Modelling cognitive decline: the impact of social isolation and loneliness on the cognitive trajectories of Alzheimer’s disease and related diseases patients

James A. C. Myers

Supervised by Dr Nemanja Vaci & Prof Tom Stafford

Submitted in partial fulfilment of the requirements for a Doctor of Philosophy from the School of Psychology at the University of Sheffield

June 2025

Acknowledgements

I would like to acknowledge my supervisors, Dr Nemanja Vaci and Prof Tom Stafford, for their support of this PhD. Your guidance and feedback, throughout, has been invaluable.

I would like to acknowledge the School of Psychology for funding this PhD position and giving me this opportunity.

I would like to acknowledge the academic support staff for your unwavering help whenever needed.

I would also like to acknowledge my PhD peers, past and present. I have shared a lot of good times with a lot of good people over these nearly-four years. Those that have already finished your PhD journeys, I wish you all the best in your future endeavours. Those that are still going, I wish you good luck!

I would also like to acknowledge my friends from outside of academia. Thanks for keeping me in touch with the ‘real world’.

I would like to acknowledge my parents. You have given me great support throughout my academic journey, as you have throughout my whole life. I love you both.

Last (but not least), I would like to acknowledge my partner, Leah. Thanks for sticking by me and supporting me through this. I’m amazed we’ve managed to still enjoy so many great times, despite how much time I’ve had to dedicate to this project. I hope we continue to enjoy many more. I love you lots.

Contents

List of Abbreviations

Abbreviation	Full form
χ^2	Chi-squared
Aβ	Amyloid Beta
ACE	Addenbrooke’s Cognitive Assessment
ACH	Amyloid Cascade Hypothesis
AD	Alzheimer’s Disease
ADAS-(J)Cog	Alzheimer’s Disease Assessment Scale - Cognitive Subscale (Japanese version)
AIC	Akaike Information Criterion
ADRD	Alzheimer’s Disease and Related Diseases
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
APOE	Apolipoprotein
APP	Amyloid Precursor Protein
BBC	British Broadcasting Corporation
BIC	Bayesian Information Criterion
BM	Brain Maintenance
BR	Brain Reserve
(r)CBF	(regional) Cerebral Blood Flow
CDR(-Sb)	Clinical Dementia Rating (Sum of boxes)
CERAD	Consortium to Establish a Registry for Alzheimer’s Disease
CI	Confidence Interval
CR	Cognitive Reserve
COVID-19	Coronavirus Disease 2019
df	Degrees of freedom
DLB	Dementia with Lewy Bodies
EDF	Effective Degrees of Freedom
EHR(s)	Electronic Health Record(s)
FAST	Functional Assessment Staging Tool
FTD	Frontotemporal Dementia
GAMM(s)	Generalised Additive Multilevel Model(s)
(r)GMV	(regional) Grey Matter Volume
HIV	Human Immunodeficiency Virus

HONOS	Health of the Nation Outcome Scales
HR	Hazard Ratio
ICC	Intraclass Correlation
ID(s)	Identity Document(s)
IQ	Intelligence Quotient
LDL	Low-Density Lipoprotein
LMRM(s)	Linear Multilevel Regression Model(s)
LSNS	Luben Social Network Scale
MCI	Mild Cognitive Impairment
MLM(s)	Multilevel Model(s)
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
NA	Not Applicable
NICE	National Institute for Health and Care Excellence
NFT(s)	Neurofibrillary Tangle(s)
NHS	National Health Service
NMDA	N-Methyl-D-Aspartate
NLP	Natural Language Processing
OR	Odds Ratio
PAF	Population Attributable Factor
PCA	Principal Component Analysis
PDD	Parkinson’s Disease Dementia
PRISMA	Preferred Reporting Items for Systematic reviews and Meta Analysis
PROSPERO	International Prospective Register of Systematic Reviews
PSEN	Presenilin
RR	Relative Risk
SD	Standard Deviation
SE	Standard Error
SEM	Structural Equation Modelling
SI	Social Isolation
UCLA	University of California, Los Angeles
UK	United Kingdom of Great Britain and Northern Ireland

VaD	Vascular Dementia
WHO	World Health Organisation

Summary

This thesis focuses on the impact of social isolation and loneliness on cognition and cognitive trajectories of patients with an Alzheimer's disease or related disease diagnosis. While social isolation and loneliness are known to impact incidence risk, their effect on cognitive trajectories in patients, particularly after diagnosis, is relatively under studied. As these factors are potentially modifiable, exploring their impact offers an opportunity to inform care plans or non-pharmacological interventions, thereby improving quality of life for patients. A retrospective cohort design of electronic healthcare records was used across three modelling studies. Study 1 aimed to develop proxies of social isolation from the records and model their impact using linear multilevel models. Study 2 looked to build upon the models from Study 1 by introducing the addition of non-linear multilevel models. Study 3 looked to further develop the models by introducing a natural language processing algorithm to detect novel proxies of both social isolation and loneliness from the records and analyse their impact on cognitive outcomes using a combination of linear and non-linear models. Findings indicated that accommodation status was a strong predictor of cognitive scores at diagnosis, regardless of cognitive measure. Reports of loneliness and social isolation predicted significant yet differing impacts on cognition as measured by the Montreal Cognitive Assessment. Patients experiencing loneliness exhibited worse overall cognition. Whereas, patients experiencing social isolation exhibited initially similar cognitive trajectories as controls with rates of cognitive decline that increased, relatively, around diagnosis. These studies demonstrate that social and demographic factors related to social isolation and loneliness contribute to cognitive performances across diagnosis trajectories and therefore have practical implications for clinical screening and routine data collection at memory clinics.

1 General Introduction

1.1 Dementia, Alzheimer's Disease and Related Diseases

1.1.1 Definitions

Dementia is a syndrome comprising acquired, progressive symptoms of cognitive impairment, primarily affecting memory, executive functions, language and the ability to perform daily activities, that is often used as an umbrella term to describe a number of related neurodegenerative diseases and/or the result of brain injury (World Health Organization, 2019, 2023). Cognitive symptoms are often observed alongside, or in some cases foreshadowed by neuropsychiatric symptoms such as low mood, low motivation, apathy, depression, deteriorated social participation, social aggression, hallucinations and/or sleep disturbances, which have an impact on daily living (Lyketsos et al., 2011; World Health Organization, 2019). Mild cognitive impairment (MCI) is a term used to describe memory or thinking difficulties that arise but do not impact daily living. In some cases, MCI may be a precursor to dementia, but can also be caused by other conditions (Alzheimer's Society, 2025a).

Alzheimer's disease (AD) is predominantly recognised as the most common neurodegenerative disease-causing cognitive impairment, accounting for approximately 65% of diagnosed cases (World Health Organization, 2023a). Given the broad range of underlying pathologies that can lead to a dementia syndrome, and due to the historical connotations of the term itself, there is a suggestion that the use of the term dementia should be phased out in favour of less stigmatising terminology (Jellinger, 2010; Trachtenberg & Trojanowski, 2008). The term, 'dementia', stems from the Latin root, 'demens', meaning to be out of one's mind (Glare, 1968), while medical text from the seventeenth and eighteenth centuries equate dementia with idiocy, stupidity, foolishness and insanity (Berrios, 1987). Understandably, the term dementia could, therefore, be considered outdated and derogatory, yet it is still widely used within clinical (including in the names of diagnoses) and academic settings, by charities and by patients themselves.

For the purposes of this thesis, to encompass the diverse conditions leading to cognitive impairment while acknowledging the need for less stigmatising language, the term Alzheimer's disease and related diseases (ADRD) is used throughout as an overarching term. This terminology broadens the scope beyond solely AD to include any disease, disorder or insult that would otherwise be considered a cause of dementia diagnosis (some studies use the term 'all-cause dementia', e.g. Sundström et al., 2020, however ADRD is preferred here for the reasons outlined), while the term 'dementia' will be reserved specifically to refer to the cognitive impairment syndrome (when used alone, i.e. not when being used as part of a diagnostic term, e.g. vascular dementia, or dementia with Lewy bodies). Chapter 2 will be an exception to this: where studies identified in the scoping review have specified a diagnosis, ADRD is used, however it was not always possible to discern this from the articles. Therefore, the term dementia is sometimes used in this chapter to mirror the term used in the study being referenced from the scoping review.

1.1.2 Context

Worldwide, as of 2018, there were at least 50 million patients living with an ADRD diagnosis (Patterson, 2018). The number of people living with dementia is greater still, due to people living without a formal ADRD diagnosis (Aldus et al., 2020). There is evidence that prevalence may be falling in specific higher income countries, potentially due to improved living conditions, improved cardiovascular health, improved access to education and/or healthcare, and/or improved awareness of risk factors (Livingston et al., 2017; Matthews et al., 2013; Wu et al., 2017). However, this may not be true for all high-income countries, as systematic reviews suggest prevalence in some countries, such as Japan (Dodge et al., 2012) and Hong Kong (Yu et al., 2012), is increasing. Projections estimate that the total number of ADRD cases could treble in the next 20-30 years, reaching over 150 million by 2050 (S. Norton et al., 2013; Office for Health Improvement and Disparities, 2022; Patterson, 2018; World Health Organization, 2023a). The total number of people living with ADRD in the UK is still projected to increase, despite reducing incidence rates, mainly due to people living longer (Ahmadi-Abhari et al., 2017). Increased life expectancy, declining fertility rates and increased ADRD incidence will inevitably have patient care and economic consequences (Ahmadi-Abhari et al., 2017; Patterson, 2018; Storey, 2018), especially so considering increased age is the greatest predictor of ADRD incidence (Alzheimer's Association, 2014; Katzman et al., 1989).

Recent pharmaceutical developments have led to two new AD medications, Lecanemab and Donanemab, that have been shown to reduce amyloid pathology (Chowdhury & Chowdhury, 2023; Mintun et al., 2021; Rashad et al., 2023; Van Dyck et al., 2023). While approved for sale and use in the UK, they have not been approved by the National Institute for Health and Clinical Excellence (NICE) for prescription through the National Health Service (NHS), due to concerns over potential side effects, as well as a perceived low cost to benefit ratio (NICE, 2024). Medications previously approved for prescription on the NHS have sought to improve or maintain cognitive function, rather than target underlying pathology. These include acetylcholinesterase inhibitors (e.g. Donepezil; Seltzer, 2005, 2007) and the glutaminergic NMDA antagonist (Memantine; Robinson & Keating, 2006). Disease modifying pharmaceutical therapies have the potential to reduce the health and economic burdens of ADRD (Selkoe, 2024). However, at least until such therapies are readily accessible and effective, approaches that focus on reducing risk and/or relieving symptoms are necessary.

1.1.3 Aetiology

The set of causes for dementia differs depending on the specific underlying disease diagnosis. Understanding these causes requires considering multiple levels of explanation across biological, genetic, and environmental domains, and considering how these factors interact. For example: at a molecular level, the Amyloid Cascade Hypothesis (ACH) theorises that abnormal protein processing leads to pathological changes within the brain (Hardy & Higgins, 1992); at a genetic level, specific gene mutations and variations increase susceptibility (e.g. Corder et al., 1993); at a population level, factors like age, vascular health and lifestyle factors contribute to overall risk (e.g. Livingston et al., 2024). In the following paragraphs, these domains are considered in more detail, while also providing a brief overview of the aetiology of three common ADRD diagnoses. Population level factors that are modifiable, such as lifestyle factors, are discussed in the subsequent subchapter (section 1.1.4).

AD is the most common single ADRD diagnosis, with age the greatest risk factor (Alzheimer’s Association, 2014; Alzheimer’s Society, 2025b; Katzman et al., 1989). Vascular dementia (VaD; a.k.a. vascular disease) is the second most common diagnosis, followed by dementia with Lewy bodies (DLB), and frontotemporal dementia, with rarer causes including early-onset dementia (a.k.a. young-onset dementia), Creutzfeldt–Jakob disease, HIV-associated neurocognitive disorder, and Huntington’s disease, amongst others (Alzheimer’s Society, 2025b; Schneider et al., 2007). Mixed dementia is the term used when there is more than one cause. Schneider and colleagues (2007) argue that mixed dementia is the most common cause of ADRD cases. In their study of a community-dwelling cohort from the Rush Memory and Ageing Project, it was found that, of those with an ADRD diagnosis, over half had more than one pathology, the most common combination being AD with vascular infarcts. While AD and VaD are the most common co-occurring diseases for mixed dementia, alternative disease combinations also contribute to diagnoses (National Health Service, 2024; Schneider et al., 2007).

AD, the most common ADRD diagnosis, is pathologically characterised by the accumulation of neuritic plaques and neurofibrillary tangles (NFTs) first described by Alois Alzheimer in 1906 (see Hippius & Neundörfer, 2003; Katzman & Saitoh, 1991). It is now known that the primary aggregated components of these plaques and NFTs are, respectively, the amino acid peptide *amyloid-beta* (Aβ), and the cytoskeletal protein *tau* (Sheppard & Coleman, 2020). AD pathology is thought to initially impact neurons within the hippocampus before spreading to nearby brain regions, leading to synapse loss and atrophy (Braak & Braak, 1997; Masurkar, 2018; Sheppard & Coleman, 2020). Amyloid plaques and neurofibrillary tau tangles can be found in affected areas and are believed to contribute to neurotoxicity (Behl, 2024; Hardy & Higgins, 1992; Selkoe & Hardy, 2016).

The amyloid cascade hypothesis (ACH) posits that abnormal proteolysis of the amyloid precursor protein (APP) leads to the deposition of Aβ as a precursor to amyloid plaques, NFTs and eventually cell death (Hardy & Higgins, 1992). The ACH has driven extensive research into genetic risk factors for AD, particularly regarding early-onset familial cases (Armstrong, 2019). Mutations of APP and presenilin genes PSEN1 and PSEN2 have been identified as the main causal factor of early-onset familial AD (Chapuis et al., 2017; Kabir et al., 2020). For sporadic and late-onset AD, variations in cholesterol transporter genes, notably APOE ε4, have been linked with increased risk (Corder et al., 1993; Leduc et al., 2010; Saunders et al., 1993). In contrast, there is accumulating evidence that APOE ε2 could be a genetic protective factor (Serrano-Pozo et al., 2011).

VaD results from vascular infarcts (damage to blood vessels), leading to a reduced supply of blood, oxygen and nutrients to the brain (Khan et al., 2016). These infarcts often stem from stroke or an accumulation of less apparent, ‘covert’ brain injuries, detectable through brain imaging or during autopsy (E. E. Smith, 2017). Post-stroke, ADRD incidence rates increase amongst survivors year upon year (Allan et al., 2011; Pendlebury & Rothwell, 2009). VaD frequently co-occurs with AD as mixed dementia (Schneider et al., 2007). Diagnosing VaD requires extra consideration as to whether functional interferences aren’t due to other consequences, such as motor or sensory impairments post-stroke (E. E. Smith, 2017). Genetic loci on the X and 17q25 chromosomes, as well as APOE allele variations, are associated with increased susceptibility to VaD (Kim et al., 2013; Schmidt et al., 2012).

DLB is characterised as the occurrence of the dementia syndrome as a probable consequence of Lewy body pathology, an accumulation of α-synuclein protein aggregates associated with neuronal atrophy (Kanazawa et al., 2008; Walker et al., 2015). Lewy body pathology often requires imaging or autopsy for confirmation (Walker et al., 2007), and also plays a key role in Parkinson’s disease (PD), whereby DLB is diagnosed if dementia occurs before or within one year of the onset of parkinsonian motor symptoms (McKeith et al., 2017; Walker et al., 2015). PD patients’ risk of cognitive impairment increases year on year following diagnosis (Williams-Gray et al., 2013), and cognitive impairment could be compounded by the co-occurrence of AD pathology (Aβ plaques and tau NFTs) in up to 50% of PD patients (Irwin et al., 2013). This co-occurrence may mask the clinical features of DLB, potentially leading to misdiagnosis (Lopez et al., 2002; McKeith et al., 2017; Outeiro et al., 2019). Siblings of patients with DLB have increased risk of DLB and DLB clinical features compared to siblings of AD patients, suggesting an inherited genetic risk for DLB (Nervi et al., 2011), though further understanding of genetic risk factors is needed (McKeith et al., 2017; Outeiro et al., 2019).

1.1.4 Modifiable Risk Factors

Unlike non-modifiable risk factors, such as age and genetics, some factors that influence ADRD risk are modifiable. Modifiable risk factors are attributable to one’s environment and lifestyle, thus function at the population level, and therefore can be potentially changed throughout the course of one’s life. Three reports by Livingston and colleagues for The Lancet Commissions in 2017 (Livingston et al., 2017), 2020 (Livingston et al., 2020), and 2024 (Livingston et al., 2024) investigate prevention, intervention and care with regards to ADRD. From these reports, 14 modifiable risk factors for ADRD are identified, considering existing evidence from published studies and meta-analyses, and conducting new meta-analyses where necessary. These 14 modifiable risk factors are estimated to be responsible for contributing to up to 45% of ADRD cases. These risk factors are less educational attainment, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, social isolation, excessive alcohol consumption, traumatic brain injury, exposure to air pollution, untreated visual loss, and high low-density lipoprotein (LDL) cholesterol. Therefore, modification of these factors has the potential to prevent or delay the onset of up to 45%

(potentially more in lower- and middle-income countries) of cases at current rates, and could have implications for post-diagnostic care and policy (Livingston et al., 2020, 2024; Patterson, 2018). Furthermore, reduction of risk via these 14 pathways remains possible regardless of APOE genetic risk (Livingston et al., 2024). This highlights the significant impact of population-level factors on dementia risk, suggesting that modifiable risk factors are at least as impactful as genetic risk factors with regards to the cause of dementia, and importantly, can act to mitigate the effect of genetic risk. Thus, underscoring the complex interaction between genetic and population level factors in ADRD incidence; genetic predispositions may increase susceptibility at the biological level, while lifestyle and environmental factors influence whether and when these predispositions manifest.

It is thought that these 14 factors contribute to risk throughout different stages of life: the main early-life (<45 years of age) risk factor is less educational attainment; the majority of factors contribute at mid-life (age 45-65 years), including hearing loss, high LDL cholesterol, traumatic brain injury, depression, hypertension, smoking, physical inactivity, diabetes, excessive alcohol consumption, and obesity; later-life (>65 years of age) factors include social isolation, exposure to air pollution, and visual loss (Livingston et al., 2017, 2020, 2024). It is unclear whether the differences between factors affecting risk at certain points in life reflects critical windows of exposure, or whether duration of exposure may play an important factor, so that people who develop early- or mid-life risk factors in late-life may also be at increased risk provided they live long enough (Livingston et al., 2024). It may be the case that the link between all risk factors and dementia is bidirectional, particularly later-life factors, though considering the long preclinical phase of some dementia causing diseases, changes in behaviour that also occur before clinical symptoms could indicate a true causal effect or reverse causation (Livingston et al., 2020, 2024). The precise mechanisms for how these risk factors could lead directly to ADRD incidence is still mostly unclear, though causal pathways including vascular, inflammatory, immunogenic, neuropathological, or relating to cognitive reserve are postulated, with the expectation that most if not all of these risk factors will follow at least one (if not some combination) of these routes, and that these pathways also interact with each other (Livingston et al., 2024). Current proposed mechanisms are discussed later in section 1.2.4.

1.2 Reserve

1.2.1 Overview

Cognitive reserve, in the context of ADRD, is a term that was derived to describe the lack of direct association between neuropathological burden and cognitive symptoms observed in autopsy studies (Stern, 2002). Numerous terms have since been used, often interchangeably, to describe the process in which brain function is protected from deterioration despite the presence of pathology or other brain injury. This thesis will primarily consider the definitions outlined in Stern et al., (2020) and later refined in Stern et al., (2023) to be the most well defined, most ubiquitous, and therefore the most relevant. In these works, Stern and colleagues first outline the concept of *Reserve* as individual differences in cognitive function or clinical status in relation to age or pathology. These individual differences are then broken down into three components: *Cognitive Reserve* (CR), *Brain Reserve* (BR), and *Brain Maintenance* (BM).

1.2.2 Definitions

CR specifically refers to the adaptability of brain networks at molecular and cellular levels to maintain functional interactions despite age, the presence of pathology, and/or brain injury. CR is a dynamic process, thought to be determined by a combination of modifiable (e.g. exposure to certain environmental conditions) and non-modifiable (e.g. genetics) factors. Individual differences in CR are proposed to influence a person’s susceptibility to negative changes, while exposure to neurocognitive stimulation may also offer protection. Through these processes, CR gives the capacity for a person to outperform their expected level of brain or cognitive function, given their age, pathology, and/or injury.

BR refers to the concept that individual differences account for people having more or less structural brain capacity (e.g. more or less grey/white matter, synapses etc.). A reduction in cognitive function would only occur after a critical threshold of ‘lost’ structural brain capacity had been reached or surpassed. It is supposed, therefore, that people with higher BR would have more capacity to lose before reaching this threshold and could theoretically delay or prevent the onset of cognitive impairment (Arenaza-Urquijo & Vemuri, 2018, 2020; Stern et al., 2020, 2023).

Whereas BR refers to a fixed status of the brain at any given time, BM refers to the dynamic process of maintaining brain function. This is thought to be achieved through avoidance of pathological hallmarks or brain injury, a reduction in the impact that pathology or brain injury exhibits, and/or a reduction in the rate of neuropathological advancement. Some combination of these processes is responsible for delaying potential cognitive decline, therefore maintaining cognitive function (Bocancea et al., 2021; Stern et al., 2020, 2023).

For additional context, the term *Cognitive Resilience* is defined by Stern and colleagues as a catch-all term for any concept, mechanism, or study generally related to the brain's ability to maintain function despite age, pathology and/or injury (Stern et al., 2020, 2023). Additionally, in modelling studies, *Cognitive Resilience* is also used to describe the residual difference between a patient's observed level of cognition and their expected level of cognition based on their pathology (Bocancea et al., 2021; Elman et al., 2022; Graham et al., 2021; Kremen et al., 2022; Wagner et al., 2022; Yao et al., 2020).

1.2.3 Cognitive Reserve and Modifiable Lifestyle Factors

When studying cognitive reserve, it is necessary to utilise readily available socio-behavioural indicators (so called 'convenience proxies'), assuming their covariance with and/or contribution to cognitive reserve (Borroni et al., 2009; Stern et al., 2020). Such convenience proxies could then, for instance, be interpreted to moderate the association between pathological change and disease severity (Stern et al., 2023). Stern and colleagues (2023) define three components needed to elucidate cognitive reserve: (1) a measure of brain changes, representing injury or disease pathology, that is thought to impact cognition; (2) a measure of cognition, as a representation of functional brain change severity; (3) some variable that is thought to influence the relationship between the first two components, as a representation of cognitive reserve. An example of this using a common proxy would be education level (e.g. Alexander et al., 1997; Bennett et al., 2006; Meng & D'Arcy, 2012; Perneczky et al., 2009; Reed et al., 2011; Rouillard et al., 2017; Scarmeas et al., 2003; Stern et al., 1992; Yao et al., 2020). In this example, a measure of cerebral blood flow would represent the impact of disease pathology on the functional metabolism of the brain, a measure of Mini-Mental State Examination would represent cognitive function; and a measure of a person's highest attained level of completed education would represent education level. Using these representations, researchers could assess how education level moderates the relationship between disease progression and cognitive function, given the known levels of each. Other commonly used convenience proxies of cognitive reserve include occupation/occupational complexity (Borroni et al., 2009; Habeck et al., 2019; Rouillard et al., 2017), engagement in (cognitively stimulating) leisure activity (Borroni et al., 2009; Casaletto, Renteíıa, et al., 2020; Casaletto, Staffaroni, et al., 2020; Sumowski et al., 2013; Yao et al., 2020), engagement in physical activity (Anatürk et al., 2021; Buchman et al., 2019; Casaletto, Renteíıa, et al., 2020; Casaletto, Staffaroni, et al., 2020; Yao et al., 2020), and premorbid reading ability/IQ (Alexander et al., 1997; Anatürk et al., 2021; Fyffe et al., 2011; Negash et al., 2013; Scarmeas et al., 2003).

The 14 modifiable ADRD risk factors identified in the Livingston and colleagues reports (Livingston et al., 2017, 2020, 2024) could be considered cognitive reserve proxies due to their protective factors, and there is scope (though, due to lack of direct measure of disease progression, outside the scope of this thesis) to investigate these modifiable risk factors further from a cognitive reserve perspective (studies investigating social connection and cognitive reserve and reviewed in section 1.3.5). Measures commonly used for evaluating cognition with regards to ADRD include the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), the Mini-Mental State Examination (MMSE; Folstein et al., 1975), and the Addenbrooke’s Cognitive Examination (ACE; Noone, 2015). Other studies utilise the Clinical Dementia Rating (CDR) scale (C. P. Hughes et al., 1982), which encompasses both cognitive and general function domains to assess dementia severity. In the case of AD specifically, imaging studies have often used regional metabolism or regional cerebral blood flow (CBF) change as an indicator for pathological change, such as neuronal loss, within the brain (Friedland et al., 1985; Hoffman et al., 2000; E. G. McGeer, McGeer, et al., 1990; E. G. McGeer, Peppard, et al., 1990; P. L. McGeer, Kamo, Harrop, Li, et al., 1986; P. L. McGeer, Kamo, Harrop, McGeer, et al., 1986; Mielke et al., 1996; Scarmeas et al., 2003; Stern et al., 1992). Other approaches have used brain atrophy, or regional density as an indication of disease progression (Perry, Roth, et al., 2022; Zhang et al., 2022).

In their systematic review, Song and colleagues (2022) identified the three models of investigating cognitive reserve that are most frequently used: the residual model, the moderation model, and the controlling model. The residual model looks to examine the impact of some lifestyle/modifiable factor(s) on the difference (i.e. residual) between an observed measure of cognition and an expected measure of cognition given a person’s level of pathology (e.g. Anatürk et al., 2021; Negash et al., 2013; Reed et al., 2011; Yao et al., 2020). The moderation model explores whether lifestyle/modifiable factor(s) influence the relationship between pathology and cognition (Amato et al., 2013; Bartrés-Faz et al., 2009; Buchman et al., 2019; Casaletto, Renteíıa, et al., 2020; Casaletto, Staffaroni, et al., 2020; Chan et al., 2018; Nunnari et al., 2016; Rouillard et al., 2017; Snitz et al., 2020; Sumowski et al., 2013). In line with cognitive reserve theory, moderation models predict that individuals with healthier lifestyles will experience less severe cognitive decline in relation to pathology than those with less healthy lifestyles (Song et al., 2022). The final model Song and colleagues outline is the controlling model, which they describe as being implemented in one of two variations in terms of approach to statistical analyses. The first variation investigates the relationship between lifestyle/modifiable factor(s) and cognition, controlling for pathology (e.g. Sumowski et al., 2010). This approach posits that healthier lifestyles are linked to better cognitive performance, even when pathology is comparable. The second variation investigates the relationship between lifestyle/modifiable factor(s) and pathology, controlling for cognition (Borroni et al., 2009; Harris et al., 2015; Scarmeas et al., 2003). This approach predicts that people with healthier lifestyles will exhibit more brain pathology while maintaining the same cognitive level as people with less healthy lifestyles and less brain pathology, suggesting a protective effect of healthier lifestyles.

1.2.4 Proposed Mechanisms

The precise mechanisms for how cognitive reserve prevents or protects from cognitive decline and dementia in ADRD are not fully understood, however several studies offer insight by exploring the association between cognitive reserve proxies and cognition considering pathological changes, or the relative absence of brain changes over time. Cognitive reserve proxies inversely associated with cognitive decline, dementia and ADRD incidence risk include education level, occupational complexity, engagement in leisure activities, amongst other socio-behavioural factors (see section 1.2.3). People with higher levels of education attainment and demanding occupational environments exhibit lower levels of cognitive decline, however whether education level and occupational complexity are associated with reduced ADRD incidence risk independent of each other is somewhat debated (Alvares Pereira et al., 2022; Dekhtyar et al., 2015; Karp et al., 2009). Access to higher education often leads to access to more complex and intellectually stimulating occupations. Consequently, it is challenging to isolate the unique contribution of each factor to cognitive reserve, as their effects may be intertwined and mutually reinforcing. Furthermore, the associated reduction in ADRD incidence risk of occupational complexity may only be present for certain ADRD subtypes (Kröger et al., 2008).

Imaging studies have aimed to identify brain regions or networks associated with cognitive reserve proxies and pathology. One mechanism may be related to metabolism. Specifically, studies have found an inverse relationship between CBF in regions associated with AD (e.g.

temporal, temporal-occipital-parietal, parieto-temporal, pre-frontal, pre-motor, and left superior parietal cortices), education level (Scarmeas & Stern, 2003; Stern et al., 1992), and premorbid reading level/IQ (Alexander et al., 1997; Scarmeas et al., 2003), when controlling for disease severity, suggesting these proxies offer some protective role in disease severity. Further imaging studies have shown associations between alcohol consumption (Topiwala et al., 2017), education level (AddNeuroMed Consortium et al., 2012), and social connection factors (Perry, Roth, et al., 2022; Zhang et al., 2022) with neuronal density, suggesting a role in brain reserve and maintenance (Alvares Pereira et al., 2022). Childhood and mid-life stressful life events have been found to be associated with neuroinflammation and various AD pathologies such as higher NFTs (Palpatzis et al., 2024). Circulating metabolites, found within the bloodstream (as well as other bodily fluids), have been found to be associated with cognition, ADRD and modifiable lifestyle factors, suggesting that vascular metabolism is another potential mechanism for reserve (van der Lee et al., 2018). Exposure to pollutants within the air may directly contribute to neurotoxicity and has been shown to increase risk of ADRD and other neurological disorders (Costa et al., 2017; Peters et al., 2019). Exercise has been linked with increased CBF, as well as an increase in levels of Orexin-A, a neuropeptide, that has in turn been found to be linked to neurogenesis in the hippocampus (Chieffi et al., 2017), which is a key area of neuronal loss in AD.

1.3 Social Connection

1.3.1 Definitions and Distinctions

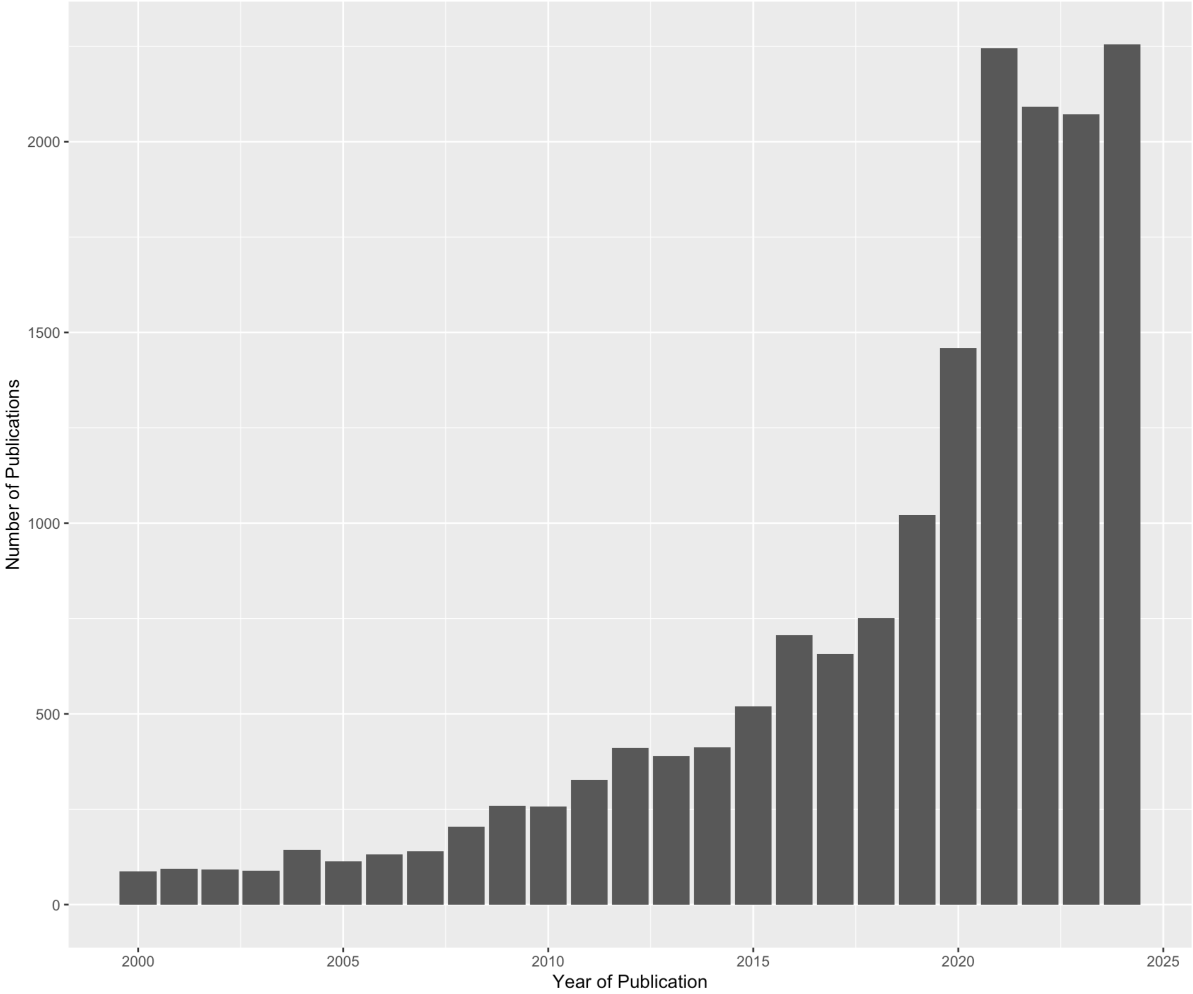
Social isolation is one of the 14 modifiable risk factors for ADRD highlighted in the Livingston reports (Livingston et al., 2017, 2020, 2024). Social isolation constitutes an objective lack of social contacts, social relationships and social roles (de Jong Gierveld et al., 2006; Holt-Lunstad, 2017; Perissinotto et al., 2019; Wenger et al., 1996). In contrast, loneliness constitutes a subjective negative experience occurring as a result of a disparity, that can be either quantitative or qualitative, between a person’s perceived level of social connection and their desired level of social connection (de Jong Gierveld et al., 2006; de Jong-Gierveld, 1987; Perlman & Peplau, 1981; Wenger et al., 1996). This negative experience is not necessarily synchronous with an objective lack of social connection; therefore a person can be alone without feeling lonely, and vice versa (Perlman & Peplau, 1981). In this sense, social isolation can be seen as an objective lack of social connection, whereas loneliness represents a subjective emotional absence of social connection. Some studies represent loneliness to be the subjective experience of isolation (Zhang et al., 2022). However, the current thesis posits that subjective experience of isolation and the subjective experience of loneliness are distinct (see section 1.3.4 and Chapter 6).

