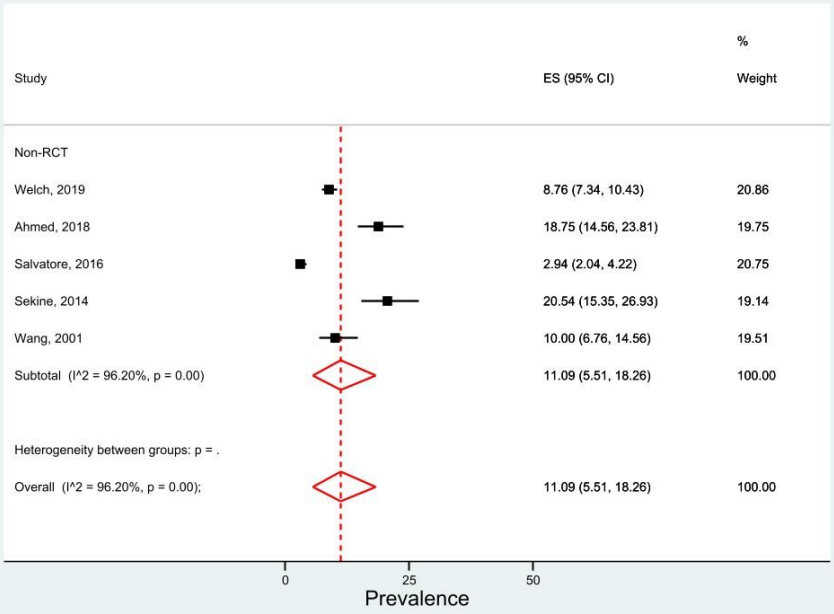
Hypertension



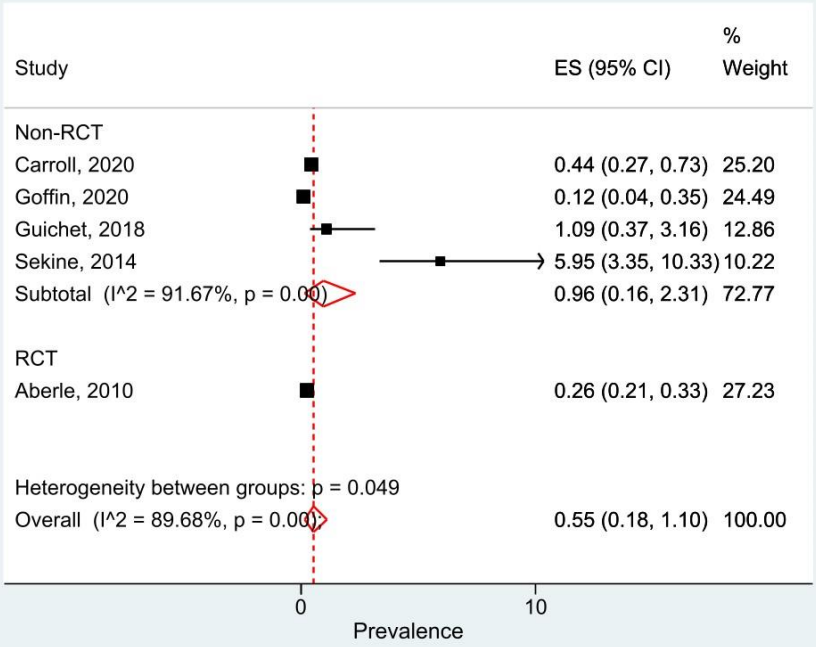
Ischaemic heart disease

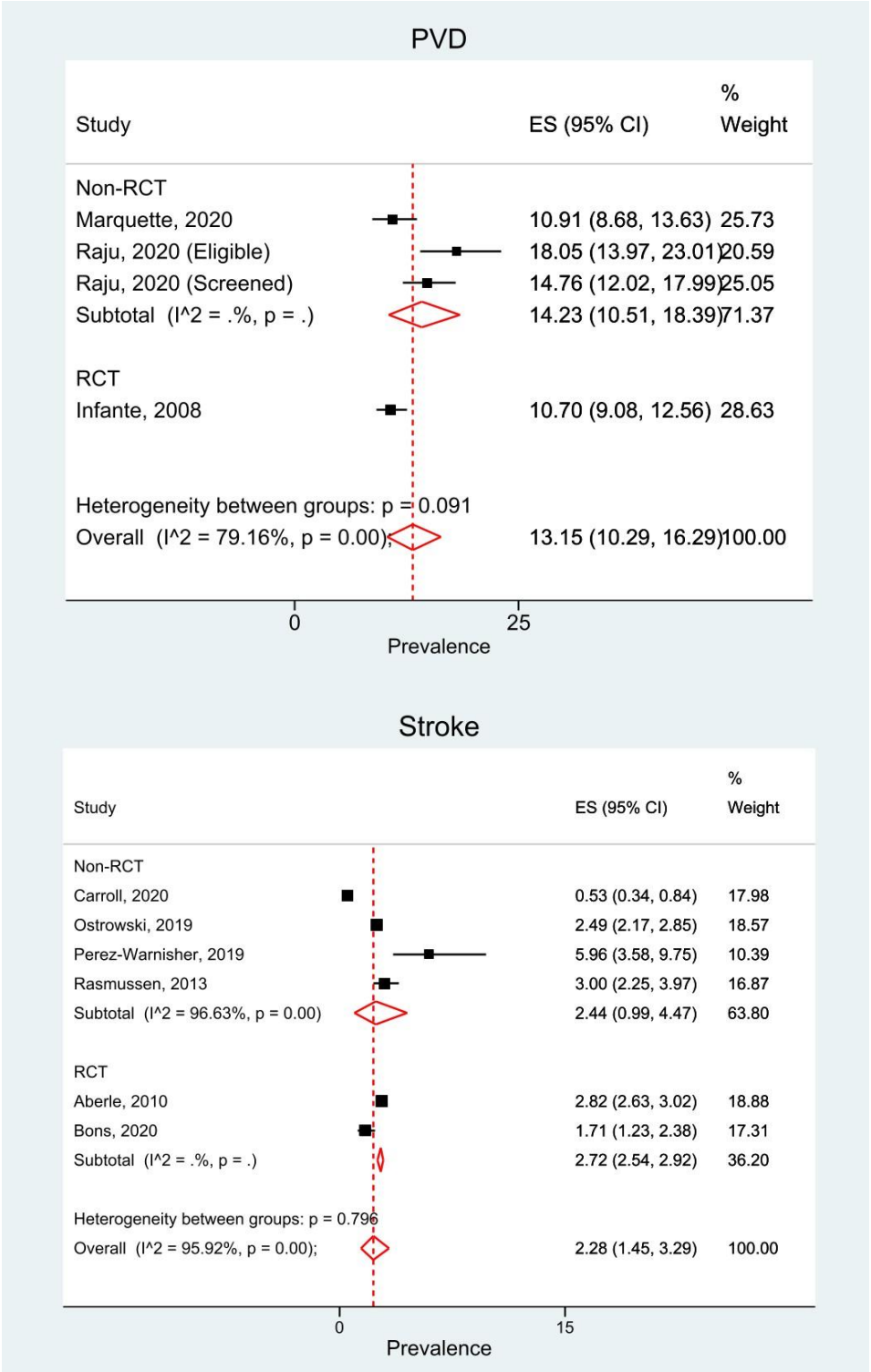


Moderate to severe Emphysema



Pulmonary Fibrosis




PVD
Study
ES (95% CI)
% Weight
Non-RCT
Marquette, 2020
10.91 (8.68, 13.63) 25.73
Raju, 2020 (Eligible)
18.05 (13.97, 23.01) 20.59
Raju, 2020 (Screened)
14.76 (12.02, 17.99) 25.05
Subtotal (I^2 = .%, p = .)
14.23 (10.51, 18.39) 71.37
RCT
Infante, 2008
10.70 (9.08, 12.56) 28.63
Heterogeneity between groups: p = 0.091
Overall (I^2 = 79.16%, p = 0.00);
13.15 (10.29, 16.29) 100.00
0
25
Prevalence
Stroke
Study
ES (95% CI)
% Weight
Non-RCT
Carroll, 2020
0.53 (0.34, 0.84) 17.98
Ostrowski, 2019
2.49 (2.17, 2.85) 18.57
Perez-Warnisher, 2019
5.96 (3.58, 9.75) 10.39
Rasmussen, 2013
3.00 (2.25, 3.97) 16.87
Subtotal (I^2 = 96.63%, p = 0.00)
2.44 (0.99, 4.47) 63.80
RCT
Aberle, 2010
2.82 (2.63, 3.02) 18.88
Bons, 2020
1.71 (1.23, 2.38) 17.31
Subtotal (I^2 = .%, p = .)
2.72 (2.54, 2.92) 36.20
Heterogeneity between groups: p = 0.796
Overall (I^2 = 95.92%, p = 0.00);
2.28 (1.45, 3.29) 100.00
0
15
Prevalence

Appendix A.3: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract page
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	NA
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Figure 2
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 5

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 20
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 4
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Tables 1-3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Tables 1-2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figure 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 20
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Figure 2
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 17-19
	23b	Discuss any limitations of the evidence included in the review.	Page 20