1.3.2 Context

The onset of the COVID-19 pandemic and associated social restrictions undoubtedly brought social connection to the fore in conversations and articles in mainstream news media (Andrew & Morava, 2021; BBC, 2020a, 2020c; Chillag, 2020; Davies, 2020; Moss & England, 2021), with some articles particularly focussing on the experience of people living in care homes, or people ‘shielding’ due to health conditions, and their relatives (BBC, 2020b, 2021; I. Bennett, 2021; Bethell, 2021). The UK appointed its first Minister for Loneliness in 2018, following the Jo Cox Commission on Loneliness (Jopling et al., 2017), while the World Health Organisation (WHO) announced its commission on social connection in 2023, to be completed between 2024 and 2026 (World Health Organization, 2023b, 2024). Social connection has been gaining prominence as a topic within the academic scope for some time, and particularly within the past 5 years. A search of ‘social isolation’, ‘loneliness’ and ‘social connect*’ (to cover social connection and social connectedness as it is otherwise known as) within the titles of published peer reviewed papers on the Web of Science database reveals a sharp increase in papers published between 2019 and 2021, coinciding with the onset of the COVID-19 pandemic, before plateauing (see Figure 1.1). The Covid-19 pandemic and associated enforced social restrictions offer an interesting opportunity to explore social connection from a natural experiment approach.

Figure 1.1

Number of Publications, by Year, of Social Connection Related Titles on Web of Science



There is evidence to suggest that the prevalence of social isolation and loneliness amongst older adults and those with an ADRD or MCI diagnosis, is particularly high compared to other age groups (Hajek et al., 2023; Hajek & König, 2025). It is suggested that this increased prevalence to lower social connection could be due to challenges related to aging, such as occupational changes, need for care, caregiving, bereavement, physical decline/disorder, cognitive decline/disorder, discriminatory societal views, or comorbidities (Hajek et al., 2023; M. L. Smith et al., 2020). As well as ADRD incidence risk (see section 1.3.3), social isolation and loneliness have been associated with a variety of negative health consequences including depression (e.g. Santini et al., 2014), coronary heart disease (e.g. Hemingway and Marmot, 1999), functional decline (e.g. Avlund et al., 2004), mortality (e.g. Holt-Lunstad et al., 2010), cognitive decline in people without dementia or ADRD diagnosis (e.g. Kuiper et al., 2016; Röhr et al., 2020), and increased neuropsychiatric symptoms (e.g. Manca et al., 2020). As well as being vulnerable to low social connection, older adults are more at risk of Covid-19 severe complications (including death), due to comorbidities (Sanyaolu et al., 2020). Efforts to limit exposure to Covid-19, such as social distancing, may counteract efforts to improve social connection amongst older adults; a situation sometimes referred to as the Covid-19 Social Connectivity Paradox (M. L. Smith et al., 2020). Some studies have investigated the impact of social restrictions associated with the COVID-19 pandemic on cognitive outcomes in people with dementia/ADRD (see Chapter 2), and those without previous cognitive impairment (e.g. Babulal et al., 2021; Lehtisalo et al., 2021; Sutton et al., 2022).

1.3.3 Proxies, Quantification and Incidence Risk

Similarly to cognitive reserve, quantification of social isolation and loneliness utilises proxies of factors that are thought to tap into aspects of their underlying properties, and/or due to their associated cooccurrences. For example, marital status has previously been identified as a key component of social isolation due to its association with varying family structures and social interaction (Livingston et al., 2020; Saito et al., 2018; Sommerlad et al., 2018; Wenger et al., 1996). Considering people in mid-late life, marital status can offer an indication of long-term social interaction (Livingston et al., 2020). Being married is thought to be associated with more frequent social interaction (or ‘social engagement’; (Livingston et al., 2020; Sommerlad et al., 2018), with more frequent interaction being associated with reduced cognitive decline (Kuiper et al., 2016) and ADRD incidence (Kuiper et al., 2015). Being married is associated with a reduction in unhealthy behaviours (Fuller & Tech, 2010; Joung et al., 1995), which could also help to decrease ADRD incidence risk (Sommerlad et al., 2018). Conversely lifelong single people, or people who are widowed have been found to be at increased risk of ADRD incidence, controlling for age and sex (Sommerlad et al., 2018). Specifically, the finding that lifelong single people are at 42% increased risk of ADRD incidence (Sommerlad et al., 2018) is comparable to findings for other known modifiable risk factors (National Institute for Health and Care Excellence, 2015; S. Norton et al., 2014). It is suggested that the increased risk in widowed people could be mediated through stress (Sommerlad et al., 2018), which has also been shown to be associated with increased ADRD incidence risk (Johansson et al., 2013). Mid-life social interaction (or ‘social contact’) has been found to be associated with follow-up cognitive performance, while more frequent mid-to-late-life social contact with friends, rather than family, has been found to be associated with reduced ADRD incidence (Sommerlad et al., 2019).

Rather than reducing aspects of social connection to one factor, others argue that it is important to take a holistic approach to social connection, as different aspects may impact health outcomes through a variety of mechanisms (Kuiper et al., 2015). A meta-analytic review by Kuiper and colleagues (2015) into social connection and the risk of ADRD incidence provided evidence towards the conclusions of Livingston and colleagues (2017), that social isolation contributes to the population attributable factor for ADRD incidence. Specifically, the meta-analysis by Kuiper and colleagues (2015) aimed to investigate the relationship between social connection and ADRD incidence by reviewing and analysing longitudinal data from 19 identified cohorts. Social connection factors were categorised into six groups: social network size; social participation; frequency of social contact; loneliness; satisfaction with social network; other social relationship factors. From the results of the meta-analysis, pooled estimates revealed statistically significant increased risk of ADRD incidence for people with low levels of social participation compared to higher levels of social participation (RR = 1.41, 95% CI [1.13, 1.75]), for people with lower frequency of social contact compared to higher frequency of social contact (RR = 1.57, 95% CI [1.32, 1.85]), and for people who are lonely compared to not lonely (RR = 1.58, 95% CI [1.19, 2.09]). No statistically significant association with ADRD incidence was found for satisfaction with social networks (RR = 1.25, 95% CI [0.96, 1.62]). Estimations for social network size and ADRD incidence could not be made due to heterogeneity in populations, outcomes, measures and methodological quality of the identified studies. It is suggested these results indicate that frequency of interactions plays a larger role in ADRD risk than size of social network with regards to social isolation, and that social connection is comparable to other known ADRD risk factors such as depression (e.g. Diniz et al., 2013), physical activity, hypertension, education attainment (e.g. Norton et al., 2014), and smoking (e.g. Beydoun et al., 2014).

Alternatively, some consider that living status (i.e. living alone or with others) is a more objective proxy for objective social connection (Desai et al., 2020; Wenger et al., 1996). In a following review and meta-analysis, Desai and colleagues (2020) argue that the use of various aspects of social connection utilised by Kuiper and colleagues (2015) in their meta-analysis, and the variety of definitions of those aspects between the studies themselves, introduces heterogeneity which is likely to lead to less accurate interpretations. Living alone has been used as a proxy for social isolation in numerous longitudinal studies (Akbaraly et al., 2009; Arai et al., 2004; Bickel & Cooper, 1994; R. Chen et al., 2011; Fratiglioni et al., 2000; He et al., 2000; Helmer et al., 1999; Holwerda et al., 2014; Paillard-Borg et al., 2009; Rawtaer et al., 2017; Rodriguez et al., 2018; Sörman et al., 2015) and pooled effect sizes reveal an association with a significant increase in ADRD incidence risk for people living alone, compared to people living with others (RR = 1.30, 95% CI [1.15, 1.46]; Desai et al., 2020).

Levels of heterogeneity within the analysis were found to be non-significant (χ^2 = 9.23, df = 11, p = .60, I^2 < .001%), and ADRD incidence risk remained at similar levels after a sensitivity analysis removed three studies at medium risk of bias (RR = 1.31, 95% CI [1.13, 1.51]). Desai and colleagues estimated the population attributable fraction (PAF) of living alone to be 8.9%, concluding that social isolation, proxied by living alone, may contribute to greater ADRD incidence rates than previously thought. Though, the latest report by Livingston and colleagues (Livingston et al., 2024) reported weighted PAF calculations of 4.6%.

Desai and colleagues (2020) do not consider loneliness in their analysis as a subjective aspect of social connection, despite some of the studies included in their review containing a measure of loneliness. The authors acknowledge that loneliness could be a more substantial driving factor than people intrinsically living alone, as some people seek living alone through preference. A systematic review and meta-analysis focusing specifically on the impact of loneliness to ADRD risk (as well as MCI risk) was conducted by Lara and colleagues (2019). In this review, the authors identified 11 longitudinal studies (R. Chen et al., 2011; He et al., 2000; Holwerda et al., 2014; Lobo et al., 2008; Rafnsson et al., 2020; Rawtaer et al., 2017; Sutin et al., 2020; Wilson, Krueger, et al., 2007; Wilson et al., 2015; Zhou et al., 2018) all of which used self-report measures of loneliness. Pooled estimates for eight studies investigating ADRD incidence (Chen et al., 2011; He et al., 2000; Holwerda et al., 2014; Lobo et al., 2008; Rafnsson et al., 2017 Sutin et al., 2018; Wilson et al., 2007; Zhou et al., 2018a) revealed an increased risk of loneliness on ADRD incidence (RR = 1.26, 95% CI [1.14, 1.40]), with the level of heterogeneity across the studies found to be non-significant (χ^2 = 9.10, df = 7, p = .25). Sensitivity analyses also confirmed these findings to be robust to potential confounding effects from exposure measurement, duration of follow-up, depression adjustment or risk of bias. Only two identified studies investigated the impact of loneliness on MCI incidence (Lobo et al., 2008; Wilson et al., 2015), however a meta-analysis could not be performed due to only one study reporting effect sizes. The study that did report effect sizes (Lobo et al., 2008) found a significant increase of loneliness on MCI incidence risk (OR = 2.05, 95% CI [1.31, 4.97]). Interestingly, the one study identified by the authors that explored the impact of loneliness on the transition between MCI and ADRD (Rawtaer et al., 2017) found no significant impact of loneliness (HR = 1.02, 95% CI [0.66, 1.57]). The authors conclude that their findings add further support to the evidence of the impact of loneliness on ADRD incidence, building upon previous findings such as those of Kuiper and colleagues (2015).

In contrast, a systematic review into social connection, loneliness and ADRD risk by Penninkilampi and colleagues (Penninkilampi et al., 2018) found an increased risk in people with poor social networks (RR = 1.59, 95% CI = 1.31, 1.96, I^2 = 0.00%) and poor social support

(RR = 1.28, 95% CI = 1.01, 1.62, I^2 = 55.51%), and decreased risk in people with good social engagement (RR = 0.88, 95% CI = 0.80, 0.96, I^2 = 0.00%). The review did not find a significant association between loneliness and associated incidence risk (RR = 1.38, 95% CI = 0.98, 1.94, I^2 = 45.32). Similarly, a longitudinal study utilising data from the UK Biobank (Elovainio et al., 2020) found a significant associated increased risk between ADRD incidence and isolation (HR = 1.34, 95% CI = 1.11, 1.60, p = 0.003), but not loneliness (HR = 0.96, 95% CI = 0.75, 1.23, p = 0.716). The latest report by Livingston and colleagues (Livingston et al., 2024) does not offer a PAF calculation for loneliness.

1.3.4 Measures of Social Connection

As well as the proxies discussed in the previous sections, studies often use measurement tools to identify aspects of social connection. Chen and colleagues (2011) used a single yes/no response item, asking if the participant had good relationships with others/ease in acquiring friends to determine loneliness. While this item may address some of the subjective disparity between desired and achieved level of social relationships, it does not seem to consider that some people may prefer solitude. Therefore, the question may instead be inadvertently tapping into the objective measure of quantity of social interactions/engagements. In their study on psychosocial risk factors for AD, He and colleagues (2000) refer to the use of a 100-item psychosocial factors questionnaire. In a results section table showing the findings from the 10-year follow-up, there is a variable referred to as simply, ‘Lonely’, along with percentages of AD incidence, relative risk, confidence intervals and population attributable factor. Holwerda and colleagues (2014) used a single-item yes/no question, “Do you feel lonely or very lonely?” This was adapted for use by Zhou and colleagues (2018) by shortening the question to, “Do you feel lonely?” with 5 response options, “never”, “seldom”, “sometimes”, “often”, or “always”. Dropping, “or very lonely” from the original question seems inconsequential, when Holwerda and colleagues did not make a distinction between lonely and very lonely people in their analysis. One study (Lobo et al., 2008) utilised the loneliness question from the Geriatric Mental State (Copeland et al., 1992).

Two studies (Rafnsson et al., 2020; Sutin et al., 2020) utilised the three-item version of the UCLA Loneliness Scale (M. E. Hughes et al., 2004). This shortened version of the questionnaire asks the participant to answer three questions prefaced by, “how much of the time do you feel… (1) you lack companionship? (2) left out? (3) isolated from others?” This last item on feelings of isolation arguably may not accurately reflect feelings of loneliness, as a person may feel they are isolated, yet not feel lonely. A further two studies (Wilson, Krueger, et al., 2007; Wilson et al., 2015) utilised a modified version of the de Jong-Gierveld Loneliness Scale (de Jong Gierveld & van Tilburg, 1999), with items answered using a 1-5 scale, with 5 indicating higher loneliness agreement. Other examples of psychometric approaches to social connection include the Lubben Social Network Scale (Lubben, 1988), a ten-item measure of social network quantity that was developed to address the use of single-item indicators of social isolation. The scale includes three items on family networks, three items on friend networks, two items on confidant relationships, one item (in two parts) on helping others, and one item on living arrangements. Several studies used a 12-item psychometric scale on frequency of social negative social interactions (Krause & Rook, 2003; Newsom et al., 2003; Wilson et al., 2015).

1.3.5 Social Connection and Cognitive Reserve

Engaging in higher levels of social connection may enhance cognitive reserve, thereby contributing to the brain's ability to withstand and adapt to neuropathological damage, thus leading to greater preservation of cognitive function (Sommerlad et al., 2018, 2019). The increased risk of ADRD incidence associated with certain social connection proxies (see section 1.3.3), such as widowed marital status, could be mediated through stress. Adverse stress negatively impacts neuronal plasticity in the hippocampus, an area of the brain critically involved in learning and memory, and brain oxidation, affecting neurons' capacity to metabolise energy. These effects parallel those observed in AD pathology (Rothman & Mattson, 2010). Such findings may elucidate the mechanisms by which certain marital statuses influence cognitive reserve, and may suggest approaches for modifying behaviour in order to preserve long-term function (Rothman & Mattson, 2010; Sommerlad et al., 2018). Furthermore, Engagement with socially rich environments may help to promote additional and/or maintain existing neuronal pathways through cognitive stimulation (Evans, et al., 2019; Wang et al., 2012). Cognitive reserve has been found to moderate the interaction between social connection and cognitive function, suggesting that individuals who are more socially integrated receive more cognitive stimulation, which is beneficial for their late-life cognitive function (Evans et al., 2018). Previous imaging studies have shown links between CBF and social activity (Scarmeas et al., 2003).

Evidence from Bennett and colleagues (Bennet et al., 2006), utilising data from the Rush Memory and Aging Project longitudinal cohort suggests that social connection, specifically social network size, moderates the interaction between cognition and global pathology, as well as cognition and NFTs, such that participants with larger social networks maintain higher cognitive function despite higher global pathology and despite higher NFTs, whereas participants with smaller social networks experience more severe cognitive decline as global pathology and NFTs increased. The interaction between Aβ load and social network size, however, was not statistically significant. The specific domains of memory moderated by social network size were episodic memory (NFTs), semantic memory (NFTs and global pathology), and working memory (NFTs). Bennett and colleagues discuss these findings in relation to brain and cognitive reserve theories and suggest limbic and associational cortical and subcortical brain regions may be involved in the underlying processes, due to their overlap in involvement in both social cognition and the episodic and semantic memory domains.

Fratiglioni and colleagues (Fratiglioni et al., 2004) suggest that the possible mechanisms underlying social connection and cognitive reserve may be linked to Berkman and colleagues' Social Integration model (Berkman et al., 2000) through its implications for health outcomes. This framework draws from attachment theory (Bowlby, 1979) and the work of Émile Durkheim on social integration (see Scheff, 2007, for an overview) to offer a multifaceted interpretation of social connection and its relation to health outcomes. From a downstream perspective, behavioural pathways include provision of social support, social influence and its impact on engagement and attachment, and access to resources and materials. These operators are proposed to then influence upstream pathways that are more closely linked to health outcomes, such as stress, health-damaging behaviours (e.g. smoking), exposure to infectious disease agents, and psychological aspects (e.g. self-esteem).

Complementary to this theoretical framework, research by Perry and colleagues (Perry, McConnell, Coleman, et al., 2022; Perry, McConnell, Peng, et al., 2022; Perry, Roth, et al., 2022) also highlights the significance of upstream social determinants in influencing cognitive ageing. They specifically propose two pathways: social bridging and social bonding (Perry, McConnell, Peng, et al., 2022). Social bridging, involving expansive social networks and diverse casual relationships, is suggested to contribute to cognitive enrichment by exposing individuals to novel social stimuli, potentially leading to neurogenesis and neuronal maintenance, and accumulation of cognitive reserve. Social bonding, characterised by cohesive networks of close ties, is proposed to influence brain health through neuroendocrine pathways and by protecting against the negative impacts of stress (Perry, McConnell, Peng, et al., 2022; Perry, Roth, et al., 2022). The authors argue that social connection, as an upstream factor, can disrupt multiple cascading pathogenic processes occurring downstream (Perry, McConnell, Coleman, et al., 2022). Their findings suggest that social bridging (e.g.

network size, density and presence of weak ties) and social bonding (e.g. marriage, cohabitation), can moderate the associations between atrophy and cognitive function, and perceived stress and cognitive stress, indicating their contribution to cognitive reserve (Perry, McConnell, Peng, et al., 2022; Perry, Roth, et al., 2022).

1.4 Research Aims

It is well established that social isolation is a risk factor for ADRD incidence and is associated with cognition in old age. Similarly, there is evidence to suggest that loneliness also plays a role. Often, studies investigating incidence risk do not continue their analyses post-diagnosis, and studies investigating cognition in old age exclude ADRD patients (or people who go on to receive a diagnosis). Therefore, it is less well understood how these two components of social connection impact cognition and rates of cognitive change in patients with an ADRD diagnosis. Electronic healthcare records (EHRs) offer rich clinical data that can be utilised retrospectively but are relatively underutilised for assessing the impact of lifestyle factors on patient outcomes (see section 3.1). A clearer understanding of how social isolation and loneliness impact pre- and post-diagnosis cognitive trajectories would provide crucial insights with potential implications for patient care. This thesis focuses on proxies of social isolation and loneliness attainable from EHRs, aiming to provide novel insights into their impact on the cognition and cognitive trajectories of patients with an ADRD diagnosis, thereby bridging the gap between the understanding of social connection's impact on pre- and post-diagnosis cognitive changes in ADRD patients. The central hypothesis posits that patients experiencing social isolation and loneliness will have more adverse outcomes with regards to cognition and rates of cognitive decline. While a direct measure of disease pathology (e.g. imaging showing atrophy) is not accessible within the EHRs, this hypothesis generally aligns with the broader concept of cognitive reserve, suggesting that social connection modulates cognitive decline.

The following chapter (Chapter 2) aims to investigate the existing literature regarding the impact of social connection on the cognition of specifically patients with an ADRD diagnosis. This is followed by an overview of the methods used throughout the modelling studies conducted as part of this thesis (Chapter 3). The first study (Chapter 4) looks to develop and test a model of social isolation, based on the literature regarding social connection and cognition, ADRD incidence, and cognitive reserve reviewed in Chapters 1 and 2. This study uses multilevel models to assess how social isolation moderates the association between cognitive function and diagnosis duration in a retrospective cohort of ADRD patients. The second study (Chapter 5) builds upon the first study by advancing the statistical analysis techniques used to better assess the non-linear change in cognition across diagnosis duration. The final study (Chapter 6) aims to further advance the model by using natural language processing to integrate proxies of both social isolation and loneliness. The non-linear modelling techniques developed in Chapter 5 are used to test the moderating effects of these new proxies on the association between cognition and diagnosis duration. Finally, Chapter 7 provides a discussion of the study findings in the context of the previous literature, as well as limitations of the current approaches and suggestions for further research.

2. The Impact of Social Connection on Cognition in Patients with Alzheimer's Disease and Related Diseases: A Scoping Review

2.1 Introduction

2.1.1 Rationale

The impact of social connection on the risk of Alzheimer’s Disease and related diseases (ADRD) incidence is well documented. Previous meta-analyses (Desai et al., 2020; Kuiper et al., 2015; Penninkilampi et al., 2018; Sommerlad et al., 2018, 2019) and subsequent longitudinal cohort studies (Elovainio et al., 2020; Shen et al., 2022) have established a connection between proxies of social isolation, the objective lack of social connection (de Jong Gierveld et al., 2006), and increased ADRD risk. Similarly, previous meta-analyses have established an association between proxies of social isolation and reduced cognitive function in older adults without an ADRD diagnosis, though warn against overinterpretation due to possible bias from heterogeneity (Evans et al., 2019; Kuiper et al., 2016; Piolatto et al., 2022). In two meta-analyses (Kuiper et al., 2015; Lara et al., 2019), loneliness – the subjective disparity between desired and perceived social connection (de Jong Gierveld et al., 2006) – has been found to be associated with increased ADRD incidence, though this association was not found in a third meta-analysis (Penninkilampi et al., 2018), nor two subsequent longitudinal cohort studies (Elovainio et al., 2020; Shen et al., 2022). Five additional longitudinal cohort studies (Akhter-Khan et al., 2021; Freak-Poli et al., 2022; Salinas et al., 2022; Shibata et al., 2021; Sutin et al., 2020) investigating the connection between loneliness and ADRD incidence did find a significant association between increased risk and some (though not all) loneliness domains. As with social isolation, meta-analyses found loneliness to be associated with reduced cognitive function in older adults, though, again, there was significant heterogeneity between included studies (Kuiper et al., 2016; Piolatto et al., 2022).

Unlike the well-documented connections to ADRD incidence risk and cognition in older adults without an ADRD diagnosis, the impact of social connection factors on the cognition and cognitive trajectories of adults at and post-ADRD diagnosis is considerably less reported, and synthesis of findings is relatively lacking. Two systematic reviews with meta-analyses provide some insight, albeit primarily focusing on the specific context of COVID-19 social restrictions. Prommas and colleagues (2023) reported that approximately 54% of ADRD patients experienced worsening cognition as a result of COVID-19. This finding was based on studies relying on structured telephone interviews and paper- and online-based surveys, the majority of which were performed with caregivers rather than the patients themselves. Landsteiner and colleagues (2025) also reviewed the impact of COVID-19 social restrictions on ADRD patients, focussing on studies using MMSE as a measure of cognitive function. Their meta-analysis revealed a significant decline in MMSE scores when comparing pre-restriction assessments (measured no more than one year prior to restrictions) to those taken during or up to one year after restrictions. For general dementia, the standardised mean difference in MMSE scores was 0.34 points lower ($p < .001$, 95% CI [0.18, 0.50]), and for AD specifically it was 0.39 points lower ($p < .001$, 95% CI [0.21, 0.57]). However, these findings were accompanied by high heterogeneity ($I^2 = 65.91\%$ and 56.16%, respectively). While these studies provide valuable insight into the impact of COVID-19 pandemic on the cognition of ADRD patients, they do not consider the impact of other social connection proxies outside of this timeframe, or other clinically used measures of cognition (e.g. MoCA, HONOS, ACE etc.).

2.1.2 Objectives

Despite previous reviews, there is still a need to further clarify what approaches to investigating the impact of social isolation and loneliness (as concepts of social connection) in people with ADRD or dementia, and to summarise their findings. As such, the aims of the current scoping review are set out below:

1. Identify the types of study designs (e.g. cross-sectional, cohort etc.) that have been used to investigate the impact of social connection on cognition in people with ADRD and dementia;
2. Identify the social connection variables used in these studies and how they are defined;
3. Identify the commonly used measures of cognition and statistical models used to analyse it;
4. Summarise the findings of the various studies, commenting on common themes.

2.2 Methods

2.2.1 Protocol and Registration

The initial protocol for this study, originally outlined as a systematic review, is registered with the PROSPERO international prospective register of international reviews: https://www.crd.york.ac.uk/PROSPERO/view/CRD42022352273. Adaptation of this protocol to a scoping review was decided due to time and resource constraints. The aims of this review are still broadly in line with the original review objectives outlined in the PROSPERO registration but have been adapted in order to better fit the strengths provided by scoping review methodology (Tricco et al., 2018).

2.2.2 Eligibility Criteria

The inclusion criteria for this review are:

- Studies that involve a sample of patients with a clinical ADRD (e.g. Alzheimer's disease, vascular dementia, dementia with lewy bodies etc.) diagnosis, or dementia, but not limited to pre-morbid conditions (e.g. mild cognitive impairment) and/or carers of people with dementia;
- Studies that report patients' social connection (i.e. level of social isolation and/or loneliness), related factors (e.g. social network size, level of social engagement, marital status etc.), exposure to prolonged periods of time with reduced social connection (e.g. periods of imposed social restrictions due to the COVID-19 pandemic), and/or participation in/exposure to interventions specifically intended to improve levels of social connection;
- Studies that report cognition as the outcome measure, using validated methods (e.g. Mini-Mental State Examination, Montreal Cognitive Assessment etc.), for at least one time point from or including the point of ADRD incidence;
- Studies that, where relevant, report comparisons between patients with poor vs good social connection, rate of cognitive change over time, and/or comparisons of pre vs post intervention/intervention group vs control;
- Studies that are published in peer-reviewed journals available in English language.

2.2.3 Information sources

Database searches were conducted for Web of Science (6th March 2022), Scopus (7th March 2022), PsycINFO (9th March 2022), and PubMed (12th March 2022). Search term development and database searches were performed by this thesis' author, JACM. Forward and backward citation searches of included articles from the database searches were performed using Rayyan (Ouzzani et al., 2016) by JACM on 16th April 2025. The length of time between the initial database search and the forward and backward search likely explains the large number of articles identified at the forward and backward search (see section 2.3.1).

2.2.4 Search Strategy

An example of the terms used to search the Web of Science database is shown in Table 2.1. The application of the search strategy for the Web of Science search is as follows. Line 1 covers terms related to social connection, such as social isolation or loneliness. Line 2 covers terms relating to cognition, such as cognitive decline or cognitive impairment. Line 3 covers terms related to Alzheimer's disease or related diseases, such as dementia, AD, or FTD. Individual search terms in Lines 1-3 are connected using the Boolean term OR, meaning that a result will be returned if either one *or* more of these terms is identified within the fields associated with the article Topic (the title, the abstract and the keywords). Lines 1-3 are connected using the Boolean term AND, meaning that a result will only be returned if it identifies at least one search term from Line 1 *and* at least one search term from Line 2 *and* at least one search term from Line 3. Line 4 provides search terms related to unwanted or irrelevant terms, separated by OR, and connected to Lines 1-3 with the Boolean term NOT, meaning a result will be returned if an article meets the criteria for the search terms in Lines 1-3 and does *not* contain any of the search terms from Line 4 in the article title. Appendix A shows complete search strategies for all remaining databases.

Table 2.1

Web of Science Search Terms

Line	Boolean term	Search terms
1	-	(Topic) "social* isolat*" OR "lonel*" OR "social connect*"
2	AND	(Topic) "cognitive decline" OR "cognition" OR "cognitive impairment"
3	AND	(Topic) "dementia" OR "alzheimer*" OR "AD" OR "FTD"
4	NOT	(Title) "parkinson*" OR "down* syndrome" OR "mouse" OR "mice" OR "rat$" OR "animal$" OR "rodent*" OR "dog$"

Note. The * is used to represent any sequence of characters, while the $ is used to represent zero or one character

2.2.5 Study Selection

Titles and abstracts of articles identified in the database search and forward/backward search were screened for relevance by JACM, after removal of duplicate articles. Full texts for articles deemed potentially relevant (or that could not be ruled out as being irrelevant), based on the titles and abstracts, were collected and reviewed against the inclusion criteria by author JACM. A screening tool was used to judge each full text article against the eligibility criteria. Examples of the screening tool can be found in Appendix B.

2.3 Results

As mentioned in section 2.2.3, the database search was conducted in March 2022. The articles identified at the database search, therefore, provided scope on the literature that informed or motivated decisions made in the three modelling chapters outlined later in this thesis (Chapters 4, 5, and 6). Forward and backwards citation searches were completed in April 2025 in order to provide a more complete and up to date picture of the literature for the sake of this scoping review, even though some of the articles identified at citation search stage were not identified until after all three modelling chapters were completed. To provide clarity the findings of the database search and citation search are presented together to give a more cohesive narrative to the scoping review findings as a whole. A table of the studies identified for inclusion at the database search and at the citation search is included in Appendix C.

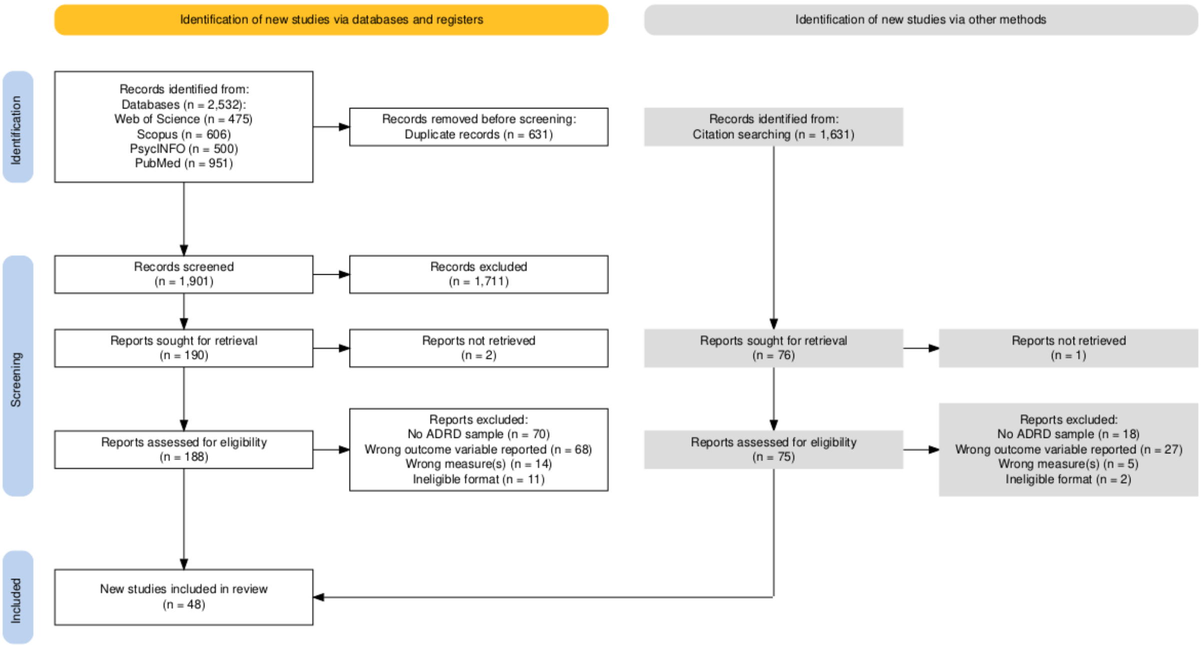
2.3.1 Search Findings

The PRISMA diagram illustrating the results of the study selection processes is shown in Figure 2.1. This figure was created using the PRISMA Flow Diagram tool (Haddaway et al., 2022). Through database searches following the search strategies outlined in section 2.2.4, 2,530 records were identified. Duplicated records were removed leaving 1,899, which had their titles and abstracts screened for relevance against the eligibility criteria. Consequently, 1,709 records were excluded, leaving 190 records to have their full-text articles assessed for eligibility. Two studies could not be retrieved. Of the 188 full-text articles assessed, a total of 165 were deemed to not meet the eligibility criteria (70 for not using a sample including people with a formal ADRD or dementia diagnosis; 68 for not reporting the desired outcome variable, e.g. only reporting incidence risk; 14 for not including a validated measure of cognition, e.g. MMSE, or measure of social connection; 11 for being an ineligible format, e.g. unpublished manuscripts or texts that had not been through peer review, posters, grey literature). The remaining 25 articles were deemed to have met the eligibility criteria and were therefore included in the review.

Forward and backward searches of articles identified through the database searches that were deemed to have met the eligibility criteria yielded 1,742 articles, of which 111 were duplicates. After removing duplicates, 1,631 articles had their titles and abstracts screened for relevance against the eligibility criteria, resulting in 1,536 articles being excluded. Of the remaining 95 articles, 19 had already been assessed as part of the database search full-text eligibility screening (9 previously included, 10 previously excluded), therefore these were not reassessed as part of the forward and backward search full-text screening. One article could not be retrieved. From the remaining 75 articles, full-text reviews led to 53 articles being deemed not to meet the eligibility criteria (18 for not using a sample including people with a formal ADRD or dementia diagnosis; 28 for not reporting the desired outcome variable; 5 for not including a validated measure of cognition, or measure of social connection; 2 for being an ineligible format). The remaining 23 articles were deemed to have met the eligibility criteria and were additionally included in the review.

Figure 2.1

PRISMA Flow Diagram



2.3.2 Study Approaches

The most commonly used study design used a prospective longitudinal approach (n = 18, database = 6, citation = 12). These studies followed participants over time using cohorts recruited from clinical settings (Z.-C. Chen et al., 2021; Defrancesco et al., 2024; Gan et al., 2021; Harsányiová & Prokop, 2018; Te Boekhorst et al., 2009; Tsatali et al., 2023), or through disease research related programmes (Bakker et al., 2023; D. A. Bennett et al., 2006; Clare et al., 2020, 2024; Ebly et al., 1999; Laininger et al., 2024; Lehmann et al., 2010; Manca et al., 2022; Perry, McConnell, Peng, et al., 2022; Perry, Roth, et al., 2022; Tsatali et al., 2021). Follow-up durations varied, ranging from 6 months to several years.

Cross-sectional approaches were also frequently employed (n = 14; database = 10, citation = 4). Of these, seven studies recruited participants through clinical and/or care settings (Azevedo et al., 2021; Balouch et al., 2019; Borelli et al., 2021; Dobrzyn-Matusiak et al., 2014; Li et al., 2022; Mohammadian et al., 2022; Nikmat, Hawthorne, et al., 2015). The other seven utilised data from longitudinal cohorts assessed at a single time point, such as at baseline (Abbott & Pachucki, 2017; Clare et al., 2020; Edwards & Morris, 2007; Lampinen et al., 2022; Missotten et al., 2009; Tuokko et al., 1999; Victor et al., 2020).

Nine Studies (database = 4, citation = 5) used a retrospective, or mixture of retrospective and prospective design. For these studies, cohorts were sourced from a variety of settings, including data from data from a hospital patient registry and follow-up telephone interview (Barguilla et al., 2020), patients identified from randomised control trials (Dura-Perez et al., 2022), data from clinical records (Gan et al., 2021; Joo et al., 2022), national health insurance data (T. W. Lee et al., 2014), adult day centre records (Sánchez-Valdeón et al., 2023), and a dementia diagnosis centre (Sun et al., 2021).

Furthermore, three studies from the database search investigated pre- and post-intervention outcomes (Fritsch et al., 2014; J. Lee & Lee, 2020; Maggio et al., 2023), while another combined a cross-sectional approach with a longitudinal analysis of a subgroup of participants with follow-up assessment data (Zhang et al., 2022). One study from the citation search combined prospective data collection with autopsy data (Lao et al., 2024), and another analysed data from a randomised control trial (Dyer et al., 2021). Finally, one study from the database search investigated an individual case of an 87-year-old woman living in a long-term care facility (LeVasseur, 2021).

2.3.3 Social Connection Variables

A variety of social connection variables were used across the studies identified for inclusion in the review. The majority of these studies (n = 41; database = 20, citation = 21) assessed at least one social isolation variable. One type of social isolation proxy utilised by 18 studies (database = 10, citation = 8) included isolation associated with the COVID-19 pandemic, such as lockdowns or social restrictions (Azevedo et al., 2021; Bakker et al., 2023; Barguilla et al., 2020; Borelli et al., 2021; Z.-C. Chen et al., 2021; Defrancesco et al., 2024; Dura-Perez et al., 2022; Gan et al., 2021; Joo et al., 2022; LeVasseur et al., 2021; Manca et al., 2022; Mohammadian et al., 2022; Perach et al., 2023; Pereiro et al., 2021; Sánchez-Valdeón et al., 2023; Tondo et al., 2021; Tsatali et al., 2021, 2023). Living status, used by 10 studies (database = 5, citation = 5), measured whether participants were living alone or with others (X. Chen et al., 2020; Clare et al., 2020; Dura-Perez et al., 2022; Ebly et al., 1999; Edwards & Morris, 2007; Harsányiová & Prokop, 2018; Lehmann et al., 2010; Sun et al., 2021; Tuokko et al., 1999; Victor et al., 2020). Accommodation status was used by a further six studies (database = 3, citation = 3) to assess whether participants were living in supported accommodation, such as nursing or care homes, or in home/community dwelling settings

(Dobrzyn-Matusiak et al., 2014; Edwards & Morris, 2007; Harsányiová & Prokop, 2018; T. W. Lee et al., 2014; Nikmat et al., 2015; Te Boekhorst et al., 2009). Two intervention studies from the database search included participation in social activities in group settings (Fritsch et al., 2014; Maggio et al., 2023).

Other studies used more direct measures of social isolation including the frequency of social contact (n = 5; database = 4, citation = 1; Abbott & Pachucki, 2017; Clare et al., 2020; LeVasseur, 2021;Perach et al., 2023; Pereiro et al., 2021), social/personal network size/connections (n = 5; database = 4, citation = 1; Abbott & Pachucki, 2017; Bennett et al., 2006; Norton et al., 2009; Perry, McConnell, Coleman, et al., 2022; Perry, Roth, et al., 2022), and responses to the Friendship Scale (Hawthorne, 2006; Hawthorne & Griffith, 2000; n = 1; Nikmat et al., 2015). Six studies (database = 6, citation = 6; Balouch et al., 2019; Dyer et al., 2021; Laininger et al., 2024; Li et al., 2022; Mohammadian et al., 2022; Victor et al., 2020) assessed responses to the Lubben Social Network Scale (Lubben, 1988).

Eight studies (database = 5, citation = 3) used at least one measure of loneliness. Four studies (Balouch et al., 2019; Mohammadian et al., 2022; Lao et al., 2024; Victor et al., 2019) from the database search included responses to the de Jong Gierveld Loneliness scale (De Jong Gierveld & Tilburg, 1999). One study (Sun et al., 2021) from the citation search utilised responses from the UCLA Loneliness scale (Russell, 1996). Two studies (database = 1, citation = 1) assessed loneliness using a binary response question (Lampinen et al., 2022; Zhang et al., 2022). One intervention study (J. Lee & Lee, 2020) from the database search focussed on combating loneliness.

2.3.4 Measures of Cognition and Analytical Approaches

The Mini-Mental State Examination (MMSE; Folstein et al., 1975) was the most used (n = 34; database = 18, citation = 16) cognitive measure from the studies identified (Abbott & Pachuki, 2017; Bakker et al., 2023; Balouch et al., 2019; Bennett et al., 2006; Borelli et al., 2021; Z.-C. Chen et al., 2021; Clare et al., 2020, 2024; Defrancesco et al., 2024; Dobrzyn-Matusiak et al. 2014; Dura-Perez et al., 2022; Ebly et al., 1999; Edwards & Morris, 2007; Gan et al., 2021; Harsányiová & Prokop, 2018; Joo et al., 2022; Laininger et al., 2024; Lampinen et al., 2022; J. Lee & Lee, 2020; Lehman et al., 2010; Maggio et al., 2022; Manca et al., 2022; Missotten et al., 2009; Nikmat et al., 2015; Norton et al., 2009; Pereiro et al., 2021; Sánchez-Valdeón et al., 2023; te Boekhorst et al., 2009; Tondo et al., 2021; Tsatali et al., 2021, 2023; Tuokko et al., 1999; Victor et al., 2020). The Montreal Cognitive Assessment (MoCA; Nasreddine, 2005) was the next most used (n = 9, database = 5, citation = 4; Z.-C. Chen et al., 2021; Gan et al., 2021; Laininger et al., 2024; Mohammadian et al., 2022; Perry, McConnell, Coleman, et al., 2022; Perry, McConnell, Peng et al., 2022; Perry, Roth, Peng et al., 2022; Tsatali et al., 2021, 2023). Another well used measure (n = 8; database = 3, citation = 5; Barguilla et al., 2020; Z.-C. Chen et al., 2021; Defrancesco et al., 2024; Dyer et al., 2021; Gan et al., 2021; Joo et al., 2022; Perach et al., 2023; Pereiro et al., 2021) included the Clinical Dementia Rating scale (CDR; Morris, 1993). Two studies (database = 1, citation = 1; Clare et al., 2020, 2024) used Addenbrooke's Cognitive Examination III (ACE-III; Noone, 2015). One study (LeVasseur, 2021) from the database search used the Brief Interview for Mental Status (Saliba et al., 2012). Another two (database = 1, citation = 1; Dyer et al., 2021; Zhang et al., 2022) used the Alzheimer’s Disease Assessment Scale-cognitive component (ADAS-cog; Rosen et al., 1984). The study by Fritsch and colleagues (2014) utilised the the CERAD Word List Memory Test (Morris et al., 1989) and the Wechsler Memory Scale (Wechsler, 1945). The study by Tsatali and colleagues (Tsatali et al., 2021), in addition to the MMSE and MoCA, also utilised Rey’s Verbal Learning Test (Rey, 1958), the Phonemic Verbal Fluency test (Borkowski et al., 1967), the Rey Complex Figure Test (see Jerskey & Meyers, 2011), and the Wechsler Adult Intelligence Scale (Wechsler, 2012). Bennett and colleagues (2006) utilised AD pathology, amyloid load, and neurofibrillary tangle data from autopsy as markers of disease progression, while Zhang and colleagues (2022) utilised amygdala volume.

In examining the analytical approaches employed across the reviewed articles, a diverse range of statistical techniques were utilised to address their respective research questions. The most prevalent category (n = 29; database = 12, citation = 17) of analysis utilised regression-based techniques, such as linear regression, multiple regression, and logistic regression (including multinomial and disordered multi-class variations; Bakker et al., 2023; Balouch et al., 2019; Bennett et al., 2008; Borelli et al., 2021; Z.-C. Chen et al., 2021; Clare et al., 2020, 2024; Defrancesco et al., 2024; Dura-Perez et al., 2022; Dyer et al., 2021; Ebly et al., 1999; Edwards & Morris, 2007; Fritsch et al., 2014; Gan et al., 2021; Harsányiová & Prokop, 2018; Joo et al., 2022; Lampinen et al., 2022; Lao et al., 2024; Lee et al., 2014; Lehmann et al., 2010; Manca et al., 2022; M. C. Norton et al., 2009; Perry, McConnell, Coleman, et al., 2022; Perry, Roth, et al., 2022; Sánchez-Valdeón et al., 2023; te Boekhorst et al., 2009; Tuokko et al., 1999 Victor et al., 2020), to model the influence of predictor variables on outcome variables and to identify potential risk factors or determinants. Another prevalent (n = 25; database = 13, citation = 12) analysis technique involved comparisons between groups or conditions, such as t-tests, ANOVA (and non-parametric equivalents like Kruskal-Wallis and Mann-Whitney U-tests) and chi-square tests to discern statistically significant differences in demographic, clinical, cognitive, and other relevant variables (Azevedo et al., 2021; Barguilla et al., 2020; Z.-C. Chen et al., 2021; Defrancesco et al., 2024; Dobrzyn-Matusiak et al., 2014; Dura-Perez et al., 2022; Ebly et al., 1999; Edwards & Morris, 2007; Gan et al., 2021; Joo et al., 2022; Laininger et al., 2024; Lampinen et al., 2022; Lee et al., 2014; J. Lee & Lee, 2020; Maggio et al., 2022; Manca et al., 2022; Missotten et al., 2009; Nikmat et al., 2015; Te Boekhorst et al., 2009; Tondo et al., 2021; Tsatali et al., 2021, 2023; Tuokko et al., 1999; Victor et al., 2019; Zhang et al., 2022).

Several studies (n = 7; database = 3, citation = 4) also used covariance-based analyses, specifically ANCOVA and repeated-measures ANCOVA and mixed-measures ANOVA (Dobrzyn-Matusiak et al., 2014; Missotten et al., 2009; Laininger et al., 2024; Manca et al., 2022; Pereiro et al., 2021; Tsatali et al., 2023; Victor et al., 2020). Additionally, seven studies (database = 4, citation = 3) assessed the relationship between variables using correlational techniques including Pearson's and Spearman's correlation coefficients (Abbott & Pachucki, 2017; Azevedo et al., 2021; Dobrzyn-Matusiak et al., 2014; Lampinen et al., 2022; Lehmann et al., 2010; Sun et al., 2021). Less commonly used analyses included Path analysis was employed by Perach and colleagues (2023) using Structural Equation Modelling (SEM) to build a path model examining loneliness as an outcome, with social resources, wellbeing, and cognitive impairment as predictors, adjusting for background variables and utilizing Latent Growth Curves for repeated measures. Finally, principal component analysis (PCA) was used by Defrancesco and colleagues (2024) to reduce the dimensionality of variables from a social factor questionnaire before including the extracted factors in a logistic regression model to predict newly occurring loneliness.

2.3.5 Summary of Included Article Findings

2.3.5.1 Cognitive Decline and COVID-19 Related Social Isolation

Studies often reported perceived cognitive decline during the COVID-19 pandemic and associated social isolation (Azevedo et al., 2021; Barguilla et al., 2020; Borelli et al., 2021). Caregivers frequently observed worsening memory, attention, and orientation in ADRD patients. Despite these perceptions, some studies did not find a significant difference in objective cognitive measures (e.g. MMSE or CDR scores) pre- and post-lockdown, despite also reporting increased neuropsychiatric issues (Bakker et al., 2023; Barguilla et al., 2020;

Borelli et al., 2021; Dura-Perez et al., 2022; Gan et al., 2021; Joo et al., 2022; Manca et al., 2022).

Conversely, other studies did find evidence linking COVID-19 related social isolation to cognitive outcomes. For instance, more severe CDR dementia groups showed lower MMSE scores, even when accounting for social contact during lockdown (Pereiro et al., 2021). A notable finding was that of a greater loss of cognitive function in patients visiting dementia centres during the pandemic compared to previous years, with cognitive decline in AD patients worsening year-on-year (Perach et al., 2023, Tondo et al., 2021; Tsatali et al., 2021). This decline was strongly linked to worsening neuropsychiatric disturbances, which the authors suggest is potentially influenced by the impact of the COVID-19 pandemic (Tsatali et al., 2021). Additional findings suggest a decline in cognition from before lockdown to during lockdown could be linked with reduced social contact, depending on ADRD diagnosis (Z.-C. Chen et al., 2021). Further studies similarly indicated increased dementia severity and faster rates of cognitive decline during the COVID-19 pandemic, particularly during periods of home confinement (Perach et al., 2023; Sánchez-Valdeón et al., 2023; Tsatali et al., 2023). In their case report, LeVasseur (2021) comments that their patient's Brief Interview for Mental Status declines from 11 to 9 to 0 over seven months of COVID-19 lockdown, indicating a progression from mild to severe cognitive impairment. Manca and colleagues (2022) reported no significant changes in MMSE from before lockdown, however time spent under social restrictions was a significant predictor of worse cognition in both immediate and delayed recall tests.

2.3.5.2 Social Network Characteristics and Cognition

Beyond the context of the COVID-19 pandemic, studies utilising other social isolation proxies, such as social network size and frequency, revealed important associations with cognition. Specifically, a larger network size, smaller network density, and weaker ties were often associated with higher cognitive function in cognitively normal adults (Perry, Roth, et al., 2022). These three variables also significantly moderated the association between amygdala atrophy and cognitive function, whereas smaller and denser networks were associated with ADRD and MCI (Perry, McConnell, Coleman, et al., 2022). Furthermore, there was not a significant relationship between marital status and cognitive function, nor stress and cognitive function, but there was a significant interaction between the three variables when considering widowed, divorced, and never married marital statuses, but not married or cohabitating. Network diversity and frequency of contact, but not size of network, were positively associated with cognitive function in ADRD patients (Perry, Roth, McConnell, et al., 2022).

However, these findings were not always consistent, as the study by Abbott and Pachucki (2017) found a significant inverse relationship between network size and cognition (as measured by MMSE) in one cohort but not the subsequent two. Balouch and colleagues (Balouch et al., 2019) found that the size of and frequency of contact with the friendship network (as measured by the LSNS), significantly predicted cognition (B = 0.284, SE = 0.107, p = 0.01, 95% CI = 0.078 to 0.492), and this finding was independent of all other predictors. However, the authors comment that the model overall did not explain a significant amount of the variance within the data. Dyer and colleagues (2021) reported that poor social networks were significantly associated with dementia severity at baseline, controlling for age, gender, diagnosis duration, and years of formal education when measured with the CDR-Sb, but not when measured with the ADAS-Cog. There was additionally no impact of social network scores at baseline on dementia progression at 18 months using either dementia severity measure. Laininger and colleagues (2024) found a significant difference between MMSE of those with poor social networks and average/good social networks. Although they found no differences in MMSE at 12-month follow-up between poor and average/good social network groups when controlling for baseline MMSE, age, gender, education, housing and activities of daily living. Li et al (2022) reported a negative association between social contact and cognitive decline. Pathway analysis revealed a significant direct effect of social contact on cognitive decline, and an indirect effect of frailty on cognitive decline through social contact.

Bennett and colleagues (2006) found that social networks were associated with social activity and cognitive activity, but did not significantly predict global AD pathology score, amyloid-beta load, nor neurofibrillary tangle density as a main effect. The interaction between social networks and global disease pathology was significant (B = 0.097, SE = 0.039, p = 0.016), as was the interaction between social networks and neurofibrillary tangles (B = 0.011, SE = 0.003, p = 0.001). Additional regression modelling revealed the interaction between social network and global disease pathology was significant predictor of semantic memory (B = 0.116, SE = 0.047, p = 0.016), but no other category of cognition (episodic memory, working memory, perceptual speed, or visuospatial ability). The interaction between social networks and neurofibrillary tangles was a significant predictor of episodic memory (B = 0.009, SE = 0.004, p = 0.023), semantic memory (B = 0.015, SE = 0.004, p = 0.0005), and working memory (B = 0.015, SE = 0.005, p = 0.005), but not perceptual speed or visuospatial activity. The interaction between social networks and amyloid burden was not a significant predictor of any cognitive function domain. The authors propose that these results suggest social network size plays a mitigating role on the impact of neurofibrillary tangles on cognition.

The quality of caregiver relationships also played a role, with closer caregiver relationships and spouse caregivers being associated with slower rates of cognitive decline (M. C. Norton et al., 2009). Furthermore, it was also found that patients with spouse caregivers were also more likely to be living at home and cohabiting patients, and cohabiting patients generally had higher MMSE scores (M. C. Norton et al., 2009). Though, generally, studies exploring living status (whether a person was living alone or cohabiting) found mixed results. Living alone was a predictor of institutionalisation, and dementia severity was a predictor of living alone (Ebly et al., 1999). Some studies found that patients living alone exhibited better cognitive scores than those living with others (Clare et al., 2020, 2024; Ebly et al., 1999; Edwards & Morris, 2007, Lehman et al., 2010). However, others found no significant effect (Tuokko et al., 1999).

When considering accommodation status (e.g. patients living in supported accommodation vs mainstream housing), severity of cognitive impairment was significantly higher in patients living in institutional long-term care and in-home care settings than in those receiving a mix of institutional day care and in-home day care (Dobrzyn-Matusiak et al., 2014; Lee et al., 2014). Harsányiová & Prokop (2018) reported patients' mean MMSE scores significantly differed between the patients living alone, patients living in nursing homes, and patients living with family. Post-hoc tests revealed patients living alone had significantly lower scores than patients living in nursing homes. Patients living with family had significantly higher scores than patients living in nursing homes. Patients living with family, and patients living alone scored significantly lower than patients living in nursing homes. Nikmat and colleagues (2015) reported patients living in community settings showed higher average cognitive scores than those living in nursing homes, but this difference did not reach statistical significance ($t = 1.86$, $df = 47$, $p = 0.07$). Place of residence has a significant impact on social interaction, depending on dementia severity, with patients with very severe dementia having higher social interaction scores when living in an at-home setting than in an institutional setting, whereas for patients with less severe dementia, this finding is reversed (Missotten et al., 2009). Rates of decline were not protected by accommodation status (Te Boekhorst et al., 2009).

2.3.5.3 Loneliness and Cognition

The evidence regarding the impact of loneliness on cognition was also mixed. Victor and colleagues (Victor et al., 2020) reported no difference in MMSE scores, loneliness severity, nor disease subtype (e.g. AD, VaD) and loneliness severity. MMSE did not predict moderate loneliness, nor severe loneliness. Additionally, Zhang and colleagues (2022) found lonely AD patients had higher (indicating more impairment) baseline scores on the Japanese adaptation of the Alzheimer Disease Assessment Scale – Cognitive subscale (ADAS-Jcog; Honma, 1992). However adjusted models did not show loneliness as a significant predictor of ADAS-Jcog score change over time in AD but was a significant predictor in MCI patients. Similarly, no significant differences in regional grey matter volume (rGMV) were found between lonely and non-lonely AD patients, however lonely people in the MCI group exhibited decreased rGMV in the cerebellar vermal lobules I-V and the region containing the middle occipital gyrus. On the other hand, Mohammadian and colleagues (2022) found positive associations between Functional Assessment Staging (FAST; Sclan & Reisberg, 1992) scores (with higher scores indicating more cognitive impairment) and avoidance scores, social loneliness, and total loneliness scores.

2.3.5.4 Intervention Efficacy

Fritsch and colleagues' (Fritsch et al., 2014) findings suggested mixed effectiveness of their memory club intervention in terms of cognition (see above for more details). In contrast, Lee and Lee (2020) report positive impacts on cognition following intervention, finding that patients recruited from dementia centres with cognitive impairment showed an increase in mean MMSE scores from pre- to post-intervention. This improvement in the cognitively impaired group was greater than the improvement seen in the cognitively normal group (0.83 points improvement, $p < 0.01$). Similarly, Maggio and colleagues (2023) reported both experimental and control groups experienced statistically significant increases in mean MMSE scores from baseline to follow-up. The experimental group also showed significant improvements in social functioning as measured by the Social Adaptation Self-Evaluation Scale.

2.4 Discussion

This scoping review aimed to further clarify and summarise the findings of studies investigating the impact of social connection on cognition specifically in people with an ADRD diagnosis or dementia by considering the types of study approaches, as well as the social connection proxies, cognitive function measures, and analytical techniques used. Longitudinal studies utilised a mixture of prospective and retrospective approaches. Less common study approaches included intervention studies and one case study. The most frequently used proxies/measures of social connection were social isolation related to the COVID-19 pandemic, living arrangements, social network measures and loneliness measures.

Loneliness was less studied than social isolation amongst the included articles. Widely adopted cognitive and functional measures such as the MMSE, MoCA, CDR and ACE-III were the most commonly used measures of cognition.

There were mixed findings with regards to the impact of social connection on cognition. Without suitable meta-analytic synthesis, it is difficult to make direct comparisons with previous systematic review and meta-analyses investigating social connection proxies in regard to ADRD risk (e.g. Penninkilampi et al., 2018) or cognitive function in people without dementia (e.g. Kuiper et al., 2016). However, through an overview of the study designs and measures, there is demonstrable heterogeneity amongst approaches of studies included in the current scoping review. That a large proportion of studies utilised a cross-sectional approach presents a limitation of the existing literature, due to the inability to assess longer term impacts on cognitive trajectories. The variation in analytical techniques, definitions and proxies of social connection and measures of cognitive outcomes likely explains a proportion of the variation in study findings. That direct cognitive impact appears less clearly evidenced across the studies in this scoping review, compared to the findings of previous meta-analyses highlighted in the introduction, suggests that mechanisms by which social connection influences cognition may differ or be compounded by other factors in individuals already experiencing neurodegeneration. This is supported by the findings of Zhang and colleagues (2022) who reported that loneliness predicted reduced rGMV in MCI patients, but not in AD patients, suggesting that changes in rGMV associated with loneliness may occur earlier in the disease course.

Studies investigating the impact of COVID-19 related social isolation described worsening self- or carer-reported cognition. However, these reports were frequently not supported by statistically significant changes in cognitive functioning. Instead, significant differences in functional ability (e.g. Borelli et al., 2021) and neuropsychiatric symptoms (e.g. Barguilla et al., 2020) were reported during the same timeframe as perceived cognitive decline. It may be the case, then, that patients and/or their caregivers were mistaking declines in functional capacity and/or an exacerbation of neuropsychiatric symptoms as worsening of cognitive functions. Neuropsychiatric symptoms, such as agitation, depression, anxiety, apathy and psychosis are highly prevalent in ADRD and can profoundly affect quality of life and functional independence (Borda et al., 2023). The findings by Z.-C. Chen et al. (2021) further support this potential connection, suggesting that worsening neuropsychiatric symptoms during COVID-19 may be associated with a reduction in social contact. Though, in their study, reduced social contact was not associated with changes in MMSE scores, the association with increased neuropsychiatric symptoms was significant. Loss of structured activity and social engagement, such as that presumably experienced by ADRD patients during periods of the COVID-19 pandemic, may directly lead to increased neuropsychiatric symptoms such as increased boredom, apathy or withdrawal due to lack of opportunities to engage, and increased neuropsychiatric symptoms may affect attention, motivation, or executive functions, potentially giving the impression of cognitive decline, even if core cognitive abilities remain intact. Increased caregivers burden (Borelli et al., 2021) and diminished contact with patients could potentially skew impressions of patient cognitive decline as well as other symptoms. Worsening of patient cognition could add further distress to caregivers, as these factors were found to be associated (Borelli et al., 2021). Changes in caregiver-patient relationship closeness may also have a direct impact on rates of cognitive and functional decline (M. C. Norton et al., 2009). ‘Brain fog’ is a well reported symptom of COVID-19 infection, though infection is not necessarily reported in these studies, this could be one pathway through which infected patients experience a temporary, or in some cases more long-term, impairment of cognitive functions during this time period (Nouraeinejad, 2022).

Studies using longitudinal analyses to explore the change in cognition over time related to social connection describe significant impacts of social isolation proxies more consistently than other study designs. For example, Balouch et al. (2021) found that frequency of social contact with friends significantly predicted cognition, such that increased frequency was associated with better cognitive function. The authors comment that it is unclear whether maintaining friendship contact acts as a protective factor, or whether severity of cognitive impairment leads to difficulties maintaining friendships. Z.-C. Chen et al. (2021) reported significant changes in MMSE scores for AD and DLB patients during their 1 year follow-up, but not MCI patients. Changes in AD MMSE were comparable with previous studies' rates of cognitive decline, but the rate of decline in DLB patients was roughly twice as much as that of AD patients, and more than a point per year higher than comparable studies. The authors suggest that DLB patients may have been particularly vulnerable to cognitive decline during the COVID-19 pandemic. Harsányiová and Prokop (2018) report different rates of cognitive decline across living arrangements, with patients living in nursing homes displaying faster rates of decline that those living with family, and those living alone displaying faster rates of decline that those living in nursing homes. Norton et al. (2009) report that patient-caregiver relationships predict rates of cognitive decline, with stronger relationships associated with slower rates of cognitive decline. In one study, Perry and colleagues (Perry, McConnell, Coleman, et al., 2022) reported that social network size, density, and strength moderate the association between brain atrophy and cognitive function (thus demonstrating cognitive reserve, i.e. Stern et al., 2020, 2023). Additionally, the authors found a moderating effect of marital status on the association between perceived stress and cognitive function. The authors suggest that their findings have implications for downstream pathophysiological processes. In another study, Perry and colleagues (Perry, Roth, et al., 2022) reported that having a more complex social network structure was associated with better cognitive outcomes, as well as moderated the association between amygdala volume and cognition. The authors suggest complex social network structures may promote cognitive stimulation and therefore increase cognitive reserve. Fritsch et al. (2014) report mixed findings of their intervention designed to, in part, improve social isolation. This may reflect the effectiveness of the intervention, rather than the specific impact of social isolation.

Some studies investigating living arrangements found a negative association between living status (whether a person lives with others vs alone) and cognitive function, in that patients living alone were more likely to have higher cognitive function (Clare et al., 2020; Edwards & Morris, 2007). Conversly, the study by Harsányiová & Prokop (2018) found a positive association between living status and cognitive function, in that patients living with others were more likely to have higher cognitive function. In line with the theory that living status is the most objective measure of social connection (Desai et al., 2020) and that higher social isolation is linked to worse cognitive outcomes in patients without ADRD diagnoses or dementia, and increased risk of incidence (Kuiper et al., 2015, 2016), living alone would be expected to have a negative impact on patient cognition, yet this is not the case in two out of the three studies that investigate this included in this review. These findings could suggest that living alone only exacerbates declines in cognitive functioning earlier in the neurodegenerative process. Alternatively, this may reflect a difference in more general function between ADRD patients, as many patients living with others may live in supported accommodation. Those living alone may retain more function to enable living independently. Clare et al (2020) report that, despite being more likely to be lonely, and more likely to have smaller social networks, people living alone are more likely to have higher frequency of social contact. Harsányiová & Prokop (2018) suggest that patients living alone and in nursing homes having increased cognitive decline compared to patients living with family may reflect patients living alone and in nursing homes living in impoverished conditions. This conclusion could represent geo-cultural issues surrounding supported accommodation standards/funding, or (lack of) support for elderly living alone etc.

Two studies found evidence for the impact of loneliness on cognition/rates of cognitive change: Mohammadian et al. (2022), found higher levels of loneliness were associated with worse cognition and functional ability; while Zhang et al. (2022), found loneliness was associated with increased loss of rGMV and increased rates of cognitive decline, though this was only in MCI patients. The study by Balouch et al. (2019), however, failed to find evidence for the impact of loneliness on cognition in ADRD patients. Studies identified at the forward and backward citation search stage mostly mirrored the findings of the main database search. There was, again, a mixture of findings with regards to cognitive changes over the COVID-19 pandemic. More studies demonstrated an association between living alone and increased cognition (Clare et al., 2024; Ebly et al., 1999; Lehmann et al., 2010), while one failed to find evidence of an effect of living alone on cognition (Tuokko et al., 1999). Patient social interaction in different accommodation settings may be mediated by dementia severity (Missotten et al., 2009). Social networks may moderate the association between NFTs and episodic, semantic and working memory (D. A. Bennett et al., 2006).

2.5 Conclusion

The articles identified at the database search provided insight into exposures for social isolation, particularly marital status, living arrangements and social networks, that would inform the analyses in the following empirical modelling chapters. Overall, the literature suggests a complex and multifaceted relationship between social factors, including social isolation and loneliness, and cognitive function in ADRD patients. While the COVID-19 pandemic highlighted a perceived and, in some cases, actual acceleration of cognitive decline in the context of increased social isolation, the impact of other social isolation proxies (e.g. marital status, living arrangements, social networks) on cognitive trajectories is not always straightforward and can vary depending on the cognitive measure used and the stage of the disease. Studies investigating the impact of social connection factors on cognitive and functional performance in patients with ADRD diagnoses and dementia found mixed evidence for its impact. These findings are hard to compare to previous meta-analyses without formal synthesis, though numerous studies reported associations between living alone and improved cognitive functioning, going against what would be expected based on previous literature regarding social isolation and cognition and ADRD incidence risk. Studies utilising longitudinal analyses were most consistent in finding evidence for the effect of social isolation on cognitive outcomes, though the effect of loneliness was not as consistently reported. Several studies utilising direct measures of disease progression, such as rGMV, suggest social connection plays a role in increasing cognitive reserve, but this effect may be more prominent earlier in the disease manifestation.

3 Overview of Methodological Approaches

This chapter outlines several methods which are used frequently throughout studies conducted as part of this thesis. The objective of this chapter is to provide the reader with an insight into these methods before reading the study chapters, in order to prepare the reader and minimise repetition across those chapters. Methods that are specific to one study will be explained in more detail in that specific study chapter.