	23c	Discuss any limitations of the review processes used.	Page 20
	23d	Discuss implications of the results for practice, policy, and future research.	Page 20
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	✓
Competing interests	26	Declare any competing interests of review authors.	✓
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplementary files

Appendix A.4: Pooled estimations of the prevalence of individual comorbidities among LCS populations

History of COPD

Author	Source	Setting	status	Comorbidity	Cases	Total	_ES	_seES	_LCI	_UCI
Carroll, 2020	Health records	Non-RCT	Screened	History_of_COPD	1098	3375	0.325333	0.017212	0.309734	0.34133
Goffin, 2020	Self-reported	Non-RCT	Screened	History_of_COPD	527	2514	0.209626	0.019942	0.194164	0.225974
Zhu, 2020	Self-reported	Non-RCT	Screened	History_of_COPD	1097	8618	0.127292	0.010772	0.120421	0.134495
Raju, 2020 (Eligible)	Health records	Non-RCT	Eligibles	History_of_COPD	100	277	0.361011	0.06003	0.306707	0.419117
Raju, 2020 (Screened)	Health records	Non-RCT	Screened	History_of_COPD	278	542	0.512915	0.042934	0.470893	0.554756
Balata, 2020	Self-reported	Non-RCT	Screened	History_of_COPD	561	2525	0.076436	0.019899	0.066704	0.087455
Aggarwal, 2019	Self-reported	Non-RCT	Screened	History_of_COPD	61	359	0.169916	0.052741	0.134611	0.212212
Iaccarino, 2018	Health records	Non-RCT	Screened	History_of_COPD	433	1203	0.359934	0.028826	0.333296	0.387463
Guichet, 2018	Self-reported	Non-RCT	Screened	History_of_COPD	54	275	0.196364	0.060248	0.153733	0.24736
Tammemagi, 2017	Self-reported	Non-RCT	Screened	History_of_COPD	569	2537	0.224281	0.019852	0.208474	0.240921
Hopkins, 2017	Self-reported	Non-RCT	Screened	History_of_COPD	3743	18714	0.200011	0.00731	0.194342	0.205803
Aberle, 2010	Self-reported	RCT	Screened	History_of_COPD	1347	26723	0.050406	0.006117	0.047847	0.053094
					9868	67662				