3.1 Electronic Healthcare Records

Electronic healthcare records (EHRs) offer an accessible yet secure means of potentially comprehensively recording patient interactions with primary and secondary healthcare providers (Goodday et al., 2020; Pagliari et al., 2007). Research utilising EHRs can lead to positive clinical outcomes, such as improving the quality of patient care, as well as improved population health (Menachemi & Collum, 2011). The longitudinal data comprising the EHRs allows the study of complex interactions between outcome effects and variables of interest (Vaci et al., 2020). However, due to the high proportion of unstructured, natural text within EHRs, it is necessary to adopt algorithm-based approaches to data extraction for the sake of time and resources (Goodday et al., 2020; Murdoch & Detsky, 2013; Vaci et al., 2020). Previous studies have demonstrated that natural language processing (NLP) algorithms can be utilised for data extraction of key variables within EHRs (Gligic et al., 2020; Kormilitzin et al., 2021; Liu et al., 2022; Senior et al., 2020; Vaci et al., 2020), and how such data can then be used to investigate the interaction(s) between variables pertaining to ADRD, such as medication and cognitive testing, from a retrospective cohort of patients (Liu et al., 2022; Vaci et al., 2021).

The data collected in the EHRs used in the studies included in this thesis are from patients from Oxford Health NHS Foundation Trust between 1995 and 2022. The data are accessible through the UK-CRIS system and have been maintained by Akrivia Health (https://akriviahealth.com/). The system allows access to structured information, e.g. demographic information and diagnosis code, as well as unstructured textual information, such as clinical records. These documents collect free-text information on the history of mental disorders under treatment, relevant cognitive assessments, and any other clinically relevant discussion between services and support that went on throughout the treatment.

3.2 Multilevel Models

The multilevel (a.k.a. hierarchical, a.k.a. mixed-effects) models conducted as part of this thesis are done so based on the author's interpretation of Gelman and Hill (2006) and Wood (2017), along with guidance and feedback from the author's supervisory team, NV and TS. Multilevel models are a form of advanced regression used to analyse data that is within a nested (or 'hierarchical') structure, therefore not assumed to be independent like traditional regression. Rather data are assumed to be more likely to be similar within nested groups compared to between groups.

Multilevel models estimate regression coefficients at a first-level (as in a traditional regression; in 'mixed-effect' models, these are referred to as 'fixed effects'), and at a higher-level ('random effects'), accounting for the variability between groups, assuming group-specific parameters are drawn from a common distribution. A classic example of a multilevel model (Gelman and Hill, 2006) gives an educational study where data are collected from students from various schools. Parameters at the student-level (e.g. sex, test results, parental education), and hyperparameters at the school-level (e.g. average class size, school funding) can be estimated. This could be expanded further by adding estimates at the district level (e.g. district policies). In this expanded example model there are students nested within schools nested within districts.

Repeated measures also follow a multilevel structure. In such cases, observations are nested within persons, and persons may be nested within other higher-level groups. A strength of multilevel models is that they are capable of handling missing data, making them particularly suitable for longitudinal studies. Assuming data are missing at random, multilevel models leverage observed data from within an individual or within their group to make estimations. As higher level effects are estimated as deviations from the grand mean, missing data estimations are pulled closer to the grand mean.

3.2.1 Linear Multilevel Regression Models

Linear multilevel regression models (LMRMs) are used across all three study chapters, with observations nested within patients. Various factors are collected at the observation level, while others are collected at the patient level. LMRMs have been previously used to assess the impact on ADRD patients’ cognitive trajectories of APOE alleles (X. R. Chen et al., 2021) and ADRD medications (Vaci et al., 2021).

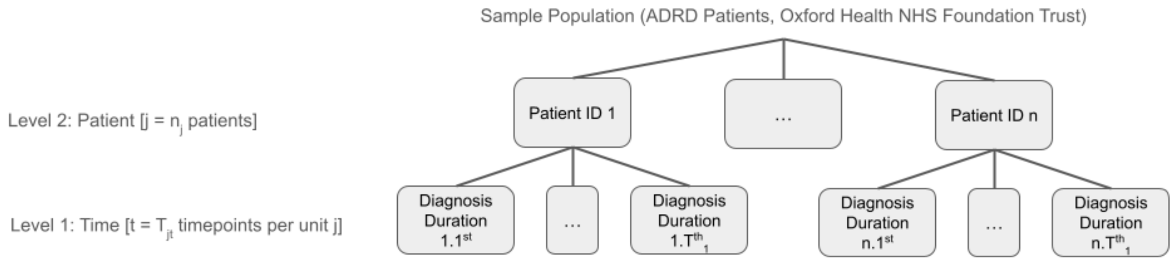
Equation 3.1

Multilevel Equation

$$Y^{\text{Cognition}}_{jt} = \beta_0 + \beta_{0j} + (\beta_1 + \beta_{1j})X^{\text{Diagnosis duration}}_{jt} * X^{\text{SI proxy}}_{j} + X^{\text{Controls}}_{j} + \varepsilon_{jt}$$

Figure 3.1

Multilevel Structure for a Two-Level Longitudinal Model for Observations of Timepoints Nested Within Patients.



3.2.2 Generalised Additive Multilevel Models

Generalised additive multilevel models (GAMMs) are used in studies 2 and 3. GAMMs are a non-linear data driven approach that can be used to model repeated measures over time. Previous studies have demonstrated how cognitive decline in ADRD patients is non-linear, often displaying a period of stabilisation around diagnosis and greater variability in the years proceeding and following diagnosis (Vaci et al., 2021). GAMMs use smooth functions to model the relationship between a predictor variable (such as diagnosis duration) and the outcome variable (such as cognition) without forcing a rigid linear assumption, while the multilevel component accounts for the repeated observations nested within the same individuals. GAMMs offer a flexible framework to model how cognition changes non-linearly over time while simultaneously acknowledging the inherent variability between patients and the dependence within patients given the repeated observations. Therefore, they may model the change in ADRD patient cognition over time more accurately than linear techniques. However, their output is often difficult to interpret and relies on coefficient estimates from parametric model outputs to ease interpretation.

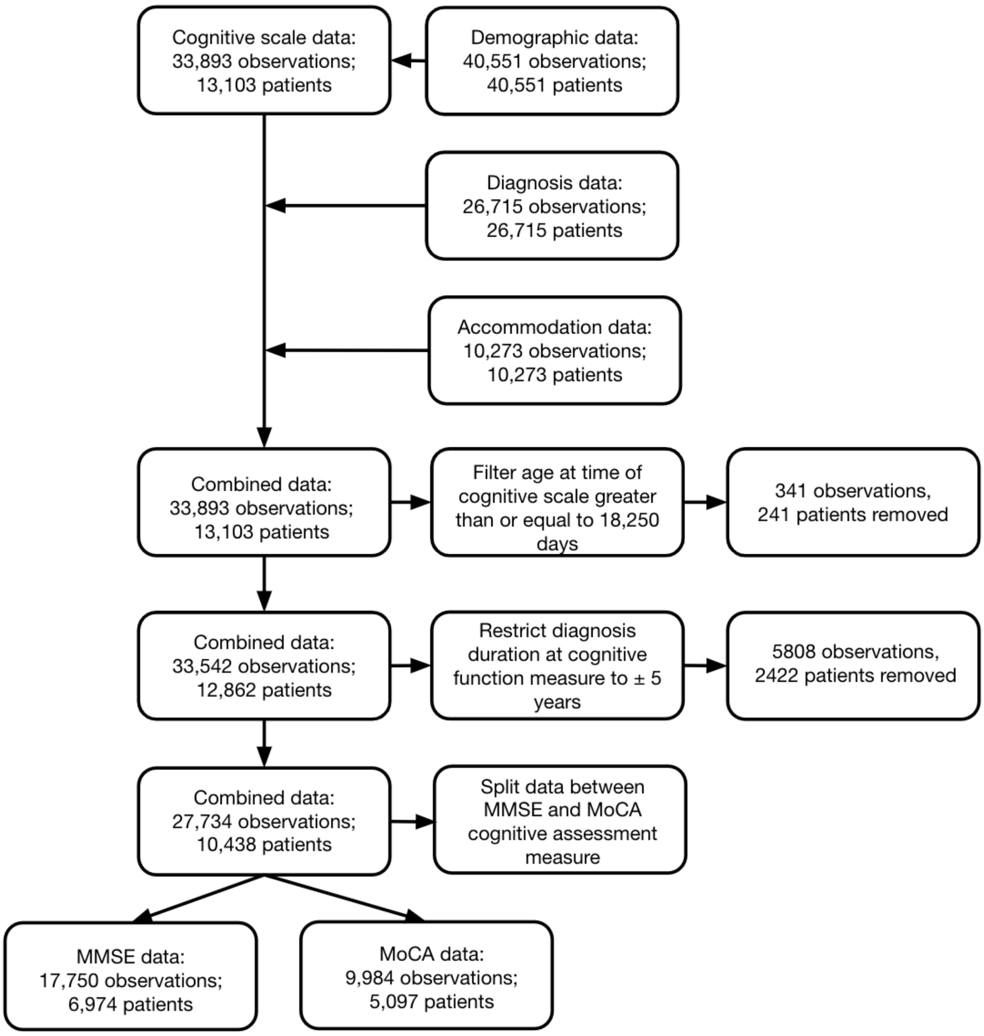
3.3 Study Design, Data Sources, and Sample

This study utilised a retrospective cohort design, collecting secondary data from EHRs of patients from Oxford Health NHS Foundation Trust. The trust employs approximately 6,500 staff over 150 sites, providing a range of health services for approximately 2.5 million people across Buckinghamshire, Oxfordshire, Wiltshire and Swindon, and Bath and North East Somerset (Oxford Health NHS Foundation Trust, 2024). EHRs were accessible through UK-CRIS, maintained by Akrivia Health (https://akriviahealth.com/). The full cohort consisted of 6,388,715 records from 34,469 patients with ICD codes matching an ADRD diagnosis (F00 – F00.9, F01, F02, F03, G30), excluding MCI (F06.7), between March 2008 and June 2022. NLP processes were implemented by the primary supervisor of this project, NV, to extract information from the rich clinical texts. Ethical approval for the use of the data was acquired from the local UK-CRIS oversight committees. The University of Sheffield Ethics Application Review Board approved the project (ID: 045869) after self-declaration that the research will involve only existing clinical data that is robustly anonymised and is unlikely to cause offence to those who originally provided the data should they become aware of it. Due to the anonymised nature of the data, it was not possible or necessary to obtained informed consent.

Data extracted from the EHRs regarding patients' demographics, type of ADRD diagnosis, accommodation status and cognitive function were imported to RStudio (v1.3.1093; RStudio Team, 2020), in long format, merged and prepared for longitudinal data analysis. Due to the nature of the clinical assessments reflected in the EHRs, timepoints between observations were sporadic. Data were amended to remove or correct for errors presumed to have occurred during the NLP extraction, or as a result of an encoding/reporting error, using a combination of functions from the 'dplyr' (v1.0.6 – Wickham et al., 2021), 'lubridate' (v1.7.10 – Grolemund & Wickham, 2011) and 'parsedate' (v1.3.0 – Csárdi & Torvalds, 2022) packages, such as removing observations of patient IDs that had been incorrectly extracted, transforming dates into a uniform format, or removing observations of impossible dates (such as those indicating a date outside of possible record date parameters). The extracted EHR data were restricted to patients aged at least 50 years. All patients had, or would go on to receive a factual, affirmed ADRD diagnosis, with data collected regarding ADRD cause and date of diagnosis. To capture the critical period of disease onset, observations were included from 5 years (18,250 days) prior to diagnosis, a timeframe during which symptoms and neuropathological processes often occur. This 5-year window was also applied post-diagnosis to capture following changes that may result from progressing neuropathology and/or care changes. This ±5-year boundary was chosen to strike a balance between observing a clinically meaningful period of change surrounding diagnosis, and ensuring data reliability, which tended to decrease the further away from diagnosis the observation was made. Figure 3.2 shows a flow chart describing the steps in the data processes.

Figure 3.

Data Processing Flow Chart



3.4 Ubiquitous Variables

3.4.1 Cognitive Function

The outcome variable, cognition, was captured using either the Mini-Mental State examination (MMSE – Folstein et al., 1975) or Montreal Cognitive Assessment (MoCA – Nasreddine et al., 2005), two cognitive assessment measures that are widely used as cognitive screening tools in memory assessment clinics within the UK National Health Service. Both measures have been found to be able to accurately discern cognitive impairment from healthy cognition (Pezzotti et al., 2008; Roalf et al., 2013) and both tests result in a score with a denominator of 30. They share several tested domains, including orientation, memory recall, and attention. However, the MoCA is considered more sensitive for detecting MCI and early AD (Ciesielska et al., 2016; Jia et al., 2021; Nasreddine et al, 2005; Pendlebury et al., 2012; Wang et al., 2013), DLB (Wang et al., 2013), and cognitive deficits in PD (Lessig et al., 2012), placing greater emphasis on executive function and visuospatial skills (Lessig et al., 2012; Nasreddine et al., 2005; Siqueira et al., 2019). Conversely, the MMSE has been used when tracking cognitive decline in more advanced AD (Panegyres et al., 2013; Ward et al., 2002; Wattmo et al., 2016), yet research suggests it could be susceptible to floor effects when adjusting for education level (Franco-Marina et al., 2010).

Mentions of patients' cognitive scores on MMSE or MoCA were derived from the free text by the NLP model (see Vaci et al., 2021). Patient's scores with denominators of 28 and 29 could have resulted from patients with difficulties reading or writing being unable to answer related questions. As such these results were transformed, adding 2 or 1 respectively to the numerator and denominator to give scores with a denominator of 30. Scores with denominators of less than 28 or more than 30 were considered NLP-related errors, possibly resulting from a misclassification of dates or other numbers as MMSE/MoCA scores, and these observations were excluded from the dataset. Similarly, patients without any cognitive assessment score data (e.g. where scores were given as 'null' or 'NA') were removed. A maximum of one cognitive measure per month per patient was retained in the dataset, prioritising the earliest cognitive measure observation when more than one was extracted. For data analyses, separate datasets and models were created for observations using MMSE as the measure of cognitive function, and observations using MoCA as the measure of cognitive function.

3.4.2 Diagnosis Duration

The time variant, diagnosis duration, was calculated for each patient by finding the difference in time between the date of diagnosis and the date of cognitive assessment, extracted from the EHRs during the NLP process, for each measure of cognitive function (MMSE or MoCA), expressed in years. Where multiple diagnosis dates were found, the oldest date attributed to a factual and affirmed ADRD diagnosis was used. When available, where patients reached full ADRD diagnosis but also had cognitive assessments prior to full diagnosis (within the 5-year threshold) those pre-diagnosis observations were included, therefore negative diagnosis duration values represent their respective time before the date of diagnosis, positive diagnosis durations represent their respective times after the date of diagnosis, and zero represents the point of diagnosis.

3.4.3 Control Variables

Variables regarding patients' diagnosis cause (e.g. AD, DLB, VaD), age, ethnicity, and sex were collected (or calculated, in the case of age) from structured clinical and demographic data. One diagnosis cause and diagnosis date were recorded per patient. Where multiple diagnosis causes were found for a given patient, the most recent cause information attributed to a factual/affirmed observation was taken to be the most accurate/up to date, and conflicting data were transformed to reflect the most recent data. Where multiple diagnosis dates were found for a given patient, the oldest diagnosis date information attributed to a factual/affirmed observation was used. Patients' ages were calculated for each observation by calculating the difference between their date of birth and the document date corresponding to each cognitive assessment observation, expressed in years. In order to avoid an uninterpretable intercept prediction from the model caused by extrapolation, the age variable was centred by transforming age of 0 years to represent a patient aged 50 years (18,250 days). The choice of 50 years was primarily motivated by improving statistical interpretation (Gelman & Hill, 2006), however, from a clinical perspective, 50 years old represents a critical mid-life point where modifiable risk-factors such as SI exert their greatest influence on dementia risk (Livingston et al., 2024).

3.5 Patient Characteristics

Table 3.1 shows the characteristics of the full sample after the data processing steps described in sections 3.3 and 3.4. The total sample included 27,734 observations from 10,438 patients. The mean age of patients at first observation was 81.13 years, while the mean age of patients across all observations was 80.78 years. Data were split into two sets depending on whether cognition was measured using MMSE or MoCA: 17,750 observations were available for 6,974 patients (2.55 average observations per patient) for the MMSE data; 9,984 observations were available for 5,097 patients for the MoCA data (1.96 average observations per patient). The exact number of units (patients and timepoints/observations) available for each model varied depending on data that were available for the predictors included in the model.

Table 3.1

Sample Cohort Characteristics

Variable	Full sample	MMSE	MoCA
Number of observations	27,734	17,750	9,984
Number of patients	10,438	6,974	5,097
Average observations per patient	2.66	2.55	1.96
Mean cognitive score at first observation* (SD)	-	21.68 (5.83)	17.93 (6.00)
Mean cognitive scores across all observations (SD)	-	21.60 (5.77)	18.19 (5.85)
Marital status, by patient (%)			
Partner†	3,031 (29.04)	2,221 (31.85)	1,298 (25.47)
Separated†	326 (3.12)	213 (3.05)	170 (3.34)
Single‡	330 (3.16)	277 (3.97)	88 (1.73)

Widowed‡	2,140 (20.50)	1,624 (23.29)	791 (15.52)
Not known	4,611 (44.18)	2,639 (37.84)	2,750 (53.95)
Marital status, by observation (%)			
Partner†	9,500 (34.25)	6,762 (38.10)	2,738 (27.42)
Separated†	914 (3.30)	582 (3.28)	332 (3.33)
Single‡	897 (3.23)	722 (4.07)	175 (1.75)
Widowed‡	5,904 (21.29)	4,316 (24.32)	1,588 (15.91)
Not known	10,519 (37.93)	5,368 (30.24)	5,151 (51.59)
Accommodation status, by patient (%)			
Mainstream housing†	2,449 (23.46)	1,077 (15.44)	1,904 (37.36)
Supported accommodation‡	887 (8.50)	563 (8.07)	509 (9.99)
Clinical‡	32 (0.31)	20 (0.29)	19 (0.37)
No fixed abode‡	32 (0.31)	13 (0.19)	23 (0.45)
Incarceration‡	2 (0.02)	-	2 (0.04)
Not known	7,036 (67.41)	5,301 (76.01)	2,640 (51.80)
Accommodation status, by observation (%)			
Mainstream housing†	6,851 (24.70)	2,828 (15.93)	4,023 (40.29)
Supported accommodation‡	2,793 (10.07)	1652 (9.31)	1,141 (11.43)
Clinical‡	92 (0.33)	42 (0.24)	50 (0.50)
No fixed abode‡	76 (0.27)	31 (0.17)	45 (0.45)
Incarceration‡	2 (< 0.01)	-	2 (< 0.01)
Not known	17,920 (64.61)	13,197 (74.35)	4,723 (47.31)

Living status, by patient (%)			
Cohabiting[†]	984 (9.43)	457 (6.55)	746 (14.64)
Alone[‡]	483 (4.63)	210 (3.01)	379 (7.44)
Not known	8,018 (76.82)	5,711 (81.89)	3419 (67.08)
Living status, by observation (%)			
Cohabiting[†]	3129 (11.28)	1,482 (8.35)	1,647 (16.50)
Alone[‡]	1233 (4.45)	480 (2.70)	753 (7.54)
Not known	20,409 (73.59)	14,063 (79.23)	6,346 (63.56)
Mean age at first observation (SD)*	81.13 (7.61)	81.33 (7.68)	80.77 (7.46)
Mean age across all observations (SD)*	80.78 (7.38)	80.97 (7.44)	80.46 (7.25)
Sex, by patient (%)			
Female	6,308 (60.43)	4308 (61.77)	2,959 (58.05)
Male	4,128 (39.55)	2664 (38.20)	2,138 (41.95)
Not known	2 (0.01)	2 (0.03)	-
Ethnicity, by patient (%)			
White	6,851 (65.64)	5,104 (73.19)	2,785 (54.64)
Non-White	141 (1.35)	96 (1.38)	66 (1.29)
Not known	3,446 (33.01)	1,774 (25.44)	2,246 (44.07)
Diagnosis, by patient (%)			
AD	4,681 (44.85)	3,142 (45.05)	2,368 (46.46)
VaD	868 (8.32)	589 (8.45)	416 (8.16)
DLB	190 (1.82)	125 (1.79)	93 (1.82)
FTD	34 (0.33)	19 (0.27)	22 (0.43)
Mixed AD-VaD	154 (1.48)	80 (1.15)	93 (1.82)

Other	1 (<0.01)	-	1 (0.02)
Unspecified	3,762 (36.04)	2,572 (36.88)	1,701 (33.47)
Not known	673 (6.45)	405 (5.81)	357 (7.00)
Patients Reports			
Social Isolation	-	545	624
Loneliness	-	694	543
No reports (controls)	-	5,735	3,930

† Considered to be a non-socially isolated category

‡ Considered to be a socially isolated category

3.6 Missingness

Missing data were present across outcome, predictor (exposures), and control variables (covariates). Missingness was addressed through a combination of pre-processing removal, explicit modelling of missing categories, and default complete case analysis (listwise deletion) by the statistical packages. Specifically, missingness in the outcome variable, cognition, was addressed prior to analyses being conducted. As detailed in section 3.4.1, observations were removed from the dataset where cognitive scores were missing or deemed to be recorded in error. For categorical control variables, such as ethnicity, sex and diagnosis (and including marital status, accommodation status and living status in the SI and loneliness report models in Chapter 6), missingness was explicitly modelled by retaining distinct categories, such as ‘not known’ or ‘unspecified’, within the analyses. Missingness in the predictor variables (e.g. the SI proxy variables marital status, accommodation status and living status), such as a record of ‘NA’, were handled by listwise deletion by *lme4::lmer* and *mgcv::bam*. The use of listwise deletion for the predictor variable relies on the assumption that the data are missing at random. This assumption posits that the probability of the predictor being missing depends only on the other observed variables in the model (i.e. the covariates, e.g. age, sex, ethnicity etc.). By explicitly modelling the covariates, systematic reasons for missingness in the predictor variable are captured, and therefore model bias is mitigated (Gelman and Hill, 2006).

It is important to distinguish the handling of missing variable data from the ‘missingness’ resulting from unbalanced timepoints, which relies on restricted maximum likelihood (REML) estimation. In practice, the pre-processing removal of observations, followed by the creation of explicit variable categories, occurs before the analyses, at the data preparation stage. When the analysis functions are run, the listwise deletion of missing predictor variable observations is undertaken by the function before completing the analysis. During the analyses, REML estimations account for the non-standardised timepoints and varying number of observations per patient by modelling the average trajectories – the fixed effects – and individual patient trajectories – the random effects – using all available data from the participants who were retained after the listwise deletion step (Gelman & Hill, 2006; Wood, 2017).

The chosen approach has two main limitations. The first is that if the assumption that the data are missing at random is incorrect, then this would likely result in biased results. There is a general impossibility of proving that data are missing at random (Gelman & Hill, 2006), however the models included all relevant explicit variables to cover for this possibility. Even so, an inherent limitation of using secondary data is that one is without full control of the data that is collected, and it could be the case that potential unobserved variables predict missingness. The second is that the use of explicit modelling of missing covariates using categories, such as ‘not known’, as distinct can potentially bias the estimated coefficients of other variables in the model, as it is likely that these explicit missing categories are heterogeneous (Gelman & Hill, 2006). Overall, despite the limitations outlined, the approach for handling missingness was chosen as the most pragmatic and robust solution for the EHR dataset.

4 Study 1: Development of Social Isolation Proxies, and their Impact on Cognitive Decline

4.1 Introduction

4.1.1 Overview

Social isolation (SI) constitutes an objective lack of social connection (Holt-Lunstad, 2021), such as a lack of social contact or living alone. SI differs from loneliness, which represents a subjective disparity between a desired level/quality of social connection and a perceived level/quality of social connection (de Jong-Gierveld, 1987; de Jong-Gierveld & Tilburg, 2006; Perlman & Peplau, 1981). SI is inversely associated with cognitive functioning in older adults without an ADRD diagnosis (Kuiper et al., 2016; Piolatto et al., 2022) as well as neuropsychiatric symptoms in ADRD patients (Leung et al., 2015; Manca et al., 2020). Furthermore, SI has been identified as a modifiable risk factor for ADRD incidence (Desai et al., 2020; Kuiper et al., 2015; Lazzari & Rabottini, 2022; Livingston et al., 2017, 2020, 2024; Penninkilampi et al., 2018; Sommerlad et al., 2018, 2019) meaning that, in contrast to non-modifiable risk factors such as age (e.g. Carone et al., 2014) or genetic factors (e.g. Corder et al., 1993), addressing and reducing SI may offer an avenue for intervention. The theoretical links between SI and cognitive reserve (Stern et al., 2020, 2023), which have been supported by studies investigating how SI moderates the relationship between disease progression and cognitive symptoms (Perry, McConnell, Coleman, et al., 2022; Perry, Roth, et al., 2022), suggest that reducing SI could have an impact on cognition throughout the disease course. If this were the case, it could have implications for patient care by considering SI's impact on patients after diagnosis, not just as a risk-factor.

Previous studies that investigated the impact of SI on cognitive change in patients with an ADRD/dementia diagnosis have found mixed evidence of its impact. As shown in Chapter 2, studies using longitudinal designs found evidence for the impact of SI on ADRD patients' cognition more frequently than studies using cross-sectional designs. EHRs offer a relatively underutilised method of collecting and assessing real-world, retrospective, longitudinal data. Data regarding SI may not be regularly collected as part of mainstream clinical practices regarding ADRD patients, however. Without direct measures of SI, such as social network size and frequency of social interactions, analysing the impact of SI relies on the identification and use of proxy variables. For example, marital status has previously been identified as a key component of SI (Livingston et al., 2020; Saito et al., 2018; Wenger et al., 1996) that can impact ADRD risk, with lifelong single and widowed people found to have a 42% and 20% increased ADRD risk, respectively, compared to married people, while no overall ADRD difference in risk was found between divorced people and married people (Sommerlad et al., 2018). Marital status is associated with the frequency of social interactions (Kuiper et al., 2015), and also with participating in more or less adverse health behaviours (Fuller & Tech, 2010; Joung et al., 1995) as well as level of stress (Rothman & Mattson, 2010), all of which are thought to influence ADRD risk and cognitive reserve (Sommerlad et al., 2018).

Living status is another key component of SI, which is argued to be a more objective and precise measure than attempting to discern the value and/or frequency of social contacts (Desai et al., 2020). Living alone has been shown to lead to increased risk of ADRD incidence in a systematic review and meta-analysis (Desai et al., 2020), as well as steeper rates of cognitive decline for patients with an existing ADRD diagnosis in a longitudinal study (Harsányiová & Prokop, 2018). Conversely, a cross-sectional comparison of older African American patients with dementia (Edwards & Morris, 2007) revealed significantly higher MMSE scores for patients living alone ($M = 18.38$, $SD = 6.9$) than patients living with others ($M = 15.05$, $SD = 7.3$, $t = 4.28$, $p = 0.001$). Similarly, a logistic regression analysis of a cross-section of ADRD patient data from the IDEAL cohort study (Clare et al., 2020) revealed that patients who were living alone were more likely to have higher MMSE than patients living with others ($OR = 1.08$, 95% $CI = 1.04, 1.13$, $p < 0.001$), including when patients were living alone with low levels of support ($OR = 1.18$, 95% $CI = 1.08, 1.28$, $p < 0.001$). Significant odds ratios were also found when using total ACE-III scores as the measure of cognition. These studies also reported that people living alone had significantly more caregivers than those living with others (Edwards & Morris, 2007) and were more likely to have higher social contact with people from other households than those living with others (Clare et al., 2020). It could be the case, therefore, that the people in these studies were experiencing higher levels of social connection, despite living alone. One study (Clare et al., 2020) also reported that patients living alone had higher self-reported general functioning than patients living with others. Functional deficiencies may create a necessity for people to live with others, in order to have support, whereas those with better functional abilities are able to live more independently. As these studies were cross-sectional, it is not possible to gauge the change in cognition over time or how living alone or with others might impact any change.

Proportionally more ADRD patients will spend some time living in supported accommodation, such as a care home, compared to non-ADRD aged-matched controls (G. E. Smith et al., 2000). Prevalence of perceived social isolation in older adults with cognitive impairment living in nursing homes could be as high as 95.5% in emerging countries with ageing populations (Nikmat, Hashim, et al., 2015). Feelings of poor social connection or lack of care network may prompt some people to seek a move to supported accommodation (Scocco et al., 2006). ADRD patients living in supported accommodation show slower rates of cognitive decline than those living alone, but faster rates of cognitive decline than those living with family (Harsányiová & Prokop, 2018). Cross-sectional comparisons (Nikmat, Hawthorne, et al., 2015) suggest that ADRD patients receiving care in community settings have higher cognitive scores on the short MMSE ($M = 6.63$, $SD = 3.11$) than patients receiving care in a supported accommodation (e.g. nursing home) setting ($M = 5.20$, $SD = 2.28$), though these differences did not reach statistical significance ($t = 1.86$, $p = 0.07$). A study (Harmand et al., 2014) utilising data from a longitudinal cohort of older adults without cognitive impairment from France revealed a significant reduction in predicted MMSE scores from participants after admittance into nursing home care by almost 3 MMSE points ($B = -2.82$, $SE = 0.137$, $p < 0.0001$). Furthermore, the predicted rate of cognitive decline was faster for participants living in institutional care by around 0.2 MMSE points per year ($B = -0.218$, $SE = 0.044$, $p < 0.0001$). Similar changes in cognition and rates of cognitive decline were observed for AD patients recruited from the Rush Alzheimer's Disease Centre in Chicago, USA (Wilson, McCann, et al., 2007), with patients estimated MMSE scores reducing by around 0.3 MMSE points after admission to nursing homes ($B = -0.340$, $SE = 0.048$, $p < 0.001$) and cognitive decline predicted around 0.3 MMSE points per year faster in nursing homes ($B = -0.303$, $SE = 0.096$, $p = 0.002$).

4.1.2 Aims and Study Expectations

Previous studies have focussed on SI as a modifiable risk factor, without consideration of its impact also on post-diagnosis trajectories. Additionally, some studies have only considered cross-sectional timepoints to make comparisons regarding cognition and SI. This study aims to address these gaps by utilising a longitudinal prospective cohort of ADRD patient data from EHRs to predict the impact of three SI proxy variables on cognitive trajectories both before and after ADRD diagnosis. Marital status, living status (i.e. whether a person is living alone or cohabiting) and accommodation status (i.e. whether a person is living independently in mainstream housing/community setting or is in supported or clinical/institutionalised accommodation) are three factors linked to SI that stand as potential proxy variables discernible from EHR records. Identification of these three proxies offers potential avenues for exploring the impact of SI on cognition and rates of cognitive change of ADRD patients, utilising a wealth of real-world longitudinal data from the EHRs. The aims of this study are to explore the use of these proxies as predictors of cognitive trajectories in ADRD patients by developing linear multilevel models and comparing the resulting models. In line with the expectation that the three proxy variables are linked to SI, and SI has been linked to ADRD incidence and worse cognitive outcomes, it is hypothesised that patients exhibiting SI will have lower cognition at diagnosis (intercept) and faster rates of cognitive decline per year of diagnosis duration (slope).

4.2 Methods

4.2.1 Study Design, Data Sources, Sample, Ubiquitous Variables, and Patient Characteristics

The study design, data sources, sample, variables that are ubiquitous to all three modelling studies – cognitive function, diagnosis duration, and control variables – and patient characteristics information is set out in the Overview of Methodological Approaches chapter (Chapter 3), sections 3.3 to 3.5. Diagnosis duration represents the time from diagnosis at which the observation of cognitive function took place, with negative times representing time before diagnosis, positive time representing the time after diagnosis, and zero representing the time at which diagnosis occurred.

4.2.2 Social Isolation Proxies

It is necessary to rely on convenience proxies of social behavioural factors that are assumed to contribute to protection to cognitive function (Stern et al., 2020). Three different SI proxies – marital status, accommodation status, and living status – were chosen based on their connection to SI and cognitive function (as outlined in section 4.1), as well as their discernability from the structured data within the EHRs.