GOLD 3-4

Author	Source of data	Setting	Country	status	Comorbidity	Cases	Total	_ES	_seES	_LCI	_UCI
Barros, 2018	Measured pre-screening using Spirometry	Non-RCT	South-America	Screened	GOLD 3-4	35	172	0.203488	0.04034	0.255409	0.327009
Goffin, 2020	Measured pre-screening using Spirometry	Non-RCT	North-America	Screened	GOLD 3-4	97	1136	0.085387	0.031838	0.062935	0.096526
Hopkins, 2017	Measured pre-screening using Spirometry	RCT	North-America	Screened	GOLD 3-4	1294	18714	0.069146	0.029663	0.070501	0.103068
Marquette, 2020	Not reported	Non-RCT	Europe	Screened	GOLD 3-4	178	614	0.289902	0.015703	0.261929	0.28942
Mets, 2012	Measured at baseline screening by Spirometry	RCT	Europe	Screened	GOLD 3-4	5	266	0.018797	0.076139	0.15011	0.269823
Rasmussen, 2013	Measured pre-screening using Spirometry	RCT	Europe	Screened	GOLD 3-4	476	1535	0.310098	0.00731	0.065599	0.07287
Regan, 2019	Measured pre-screening using Spirometry	Non-RCT	North-America	Screened	GOLD 3-4	1117	4055	0.275462	0.01829	0.061636	0.079982
Ruparel, 2020	Measured pre-screening using Spirometry	RCT	Europe	Screened	GOLD 3-4	77	986	0.078093	0.075919	0.019736	0.081154
Sanchez-Salcedo, 2015	Measured pre-screening using Spirometry	Non-RCT	Europe	Screened	GOLD 3-4	210	2989	0.070258	0.025816	0.008124	0.019699
Sekine, 2014	Measured post-screening using Spirometry in a LC screened cohort	Non-RCT	Asia	Screened	GOLD 3-4	7	173	0.040462	0.02552	0.287457	0.333686
Sekine, 2014	Measured post-screening using Spirometry in a LC screened cohort	Non-RCT	Asia	Screened	GOLD 3-4	19	1500	0.012667	0.061256	0.008055	0.04324
Wilson, 2008	Measured at baseline screening by Spirometry	Non-RCT	North-America	Screened	GOLD 3-4	232	3638	0.063771	0.016578	0.056282	0.072181
						3747	35778				

Chronic Bronchitis

Author	Setting	status	Comorbidity	Cases	Total	_ES	_seES	_LCI	_UCI
Carroll, 2020	Non-RCT	Screened	Chronic bronchitis	725	3375	0.214815	0.017212	0.201287	0.228991
Guo, 2020 (Screened)	Non-RCT	Screened	Chronic bronchitis	13123	22260	0.589533	0.006702	0.583056	0.595979
Guo, 2020 (Eligible)	Non-RCT	Eligible	Chronic bronchitis	13906	33168	0.41926	0.005491	0.413959	0.424579
Wilshire, 2020	Non-RCT	Referrals	Chronic bronchitis	20	571	0.035026	0.04183	0.022787	0.05348
Regan, 2019	Non-RCT	Screened	Chronic bronchitis	892	4055	0.219975	0.015703	0.207494	0.232987
Sekine, 2014	Non-RCT	Screened	Chronic bronchitis	59	1500	0.039333	0.025816	0.030615	0.050405
Li, 2011	Non-RCT	screened	Chronic bronchitis	12	450	0.026667	0.047114	0.015319	0.046027
Aberle, 2010	RCT	Screened	Chronic bronchitis	2592	26723	0.096995	0.006117	0.093505	0.100602
				31329	92102				

Bronchiectasis

Author	Setting	status	Comorbidity	Cases	Total	_ES	_seES	_LCI	_UCI
Carroll, 2020	Non-RCT	Screened	Bronchiectasis	4	3375	0.001185	0.017212	0.000461	0.003044
Guo, 2020 (Screened)	Non-RCT	Screened	History of asthma bronchiectasis	4257	22260	0.19124	0.006702	0.186127	0.196459
Guo, 2020 (Eligible)	Non-RCT	Eligible	History of asthma bronchiectasis	8097	33168	0.244121	0.005491	0.239528	0.248773
Raju, 2020 (Eligible)	Non-RCT	Eligible	Bronchiectasis (eligible controls)	3	277	0.01083	0.06003	0.00369	0.031353
Raju, 2020 (Screened)	Non-RCT	Screened	Bronchiectasis (Participants)	4	542	0.00738	0.042934	0.002874	0.01882
Sekine, 2014	Non-RCT	Screened	Bronchiectasis	2	185	0.010811	0.073422	0.00297	0.038554
Aberle, 2010	RCT	Screened	Bronchiectasis	854	26723	0.031958	0.006117	0.029915	0.034135
				13221	86530				

Asthma

Author	Setting	status	Comorbidity	Cases	Total	_ES	_seES	_
Carroll, 2020	Non-RCT	Screened	Asthma	788	3375	0.2334815	0.017212	0
Goffin, 2020	Non-RCT	Screened	Asthma	244	2514	0.0970565	0.019942	0
Raju, 2020 (Eligible)	Non-RCT	Eligible	Asthma Non participants (eligible controls):	37	277	0.133574	0.06003	0
Raju, 2020 (Screened)	Non-RCT	Screened	Asthma (participants)	93	542	0.1715867	0.042934	0
Iaccarino, 2018	Non-RCT	Screened	Asthma	224	1203	0.1862012	0.028826	0
Sekine, 2014	Non-RCT	Screened	Asthma	56	1500	0.0373333	0.025816	0
Aberle, 2010	RCT	Screened	Asthma first diagnosed as an adult	2601	26723	0.0973319	0.006117	0
				4043	36134			

Pulmonary Fibrosis

Author	Setting	status	Comorbidity	Cases	Total	_ES	_seES	_LCI	_UCI	_WT
Carroll, 2020	Non-RCT	Screened	Fibrosis	15	3375	0.0044444	0.017212	0.002695	0.00732	25.20349
Goffin, 2020	Non-RCT	Screened	Pulmonary Fibrosis	3	2514	0.0011933	0.019942	0.000406	0.003503	24.48813
Guichet, 2018	Non-RCT	Screened	Pulmonary fibrosis	3	275	0.0109091	0.060248	0.003717	0.031577	12.85918
Sekine, 2014	Non-RCT	Screened	Pulmonary fibrosis	11	185	0.0594595	0.073422	0.033522	0.10332	10.21583
Aberle, 2010	RCT	Screened	Fibrosis of the lung	70	26723	0.0026195	0.006117	0.002074	0.003308	27.23337
				102	33072					

IHD

Author	Setting	status	Comorbidity	Cases	Total	_ES	_seES	_LCI	_UCI
Marquette, 2020	Non-RCT	Screened	Coronary heart disease	146	614	0.237785	0.04034	0.205807	0.273024
Bons, 2020	RCT	Screened	History of ischemic heart disease	40	1987	0.020131	0.022431	0.014818	0.027295
Lewis, 2020	Non-RCT	Screened	Coronary artery disease	19240	80819	0.238063	0.003518	0.235139	0.241012
Ruparel, 2020	Non-RCT		Coronary heart disease	106	986	0.107505	0.031838	0.089672	0.128385
Raju, 2020 (Eligible)	Non-RCT	Screened	CAD non participants	54	277	0.194946	0.060038	0.152598	0.245639
Raju, 2020 (Screened)	Non-RCT	Screened	CAD participants	191	542	0.352399	0.042934	0.313348	0.393527
Ruparel, 2019	Non-RCT	Screened	History of coronary heart disease	85	770	0.110396	0.036026	0.090168	0.134488
Perez-Warnisher, 2019	Non-RCT	Screened	Ischemic heart disease	18	235	0.076596	0.065164	0.048997	0.117814
Ostrowski, 2019	Non-RCT	Screened	Chronic ischaemic heart disease	2356	8149	0.289115	0.011077	0.279373	0.299056
				22236	94379				

Stroke

Author	Setting	status	Comorbidity	Cases	Total	_ES	_seES	_LCI	_UCI
Carroll, 2020	Non-RCT	Screened	Stroke	18	3375	0.005333	0.017212	0.003376	0.008415
Aberle, 2010	RCT	Screened	Stroke	753	26723	0.028178	0.006117	0.026261	0.030231
Bons, 2020	RCT	Screened	History of stroke	34	1987	0.017111	0.022431	0.012271	0.023815
Ostrowski, 2019	Non-RCT	Screened	Ischaemic stroke	203	8149	0.024911	0.011077	0.021744	0.028525
Perez-Warnisher, 2019	Non-RCT	Screened	Stroke	14	235	0.059575	0.065164	0.035815	0.097501
Rasmussen, 2013	Non-RCT	Screened	Stroke	46	1535	0.029967	0.02552	0.022542	0.03974

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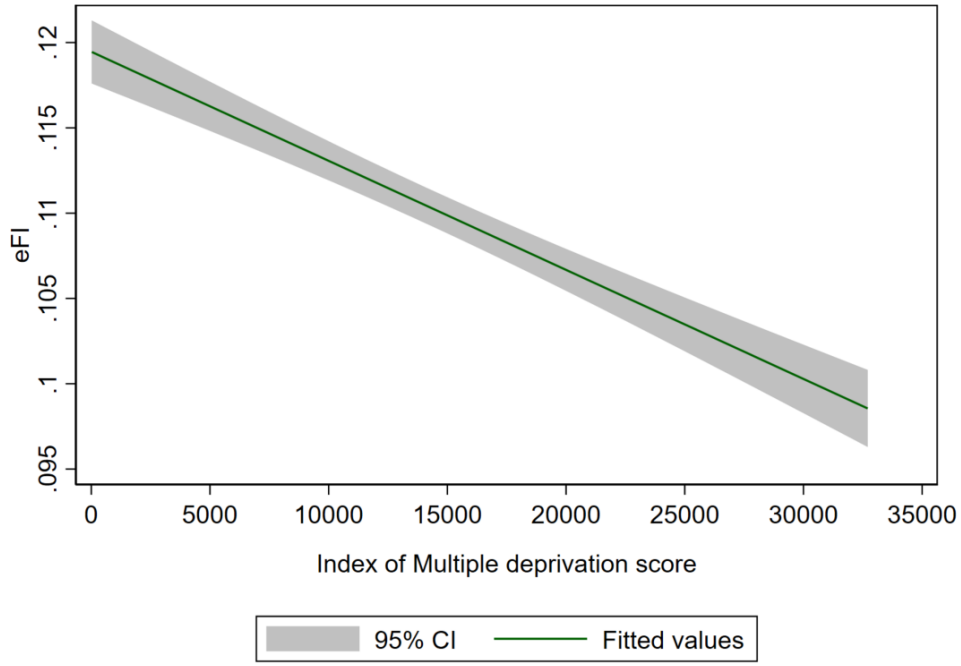
Appendix B: Study Two supplementary data

Appendix B.1: Table S1: Prevalence of 36 individual deficits in the YLST frailty cohort (n=27,761)