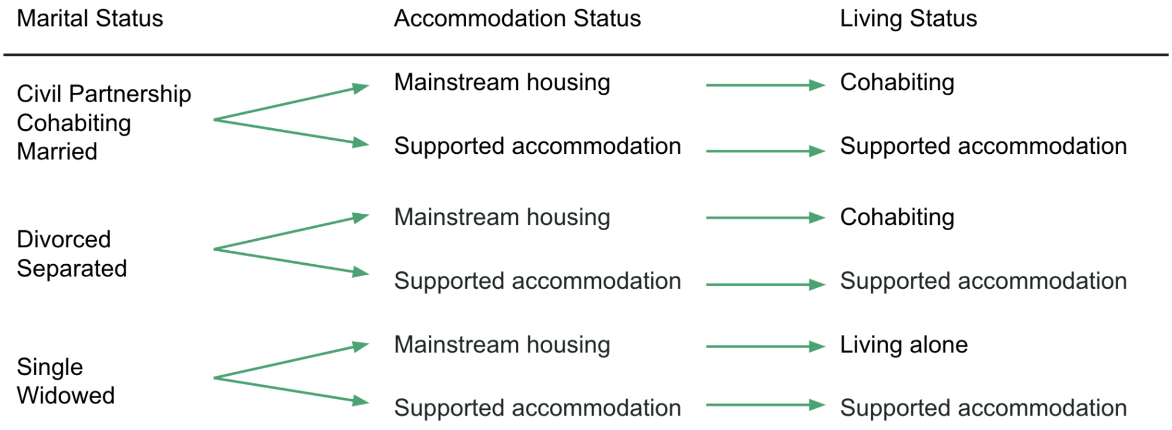
Marital status data are routinely collected in clinical settings, therefore frequently available within the structured EHR data. Married patients, patients in a civil partnership and patients who were cohabiting were assumed to share a similar partner structure (i.e. the presence of a significant other) and levels of social engagement, and therefore these categories represent the absence of SI (non-SI). The family/partner structure of divorced patients was less clear, leading to the possibility of three theoretical assumptions. The first assumes that divorced patients, considering their age and previous marriage, would have a similar family structure as married/civil partnership patients, such as possibly having children, grandchildren, and a new partner, and should be considered a non-SI category. The second assumes that divorced patients instead share similarities with widowed patients, in that they no longer have the presence of a significant other and should be considered an SI category. The third assumes that they are somewhere in-between the first two assumptions and should be considered separately to the SI and non-SI categories. A previous finding that divorced people do not differ significantly from married couples in terms of ADRD risk (Sommerlad et al., 2018), supports the first assumption, and therefore divorced patients were considered non-SI proxies for the final marital status model. Separated patients were grouped with divorced patients due to relatively few observations and assumed similarities, resulting in comparisons of two non-SI categories in the main analyses (separated/divorced patients compared to patients with partners). Single (never married) and widowed marital statuses were considered as proxies for SI, based on their assumed partner/family structure and level of social engagement, and their association with higher ADRD risk (Sommerlad et al., 2018).

A previous study had established that living in supported accommodation, compared to living in one’s own home, contributed to faster rates of cognitive decline in dementia patients (Harsányiová & Prokop, 2018). Accommodation status was derived from structured EHR data of patients’ accommodation at the time of clinical assessment. Accommodations were grouped based on similar characteristics to form six living status levels: mainstream housing, no fixed abode, supported accommodation, clinical, incarceration, not specified. Living in mainstream housing was considered a non-SI proxy, whereas the other categories were considered SI proxies.

Living status is not a variable that is routinely collected in the clinical setting, therefore this data was not readily available from the EHRs. Instead, the living status proxy used in this study was developed by assuming whether each patient was likely to be living alone or not, based on a combination of their marital status and accommodation status. Patients whose marital status indicated they would be living with a partner (civil partnership, cohabiting, married) were assumed to have a ‘cohabiting’ living status if they were living in mainstream housing. Following the previously described findings that divorced and married people do not differ significantly in ADRD risk (Sommerlad et al., 2018), divorced and separated patients were again assumed to be equivalent to married patients, therefore divorced and separated patients were considered to have a ‘cohabiting’ living status if they were also living in mainstream housing. Patients who had single or widowed marital statuses and were living in mainstream housing were considered to have a ‘living alone’ living status. As patients living in supported accommodation or clinical settings may be living away from their partner, even if their marital status indicates they are likely to have one, it was decided that ‘supported accommodation’ living status would be assigned to any patient living in supported accommodation or clinical setting regardless of marital status. Patients with unknown accommodation or marital statuses could not have a living status assigned and these observations were excluded in listwise fashion from the living status analyses, as were patients with no fixed abode, living in a clinical setting and incarcerated patients due to having too few observations to make meaningful interpretations from. Figure 4.1 shows a flow diagram describing the processing of living status categories from marital status and accommodation status.

Figure 4.1

Flow Chart of Living Status Processing



4.2.3 Data Analysis

Multilevel models were conducted using the ‘lme4’ (v1.1-29; Bates et al., 2015) R package, using restricted maximum likelihood estimation, with ‘lmerTest’ (v3.1-3; Kuznetsova et al., 2017) for additional interpretation of output. Additionally, ‘insight’ (v0.19.7; Lüdecke et al.,

2019) and ‘performance’ (v0.9.1; Daniel Lüdecke et al., 2021) packages were used for model assessment. In order to avoid errors with model convergence, a maximal approach to model fitting was used in which all possible model variables were included as coefficients based on the data structure, removing variables based on the data where appropriate (Gelman & Hill, 2006).

Multilevel models were developed with two levels: multiple observations over time (Level 1) nested within patients (Level 2). The outcome variable *cognition* and the time variable *diagnosis duration* were recorded at Level 1, while the predictor variables *SI proxy*, and control variables *age*, *ethnicity*, *sex*, and *diagnosis cause* were recorded at Level 2. Table 4.1 shows a multilevel table containing information on the levels, subindexes, variable identifiers and variables used within the models. Random slopes and intercepts were added to account for the outcome measure variance between and within patients. Separate analyses were conducted for models where the outcome variable was measured using MMSE and using MoCA. Separate analyses were conducted for the models where the predictor variable *SI proxy* used marital status, accommodation status and living status. Model equations for the final models presented in this chapter are presented in Appendix D. Due to relatively few observations of civil partnership and cohabitation levels of marital status, these patients were grouped with married and separated patients to create a ‘partner’ marital status category. The combination of variables and interactions used for the final models resulted in six model outputs reported in the main results section for this study. Unconstrained models are reported in Appendices E-G.

Table 4.1

A Multilevel Table to Show the Levels, Subindexes, Variable Identifiers, and Predictors (X) and Outcome (Y) Variables.

Level	Subindex*	Variable identifier	Variables**
Patient	$j = 1, \ldots, n$	Patient ID	$X2^{\text{SI proxy}}{}_{j}$ $X4^{\text{Ethnicity}}{}_{j}$ $X5^{\text{Sex}}{}_{j}$ $X6^{\text{Diagnosis cause}}{}_{j}$
Time	$t = 1, \ldots, T_j$	Diagnosis duration (years)	$Y^{\text{Cognition}}{}_{jt}$ $X1^{\text{Diagnosis duration}}{}_{jt}$ $X3^{\text{Age}}{}_{jt}$

Note.

* The total number of patients, n, differs depending on the model and complete data available for all variables. Similarly, the total number of timepoints, T_j, differs from patient to patient; timepoints are determined by assessments at memory clinics, therefore timepoint spacing between and within patients is sporadic.

** Variables index: $Y^{Cognition}_{jt}$ a continuous outcome variable, representing measures of cognitive function using either Mini-Mental State examination or Montreal Cognitive assessment depending on the specific model; $X1^{Diagnosis\ duration}_{jt}$ a continuous time variable, representing time from diagnosis in years, with minus times being pre-, positive times being post-, and zero times being at-the-point-of-diagnosis, calculated as the difference in diagnosis date and cognitive assessment date; $X2^{SI\ proxy}_{j}$ a categorical predictor variable, representing a proxy of social isolation, either a factor value of marital status, or accommodation status depending on the specific model; $X3^{Age}_{j}$ a continuous control variable, representing the patients age in years, adjusted for the sake of interpretation so that age 0 in the variable is equivalent to a person aged 50 years in real life, calculated by finding the difference between the date of the cognitive assessment and the patient's date of birth (expressed in years) minus 50; $X4^{Ethnicity}_{j}$ a categorical control variable, representing a patient's ethnicity; $X5^{Sex}_{j}$ a bivariate control variable, representing the patient's sex as either female or male; $X6^{Diagnosis\ cause}_{j}$ a categorical control variable, representing a patient's diagnosis cause.

4.3 Results

4.3.1 Model Comparisons

Null models predicting cognition as a result of diagnosis duration (in years) were developed to compare random-intercept-random-slope designs against fixed-intercept-random-slope and random-intercept-fixed-slope designs. For models with MMSE as the cognitive measure, adjusted intraclass correlation coefficient calculations (ICC; *performance::icc*) revealed that the random-intercept-random-slope model accounted for the greatest proportion of total variance within the cognitive scores (ICC = 0.76 vs fixed-intercept-random-slope ICC = 0.23 vs random-intercept-fixed-slope = 0.70). Specifically, approximately 76% of the total variance in MMSE scores can be explained by individual-level differences in baseline MMSE performance and individual-specific rates of cognitive change associated with diagnosis duration. Furthermore, model comparisons (*stats::anova*) consistently showed that the random-intercept-random-slope model was the best fit for the data based on Akaike's Information Criterion (AIC; Akaike, 1974) and Bayesian Information Criterion (BIC; Schwarz, 1978).

Similarly, with MoCA as the cognitive measure, adjusted intraclass correlation coefficient calculations revealed that the random-intercept-random-slope model accounted for the greatest proportion of total variance within the cognitive scores (ICC = 0.75 vs fixed-intercept-random-slope ICC = 0.20 vs random-intercept-fixed-slope = 0.74). Specifically, approximately 75% of the total variance in MoCA scores can be explained by individual-level differences in baseline MoCA performance and individual-specific rates of cognitive change associated with diagnosis duration. Again, model comparisons consistently showed that the random-intercept-random-slope model was the best fit for the data based on AIC, BIC. A comparison of model statistics is shown in Table 4.2. All together, these indicators suggest that the random-slope-random-intercept model provides a more appropriate and comprehensive representation of the data structure. With the random-slope-random-intercept model, the slopes represent the trajectories of cognitive scores over time (from diagnosis, termed 'diagnosis duration'), whereas the intercept represents the value at which the slope crosses 0 on the x-axis. In this case, the x-axis represents diagnosis duration, therefore the intercept is the predicted value when diagnosis duration is equal to zero, i.e. the point of diagnosis. The term 'random' means the slopes and intercepts are allowed to vary by the random-effect, which in this case is the patient ID. Hence, the model can capture both individual differences in initial cognitive status and individual variations in the trajectories of cognitive change over diagnosis duration and at diagnosis.

Table 4.2
Model Comparison Statistics for Different Random Effect Structures

Structure	Adjusted ICC*	AIC**	BIC***
MMSE			
Random slopes, random intercepts	0.76	103,605	103,652
Random slopes fixed intercept	0.23	110,948	110,948
Fixed slopes, random intercepts	0.70	104,298	104,329
MOCA			
Random slopes, random intercepts	0.75	28,474	28,532
Random slopes, fixed intercept	0.20	30,313	30,359
Fixed slopes, random intercepts	0.74	28,494	28,593

Note.
*Adjusted intraclass correlation coefficient (ICC) quantifies the proportion of total variance in the outcome variable that is attributable to the grouping structure.
** Akaike's information criterion (AIC) quantifies a goodness of fit for the model, with lower scores preferable.
*** Bayesian information criterion (BIC) also quantifies goodness of fit, utilising different penalisations than AIC. Again, lower scores are preferable.

4.3.2 Effects of SI Proxies on MMSE Trajectories

4.3.2.1 Marital Status

Controlling for age, sex, diagnosis cause and ethnicity, the constrained model investigating the effect of marital status on MMSE scores predicted that the average score of the reference group, female, White, AD patients with partners, at diagnosis (intercept) was 25.46 points (β

= 25.46, SE = 0.38, t-value = 66.75, p < 0.001). There was no significant main effect of being widowed on diagnosis scores, indicating similar scores to patients with partners. Single patient MMSE scores at diagnosis were also estimated to be similar to patients with partners. Separated marital status was a significant predictor of higher MMSE scores at diagnosis, estimated to be 1.09 points higher on average (β = 1.09, SE = 0.39, t-value = 2.78, p = 0.005). Rates of cognitive change for the reference group were estimated to decline at 0.96 MMSE points per year (β = -0.96, SE = 0.05, t-value = -17.49, p < 0.001). There was a significant interaction between single marital status and diagnosis duration, with estimates showing that single patients' decline was 0.42 MMSE points per year better off, indicating slower rates of decline (β = 0.42, SE = 0.16, t-value = 2.58, p = 0.010). There were no other significant interactions between marital status and diagnosis duration, indicating that separated and widowed patients' rates of cognitive change were similar to that of patients with partners. Estimates for the control variables revealed average MMSE scores reduced by 0.12 points per additional year of age of the patient (β = -0.12, SE = 0.01, t-value = -10.83, p < 0.001). Furthermore, average MMSE scores for male patients were 0.51 points higher than female patients (β = 0.51, SE = 0.18, t-value = 2.84, p = 0.005), while scores for non-White patients were 1.70 points lower on average than White patients (β = -1.71, SE = 0.61, t-value = -2.79, p = 0.005). Estimates for MMSE scores reduced by -0.12 points for each advanced year of age at cognitive measure (β = -0.12, SE = 0.01, t-value = -10.83, p < 0.001). The model coefficients are shown in Table 4.3.

Table 4.3

Model Coefficients for a Linear Multilevel Regression Model Predicting MMSE as a Function of the Interaction Between Marital Status and Diagnosis Duration Controlling for Age, Sex, Ethnicity and Diagnosis Cause

Factor	Estimate	Standard Error	df	t-value	p-value
Main Exposures					
Intercept*†	**25.46**	**0.38**	**4156**	**66.75**	**< 0.001**
Diagnosis duration**	**-0.96**	**0.05**	**1358**	**-17.49**	**< 0.001**
Separated / Divorced†	**1.09**	**0.39**	**4136**	**2.78**	**0.005**

Single[‡]	-0.03	0.45	4175	-0.10	0.924
Widowed[‡]	0.32	0.19	4088	1.64	0.100
Diagnosis duration x Separated	0.23	0.18	1349	1.28	0.201
Diagnosis duration x Single	**0.42**	**0.16**	**1538**	**2.58**	**0.010**
Diagnosis duration x Widowed	0.11	0.09	1406	1.23	0.218
Demographic Factors					
Years of age at cognitive measure	**-0.12**	**0.01**	**4166**	**-10.83**	**< 0.001**
Male	**0.51**	**0.18**	**4083**	**2.84**	**0.005**
Non-White	**-1.71**	**0.61**	**4071**	**-2.79**	**0.005**
Ethnicity not known	0.43	0.32	4187	1.36	0.174
Diagnosis Factors					
VaD	**-0.76**	**0.34**	**4252**	**-2.22**	**0.026**
DLB	-0.19	0.61	4025	-0.31	0.757
FTD	2.72	1.46	4122	1.86	0.063
Mixed AD-VaD	-0.14	0.72	3586	-0.20	0.842
PPD	-1.87	1.15	4204	-1.63	0.103
Unspecified	**-0.42**	**0.18**	**4092**	**-2.33**	**0.020**
Diagnosis not known	**0.83**	**0.35**	**3846**	**2.35**	**0.019**

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD patients with partners. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

** The diagnosis duration represents the change in estimated coefficient given a one unit increase in time for the reference group. Estimates for other interaction effects, such as diagnosis duration x single, are relative to the diagnosis duration for the reference group.

† Considered to be a non-socially isolated category

‡ Considered to be a socially isolated category

4.3.2.2 Accommodation Status

Controlling for age, sex, diagnosis cause and ethnicity, the constrained model investigating the effect of accommodation status on MMSE scores predicted that the average score of the reference group, female, White, AD patients living in mainstream housing, at diagnosis (intercept) was 25.14 points (β = 15.14, SE = 0.54, t-value = 46.91, p < 0.001). There was a significant main effect of living in a clinical setting, despite low numbers in the sample for this category (43 observations from 20 patients), with estimated MMSE scores at diagnosis predicted to be 2.85 points lower than that of patients living in mainstream housing (β = -2.85, SE = 1.11, t-value = -2.57, p < 0.010). There was also a significant main effect of supported accommodation status, with estimates for MMSE scores at diagnosis for these patients being predicted to be 1.67 points lower (β = -1.67, SE = 0.25, t-value = -6.60, p < 0.001). The main effect of no fixed abode accommodation status was not significant, indicating similar MMSE scores to the reference group. MMSE scores for people living in mainstream housing were predicted to decline by 0.66 points per year (β = -0.66, SE = 0.07, t-value = -9.82, p < 0.001). There were no additional significant interactions with diagnosis duration, suggesting rates of cognitive change were similar across all accommodation status groups. Age at cognitive measure predicted worse MMSE scores by 0.06 points for every advanced year of age (β = -0.06, SE = 0.02, t-value = -3.78, p = 0.002). The model coefficients are shown in Table 4.4.

Table 4.4.

Model Coefficients for a Linear Multilevel Regression Model Predicting MMSE as a Function of the Interaction Between Accommodation Status and Diagnosis Duration Controlling for Age, Sex, Ethnicity and Diagnosis Cause

Factor	Estimate	Standard Error	df	t-value	p-value
Main Exposures					
Intercept*†	**25.14**	**0.54**	**1528**	**46.91**	**< 0.001**
Diagnosis duration**	**-0.66**	**0.07**	**593**	**-9.82**	**< 0.001**
Supported accommodation‡	**-1.67**	**0.25**	**1537**	**-6.60**	**< 0.001**
Clinical‡	**-2.85**	**1.11**	**1663**	**-2.57**	**0.010**
No fixed abode‡	0.59	1.39	1675	0.43	0.668
Diagnosis duration x supported accommodation	-0.04	0.11	529	-0.33	0.739
Diagnosis duration x clinical	-0.51	0.52	674	-0.97	0.335
Diagnosis duration x no fixed abode	-0.80	0.52	393	-1.52	0.129
Demographic Factors					
Years of age at cognitive measure	**-0.06**	**0.02**	**1559**	**-3.78**	**< 0.001**

Male	0.28	0.24	1545	1.13	0.257
Non-White	-0.37	0.82	1519	-0.45	0.652
Ethnicity not known	**-0.75**	**0.26**	**1596**	**-2.88**	**0.004**
Diagnosis Factors					
VaD	-0.33	0.46	1665	-0.72	0.469
DLB	0.09	0.83	1504	0.11	0.914
FTD	3.29	1.76	1284	1.87	0.062
Mixed AD-VaD	-0.04	1.09	1355	-0.04	0.972
PPD	0.66	1.47	1528	0.45	0.652
Unspecified	-0.11	0.26	1542	-0.41	0.684
Diagnosis not known	0.74	0.51	1444	1.43	0.152

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD patients with living in mainstream housing. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

** The diagnosis duration represents the change in estimated coefficient given a one unit increase in time for the reference group. Estimates for other interaction effects, such as diagnosis duration x supported accommodation, are relative to the diagnosis duration for the reference group.

† Considered to be a non-socially isolated category

‡ Considered to be a socially isolated category

4.3.2.3 Living Status

Controlling for age, sex, diagnosis cause and ethnicity, the constrained model investigating the effect of living status on MMSE scores predicted that the average score of the reference group, female, White, AD, patients assumed to be cohabiting, at diagnosis (intercept) was 25.00 points (β = 25.00, SE = 0.60, t-value = 41.38, $p < 0.001$). There was no significant effect of living alone on diagnosis scores, indicating that patients who were living alone and patients who were cohabiting had similar MMSE scores at diagnosis. There was a significant effect of patients living in supported accommodation, with model estimates predicting their MMSE scores to be 1.91 points lower than cohabiting patients (β = -1.91, SE = 0.32, t-value = -5.91, p < 0.001). Similarly, patients living in clinical care settings also had lower predicted MMSE scores at diagnosis by 2.99 points (β = -2.99, SE = 1.13, t-value = -2.64, p = 0.008), though this was again based on relatively few observations. Estimates for the reference group predicted a 0.72 loss in MMSE score per year of diagnosis duration (β = -0.72, SE = 0.09, t-value = -7.63, p < 0.001). There were no other significant interactions between other living status groups and diagnosis duration, indicating that all patients, regardless of living status, experienced similar rates of cognitive decline. There was a significant effect of age, with estimates predicting that, for each increased year of age at the time of cognitive measure, cognitive scores decreased by 0.05 points (β = -0.05, SE = 0.02, t-value = -2.83, p = 0.005) There were no significant effects of any of the other control variables. The model coefficients are shown in Table 4.5.

Table 4.5

Model Coefficients for a Linear Multilevel Regression Model Predicting MMSE as a Function of the Interaction Between Living Status and Diagnosis Duration Controlling for Age, Sex, Ethnicity and Diagnosis Cause

Factor	Estimate	Standard Error	df	t-value	p-value
Main Exposures					
Intercept*†	**25.00**	**0.60**	**1156**	**41.38**	**< 0.001**
Diagnosis duration**	**-0.72**	**0.09**	**440**	**-7.63**	**< 0.001**
Alone‡	0.18	0.43	1225	0.42	0.674
Supported accommodation‡	**-1.91**	**0.32**	**1155**	**-5.91**	**< 0.001**
Clinical‡	**-2.99**	**1.13**	**1274**	**-2.64**	**0.008**
No fixed abode‡	0.35	1.41	1288	0.25	0.802
Diagnosis duration x alone	0.18	0.18	450	1.03	0.302

Diagnosis duration x supported accommodation	0.02	0.13	431	0.12	0.906
Diagnosis duration x clinical	-0.47	0.53	579	-0.88	0.381
Diagnosis duration x no fixed abode	-0.76	0.53	343	-1.43	0.154
Demographic Factors					
Years of age at cognitive measure	**-0.05**	**0.02**	**1170**	**-2.83**	**0.005**
Male	0.367	0.286	1161	1.28	0.200
Non-White	-0.17	0.92	1174	-0.19	0.853
Ethnicity not known	-0.35	0.36	1121	-0.97	0.332
Diagnosis Factors					
VaD	-0.53	0.52	1253	-1.02	0.307
DLB	0.15	0.92	1111	0.17	0.868
FTD	**3.83**	**1.90**	**926**	**2.02**	**0.044**
Mixed AD-VaD	-0.30	1.20	1098	-0.25	0.804
PPD	-0.27	1.82	1053	-0.15	0.884
Unspecified	-0.05	0.30	1166	-0.17	0.862
Diagnosis not known	0.89	0.59	1070	1.50	0.133

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD, patients assumed to be cohabiting. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

** The diagnosis duration represents the change in estimated coefficient given a one unit increase in time for the reference group. Estimates for other interaction effects, such as diagnosis duration x alone, are relative to the diagnosis duration for the reference group.

† Considered to be a non-socially isolated category

‡ Considered to be a socially isolated category

4.3.3 Effects of SI Proxies on MoCA Trajectories

4.3.3.1 Marital Status

Controlling for age, sex, diagnosis cause and ethnicity, the constrained model investigating the effect of marital status on MoCA scores predicted that the average score of the reference group, female, White, AD patients with partners, at diagnosis (intercept) was 20.91 points (β = 20.91, SE = 0.54, t-value = 38.65, $p < 0.001$). Single patients were predicted to have lower MoCA scores at diagnosis than patients with partners by 1.45 points (β = -1.45, SE = 0.63, t-value = -2.30, p = 0.022). Estimates for separated and widowed patients were not significantly different from patients with partners, indicating similar MoCA scores at diagnosis. Patients with partners were predicted to lose 0.48 MoCA points per year (β = -0.48, SE = 0.07, t-value = -7.20, $p < 0.001$). Interactions between other marital statuses and diagnosis duration were not significant indicating rates of cognitive change were similar amongst all martial statuses. For each year of increased age of the patient, the model estimated a reduction in MoCA scores by 0.10 (β = -0.10, SE = 0.02, t-value = -5.80, $p < 0.001$). Being male increased predicted MoCA scores by 1.12 point compared to being female (β = 1.12, SE = 0.24, t-value = 4.59, $p < 0.001$). Non-White patients' scores were predicted to decrease by 1.59 MoCA points compared to White patients (β = -1.59, SE = 0.80, t-value = -1.99, p = 0.046). The model coefficients are shown in Table 4.6.

Table 4.6

Model Coefficients for a Linear Multilevel Regression Model Predicting MoCA as a Function of the Interaction Between Marital Status and Diagnosis Duration Controlling for Age, Sex, Ethnicity and Diagnosis Cause

Factor	Estimate	Standard Error	df	t-value	p-value
Main Exposures					
Intercept*†	**20.91**	**0.54**	**2332**	**38.65**	**< 0.001**
Diagnosis duration**	**-0.48**	**0.07**	**465**	**-7.20**	**< 0.001**
Separated / Divorced†	0.03	0.47	2187	0.07	0.946
Single‡	**-1.45**	**0.63**	**2074**	**-2.30**	**0.022**
Widowed‡	-0.14	0.28	2180	-0.50	0.615
Diagnosis duration x Separated	0.19	0.21	487	0.91	0.365
Diagnosis duration x Single	0.30	0.29	628	1.04	0.300
Diagnosis duration x Widowed	-0.03	0.12	482	-0.29	0.772
Demographic Factors					
Years of age at cognitive measure	**-0.10**	**0.02**	**2330**	**-5.80**	**< 0.001**
Male	**1.12**	**0.24**	**2262**	**4.59**	**< 0.001**
Non-White	**-1.59**	**0.80**	**2296**	**-1.99**	**0.046**
Ethnicity not known	0.45	0.37	2257	1.24	0.216

Diagnosis Factors					
VaD	-0.444	0.50	2258	-0.89	0.376
DLB	0.50	0.88	2102	0.57	0.568
FTD	-0.80	1.73	2367	-0.46	0.643
Mixed AD-VaD	-0.16	0.89	2142	-0.18	0.860
PPD	-1.36	1.22	1992	-1.12	0.263
Unspecified	0.359	0.261	2285	1.38	0.169
Diagnosis not known	**1.37**	**0.43**	**2081**	**3.17**	**0.002**

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD patients with partners. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

** The diagnosis duration represents the change in estimated coefficient given a one unit increase in time for the reference group. Estimates for other interaction effects, such as diagnosis duration x separated, are relative to the diagnosis duration for the reference group.

[†] Considered to be a non-socially isolated category

[‡] Considered to be a socially isolated category

4.3.3.2 Accommodation Status

Controlling for age, sex, diagnosis cause and ethnicity, the constrained model investigating the effect of accommodation status on MoCA scores predicted that the average score of the reference group, female, White, AD patients in mainstream accommodation, at diagnosis (intercept) was 18.77 points (β = 18.77, SE = 0.51, t-value = 36.97, p < 0.001). Patients living in supported accommodation were predicted to have lower MoCA scores than patients living in mainstream accommodation by 1.77 points (β = -1.77, SE = 0.27, t-value = -6.55, p < 0.001). Incarcerated patients had much lower predicted MoCA scores still, predicted to be 10.65 points lower than patients living in mainstream accommodation (β = -10.66, SE = 5.38, t-value = -1.98, p = 0.048). While this estimation did reach statistical significance, it is likely that there are too few patients in this group to draw strong conclusions, and this is reflected by the high

SE and relatively low t-value. Cognition change for the reference group was estimated to be a loss of 0.58 MoCA points per year (β = -0.58, SE = 0.06, t-value = -9.96, p < 0.001). There were no other significant interactions with diagnosis duration for any of the other accommodation statuses, indicating rates of change amongst patients in different accommodation status groups was similar. Male patients had higher predicted MoCA scores by 1.18 points (β = 1.18, SE = 0.22, t-value = 5.36, p < 0.001). The model coefficients are shown in Table 4.7.

Table 4.7

Model Coefficients for a Linear Multilevel Regression Model Predicting MoCA as a Function of the Interaction Between Accommodation Status and Diagnosis Duration Controlling for Age, Sex, Ethnicity and Diagnosis Cause

Factor	Estimate	Standard Error	df	t-value	p-value
Main Exposures					
Intercept*†	**18.77**	**0.51**	**2389**	**36.97**	**< 0.001**
Diagnosis duration**	**-0.58**	**0.06**	**477**	**-9.96**	**< 0.001**
Supported accommodation	**-1.77**	**0.27**	**2373**	**-6.55**	**< 0.001**
Clinical‡	-2.30	1.24	2338	-1.85	0.064
No fixed abode‡	-0.12	1.13	2415	-0.10	0.92
Incarceration‡	**-10.66**	**5.38**	**2749**	**-1.98**	**0.048**
Diagnosis duration x supported accommodation	-0.10	0.12	491	-0.82	0.412
Diagnosis duration x clinical	0.64	0.46	337	1.38	0.168

Diagnosis duration x no fixed abode	-0.62	0.55	629	-1.14	0.256
Diagnosis duration x incarceration	-8.69	6.29	2493	-1.38	0.167
Demographic Factors					
Years of age at cognitive measure	-0.03	0.02	2405	-1.95	0.051
Male	**1.18**	**0.22**	**2375**	**5.36**	**< 0.001**
Non-White	-1.06	0.81	2386	-1.30	0.194
Ethnicity not known	**-0.73**	**0.23**	**2388**	**-3.24**	**0.001**
Diagnosis Factors					
VaD	-0.58	0.44	2345	-1.33	0.185
DLB	0.79	0.74	2253	1.07	0.284
FTD	-0.34	1.59	2520	-0.21	0.833
Mixed AD-VaD	-061	0.82	2278	-0.74	0.457
PPD	-0.31	1.06	2155	-0.30	0.768
Unspecified	-0.35	0.25	2407	-1.40	0.162
Diagnosis not known	0.65	0.42	2200	1.56	0.119

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD patients in mainstream accommodation. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

** The diagnosis duration represents the change in estimated coefficient given a one unit increase in time for the reference group. Estimates for other interaction effects, such as diagnosis duration x supported accommodation, are relative to the diagnosis duration for the reference group.

† Considered to be a non-socially isolated category

‡ Considered to be a socially isolated category

4.3.3.3 Living Status

Controlling for age, sex, diagnosis cause and ethnicity, the constrained model investigating the effect of living status on MoCA scores predicted that the average score of the reference group, female, White, AD patients assumed to be cohabiting, at diagnosis (intercept) was 19.15 (β = 19.15, SE = 0.60, t-value = 32.10, p < 0.001). Estimates for patients living alone were not significant, indicating scores were similar to cohabiting patients. Patients living supported accommodation had lower predicted MoCA scores at diagnosis by 2.37 points (β = -2.37, SE = 0.33, t-value = -7.14, p < 0.001). Incarcerated patients (β = -11.39, SE = 5.32, t-value = -2.14, p = 0.032) and patients living in clinical settings (β = -3.08, SE = 1.25, t-value = -2.47, p = 0.014) had lower MoCA estimates at diagnosis, yet these findings are unlikely to be meaningful, despite statistical significance, due to relatively few observations. The estimated change in MoCA scores for cohabiting patients was a decline of 0.57 points per year (β = -0.57, SE = 0.08, t-value = -6.83, p = 0.001). No other significant interactions between living status and diagnosis duration were found, indicating rates of cognitive change were similar across all living status groups. Male patients were predicted to have higher scores than female patients by 1.33 MoCA points (β = 1.33, SE = 0.27, t-value = 4.89, p < 0.001). For every increase in year of age at time of cognitive measure, MoCA estimates reduced by 0.04 points (β = -0.04, SE = 0.02, t-value = -2.19, p = 0.029). The model coefficients are shown in Table 4.8.

Table 4.8

Model Coefficients for a Linear Multilevel Regression Model Predicting MoCA as a Function of the Interaction Between Living Status and Diagnosis Duration Controlling for Age, Sex, Ethnicity and Diagnosis Cause

Factor	Estimate	Standard Error	df	t-value	p-value
Main Exposures					
Intercept*†	**19.15**	**0.60**	**1628**	**32.10**	**< 0.001**
Diagnosis duration**	**-0.57**	**0.08**	**308**	**-6.83**	**< 0.001**
Alone‡	-0.09	0.36	1619	-0.27	0.791
Supported	**-2.37**	**0.33**	**1614**	**-7.11**	**< 0.001**

accommodation					
Clinical‡	**-3.08**	**1.25**	**1584**	**-2.47**	**0.014**
Incarceration‡	**11.39**	**5.32**	**1864**	**-2.14**	**0.032**
No fixed abode‡	-0.57	1.14	1633	-0.50	0.617
Diagnosis duration x alone	0.07	0.16	361	0.43	0.667
Diagnosis duration x supported accommodation	-0.08	0.14	331	-0.61	0.546
Diagnosis duration x clinical	0.66	0.46	238	1.43	0.155
Diagnosis duration x no fixed abode	-0.64	0.54	449	-1.18	0.239
Diagnosis x incarceration	-8.84	6.23	1667	-1.42	0.156
Demographic Factors					
Years of age at cognitive measure	**-0.04**	**0.02**	**1636**	**-2.19**	**0.029**
Male	**1.33**	**0.27**	**1613**	**4.89**	**< 0.001**
Non-White	-0.80	0.93	1650	-0.86	0.388
Ethnicity not known	-0.03	0.34	1626	-0.10	0.923
Diagnosis Factors					
VaD	-0.38	0.53	1601.83	-0.71	0.479

DLB	0.39	0.91	1538	0.43	0.667
FTD	0.38	1.83	1776	0.21	0.834
Mixed AD-VaD	-0.68	1.00	1486	-0.69	0.493
PPD	-0.85	1.15	1486	-0.74	0.457
Unspecified	0.07	0.30	1637	0.23	0.815
Diagnosis not known	0.92	0.50	1530	1.83	0.068

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD patients assumed to be cohabiting. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

** The diagnosis duration represents the change in estimated coefficient given a one unit increase in time for the reference group. Estimates for other interaction effects, such as diagnosis duration x alone, are relative to the diagnosis duration for the reference group.