Deficit	n (%)
Activity limitation	52 (0.2)
Anaemia and haematinic deficiency	6988 (25.2)
Arthritis	9519 (34.3)
Atrial fibrillation	1729 (6.2)
Cerebrovascular disease	1457 (5.2)
Chronic kidney disease	4462 (16.1)
Diabetes	4160 (15.0)
Dizziness	4206 (15.2)
Dyspnoea	4171 (15.0)
Falls	1559 (5.6)
Foot problems	818 (2.9)
Fragility fracture	1955 (7.0)
Hearing impairment	3655 (13.2)
Heart failure	857 (3.1)
Heart valve disease	183 (0.7)
Housebound	1747 (6.3)
Hypertension	10473 (37.7)
Hypotension / syncope	1989 (7.2)
Ischaemic heart disease	2755 (9.9)
Memory and cognitive problems	787 (2.8)
Mobility and transfer problems	711 (2.6)
Osteoporosis	1739 (6.3)
Parkinsonism and tremor	336 (1.2)
Peptic ulcer	1218 (4.4)
Peripheral vascular disease	1174 (4.2)
Polypharmacy*	11914 (42.9)
Requirement for care	406 (1.5)
Respiratory disease	6707 (24.2)
Skin ulcer	821 (3.0)
Sleep disturbance	2100 (7.6)
Social vulnerability	1936 (70)
Thyroid disease	3142 (11.3)
Urinary incontinence	1518 (5.5)
Urinary system disease	5516 (19.9)
Visual impairment	5862 (21.1)
Weight loss and anorexia	1691 (6.1)

*Imputed based on eFI development cohort polypharmacy prevalence

Appendix B.2: Figure S1: A linear fit prediction plot of the association between eFI and IMD rank. The higher the IMD rank, the less deprived the neighbourhood.



Appendix B.3: polypharmacy sensitivity analysis

Role of frailty severity on the response to the risk assessment invitation considering different prevalences of polypharmacy

	Univariate models				Multivariable models			
tt response	Odds ratio	P> |z|	[95% conf.	interval]	Odds ratio	P> |z|	[95% conf.	interval]
eFIv1 Category 26% polypharmacy								
Mild	1.515167	0	1.431811	1.603377	1.328897	0	1.250444	1.412271
Moderate	1.452004	0	1.326354	1.589557	1.249489	0	1.133868	1.376901
Severe	1.507622	0	1.223623	1.857537	1.330916	0.01	1.069521	1.656196
eFIv1 Category 43% polypharmacy								
Mild	1.52926	0	1.445113	1.618308	1.33917	0	1.260163	1.423131
Moderate	1.469879	0	1.347489	1.603386	1.275311	0	1.16143	1.400359
Severe	1.543765	0	1.276575	1.866879	1.317607	0.006	1.080897	1.606154
eFIv1 Category 57% polypharmacy								
Mild	1.533702	0	1.451529	1.620526	1.361822	0	1.283683	1.444717
Moderate	1.474238	0	1.353638	1.605584	1.261783	0	1.151015	1.38321
Severe	1.514638	0	1.25991	1.820867	1.303347	0.007	1.073927	1.581778
eFIv1 Category 100% polypharmacy								
Mild	1.558435	0	1.478633	1.642544	1.367653	0	1.292425	1.44726
Moderate	1.534017	0	1.409045	1.670072	1.305451	0	1.191014	1.430885
Severe	1.576213	0	1.312369	1.8931	1.353181	0.002	1.115894	1.640925

Role of frailty severity on the LDCT uptake invitation considering different prevalences of polypharmacy

LHC Uptake	Odds ratio	P>z	[95% conf.	interval]	Odds ratio	P>z	[95% conf.	interval]
eFIv1 Category 26% polypharmacy								
Mild	0.850674	0.086	0.70731	1.023095	0.9143286	0.358	0.755331	1.106796
Moderate	0.680327	0.002	0.533336	0.86783	0.7653116	0.038	0.59443	0.985316
Severe	0.575029	0.023	0.356404	0.927763	0.7147078	0.18	0.437524	1.167495
eFIv1 Category 43% polypharmacy								
Mild	0.926779	0.428	0.768012	1.118367	0.9216959	0.408	0.759711	1.118219
Moderate	0.658304	0	0.520765	0.832168	0.7528636	0.024	0.588721	0.962772
Severe	0.599317	0.023	0.385331	0.932136	0.6675497	0.072	0.429512	1.03751
eFIv1 Category 57% polypharmacy								
Mild	0.870662	0.145	0.722661	1.048973	0.9312355	0.467	0.768451	1.128504
Moderate	0.640442	0	0.507146	0.808773	0.7186351	0.008	0.563404	0.916635
Severe	0.565996	0.009	0.368491	0.869359	0.6880656	0.097	0.442567	1.069745
eFIv1 Category 100% polypharmacy								
Mild	0.931474	0.452	0.774033	1.120939	1.015501	0.875	0.838205	1.230298
Moderate	0.674128	0.001	0.532557	0.853334	0.7657915	0.034	0.598399	0.98001
Severe	0.606715	0.023	0.394851	0.932259	0.7566661	0.217	0.485914	1.178281

Appendix C: Study Three supplementary data

Appendix C.1: Table S1. Baseline factors by risk strategy among those aged 55-80 years