† Considered to be a non-socially isolated category

‡ Considered to be a socially isolated category

4.4 Discussion

4.4.1 Summary of Findings

This study aimed to utilise ADRD patient data from EHRs to investigate the impact of three SI proxies – marital status, accommodation status, and living status – and their interaction with diagnosis duration – the time from diagnosis at which the observation of cognitive function took place, with negative time representing time before diagnosis, positive time representing the time after diagnosis, and zero representing the time at which diagnosis occurred. Controlling for demographic and diagnostic characteristics, multilevel linear regression models gave estimates for patients' cognitive function scores at diagnosis, measured by either MMSE or MoCA, and rates of cognitive change relative to the SI proxy group. It was hypothesised that patients in proxy groups associated with greater SI would experience worse overall cognition as well as faster rates of cognitive decline. However, only partial evidence for this hypothesis was found. In one model, contradictory evidence was found.

Considering marital status as the SI proxy, MMSE models did not predict statistically significant differences between the intercept scores (scores at diagnosis) of patients with partners (non-SI) and single (SI) nor widowed (SI) patients. Separated (non-SI) patients, however, were predicted to have higher intercepts by more than 1.09 points. Previous studies have equated married people and divorced people with regards to ADRD incident risk (Sommerlad et al., 2018), therefore it is surprising that the current model indicates that patients that have separated/divorced marital status (either divorced or separated) show higher cognitive scores at diagnosis. Conversely, MoCA models do not show greater cognitive scores for separated patients at diagnosis, with estimates instead showing scores for these patients are comparable to patients with partners, in line with expectations based on previous literature (Sommerlad et al., 2018). Furthermore, the MoCA model predicted that single patients had lower cognitive intercept scores than patients with partners by 1.45 points. This finding is in line with the study expectations that low SI proxy groups would experience lower cognitive function at diagnosis. The difference in findings regarding single patients' intercept scores between the MMSE and MoCA models could reflect a difference in sensitivities between the two measures. For instance, it could be that the cognitive domain most affected by SI related to life-long single marital status is more acutely captured by the MoCA than the MMSE. Widowed patients were not found to have intercept scores that were significantly different to patients with partners when measured with either MMSE or MoCA in the full models. However, the unconstrained MMSE and MoCA models showed a significant effect of widowed marital status on patient intercept scores (see Appendix E). Therefore, it seems that introducing control variables mitigated the effect of marital status for this group. Single patients' rates of cognitive decline predicted by the MMSE model was slower than the other marital statuses. This finding directly contradicts the study expectations, as single marital status was considered an SI proxy. However, in the MoCA model, single patients had worse cognition at intercept, while all marital statuses were predicted to decline at similar rates, indicating that single patients have lower MoCA scores throughout the diagnosis window. The improvements in MMSE slopes for single patients may indicate these patients are exposed to other protective factors that protects their decline. For example, previous studies have found that patients living alone, as single patients are assumed to be, display higher levels of cognitive and functional ability that enable their independence (Clare et al., 2020). However, as similar findings were not predicted in the MoCA model, such differences could again indicate differences in the measures and their sensitivity regarding different cognitive domains.

For the accommodation status proxy, models consistently predicted lower cognitive scores at diagnosis for patients living in supported accommodation compared to the reference group of patients living in mainstream housing. This remained true regardless of which cognitive measure was used. There were no significant interactions between the accommodation status groups and diagnosis duration (time from diagnosis duration), indicating that the predicted lower cognitive scores for patients in supported accommodation persists across the diagnosis duration window (± 5 years either side of diagnosis). This finding partially supports the study expectation in that intercept scores for patients living in supported accommodation (SI) were lower than patients living in mainstream housing (non-SI), however slopes were not statistically different, indicating rates of decline were similar. The model predictions for patients in clinical, no fixed abode and incarcerated accommodation statuses are likely uninterpretable, despite some reaching statistical significance, due to relatively small numbers of patient observations represented in these groups (see section 3.5). Rates of decline were shown to be similar across all accommodation statuses across the two different cognition measure models, and therefore does not provide evidence to support the study expectation that SI proxy groups would experience faster rates of decline than non-SI proxy groups. A previous study found increased rates of cognitive decline in those living in a supported accommodation setting compared to those living with others attributed this finding, at least in part, to exposure to inadequate conditions within the supported accommodation (Harsányiová & Prokop, 2018). That the current study finds patients living in supported accommodation have lower cognitive scores at diagnosis may partially reflect those patients' need to be in supported accommodation in the first place, for instance if this impaired cognition also impairs activities of daily living. The current study, unlike the previously mentioned study, did not find differences in rates of decline of patients living in supported accommodation and those living in mainstream housing. This may reflect national differences in mainstream or supported accommodation conditions. A further explanation could be the misclassification of patients living in mainstream housing as a non-SI proxy, for instance if the majority of those patients are living alone.

This is somewhat addressed by the living status model which attempted to further define patients as either living alone or cohabiting based on a combination of their marital status and accommodation status. In these models, patients living in supported accommodation again had lower intercept scores, but again there were no significant interactions between the living statuses and diagnosis duration, indicating that rates of cognitive change across all living statuses were similar to the reference group, cohabiting patients (a loss of around 0.72 MMSE or 0.57 MoCA points per year). Interestingly, neither the MMSE nor the MoCA model predicted a significant difference in intercept or slope scores between cohabiting patients and patients living alone. Assuming alone living status represents an SI proxy, and cohabiting living status represents a non-SI proxy, these findings do not provide evidence towards the study expectations that SI patients would experience worse cognition and faster rates of cognitive decline. That there were no differences between patients living alone and patients living with others in the current study perhaps reflects the difference in findings amongst the literature, with some previous studies suggesting that living alone increased ADRD incidence risk (Desai et al., 2020) and worse cognition in later life, and others indicating those living alone may have increased cognition and social participation outside of the home than those living with others (Clare et al., 2020; Edwards & Morris, 2007).

4.4.2 Limitations and Suggestions for Further Research

The finding across most models that rates of cognitive decline were similar across SI proxies may reflect a limitation in the choice of analysis approach used in the current study. Previous studies have demonstrated that decline in ADRD may not accurately be represented by linear modelling. For example, a study by Vaci and colleagues (Vaci et al., 2021) demonstrated that ADRD patients experience a period of cognitive stability around diagnosis, likely due to early clinical interventions such as the administration of acetylcholinesterase inhibitors or other medication. Further research should look to use non-linear models to better capture these nuanced changes in cognition over time. Another limitation of the current study is its reliance on assumed patient characteristics. For example, due to lack of more objective measures within the EHRs, assumptions were made about associations between patients' demographic factors and their level of social isolation. This may not accurately reflect levels of patients' social connection, and future research should look to develop a method of quantifying social connection from the EHRs that makes less assumptions about the data.

4.4.3 Conclusion

In conclusion, the models tested in this study provide limited evidence that SI negatively impacts the cognition and rates of cognitive decline of ADRD patients. In one circumstance, rates of cognitive decline were actually improved by belonging to a SI group. Lifelong single patients experience lower cognition across the five years either side of diagnosis when MoCA is used as the cognitive outcome measure, however they experience similar cognitive scores at diagnosis groups as other marital statuses and slower rates of cognitive decline when MMSE is the measure. Patients living in supported accommodation were consistently predicted to have lower cognition across the diagnosis window but were predicted to have similar rates of decline. Rates of decline were similar across most models, which could indicate more nuanced modelling techniques are required to find any meaningful differences between groups. Differences in MMSE and MoCA models may reflect differences in the sensitivities of the two measures to the cognitive domains that may be impacted by SI proxies. Specifically, the MoCA is known to be more sensitive to early cognitive deficits, whereas MMSE can be prone to ceiling effects. As such, the cognitive deficits related to social isolation may be more pronounced in domains more sensitively measured by the MoCA, such as executive functions and visuospatial skills. These deficits may be missed by the MMSE, particularly in patients with milder impairments, due to the MMSE's known ceiling effects.

5 Study 2: Linear and Non-Linear Approaches to Modelling ADRD Patient Cognitive Trajectories Using Linear Multilevel Regression and Generalised Additive Multilevel Models

5.1 Introduction

5.1.1 Overview

Multilevel models (MLMs) are useful tools for analysing longitudinal data due to their ability to accommodate within person variance and due to their flexibility of use with missing data, non-randomised and non-counterbalanced repeated measures conditions, and non-uniform observation increments (Long, 2011; Wagner et al., 2024). MLMs are also capable of performing inferences for small sample size groups by striking a middle ground between overly noisy within-group estimates and overly simplistic regression models that neglect group-specific characteristics (Gelman & Hill, 2006). Various forms of analyses have been used in previously published articles to explore late-life cognitive trajectories in adults with no neuropathology at study outset (Jo et al., 2021; Sørensen et al., 2023; Wagner et al., 2020, 2024; Wilson et al., 2020a, 2020b) and those with ADRD neuropathology (Ito et al., 2011; Vaci et al., 2021; Wilkosz et al., 2010), to predict the impact of modifiable (Amieva et al., 2014; Harsányiová & Prokop, 2018; Hsu & Bai, 2022; Terrera et al., 2014) and non-modifiable (Casanova et al., 2020; Martins et al., 2005) risk factors for ADRD on rates of cognitive change, to explore the changes clinical symptoms prior to ADRD diagnosis (Amieva et al., 2008; Cavaillès et al., 2022; Jacqmin-Gadda et al., 2006), and to examine the impact of neuropathology on cognition in the lead up to death (Boyle et al., 2017).

Study 1 used linear multilevel regression models (LMRMs) to analyse the relationship between cognition, diagnosis duration and various proxies of SI (marital status, accommodation status, and living status), controlling for age, sex, diagnosis cause (e.g. Alzheimer's disease, vascular dementia, Lewy body disease), and ethnicity. The LMRMs used in Study 1 (Chapter 4) included an interaction term between diagnosis duration and the SI proxy as fixed effects at the patient level (Level 2) and diagnosis duration varying by Patient ID as random effects at the observation level (Level 1). By using this random effect structure, the models accounted for variations in the effect of diagnosis duration across individual patients, predicting individual-specific slopes. Overall, this gave an indication of patient cognition at the moment of diagnosis and how cognition changed over time (± 5 years from diagnosis) between SI proxy groups. While the models found varying intercept scores across SI proxies, all but one (using marital status as the SI proxy predictor, and MMSE as the measure of cognition) interaction terms were not significant, indicating that rates of cognitive decline were similar across SI proxies. This finding did not support the expected finding that socially isolated groups would experience faster rates of cognitive decline based on the presumed association between SI proxies and ADRD incidence (Desai et al., 2020; Livingston et al., 2017, 2020, 2024; Sommerlad et al., 2018), and with cognition (Harmand et al., 2014; Harsányiová & Prokop, 2018; Wilson, McCann, et al., 2007). Nor with SI's presumed impact on cognitive reserve (Perry, McConnell, Coleman, et al., 2022; Perry, Roth, et al., 2022; Zhang et al., 2022).

One possible explanation for the results of Study 1 not meeting the pre-study expectation that socially isolated patients would exhibit faster rates of cognitive decline is that LMRM slopes may not be able to capture the nuanced changes in cognition over time. It has been proposed that the rate of cognitive change in later life is not linear, but instead exhibits a sudden, non-linear drop towards the end of life (the 'terminal drop' hypothesis), indicating an association between cognition and general health rather than being specifically an age-related decline (Kleemeier, 1962; Riegel & Riegel, 1972). Findings from a more recent meta-analysis from Boyle and colleagues (Boyle et al., 2017) support cognitive trajectories experiencing a sudden drop off within the last 5 years of a person's life, in line with the terminal drop hypothesis. In ADRD, cognitive trajectories have been shown to experience a period of stability around diagnosis following prescription of medications, preceded and succeeded by periods of cognitive decline (Vaci et al., 2021). There is evidence to suggest that a person's level of cognition before the initial decline and the rate of that decline influences the length of time before diagnosis (Amieva et al., 2014). For example, people with higher theorised cognitive reserve may exhibit more years of slower cognitive decline before reaching a 'threshold' for diagnosis (see section 1.2), whereas people with lower theorised cognitive reserve may exhibit less years of cognitive decline and/or faster rates of decline to reach the same threshold. Rates of cognitive decline following stabilisation around diagnosis have been shown to be similar to pre-stabilisation rates of decline (Vaci et al., 2021). Generalised additive multilevel models (GAMMs) offer a flexible, data-driven, non-parametric approach to fitting smooth functions of covariates (Wood, 2017) that could be used to capture the nuanced changes in cognition in later life and in ADRD patients (Sørensen et al., 2023; Vaci et al., 2021).

5.1.2 Aims and Study Expectations

The aims of the current study are to expand upon the LMRMs used in Study 1 by (1) exploring non-linear changes in patient cognition by using GAMMs and (2) to investigate whether the expected impact of SI on cognition is predicted by these models. The hypothesis for the current study remains much the same as Study 1, that patients in more socially isolated groups will exhibit lower cognition at diagnosis and steeper rates of cognitive decline across the diagnosis duration window.

5.2 Methods

5.2.1 Study Design, Data Sources, Sample, Variables, and Patient Characteristics

The study design, data sources, sample, variables that are ubiquitous to all three modelling studies – cognitive function, diagnosis duration, and control variables – and patient characteristics information is set out in the Overview of Methodological Approaches chapter (Chapter 3), sections 3.3 to 3.5. The SI proxies used as predictor variables in this study – *marital status*, *accommodation status*, and *living status* – are the same as those developed in Study 1 (Chapter 4). See section 4.2.2 for an overview. Diagnosis duration represents the time from diagnosis at which the observation of cognitive function took place, with negative times representing time before diagnosis, positive time representing the time after diagnosis, and zero representing the time at which diagnosis occurred.

5.2.2 Data Analysis

GAMMs were performed using the *bam* function from the *mgcv* package (v1.8-31; see Wood, 2017). The *bam* function is particularly useful for larger datasets because it is computationally more efficient than the standard *gam* function, resulting in less memory use and faster computation (Wood et al., 2015). The *bam* function simultaneously estimates the parametric (linear) effects of the covariates and the non-parametric (smooth) relationships, presenting the parametric coefficients as fixed effects in the output in a similar way to linear mixed effect regression models (e.g. *lme4::lmer*; see Chapter 4). The non-parametric estimates are more difficult to interpret without the use of visualisations, therefore figures have been added to aid interpretation (see section 5.3). The *itsadug* package (v2.4.1; van Rij et al., 2022) was also used to aid the evaluation, interpretability and visualisation of the models.

For the model structure, cognition (MMSE or MoCA) was defined as the outcome variable. Fixed effect term variables had a direct, linear, or categorical effect on cognition. The SI proxy (marital status, accommodation status, or living status) was the main effect predictor, while the control variables (age, sex and ethnicity) were also defined as fixed terms. The smooth terms allowed for non-linear relationships between predictors and cognition. A smooth interaction term was added for diagnosis duration (years) by SI proxy, allowing the smooth effect of diagnosis duration on cognition to vary depending on the levels of the SI proxy (e.g. partner, separated, single, widowed). A cubic spline basis term for this interaction was chosen as a balance between providing flexibility and smoothness. A smooth random effects term for patient ID was also added to account for the non-independence of observations within the same patient, and therefore the variability in cognition that is attributable to individual differences. Separate models were run (*mgcv::bam*) for each cognitive measure and for each SI proxy, controlling for Age, Sex, Diagnosis Cause and Ethnicity, utilising a maximal approach to model building, resulting in 6 final models: (1) MMSE as a function of marital status; (2) MMSE as a function of accommodation status; (3) MMSE as a function of living status; (4) MoCA as a function of marital status; (5) MoCA as a function of accommodation status; and (6) MoCA as a function of living status. Previously included accommodation status and living status proxies represented by less than 25 patients, ‘clinical’, ‘no fixed abode’, and ‘incarceration’, were removed from the final models.

5.3 Results

5.3.1 Effects of SI Proxies on MMSE Trajectories

5.3.1.1 Marital Status

The significant random effects term indicates significant between-patient variability in MMSE scores that are not explained by the fixed or smooth predictors (EDF = 3511.05, F = 5.90, $p < 0.001$). The model performance output suggests that this model accounts for between 69.3% and 78.1% of the variance in MMSE scores (adjusted $R^2 = 0.693$, explained deviance = 78.1%). Controlling for age, diagnosis cause, sex, and ethnicity, the results of the GAMM for the linear effects of marital status on MMSE intercepts shows average MMSE scores at diagnosis for the reference group, female, White, AD patients with a partner to be 24.73 ($\beta = 24.73$, SE = 0.29, t-value = 63.90, $p < 0.001$). The prediction for average MMSE scores for separated patients was significantly higher than patients with a partner ($\beta = 1.27$, SE = 0.40, t-value = 3.19, $p = 0.001$). No significant difference was predicted between patients with a partner and single patients ($\beta = 0.18$, SE = 0.35, t-value = 0.50, $p = 0.614$), nor widowed patients ($\beta = 0.38$, SE = 0.20, t-value = 1.85, $p = 0.065$). Of the control variables, there was a significant effect of age, with MMSE scores decreasing by 0.12 points for every increased year of age at the time of cognitive measurement ($\beta = -0.12$, SE = 0.01, t-value = -10.43, $p < 0.001$). There were also significant effects of sex and ethnicity, with male patients predicted to have higher MMSE scores by 0.58 points compared to female patients ($\beta = 0.58$, SE = 0.18, t-value = 3.22, $p = 0.001$), and non-White patients predicted to have lower MMSE scores by 1.77 points compared to white patients ($\beta = -1.77$, SE = 0.62, t-value = -2.84, $p = 0.005$). The model coefficients are shown in Table 5.1.

Table 5.1

Model Coefficients for the Parametric Output from a Generalised Additive Multilevel Model Predicting MMSE as a Function of the Interaction Between Marital Status and Diagnosis Duration Controlling for Age, Sex, Ethnicity and Diagnosis Cause

Factor	Estimate	Standard Error	t-value	p-value
Main Exposures				
Intercept*†	**24.73**	**0.39**	**63.90**	**< 0.001**
Separated / Divorced†	**1.27**	**0.40**	**3.19**	**0.001**
Single‡	0.18	0.35	0.50	0.614
Widowed‡	0.36	0.20	1.83	0.067
Demographic Factors				
Years of age at cognitive measure	**-0.12**	**0.01**	**-10.43**	**< 0.001**
Male	**0.58**	**0.18**	**3.22**	**0.001**
Non-White	**-1.77**	**0.62**	**-2.84**	**0.005**
Ethnicity not known	0.50	0.32	1.56	0.119
Diagnosis Factors				
VaD	-0.62	0.35	-1.80	0.073
DLB	-0.02	0.61	-0.03	0.975
FTD	**3.08**	**1.45**	**2.12**	**0.034**
Mixed AD-VaD	0.01	0.74	0.02	0.984
PPD	-1.76	1.13	-1.56	0.119
Unspecified	-0.26	0.18	-1.46	0.145
Diagnosis not known	**1.11**	**0.36**	**3.09**	**0.002**

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD patients with a partner. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

† Considered to be a non-socially isolated category

‡ Considered to be a socially isolated category

The non-linear effects of marital status on MMSE trajectories predicted by the GAMM indicates that the association between diagnosis duration and MMSE score is non-linear for all levels of marital status. The smooth term for patients with partners is significant, and the estimated degrees of freedom being above 5 suggests a highly complex non-linear shape (EDF = 5.50, F = 771.05, $p < 0.001$). The predicted smooth terms for separated patients (EDF = 4.25, F = 30.46, $p < 0.001$), single patients (EDF = 3.09, F = 32.93, $p < 0.001$) and widowed patients (EDF = 4.60, F = 285.34, $p < 0.001$), suggest moderate to complex non-linear shapes, with estimated degrees of freedom between 3 and 5. Figure 5.1 displays the non-linear change in MMSE over diagnosis duration for the four levels of marital status. Figure 5.2A shows that the significant difference in MMSE scores between patients with partners and separated patients begins around 2 years before diagnosis and persists for the remainder of the diagnosis duration window, with separated patients observed to have higher MMSE scores than patients with partners. Figure 5.2B shows that single patients experience a period of higher MMSE scores than patients with partners between 5 and 4 years prior to diagnosis and then again 2 to 5 years after diagnosis, despite similar scores around the time of diagnosis. Figure 5.2C shows that widowed patients experience significantly higher MMSE scores than patients with partners from around 2 years prior to diagnosis until the end of the diagnosis duration window.

Figure 5.1

Predicted Non-Linear Changes in MMSE Over Diagnosis Duration by Marital Status Group

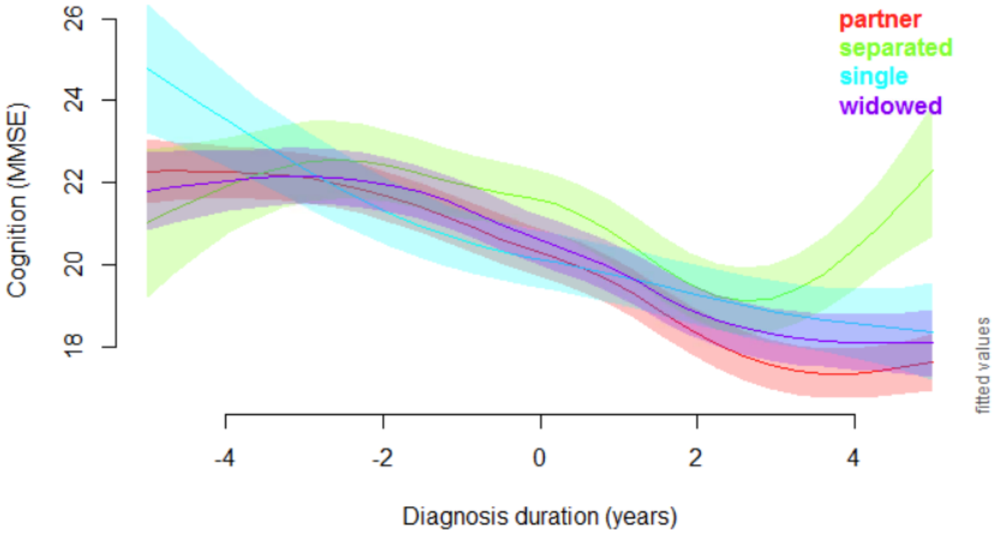
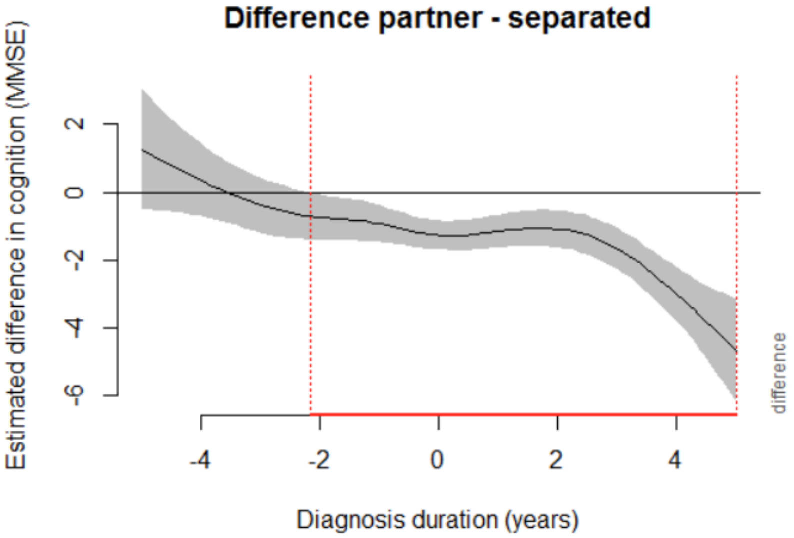


Figure 5.2A

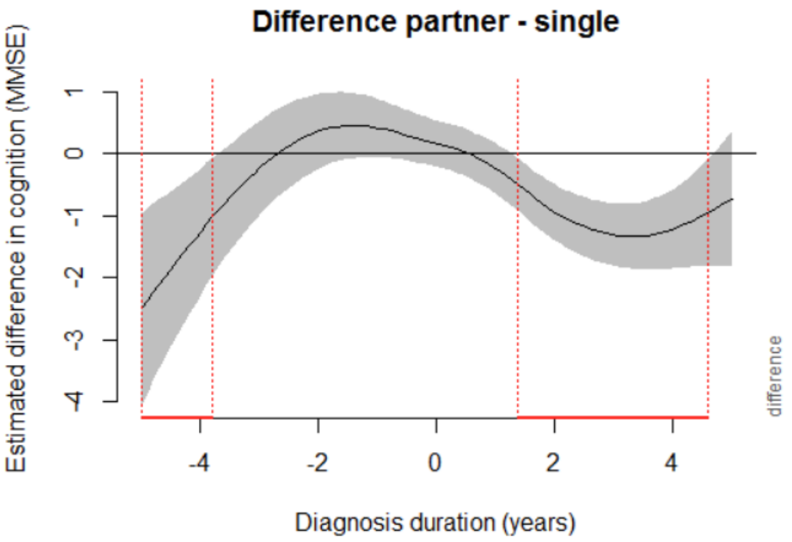
The Predicted Non-Linear Difference Between Partner and Separated Marital Statuses



Note. The red lines indicate periods of statistically significant scores

Figure 5.2B

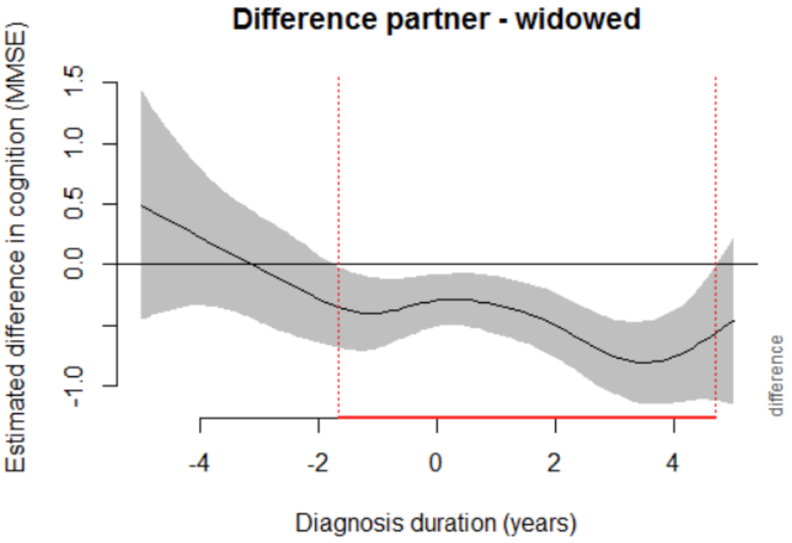
The Predicted Non-Linear Difference Between Partner and Single Marital Statuses



Note. The red lines indicate periods of statistically significant scores

Figure 5.2C

The Predicted Non-Linear Difference Between Partner and Widowed Marital Statuses



Note. The red lines indicate periods of statistically significant scores

5.3.1.2 Accommodation Status

The significant random effects term indicates significant between-patient variability in MMSE scores that are not explained by the fixed or smooth predictors (EDF = 1211.61, F = 4.07, $p < 0.001$). The model performance output suggests that this model accounts for between 62.8% and 73% of the variance in MMSE scores (adjusted $R^2 = 0.628$, explained deviance = 73.0%). Controlling for age, diagnosis cause, sex, and ethnicity, the results of the GAMM for the linear effects of accommodation status on MMSE intercepts shows average MMSE scores at diagnosis for the reference group, female, White, AD patients living in mainstream housing to be 24.85 ($\beta = 24.85$, SE = 0.55, t-value = 45.28, $p < .001$). Patients living in supported accommodation had predicted MMSE scores that were 1.77 points lower than patients living in mainstream housing ($\beta = -1.77$, SE = 0.25, t-value = -7.01, $p < 0.001$). There was a significant effect of age, with MMSE scores decreasing by 0.06 points for every increased year of age at the time of cognitive measurement ($\beta = -0.06$, SE = 0.02, t-value = -3.61, $p < 0.001$). The model coefficients are shown in Table 5.2.

Table 5.2

Model Coefficients for a the Parametric Output from a Generalised Additive Multilevel Model Predicting MMSE as a Function of the Interaction Between Accommodation Status and Diagnosis Duration Controlling for Age, Sex, Ethnicity and Diagnosis Cause

Factor	Estimate	Standard Error	t-value	p-value
Main Exposures				
Intercept*†	**24.85**	**0.55**	**45.28**	**< 0.001**
Supported accommodation‡	**-1.77**	**0.25**	**-7.01**	**< 0.001**
Demographic Factors				
Years of age at cognitive measure	**-0.06**	**0.02**	**-3.61**	**< 0.001**
Male	0.24	0.25	0.97	0.332
Non-White	-0.72	0.93	-0.87	0.387

Ethnicity not known	**-0.81**	**0.27**	**-3.05**	**0.002**
Diagnosis Factors				
VaD	-0.06	0.47	-0.13	0.898
DLB	0.18	0.84	0.22	0.829
FTD	3.33	1.83	1.82	0.068
Mixed AD-VaD	0.15	1.11	0.14	0.891
PPD	0.31	1.53	0.20	0.841
Unspecified	-0.02	0.27	-0.09	0.926
Diagnosis not known	0.91	0.53	1.72	0.085

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD patients living in mainstream housing. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

[†] Considered to be a non-socially isolated category

[‡] Considered to be a socially isolated category

The non-linear effects of accommodation status on MMSE trajectories predicted by the GAMM indicate that the association between diagnosis duration and MMSE score is non-linear for both patients living in mainstream housing (EDF = 4.36, F = 149.29, $p < 0.001$) and patients living in supported accommodation (EDF = 2.32, F = 90.57, $p < 0.001$). The estimated degrees of freedom predictions of between approximately 2 to 4 indicate moderately complex non-linear interactions. Figure 5.3 demonstrates the complexity of the non-linear smooth term for mainstream housing is more complex than for supported accommodation, with patients in mainstream housing maintaining cognition for longer prior to diagnosis before rates of change around diagnosis matching those of supported accommodation. Rates of MMSE change of patients living in supported accommodation remain relatively stable. Figure 5.4 demonstrates that there is a significant difference between the MMSE scores of the two groups throughout the diagnosis duration window, with mainstream housing estimates consistently higher.

Figure 5.3

Predicted Non-Linear Changes in MMSE Over Diagnosis Duration by Accommodation Status Group

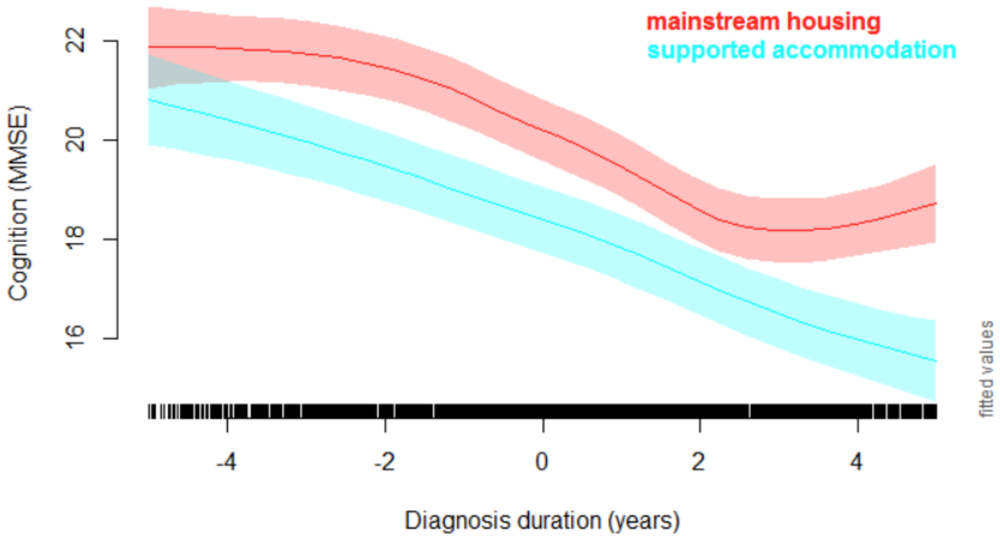
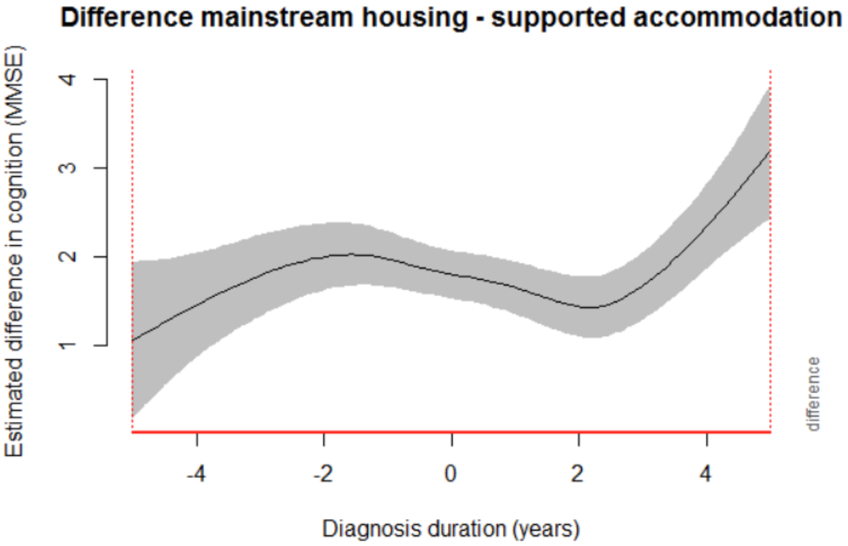


Figure 5.4

The Predicted Non-Linear Difference Between Mainstream Housing and Supported Accommodation Statuses



Note. The red lines indicate periods of statistically significant scores

5.3.1.3 Living Status

The significant random effects term indicates significant between-patient variability in MMSE scores that are not explained by the fixed or smooth predictors (EDF = 917.06, F = 4.33, p < 0.001). The model performance output suggests that this model accounts for between 63% and 72.6% of the variance in MMSE scores (adjusted R^2 = 0.630, explained deviance = 72.6%). Controlling for age, diagnosis cause, sex, and ethnicity, the results of the GAMM for the linear effects of living status on MMSE intercepts shows average MMSE scores at diagnosis for the reference group, female, White, AD patients assumed to be living with at least one other person to be 24.62 (β = 24.62, SE = 0.62, t-value = 39.76, p < .001). Like the accommodation status model, patients living in supported accommodation had predicted MMSE scores that were 2.02 points lower than cohabiting patients (β = -2.02, SE = 0.32, t-value = -6.26, p < 0.001). There was a significant effect of age, with MMSE scores decreasing by 0.05 points for every increased year of age at the time of cognitive measurement (β = -0.05, SE = 0.02, t-value = -2.66, p = 0.008). The model coefficients are shown in Table 5.3.

Table 5.3

Model Coefficients for a the Parametric Output from a Generalised Additive Multilevel Model Predicting MMSE as a Function of the Interaction Between Living Status and Diagnosis Duration Controlling for Age, Sex, Ethnicity and Diagnosis Cause

Factor	Estimate	Standard Error	t-value	p-value
Main Exposures				
Intercept*†	**24.62**	**0.62**	**39.76**	**< 0.001**
Alone‡	0.32	0.43	0.76	0.449
Supported accommodation‡	**-2.02**	**0.32**	**-6.26**	**< 0.001**
Demographic Factors				
Years of age at cognitive measure	**-0.05**	**0.02**	**-2.66**	**0.008**
Male	0.31	0.29	1.06	0.287

Non-White	-0.575	0.94	-0.61	0.541
Ethnicity not known	-0.38	0.37	-1.03	0.305
Diagnosis Factors				
VaD	-0.20	0.53	-0.38	0.702
DLB	0.15	0.95	0.16	0.871
FTD	**3.99**	**1.96**	**2.03**	**0.042**
Mixed AD-VaD	-0.10	1.22	-0.08	0.937
PPD	-0.86	1.91	-0.45	0.653
Unspecified	0.05	0.31	0.15	0.879
Diagnosis not known	1.13	0.60	1.87	0.062

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD patients assumed to be living with at least one other person. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

† Considered to be a non-socially isolated category

‡ Considered to be a socially isolated category

The non-linear effects of living status on MMSE intercepts predicted by the GAMM indicates that the association between diagnosis duration and MMSE score is non-linear for all levels of living status. The smooth term for cohabiting patients is significant, and the estimated degrees of freedom between 3 and 4 suggests a moderately complex, non-linear shape (EDF = 3.51, F = 84.34, $p < 0.001$). The smooth term for patients living alone is also significant, and the estimated degrees of freedom suggests around 2 effective parameters (EDF = 2.46, F = 10.40, $p < 0.001$). The smooth term for patients living in supported accommodation is also significant, with estimated degrees of freedom between 4 and 5, suggesting a complex non-linear relationship (EDF = 4.72, F = 93.67, $p < 0.001$). Figure 5.5 shows the non-linear changes in MMSE over diagnosis duration depending on level of living status. Figure 5.6A shows estimates for cohabiting patients are consistently significantly higher than patients in supported accommodation throughout the diagnosis duration window. Conversely, Figure 5.5 demonstrates that while cohabiting patients and patients living alone experience similar MMSE scores prior to and around the time of diagnosis, patients living alone begin to experience a relatively stable period of cognition after diagnosis, whereas cohabiting patients continue to decline. As can be seen in Figure 5.6B, this difference becomes statistically significant from around 2 years after diagnosis.

Figure 5.5

Predicted Non-Linear Changes in MMSE Over Diagnosis Duration by Living Status Group

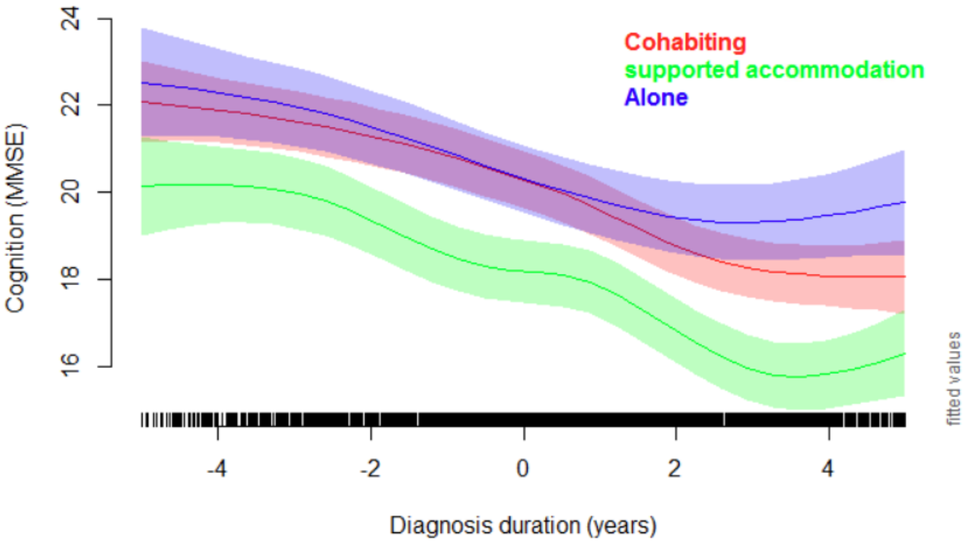
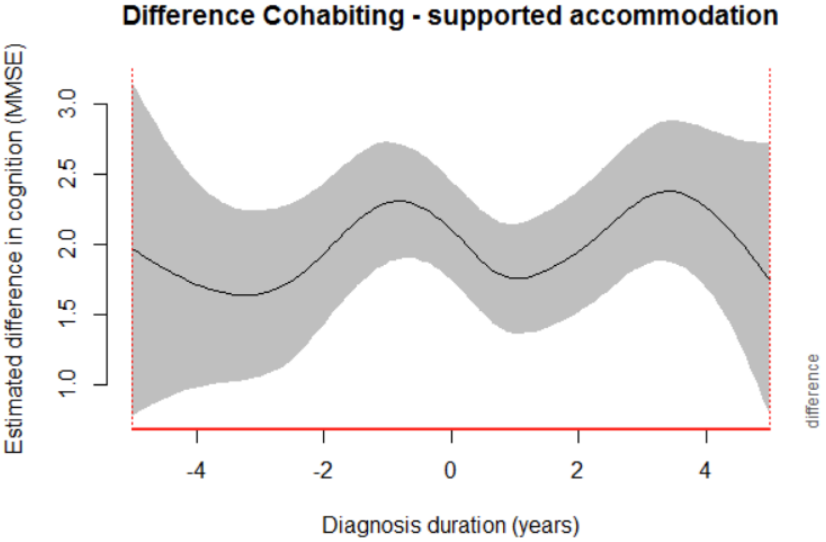


Figure 5.6A

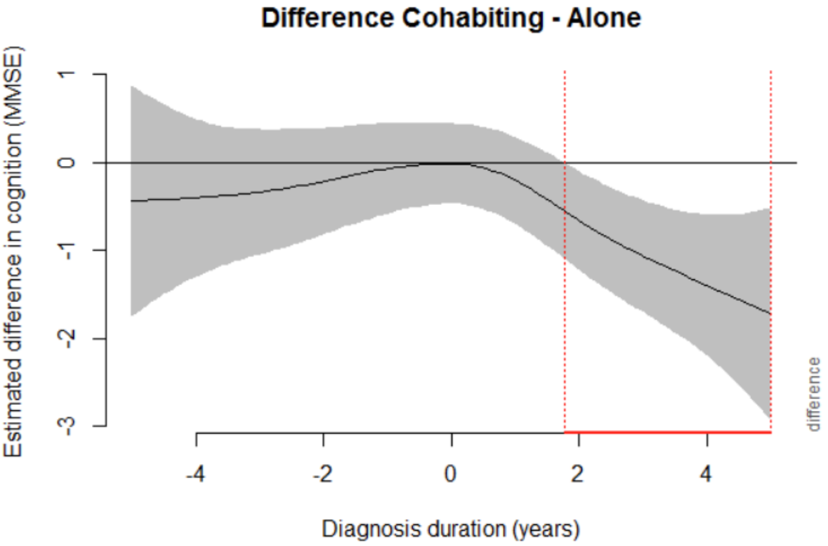
The Predicted Non-Linear Difference Between Cohabiting and Supported Living Statuses



Note. The red lines indicate periods of statistically significant scores

Figure 5.6B

The Predicted Non-Linear Difference Between Cohabiting and Alone Living Statuses



Note. The red lines indicate periods of statistically significant scores

5.3.2 Effects of SI Proxies on MoCA Trajectories

5.3.2.1 Marital Status

The significant random effects term indicates significant between-patient variability in MoCA scores that are not explained by the fixed or smooth predictors (EF = 1887.97, F = 5.41, $p < 0.001$). The model performance output suggests that this model accounts for between 73.4% and 83.9% of the variance in MoCA scores (adjusted $R^2 = 0.734$, explained deviance = 83.9%). Controlling for age, diagnosis cause, sex, and ethnicity, the results of the GAMM for the linear effects of marital status on MoCA intercepts shows average MoCA scores at diagnosis for the reference group, female, White, AD patients with a partner to be 20.84 ($\beta = 20.84$, SE = 0.55, t-value = 38.15, $p < 0.001$). The prediction for average MoCA scores for separated patients was not significantly different than patients with a partner ($\beta = 0.08$, SE = 0.47, t-value = 0.17 $p = 0.869$). Single patients had predicted MoCA scores that were lower than patients with a partner by 1.38 points ($\beta = -1.38$, SE = 0.62, t-value = -2.24, $p = 0.025$). Whereas, widowed patients' predicted cognitive scores were not significantly different from the reference group (β = -0.16, SE = 0.28, t-value = -0.56, p = 0.574). Of the control variables, there was a significant effect of age, with MoCA scores decreasing by 0.10 points for every increased year of age at the time of cognitive measurement (β = -0.10, SE = 0.02, t-value = -6.23, p < 0.001). There was also a significant effect of sex, with male patients predicted to have higher MoCA scores by 1.12 points compared to female patients (β = 1.12, SE = 0.25, t-value = 4.57, p < 0.001). The model coefficients are shown in Table 5.4.

Table 5.4

Model Coefficients for a the Parametric Output from a Generalised Additive Multilevel Model Predicting MoCA as a Function of the Interaction Between Marital Status and Diagnosis Duration Controlling for Age, Sex, Ethnicity and Diagnosis Cause

Factor	Estimate	Standard Error	t-value	p-value
Main Exposures				
Intercept*†	**20.84**	**0.55**	**38.15**	**< 0.001**
Separated / Divorced†	0.08	0.47	0.17	0.869
Single‡	**-1.38**	**0.62**	**-2.24**	**0.025**
Widowed‡	-0.16	0.28	-0.56	0.574
Demographic Factors				
Years of age at cognitive measure	**-0.10**	**0.02**	**-6.23**	**< 0.001**
Male	**1.12**	**0.25**	**4.57**	**< 0.001**
Non-White	-1.56	0.80	-1.95	0.051
Ethnicity not known	0.38	0.37	1.03	0.304
Diagnosis Factors				
VaD	-0.38	0.50	-0.76	0.447
DLB	0.56	0.88	0.63	0.528
FTD	-0.93	1.72	-0.54	0.589

Mixed AD-VaD	-0.07	0.90	-0.07	0.941
PPD	-1.42	1.23	-1.16	0.248
Unspecified	0.42	0.26	1.60	0.109
Diagnosis not known	**1.54**	**0.44**	**3.53**	**< 0.001**

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD patients with a partner. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

† Considered to be a non-socially isolated category

‡ Considered to be a socially isolated category

The non-linear effects of marital status on MoCA trajectories predicted by the GAMM indicates that the association between diagnosis duration and MoCA score is non-linear for both patients with partners (EDF = 3.31, F = 201.17, $p < 0.001$) and widowed patients (EDF = 2.56, F = 97.16, $p < 0.001$), however not for separated patients (EDF = 0.90, F = 2.53, $p = 0.098$), nor single patients (EDF = 0.56, F = 0.71, $p = 0.208$). Figure 10 displays the cognitive trajectories from the model. Patients with partners have higher MoCA scores earlier in the diagnosis window than separated and single partners, then experience sharper declines. A similar pattern is seen with widowed patients. Figure 5.8A demonstrates that the difference in scores between patients with partners and separated patients is such that patients with partners have significantly higher scores approximately 5 to 2 years before diagnosis, followed by a period of similar scores around diagnosis, then by scores that a significantly lower than separated patients from approximately 2 years after diagnosis until the end of the diagnosis duration window. Despite similar rates of change between single and separated patients, average MoCA scores for single patients is lower throughout the diagnosis window. Compared to patients with partners, single patients exhibit significantly lower cognitive scores from the start of the diagnosis duration window until approximately 2 years after diagnosis, at which point the scores for the two groups become similar.

Figure 5.7

Predicted Non-Linear Changes in MoCA Over Diagnosis Duration by Marital Status Group

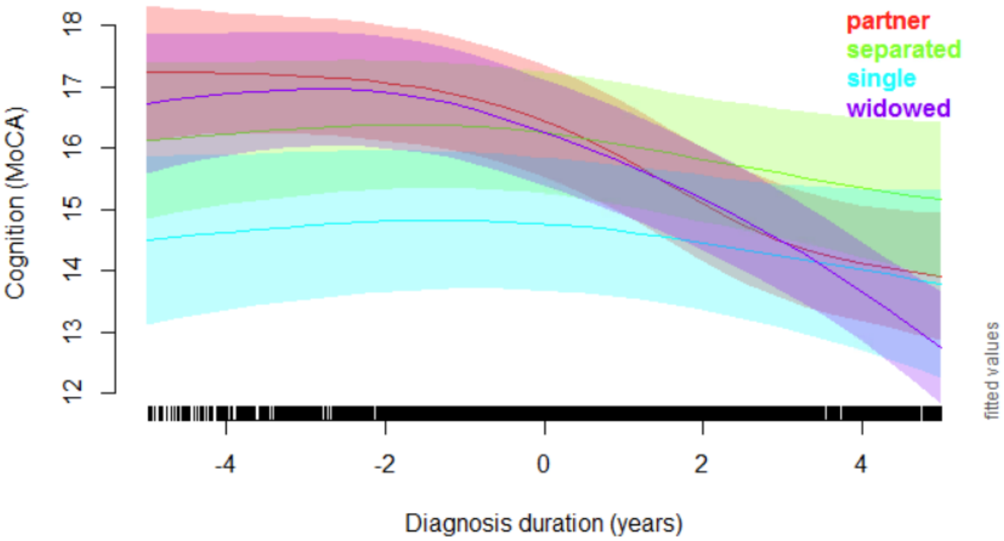
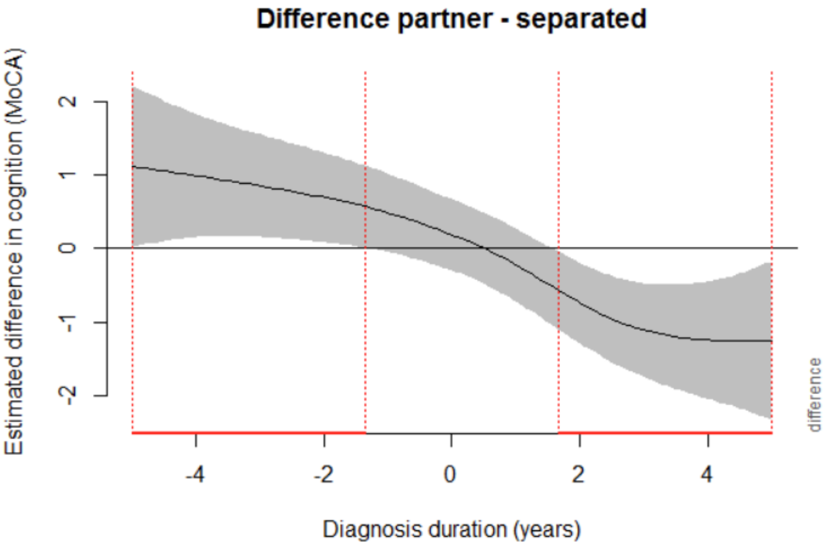


Figure 5.8A

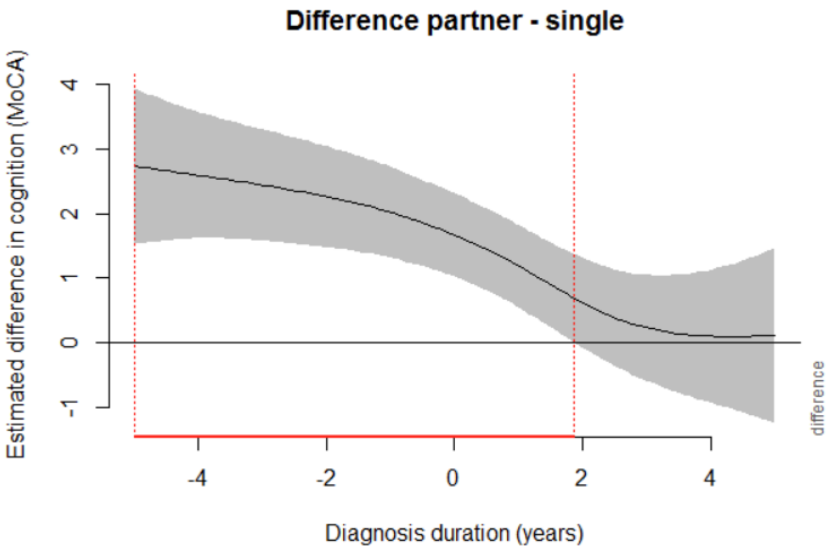
The Predicted Non-Linear Difference Between Partner and Separated Marital Statuses



Note. The red lines indicate periods of statistically significant scores

Figure 5.8B

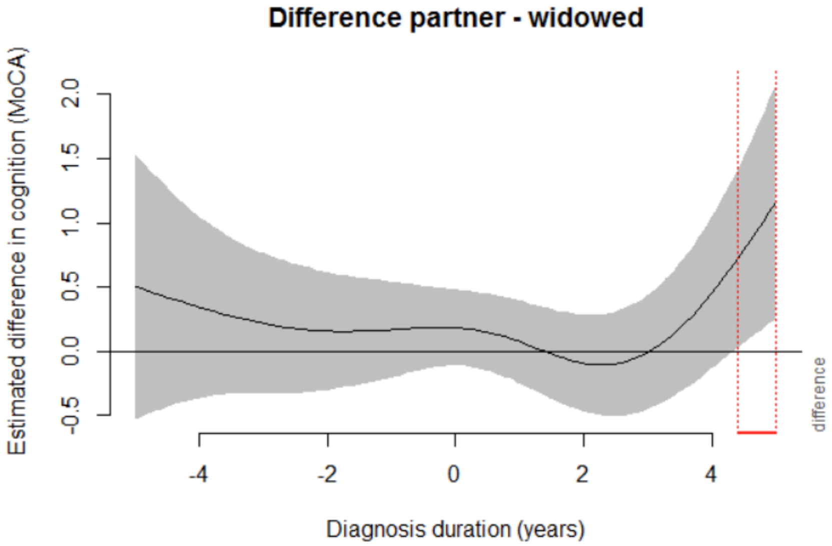
The Predicted Non-Linear Difference Between Partner and Single Marital Statuses



Note. The red lines indicate periods of statistically significant scores

Figure 5.8C

The Predicted Non-Linear Difference Between Partner and Widowed Marital Statuses



Note. The red lines indicate periods of statistically significant scores

5.3.2.2 Accommodation Status

The significant random effects term indicates significant between-patient variability in MoCA scores that are not explained by the fixed or smooth predictors (EF = 1930.41, F = 5.29, $p < 0.001$). The model performance output suggests that this model accounts for between 73% and 83.2% of the variance in MoCA scores (adjusted $R^2 = 0.730$, explained deviance = 83.2%). Controlling for age, diagnosis cause, sex, and ethnicity, the results of the GAMM for the linear effects of marital status on MoCA intercepts shows average MoCA scores at diagnosis for the reference group, female, White, AD patients assumed to be living in mainstream housing to be 18.78 ($\beta = 18.78$, SE = 0.51, t-value = 36.52, $p < 0.001$). Patients living in supported accommodation had predicted MoCA scores that were 1.78 points lower than the reference group ($\beta = -1.78$, SE = 0.27, t-value = -6.59, $p < 0.001$). There was a significant effect of age, with MoCA scores decreasing by 0.04 points for every increased year of age at the time of cognitive measurement ($\beta = -0.04$, SE = 0.02, t-value = -2.31, $p = 0.021$). There was also a significant effect of sex, with male patients predicted to have higher MoCA scores by 1.19 points compared to female patients ($\beta = 1.19$, SE = 0.22, t-value = 5.33, $p < 0.001$). The model coefficients are shown in Table 5.5.

Table 5.5

Model Coefficients for the Parametric Output from a Generalised Additive Multilevel Model Predicting MoCA as a Function of the Interaction Between Accommodation Status and Diagnosis Duration Controlling for Age, Sex, Ethnicity and Diagnosis Cause

Factor	Estimate	Standard Error	t-value	p-value
Main Exposures				
Intercept*†	**18.75**	**0.51**	**36.52**	**< 0.001**
Supported accommodation‡	**-1.78**	**0.27**	**-6.59**	**< 0.001**
Demographic Factors				
Years of age at cognitive measure	**-0.04**	**0.02**	**-2.31**	**0.021**
Male	**1.19**	**0.22**	**5.33**	**< 0.001**

Non-White	-0.97	0.83	-1.16	0.244
Ethnicity not known	**-0.78**	**0.23**	**-3.42**	**0.001**
Diagnosis Factors				
VaD	-0.66	0.44	-1.50	0.135
DLB	0.81	0.74	1.09	0.276
FTD	-0.44	1.59	-0.28	0.783
Mixed AD-VaD	-0.57	0.82	-0.70	0.487
PPD	-0.26	1.07	-0.24	0.807
Unspecified	-0.30	0.25	-1.19	0.236
Diagnosis not known	0.80	0.42	1.91	0.057

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD patients assumed to be living in mainstream housing. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

† Considered to be a non-socially isolated category

‡ Considered to be a socially isolated category

The non-linear effects of accommodation status on MoCA trajectories predicted by the GAMM indicates that the association between diagnosis duration and MoCA score is non-linear for both patients living in mainstream housing (EDF = 3.67, F = 241.47, $p < 0.001$) and patients living in supported accommodation (EDF = 3.05, F = 98.93, $p < 0.001$). The estimated degrees of freedom predictions of between 3 to 4 indicate moderately complex non-linear interactions. Figure 5.9 plots the non-linear cognitive trajectories as predicted by the model. The smooth terms for mainstream housing and supported accommodation show similarities, with both experiencing periods of relative stability up until approximately 2 years prior to diagnosis, at which point both begin to experience increased rates of decline, with patients living in supported accommodation appearing to experience faster rates of decline than patients in mainstream housing. The term for patients in supported accommodation is lower than those for patients in mainstream housing throughout the diagnosis duration window, and this is further supported by Figure 5.10 which shows a statistically significant difference between the level lasts throughout, with patients in mainstream housing exhibiting higher MoCA scores.

Figure 5.9

Predicted Non-Linear Changes in MoCA Over Diagnosis Duration by Accommodation Status Group

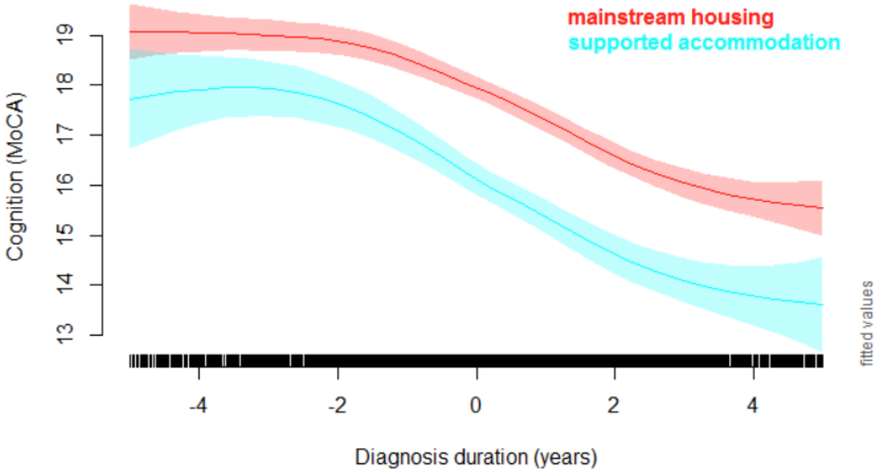
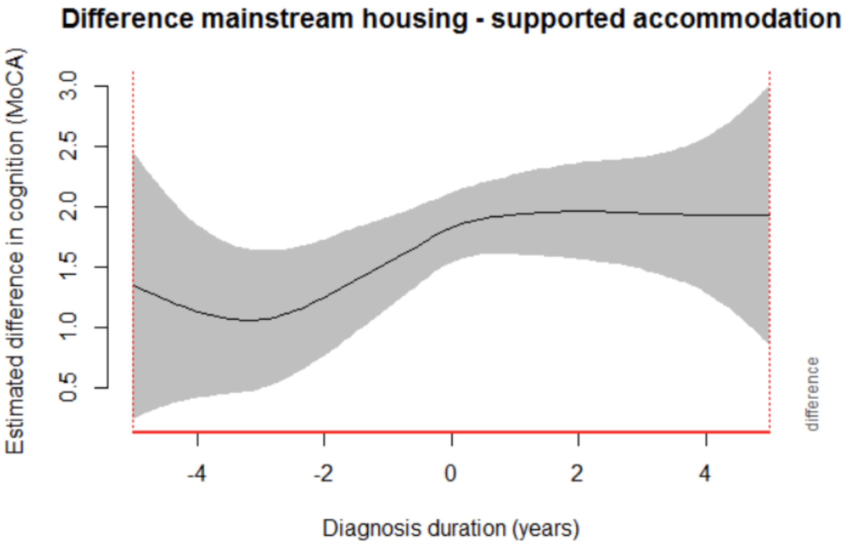


Figure 5.10

The Predicted Non-Linear Difference Between Mainstream Housing and Supported Accommodation Statuses



Note. The red lines indicate periods of statistically significant scores

5.3.2.3 Living Status

The significant random effects term indicates significant between-patient variability in MoCA scores that are not explained by the fixed or smooth predictors (EDF = 1303.95, F = 5.33, $p < 0.001$). The model performance output suggests that this model accounts for between 73.5% and 83.4% of the variance in MoCA scores (adjusted $R^2 = 0.735$, explained deviance = 83.5%). Controlling for age, diagnosis cause, sex, and ethnicity, the results of the GAMM for the linear effects of living status on MoCA intercepts shows average the MoCA score at diagnosis for the reference group, female, White, AD patients assumed to be living with at least one other person was 19.26 ($\beta = 19.26$, SE = 0.61, t-value = 31.78, $p < 0.001$). There was no significant difference in predicted MoCA scores between cohabiting patients and patients living alone ($\beta = 0.02$, SE = 0.36, t-value = 0.04, $p = 0.965$). Patients living in supported accommodation, however, had predicted MoCA scores that were 2.29 points lower than the reference group ($\beta = -2.29$, SE = 0.33, t-value = -6.91, $p < 0.001$). There was a significant effect of age, with MoCA scores decreasing by 0.05 points for every increased year of age at the time of cognitive measurement ($\beta = -0.05$, SE = 0.02, t-value = -2.74, $p = 0.006$). There was also a significant effect of sex, with male patients predicted to have higher MoCA scores by 1.37 points compared to female patients ($\beta = 1.37$, SE = 0.28, t-value = 4.97, $p < 0.001$). The model coefficients are shown in Table 5.6.

Table 5.6

Model Coefficients for the Parametric Output from a Generalised Additive Multilevel Model Predicting MoCA as a Function of the Interaction Between Living Status and Diagnosis Duration Controlling for Age, Sex, Ethnicity and Diagnosis Cause

Factor	Estimate	Standard Error	t-value	p-value
Main Exposures				
Intercept*†	**19.26**	**0.61**	**31.78**	**< 0.001**
Alone‡	0.02	0.36	0.04	0.965
Supported accommodation‡	**-2.29**	**0.33**	**-6.61**	**< 0.001**
Demographic Factors				

Years of age at cognitive measure	**-0.05**	**0.02**	**-2.74**	**0.006**
Male	**1.37**	**0.28**	**4.97**	**< 0.001**
Non-White	-0.71	0.96	-0.75	0.455
Ethnicity not known	-0.11	0.35	-0.31	0.757
Diagnosis Factors				
VaD	-0.55	0.54	-1.03	0.304
DLB	0.36	0.91	0.40	0.690
FTD	0.29	1.83	0.16	0.874
Mixed AD-VaD	-0.60	1.00	-0.60	0.551
PPD	-0.88	1.16	-0.76	0.447
Unspecified	0.08	0.30	0.28	0.781
Diagnosis not known	**1.00**	**0.51**	**1.97**	**0.049**

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD patients assumed to be living with at least one other person. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

† Considered to be a non-socially isolated category

‡ Considered to be a socially isolated category

The non-linear effects of living status on MoCA trajectories predicted by the GAMM indicates that the association between diagnosis duration and MoCA score is non-linear for all levels of living status. The smooth term for cohabiting patients is significant, and the estimated degrees of freedom being close to 4 suggests a fairly complex, non-linear shape (EDF = 3.98, F = 141.06, p < 0.001). The smooth term for patients living alone is also significant, and the estimated degrees of freedom suggests around 2 effective parameters (EDF = 1.91, F = 28.77, p < 0.001). The smooth term for patients living in supported accommodation is also significant, with estimated degrees of freedom close to 3, suggesting a moderately complex non-linear relationship (EDF = 2.90, F = 90.39, p < 0.001). Figure 5.11 displays the smooth terms estimated by the model for the three levels of living status. As the estimated degrees of freedom suggest, the term for cohabiting is more complex than the terms for alone and supported accommodation. The estimated MoCA scores for supported accommodation are consistently below those of cohabiting and alone living statuses, as supported by Figure 5.12A. Patients living alone and those cohabiting exhibit mostly similar cognitive scores except for a small period around 1.5 to 3 years after diagnosis. Estimates for this time period suggest patients living alone have significantly higher MoCA scores during this time, as evidenced in Figure 5.12B.