	$USPSTF_{2021}$	PLCO ≥1.62%*	LLP_{V2} ≥3.75%*	$PLCO_{M2012}$ ≥1.51%	LLP_{V2} 2.5%
eligible subjects	n=3922	n= 3918	n= 3932	n= 4108	n= 5450
Age, years	65.5 ±6.5	69.2 ±6.7	70.8 ±6.0	69.1 ±6.7	70.2 ±6.3
Age group					
<60	1,019 (26.0%)	434 (11.1%)	226 (5.7%)	480 (11.7%)	390 (7.2%)
60-64	919 (23.4%)	663 (16.9%)	481 (12.2%)	701 (17.1%)	825 (15.1%)
65-69	918 (23.4%)	940 (24.0%)	914 (23.2%)	979 (23.8%)	1,257 (23.1%)
70-74	665 (17.0%)	966 (24.7%)	1,176 (29.9%)	1,003 (24.4%)	1,520 (27.9%)
≥ 75	401 (10.2%)	915 (23.4%)	1,135 (28.9%)	945 (23.0%)	1,458 (26.8%)
Gender					
Female	2,029 (51.7%)	1,941 (49.5%)	1,657 (42.1%)	2,035 (49.5%)	2,224 (40.8%)
Male	1,893 (48.3%)	1,977 (50.5%)	2,275 (57.9%)	2,073 (50.5%)	3,226 (59.2%)
IMD rank: median (IQR)	10,149 (3,267-21,210)	11,833 (3,531-21,322)	13,900 (4,092-22,110)	11,833 (3,551-21,322)	14,332 (4,437-22,188)
IMD quintile					
1	1,333 (34.0%)	1,264 (32.3%)	1,160 (29.5%)	1,320 (32.1%)	1,547 (28.4%)
2	848 (21.6%)	836 (21.3%)	784 (19.9%)	867 (21.1%)	1,099 (20.2%)
3	618 (15.8%)	623 (15.9%)	646 (16.4%)	658 (16.0%)	903 (16.6%)
4	749 (19.1%)	808 (20.6%)	909 (23.1%)	855 (20.8%)	1,272 (23.3%)
5	372 (9.5%)	386 (9.9%)	432 (11.0%)	407 (9.9%)	627 (11.5%)
missing	2	1	1	1	1
Ethnicity (self-reported)					
White	3,745 (95.5%)	3,806 (97.1%)	3,797 (96.6%)	3,986 (97.0%)	5,246 (96.3%)
Black	28 (0.7%)	26 (0.7%)	25 (0.6%)	28 (0.7%)	41 (0.8%)
Hispanic	4 (0.1%)	-	1 (0.0%)	-	3 (0.1%)
Asian	68 (1.7%)	33 (0.8%)	60 (1.5%)	35 (0.9%)	80 (1.5%)
Other	55 (1.4%)	35 (0.9%)	29 (0.7%)	39 (0.9%)	48 (0.9%)
Prefer not to say	22 (0.6%)	18 (0.5%)	20 (0.5%)	20 (0.5%)	32 (0.6%)

Smoking status (self-reported)					
Previously smoked	2,301 (58.7%)	2,430 (62.0%)	2,636 (67.0%)	2,584 (62.9%)	3,859 (70.8%)
Currently smoking	1,621 (41.3%)	1,488 (38.0%)	1,296 (33.0%)	1,524 (37.1%)	1,591 (29.2%)
Pack-years	36.8 (28.5-46.2)	38 (29.5-48)	33 (20-45)	37.8 (29.1-48)	30 (17-43)
Quit time (previously smoked)	7 (4-11)	11 (5-20)	13 (6-27)	11 (5-20)	18 (7-31)
eFI score: mean ±SD	0.12 ±0.9	0.14 ±0.1	0.15 ±0.09	0.14 ±0.09	0.14 ±0.9
eFI category					
Fit	2,320 (59.2%)	1,968 (50.2%)	1,836 (46.7%)	2,082 (50.7%)	2,722 (49.9%)
Mild	1,112 (28.4%)	1,278 (32.6%)	1,356 (34.5%)	1,334 (32.5%)	1,802 (33.1%)
Moderate	409 (10.4%)	553 (14.1%)	596 (15.2%)	569 (13.9%)	757 (13.9%)
Severe	**81 (2.1%)**	**119 (3.0%)**	**144 (3.7%)**	**123 (3.0%)**	**169 (3.1%)**
Comorbidity count					
0	1,454 (37.1%)	1,109 (28.3%)	956 (24.3%)	1,191 (29.0%)	1,531 (28.1%)
1	1,157 (29.5%)	1,211 (30.9%)	1,202 (30.6%)	1,256 (30.6%)	1,638 (30.1%)
2	638 (16.3%)	718 (18.3%)	786 (20.0%)	749 (18.2%)	1,045 (19.2%)
3	355 (9.1%)	452 (11.5%)	492 (12.5%)	471 (11.5%)	634 (11.6%)
≥4	**318 (8.1%)**	**428 (10.9%)**	**496 (12.6%)**	**441 (10.7%)**	**602 (11.0%)**

* $USPSTF_{2021}$ equivalent population

**Current NHS LHC recommendation

Appendix C.2: Table S2. Comparison of individuals selected for lung cancer screening by USPSTF2021 versus PLCOm2012 and LLPv2 different risk thresholds in individuals aged 55-80 years

	$USPSTF_{2021}$	**PLCO ≥1.62%***	**LLP_{V2} ≥3.75%***	**$PLCO_{M2012}$ ≥1.51%**	**LLP_{V2} ≥2.5%**
eFI category					
Moderate/severe selection rate	490/3922 (12.5% [11.5-13.3])	672/3918 (17.2% [16.0-18.3])	740/3932 (18.8% [17.6-20.0])	692/4108 (16.8% [15.7-18.0])	926/5450 (17.0% [16.0-18.0])
p-value**	-	**<0.001** (0.173)‡	**<0.001**	**<0.001** (0.893)$	**<0.001**
Comorbidity count					

≥2 selection rate	1602/3922 (40.8% [39.3-42.4])	1950/3918 (49.8% [48.2-51.4])	2096/3932 (53.3% [51.7-54.9])	2026/4108 (49.3% [47.8.5-50.8])	2728/5450 (50.1% [48.7-51.4])
p-value**	-	**<0.001 (0.026)**‡	**<0.001**	**<0.001** (0.703)$	**<0.001**

Data presented as n/N (% [95% CI]), PLCOm2012: Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial risk model, LLP_{v2}: the Liverpool Lung Project risk model (version 2), $USPSTF_{2021}$: the US Preventive Services Task Force 2021 lung cancer screening criteria. * =$USPSTF_{2021}$ equivalent population. ** =p-value for the difference in selection rates between $USPSTF_{2021}$ as a reference group and PLCOm2012 or LLPv2 thresholds. ‡=p-value between parentheses is for the difference in selection rates between $PLCO_{m2012}$ ≥1.62% and LLP_{v2} ≥3.75%. $=p-value between parentheses is for the difference in selection rates between $PLCOm_{2012}$ ≥1.51% and LLPv2 ≥2.5%.

Appendix C.3: Table S3. Distribution of 3-year survival from all causes at each frailty/comorbidity level by risk strategy among those aged 55-80 years

	$USPSTF_{2021}$			**$PLCO_{m2012}$ >=1.62%***			**LLP_{v2} >=3.75%***			**$PLCO_{m2012}$ >=1.51%**			**LLP_{V2} >=2.5%**		
	N	**3-Years survival rate (%)**	**95% CI**	**N**	**3-Years survival rate (%)**	**95% CI**	**N**	**3-Years survival rate (%)**	**95% CI**	**N**	**3-Years survival rate (%)**	**95% CI**	**N**	**3-Years survival rate (%)**	**95% CI**
All eligible subjects	**3922**	**95.3**	**94.6 - 95.9**	**3918**	**93.9**	**93.1 - 94.6**	**3932**	**93.3**	**92.4 - 94.0**	**4108**	**93.9**	**93.2 - 94.6**	**5450**	**94.3**	**93.6 - 94.9**
Frailty category															
Fit	2320	97.9	97.3 - 98.4	1,968	97.1	96.3 - 97.8	1836	97.2	96.4 - 97.9	2082	97.3	96.5 - 97.9	2722	97.6	96.9 - 98.1
Mild	1112	93.4	91.8 - 94.8	1,278	92.9	91.3 - 94.2	1356	92.0	90.5 - 93.4	1334	92.9	91.4 - 94.1	1802	93.2	91.9 - 94.3
Moderate	409	88.8	85.3 - 91.5	553	87.9	84.9 - 90.3	596	87.8	84.8 - 90.1	569	87.7	84.7 - 90.1	757	88.5	86.0 - 90.6
Severe	81	77.8	67.1 - 85.4	119	79.0	70.5 - 85.3	144	77.1	69.3 - 83.1	123	78.1	69.7 - 84.4	169	79.3	72.4 - 84.7
Comorbidity count															
0	1,454	98.4	97.6 - 98.9	1,109	97.7	96.6 - 98.4	956	98.1	97.0 - 98.8	1191	97.7	96.7 - 98.4	1531	98.0	97.2 - 98.63
1	1,157	96.8	95.6 - 97.7	1,211	96.4	95.2 - 97.3	1,202	95.8	94.6 - 96.8	1256	96.5	95.3 - 97.4	1638	96.6	95.6 - 97.36
2	638	93.1	90.8 - 94.8	718	92.6	90.5 - 94.3	786	92.1	90.0 - 93.8	749	92.8	90.7 - 94.4	1045	92.9	91.2 - 94.32
3	355	88.7	85.0 - 91.6	452	87.4	84.0 - 90.1	492	87.6	84.4 - 90.2	471	87.3	83.9 - 90.0	634	89.0	86.3 - 91.16
≥4	318	87.4	83.3 - 90.6	428	86.0	82.3 - 88.9	496	85.1	81.6 - 87.9	441	85.5	81.8 - 88.5	602	86.5	83.6 - 89.0

* $USPSTF_{2021}$ equivalent population

Appendix C.4: Table S4. Distribution of 12 Individual comorbidities by risk strategy and age

	55-74 years				
	$USPSTF_{2021}$	**PLCO ≥1.32%***	**LLP_{V2} ≥2.96%***	**$PLCO_{m2012}$ ≥1.51%**	**LLP_{V2} 2.5%**
No of eligible subjects	n=3521	n= 3515	n= 3518	n= 3163	n= 3992
Individual Comorbidity					
Cancer	396 (11.2%)	474 (13.5%)	606 (17.2%)	448 (14.2%)	665 (16.7%)
Stroke	189 (5.4%)	215 (6.1%)	221 (6.3%)	202 (6.4%)	246 (6.2%)
Heart failure	124 (3.5%)	138 (3.9%)	161 (4.6%)	124 (3.9%)	187 (4.7%)
PVD	317 (9.0%)	349 (9.9%)	352 (10.0%)	324 (10.2%)	377 (9.4%)
Inflammatory arthritis	530 (15.1%)	598 (17.0%)	664 (18.9%)	529 (16.7%)	759 (19.0%)
Liver problems	55 (1.6%)	53 (1.5%)	46 (1.3%)	44 (1.4%)	54 (1.4%)
Mono/hemiparesis	43 (1.2%)	44 (1.3%)	42 (1.2%)	42 (1.3%)	46 (1.2%)
PUD	17 (0.5%)	17 (0.5%)	24 (0.7%)	17 (0.5%)	32 (0.8%)
Diabetes	542 (15.4%)	605 (17.2%)	622 (17.7%)	556 (17.6%)	697 (17.5%)
IHD	470 (13.3%)	527 (15.0%)	579 (16.5%)	480 (15.2%)	642 (16.1%)
COPD	840 (23.9%)	959 (27.3%)	990 (28.1%)	917 (29.0%)	1,028 (25.8%)
CKD	616 (17.5%)	682 (19.4%)	737 (20.9%)	631 (19.9%)	817 (20.5%)
	55-80 years				
	$USPSTF_{2021}$	**PLCO ≥1.62%***	**LLP_{V2} ≥3.75%***	**$PLCO_{m2012}$ ≥1.51%**	**LLP_{V2} 2.5%**
No of eligible subjects	n=3922	n= 3918	n= 3932	n= 4108	n= 5450
Individual Comorbidity					
Cancer	664 (16.2%)	1,030 (18.9%)	469 (12.0%)	642 (16.4%)	816 (20.8%)
Stroke	302 (7.4%)	387 (7.1%)	229 (5.8%)	293 (7.5%)	296 (7.5%)
Heart failure	193 (4.7%)	289 (5.3%)	160 (4.1%)	189 (4.8%)	224 (5.7%)
PVD	452 (11.0%)	552 (10.1%)	386 (9.8%)	439 (11.2%)	462 (11.7%)
Inflammatory arthritis	757 (18.4%)	1,140 (20.9%)	610 (15.6%)	724 (18.5%)	827 (21.0%)
Liver problems	55 (1.3%)	73 (1.3%)	57 (1.5%)	52 (1.3%)	53 (1.3%)
Mono/hemiparesis	50 (1.2%)	62 (1.1%)	47 (1.2%)	47 (1.2%)	47 (1.2%)
PUD	23 (0.6%)	43 (0.8%)	19 (0.5%)	23 (0.6%)	30 (0.8%)
Diabetes	777 (18.9%)	1,038 (19.0%)	640 (16.3%)	735 (18.8%)	772 (19.6%)
IHD	722 (17.6%)	1,025 (18.8%)	571 (14.6%)	695 (17.7%)	777 (19.8%)
COPD	1,207 (29.4%)	1,389 (25.5%)	986 (25.1%)	1,181 (30.1%)	1,188 (30.2%)
CKD	985 (24.0%)	1,352 (24.8%)	768 (19.6%)	945 (24.1%)	1,035 (26.3%)

Appendix C.5: Figure S1

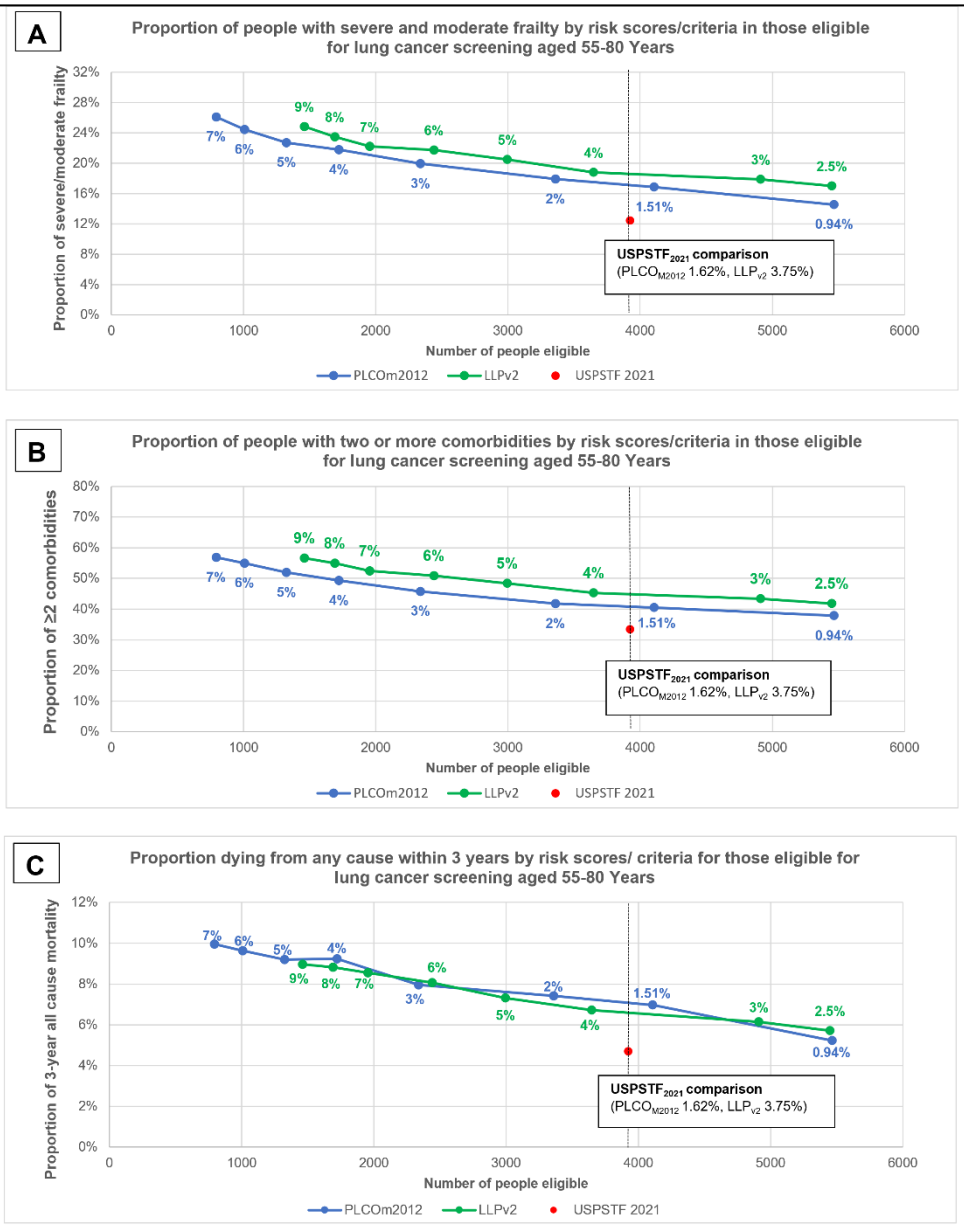


Figure S1. The proportion (%) of **A**) severe/moderate frailty, **B**) ≥2 comorbidities, and **C**) dying from any cause within 3 years in those eligible for lung cancer screening by different risk scores ($PLCO_{m2012}$ and LLP_{v2}) vs risk criteria ($USPSTF_{2021}$) in individuals aged 55-80 years. Dotted line to compare % between the three selection strategies when selecting the same number.