Figure 5.11

Predicted Non-Linear Changes in MoCA Over Diagnosis Duration by Living Status Group

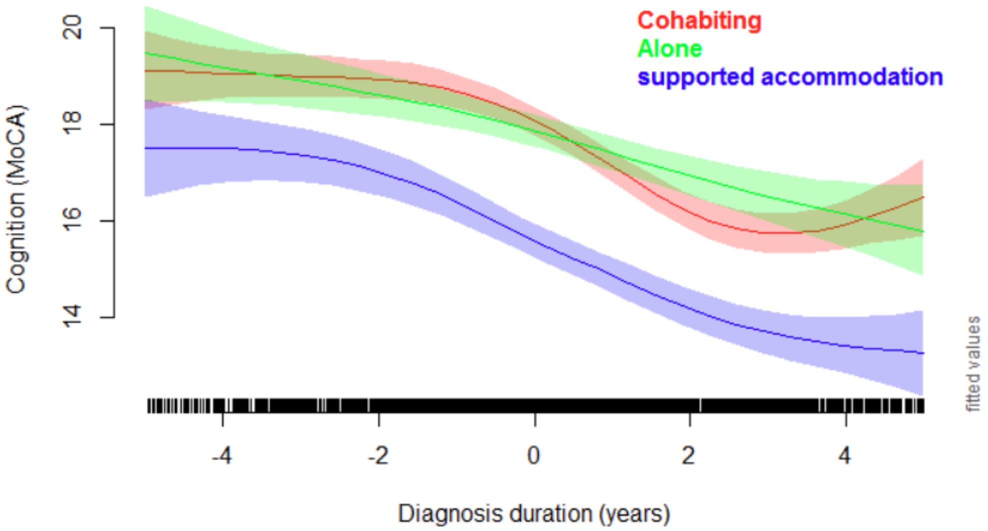
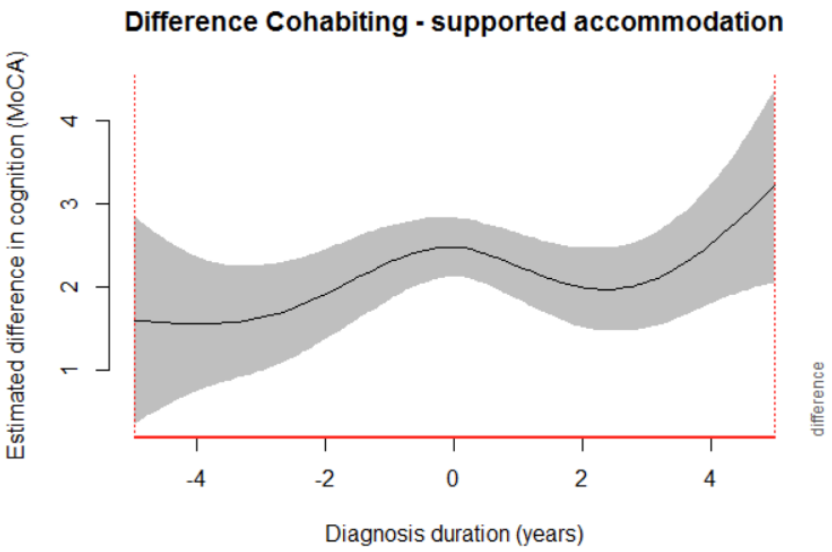


Figure 5.12A

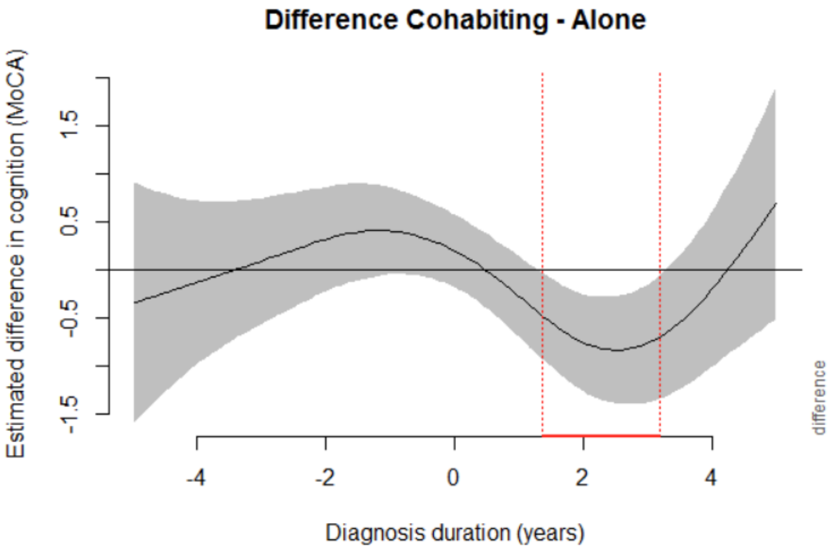
The Predicted Non-Linear Difference Between Cohabiting and Supported Living Statuses



Note. The red lines indicate periods of statistically significant scores

Figure 5.12B

The Predicted Non-Linear Difference Between Cohabiting and Alone Living Statuses



Note. The red lines indicate periods of statistically significant scores

5.4 Discussion

5.4.1 Summary of findings

This study aimed to build upon the models developed in Study 1 by introducing non-linear terms to investigate the impact of SI proxies identified from EHRs on cognition and cognitive trajectories of ADRD patients from Oxford Health NHS Foundation Trust. As with Study 1, the expectation for the current study was that patients attributed to SI proxy groups – 'single' and 'widowed' marital statuses, 'supported accommodation' accommodation status, and 'supported accommodation' and 'alone' living statuses – would exhibit lower cognitive function scores and faster rates of decline than non-SI proxy groups – 'partner' and 'separated' marital statuses, 'mainstream housing' accommodation status, and 'cohabiting' living status. As with Study 1, the current study found only partial evidence to support this expectation.

Considering marital status as the SI proxy and MMSE as the cognitive measure, model estimates for cognition at diagnosis showed patients with partners, single patients and widowed patients had similar levels of cognition, with separated patients having higher predicted scores. Age at cognitive measure decreased cognitive function by 0.12 MMSE points per increased year of age. Male participants had higher cognition at diagnosis than female patients by 0.58 MMSE points. Non-white patients had lower MMSE scores at diagnosis than white patients by 1.77 points on average. Non-linear analysis reveals that the difference between separated patients and patients with partners becomes statistically significant roughly 2.5 years before diagnosis, suggesting that separated patients are able to maintain stable cognitive function for longer, with their rate of cognitive decline less than patients with partners until around 0.5-1 year(s) after diagnosis, at which points rates of cognitive decline increase. Further analysis revealed more complex interactions between diagnosis duration – the time from diagnosis at which the observation of cognitive function took place, with negative times representing time before diagnosis, positive time representing the time after diagnosis, and zero representing the time at which diagnosis occurred – and cognition. Patients with partners remained similar to widowed patients throughout the diagnosis duration window. Whereas single patients had significantly higher cognitive scores in the years before diagnosis, experienced faster rates of decline to exhibit similar cognitive scores around diagnosis as widowed patients and patients with partners, then rates of decline become slower, resulting in significantly higher cognitive scores again from around 2 years after diagnosis. Such slowing rates of decline may be, at least partially, explained by patient mortality: it would be expected that patients with faster rates of decline are experiencing more severe disease pathology and therefore may die sooner than patients experiencing less severe decline. As the model estimates group averages over time, the model may reach a point where it is observing disproportionately more relatively healthy patients, giving the illusion that rates of decline are slowing down.

These findings give partial support to study expectations in that patients with partners and separated patients, as designated non-SI groups, were expected to have higher cognition and slower rates of cognitive decline, however this only seems to be the case for separated patients. Single and widowed patients were expected to have lower cognitive function estimates due their association with increased ADRD incidence risk (Sommerlad et al., 2018). Widowed patients were predicted by the model to have similar cognition and rates of cognitive change across the diagnosis window, whereas the study expectation was that, as an SI designated group, widowed patients would experience lower cognition and faster rates of decline than the non-SI groups. That this is the case for separated patients, but not patients with partners, could suggest an overlap between partner and widowed marital statuses within the EHRs. These variables are defined at the level of the patient, rather than the level of observation, therefore it is unclear whether some patients with partners become widowed over the course of their diagnosis or in the years before. Whether this is reflected in the EHRs likely relies on whether this is updated by the clinic, however it is not possible to see whether or when changes in marital status are recorded in the EHRs.

When considering marital status as the SI proxy and MoCA as the cognitive measure, the model findings are more aligned with study expectations. Estimates of cognitive scores at diagnosis show patients with partners and separated patients have similar scores, as do widowed patients, however single patients have lower predicted MoCA scores by an average of 1.38 points. Age at cognitive measure decreased cognitive function by 0.10 MoCA points per increased year of age and male participants had higher cognition at diagnosis than female patients by 1.12 MoCA points. However, unlike the MMSE model, there were no predicted differences between White and non-White patients in terms of MoCA scores at diagnosis. Looking at the interactions between diagnosis duration and cognition predicted by this model, trajectories for partner and widowed patients are shown to be non-linear, whereas single and widowed are not. This suggests the change in cognition over time for partner and widowed marital statuses is more complex than for single and separated, which visualisations for the model show does not change much over time. This results in predictions for single patients that are significantly lower than patients with partners throughout the diagnosis duration window, until around 2 years after diagnosis, where scores for patients with partners have declined to meet single patient predictions. Widowed patients appear similar to patients with partners throughout, which could again suggest an overlap in the categorisation of these patients within the EHRs. That such differences between the MMSE and MoCA models exist could suggest a difference in sensitivity between the two measures and the domains of cognition that could be affected by SI under the different circumstances observed and modelled. For example, the MoCA is more sensitive to early cognitive changes in executive functions and visuospatial memory, whereas MMSE can capture cognitive changes in established ADRD cases (Nasreddine et al., 2005; Smith et al., 2007; Trzepacz et al., 2015; Zadikoff et al., 2008). This may also, therefore, reflect differences in the patient populations that each measure capture, if MoCA is capturing cognition in patients earlier in their disease and MMSE later in their disease.

Accommodation status and living status models are more consistent with their outcomes regardless of which measure of cognition is used. In accommodation status models, patients living in supported accommodation have cognitive scores that are consistently estimated to be lower at diagnosis than those of patients living in mainstream housing (average scores are 1.77 points lower for the MMSE model and 1.78 points lower for the MoCA model). The non-linear visualisation for the MoCA model shows that both accommodation status levels experience moderate cognitive stability up until 2 years before diagnosis, at which point the rate of decline for patients in supported accommodation increases. Patients in mainstream housing maintain cognition for longer, before rates of decline start to increase 1 year prior to diagnosis. The MMSE model visualisation is similar for patients in mainstream housing, however the estimated change in cognition over time for patients in supported accommodation seems to be stable (a more consistent decline from 5 years before diagnosis to five years after diagnosis). Living status models consistently show patients in supported accommodation have lower estimated cognition at diagnosis and throughout the diagnosis duration window than cohabiting patients and patients living alone. Patients living alone exhibit similar cognitive scores at diagnosis as cohabiting patients at diagnosis, and non-linear analysis shows scores are similar over time, with patients living alone having significantly higher cognitive scores for a period of time towards the end of the diagnosis duration window.

5.4.2 Limitations and Suggestions for Further Research

That the models consistently did not find evidence for a difference in cognition, whether at diagnosis or over the diagnosis duration window, between patients with partners and widowed patients suggests there could be some level of overlap between these groups. That it is not possible to understand more clearly the nature of the marital relationship each patient is experiencing at the time of their observations is a limitation of using secondary data in this manner. Similarly, that assumptions had to be made regarding the patients' levels of SI limits the conclusiveness of the study findings, though convenience proxies are often relied on, due to their association with cognition or disease progression (Stern et al., 2020).

A further limitation that may influence all the non-linear trajectories presented is selective attrition due to mortality. This study includes a high-mortality population of ADRD patients. If patients with more severe disease progression and faster cognitive decline are also more likely to die (or be lost to follow-up) during the diagnosis duration window, this selective dropout of the patients with faster rates of decline at later time points can create an artificial survivorship bias. This bias could make the average cognitive decline for any group appear to slow down or flatten, as the remaining sample is composed of a relatively healthier surviving cohort and could explain some of the unexpected findings, such as the slowing rate of cognitive decline observed for single patients in the MMSE model.

Imbalance in sample sizes for ethnicity (see table 3.1) presents another limitation. The non-white category represents only 1% of the overall sample compared to 66% white and 33% non-known. Such a discrepancy could lead to imprecise estimates and likely explains the relatively large standard error estimates for non-white ethnicity across the models in this chapter. Furthermore, a catch-all category of non-white is likely to be heterogeneous, combining diverse populations into a single category. Modelling these patients as a single group could further reduce the interpretability of the model estimates. These limitations could explain the inconsistent findings regarding ethnicity across the models.

Another limitation of the current study is that it does not assess the impact of loneliness on rates of cognitive decline. Loneliness constitutes a negative feeling regarding a subjective discrepancy between desired and perceived social connection (de Jong Gierveld et al., 2006) and has been shown to be associated to cognitive decline and dementia (Freak-Poli et al., 2022; Lara et al., 2019) as well as cognitive reserve (Lao et al., 2024; Zhang et al., 2022). Further research, therefore, could look to define a more objective measure of SI from the EHRs, as opposed to relying solely on convenience proxies. A measure of loneliness would also help to provide a more holistic picture of the impact of social connection on cognition and cognitive trajectories in ADRD patients than an assessment that only utilises measures of SI.

5.4.3 Conclusion

Overall, the current study shows that the use of non-linear modelling reveals more complex interactions between diagnosis duration and cognition than when using linear modelling (e.g. Study 1). In models using MoCA as the measure of cognition, SI proxies moderated the association between cognition and diagnosis duration in line with study expectations more than MMSE when marital status was the SI proxy. Models using accommodation status and living status as the SI proxy were similar regardless of cognitive measure. That patients living alone were found to have similar cognitive scores and trajectories as cohabiting patients suggests that other factors (e.g. whether a patient is living in mainstream housing or supported accommodation) are stronger predictors of cognition for ADRD patients.

6 Study 3: Integrating a Novel Natural Language Processing Algorithm to Assess the Effect of Social Isolation and Loneliness on ADRD Patient Cognitive Trajectories

A manuscript detailing motivations, analyses and a discussion of the study covered in this chapter has been recently published (see Myers et al., 2025) and is also presented in Appendix I. The novel NLP algorithm described in this chapter was mainly developed by the primary supervisor of this PhD project, NV. The main contribution of this thesis' author, JACM, to the NLP involved defining examples of social isolation and loneliness within the EHR data and evaluating the NLP model accuracy with regards to correctly identifying reports of social isolation or loneliness. The data used in the final models were cleaned and processed by JACM. The analyses presented in this chapter were conducted by JACM. The figures were jointly created by JACM and NV.

6.1 Introduction

6.1.1 Overview

Previous findings have shown that a lack of both objective and subjective social connection (i.e. social isolation and loneliness, respectively) are associated with an increased risk of ADRD incidence risk (Desai et al., 2020; Kuiper et al., 2015; Lara et al., 2019; Livingston et al., 2017, 2020; Sommerlad et al., 2018, 2019), however less is known about the impact of reduced social connection on the cognitive trajectories of patients with an ADRD diagnosis. Study 1 and 2 of this thesis aimed to explore this impact, utilising proxies of social connection from the EHRs. Marital status, accommodation status and living status proxies were developed due to their previously established links to social isolation (see section 4.1) and due to their attainability from the EHR data. However, the models run in Study 1 and Study 2, using these proxies, failed to consider the impact of loneliness. Loneliness is another key component of social connection, along with social isolation. Whereas social isolation represents an objective absence of social connection (e.g. contacts, relationships and roles), loneliness represents a subjective negative emotional experience occurring as a result of a difference between a person’s desired and a person’s perceived level of social connection (de Jong Gierveld et al., 2006; Holt-Lunstad, 2017; Perlman & Peplau, 1981). Previous evidence supports association between loneliness and increased ADRD incidence risk (Kuiper et al., 2015; Lara et al., 2019) and its negative impact on cognition in older adults (Kuiper et al., 2016; Piolatto et al., 2022). Therefore, it was of interest to further develop the model previously used in Studies 1 and 2 by incorporating loneliness as a subjective social connection variable.

6.1.2 Aims and Study Expectations

The aim of this third study was first to develop proxy variables for social isolation and loneliness from the EHRs, utilising a novel natural language processing (NLP) algorithm. Secondly, these variables would be used to assess their impact on the interaction between cognition and diagnosis duration in ADRD patients, thereby providing a more holistic view of the impact of social connection in ADRD patient cognitive trajectories. Due to the previously established links between social isolation and loneliness and ADRD incidence and cognition, the study expectation was that participants experiencing social isolation or loneliness would exhibit worse cognitive outcomes at diagnosis and over time.

6.2 Methods

6.2.1 Study Design, Data Sources, Sample, Variables, and Patient Characteristics

The study design, data sources, sample, variables that are ubiquitous to all three modelling studies – cognitive function, diagnosis duration, and control variables – and patient characteristics information is set out in the Overview of Methodological Approaches chapter (Chapter 3), sections 3.3 to 3.5. The SI proxies developed in Studies 1 and 2 – *marital status*, *accommodation status*, and *living status* – are used as control variables in this study. See section 4.2.2 for an overview of these SI proxies. Diagnosis duration represents the time from diagnosis at which the observation of cognitive function took place, with negative times representing time before diagnosis, positive time representing the time after diagnosis, and zero representing the time at which diagnosis occurred.

6.2.2 Social Isolation and Loneliness Proxy Development

Approaches utilising lifestyle proxies or self-report have been the cornerstone of social connection research. In particular, the study of loneliness and its impact on ADRD risk/cognitive outcomes has often relied on either binary, such as “Do you feel lonely?” (e.g. Lampinen et al., 2022; Zhang et al., 2022), or questionnaire, such as the UCLA Loneliness scale (Russell, 1996; e.g. Sun et al., 2021) self-report measures. With regards to large retrospective cohort data, such as the data utilised in this thesis, analysing such self-report measures relies on those measures being collected as part of clinical practice, which is often not the case. Studies 1 and 2 relied on lifestyle variables as proxies of social isolation, yet no equivalent proxies existed within the data, as it was, that could be used as a proxy for loneliness. Therefore, in order to enhance the model developed in Studies 1 and 2 further, it was necessary to develop new proxies of social connection that encapsulate both social isolation and loneliness, considering the range of data that were available within the EHRs. EHRs contain a mixture of structured data, organised in a predefined format, making it more easily searchable and analysable (e.g. demographics, diagnosis codes, medication details), and unstructured data, lacking a predefined structure, but potentially providing rich contextual information about patient health and clinical encounters (Goodday et al., 2020; Pagliari et al., 2007). NLP offers a viable route for probing the unstructured data for new information pertaining to previously unexplored factors, in this case, social connection (Gligic et al., 2020; Kormilitzin et al., 2021; Liu et al., 2022; Senior et al., 2020; Vaci et al., 2020).

One such proxy attainable within the unstructured data was clinical notes of patients’ reports of being socially isolated or lonely. In previous studies, self-report of isolation has been considered an indicator of subjective connection and therefore used to measure loneliness, however this approach may lack nuance with regards to distinctions between social isolation and loneliness as separate (though connected) concepts. For instance, in the context of ADRD patients, reports of social isolation may reflect objective, observable circumstances. These may include descriptions of limited social interactions, geographic or transportation constraints, or other physical limitations hindering social interaction. In contrast, in the same context, reports of loneliness may reflect a more subjective emotional state. In this case, reports may describe feelings of emotional disconnection that are internal to the patient. While the expression of social isolation and loneliness through report is inherently subjective, it is expected that these reports extracted from EHRs via NLP reliably proxy distinct, latent constructs appropriately representing social isolation and loneliness as separate constructs. Furthermore, this NLP approach may help to mitigate reporting biases inherent in self-report (i.e. over or under reporting from patients due to e.g. social stigma or psychiatric factors), as clinical notes are written by trained professionals, potentially providing a more objective assessment.

6.2.3 NLP Development

A novel NLP model was developed for the social isolation and loneliness reports. The model was implemented in Python and processed textual records for reports of SI and loneliness in two stages: pattern matching and classification stage. In the pattern matching stage, a statistical model for word processing from the Spacy library was used to identify words that described social isolation and loneliness. This allowed identification of all documents including expressions such as ‘loneliness’, ‘social isolation’, ‘living alone’, etc. In the classification stage, sentence transformer models from Huggingface’s Spacy-Setfit library were used to process and classify sentences with social isolation and loneliness mentions. Sentence transformers, categorising semantically similar sentences, were trained to classify sentences with reports of social isolation and loneliness into four different categories: (1) social isolation, (2) loneliness, (3) non-informative isolation, and (4) non-informative sentences. Reports that mentioned lack of social contact, living alone, and being away from family, or that mentioned barriers in receiving social contact were used as indicators of social isolation. Reports mentioning emotional aspects of feeling lonely or suffering due to lack of social contact were used as indicators of loneliness. The non-informative isolation category included reports of temporary and physical isolation (e.g. “isolated fall” or “isolating in the tv-room”), while the non-informative sentences category covered all incorrectly included sentences from the pattern matching stage forwarded to the sentence classification stage. Most of the time, such sentences were identified due to the misspelling of words, such as ‘lovely’ instead of ‘lonely’. Table 6.1 shows examples of clinical reports and the category they were classified to.

Table 6.1

Example Clinical Reports by Classified Category

Classified category	Example report
Social isolation	"As a result of XXXXXs impairments, she has become increasingly more isolated and has been suffering from increasing distress, confusion and deterioration" "XXXXX lives alone in her own home" "Social isolation, lives in 2nd floor flat with no lift" "No longer drives which has resulted in her becoming more isolated"
Loneliness	"She reports she feels lonely but does not appear to be proactive in finding ways to address this" "Lonely and unfriended" "XXXXX did say that she felt lonely at times throughout the day" "XXXXX did say that she felt lonely at times throughout the day" "I could die of loneliness"
Non-informative isolation	"Isolated in the TV lounge for much of the morning as wanting some peace and quiet" "But this is currently an isolated incidence" "Has merely suffered one isolated fall"
Non-informative sentence	"She has also complained of feeling dizzy recently and today suffered dizziness on standing from seated position" "Mrs XXXXX will now be discharged from memory clinic back to your care" "PSA raised but not above threshold for re-referral as per urology"

6.2.4 NLP Accuracy

Accuracy evaluation involved this thesis' author and the project supervisor independently categorising sentences from a random sample of 5,000 previously unseen documents into one of the four previously defined categories. Each annotator reviewed and labelled the sentences independently to minimise bias. Annotations were then compared and disagreements discussed and resolved collaboratively through consensus to ensure consistent labelling.

The annotated data served as the ground truth for evaluating the model's classification performance. Standard classifier performance metrics were employed, including *sensitivity* (the model's ability to correctly identify true positives), *specificity* (the model's ability to correctly identify true negatives), and *balanced* or *F1 accuracy* (a metric that accounts for imbalances in the dataset by averaging sensitivity and specificity). Across four different categories, the NLP model achieved average F1 accuracy of .74, reaching .83 accuracy for social isolation sentences (sensitivity: .73 and specificity: .93) and .91 accuracy for sentences reporting loneliness (sensitivity: .88 and specificity: .95). Positive predictive values for SI were 0.83, and 0.88 for loneliness. For further details on NLP development, accuracy and training, please refer to the manuscript by Myers and colleagues (2025).

6.2.5 Statistical Analyses

As with Study 2, the data here were analysed using GAMM, with LMRM for the parametric estimates. This allowed visualisation and estimation of average change in cognitive function throughout the disease, testing how trajectories differ between patients who reported loneliness or social isolation in comparison to a group of patients without such reports (control group). The primary outcome was cognition, measured by MMSE or MoCA, testing the effect of social isolation or loneliness complaint and the interaction with diagnosis duration, controlling for age, ADRD diagnosis, sex, marital status, accommodation status, and whether patients had a diagnosis of depression in their medical history. In case of missing information for marital and accommodation status, these patients were included in the analysis as Missing categories, while models without these predictors or cases with missing data are reported in the sensitivity analysis. The random by-patient intercept effects were adjusted in all models, which allowed intercepts to vary for each patient. The analyses were conducted in RStudio (v v1.3.1093; RStudio Team, 2020) using the *lme4* (v1.1-29; Bates et al., 2015), *mgcv* (v1.8-31, see Wood, 2017) and *itsadug* (v2.4.1; van Rij et al., 2022) packages.

6.3 Results

6.3.1 Patient Characteristics

For patients with cognitive assessment(s) measured using MMSE who also reported social isolation, the mean age across all observations was 78.82 years (SD = 8.37), while the mean cognitive score was 21.98 (SD = 5.74). For patients with cognitive assessment(s) measured using MMSE who also reported loneliness, the mean age across all observations was 82.16 years (SD = 6.82), while the mean cognitive score was 21.63 (SD = 5.29). For patients with cognitive assessment(s) measured using MMSE who did not report social isolation or loneliness (controls), the mean age across all observations was 91.38 years (SD = 7.24), while the mean cognitive score was 21.46 (SD = 5.83).

For patients with cognitive assessment(s) measured using MoCA who also reported social isolation, the mean age across all observations was 79.04 years (SD = 7.91), while the mean cognitive score was 17.66 (SD = 5.93). For patients with cognitive assessment(s) measured using MoCA who also reported loneliness, the mean age across all observations was 81.72 years (SD = 6.87), while the mean cognitive score was 17.27 (SD = 5.60). For patients with cognitive assessment(s) measured using MoCA who did not report social isolation or loneliness (controls), the mean age across all observations was 80.85 years (SD = 7.08), while the mean cognitive score was 18.34 (SD = 5.87).

6.3.2 Reports

The total number of loneliness reports peaked in 2020, possibly reflecting the transition to restricted social activities following Covid-19 lockdowns. A similar spike in complaints was seen in social isolation reports in 2020, though peaked in 2013. Figure 6.1 displays the number of loneliness (A) and social isolation (B) complaints per 1000 medical notes from 2011 to 2022.

Figure 6.1A

Loneliness complaints per 1000 medical notes from 2011 to 2022

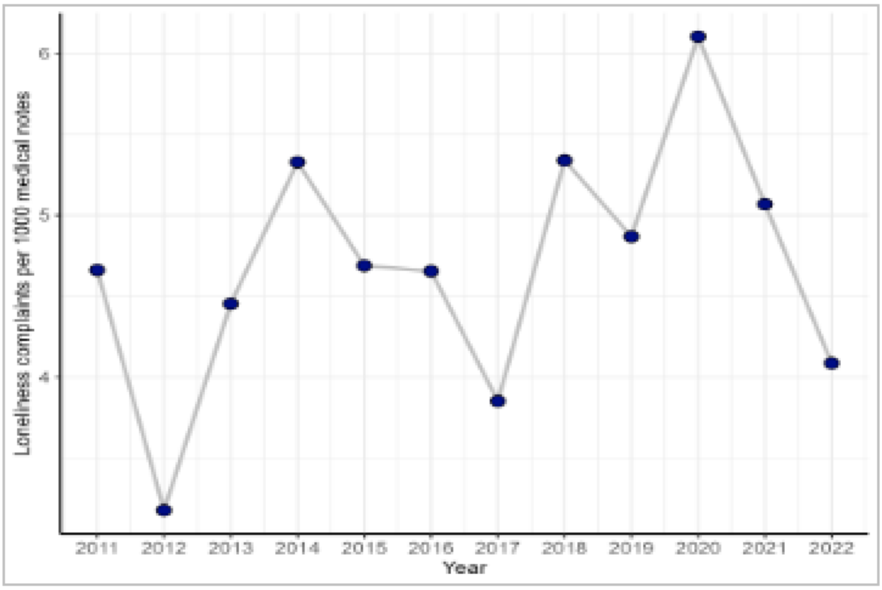
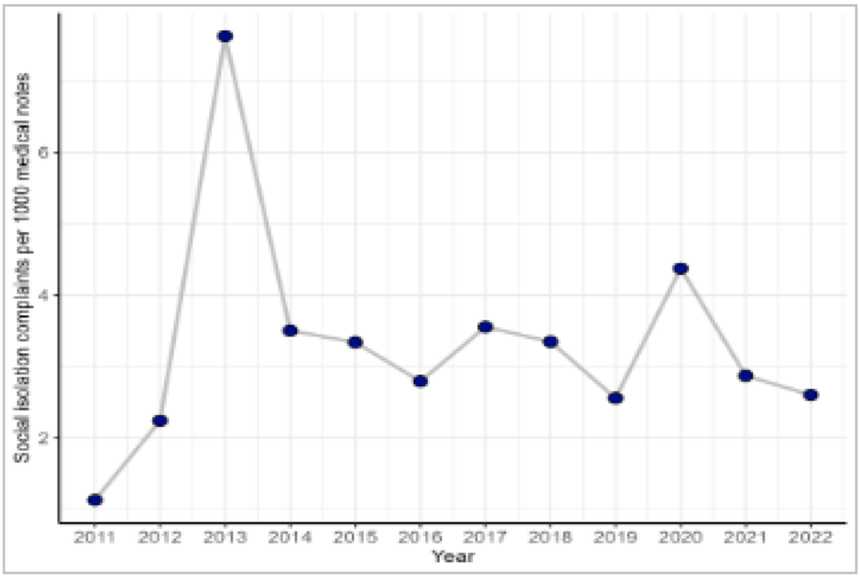


Figure 6.1B

Social isolation complaints per 1000 medical notes from 2011 to 2022



6.3.3 The Effect of Social Connection Reports on MMSE Trajectories

In the case of patients with loneliness reports (Figure 6.2A), the results for the MMSE GAMM analysis show a significant effect of loneliness around 4-5 years before diagnosis and an approximately 6-month window around diagnosis (Figure 6.3A). Against study expectations, the results showed this effect to reflect increased MMSE for patients during these times, in comparison to controls. In the case of patients with social isolation reports (Figure 6.2B), there was no significant effect of social isolation reports, suggesting that these patients have similar trajectories as those patients with no reports of either social isolation or loneliness (Figure 6.3B). Table 6.2 shows the parametric estimates

Figure 6.2A

Predicted Non-Linear Changes in MMSE Over Diagnosis Duration by Loneliness Group

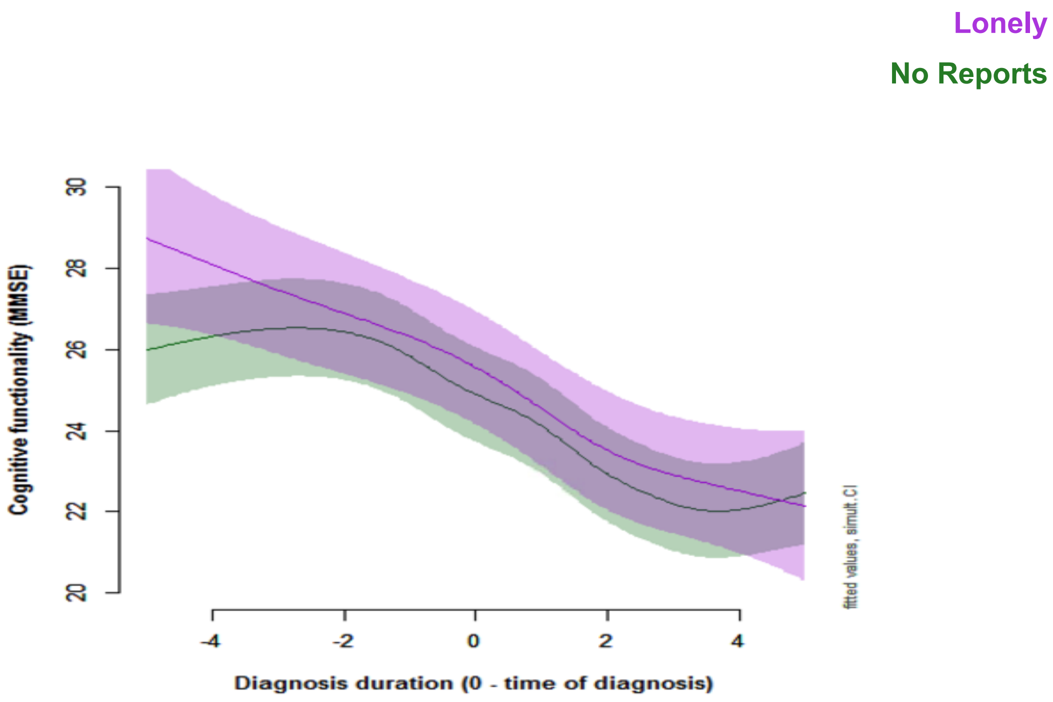


Figure 6.2B

Predicted Non-Linear Changes in MMSE Over Diagnosis Duration by Isolation Group

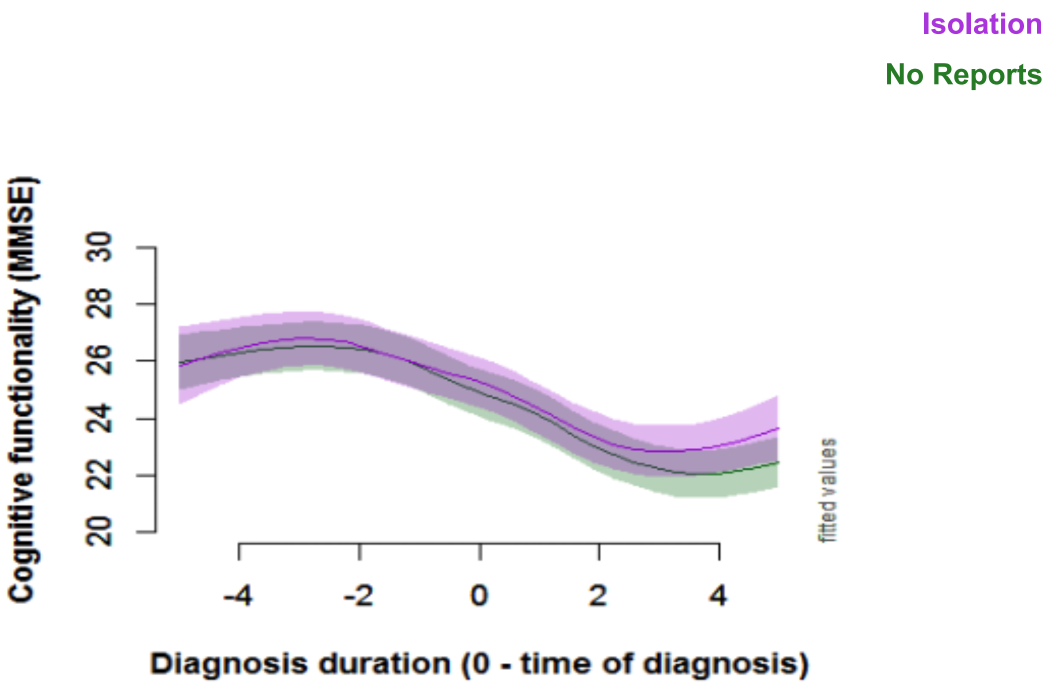


Figure 6.3A

The Predicted Non-Linear Difference Between No Reports and Loneliness Reports

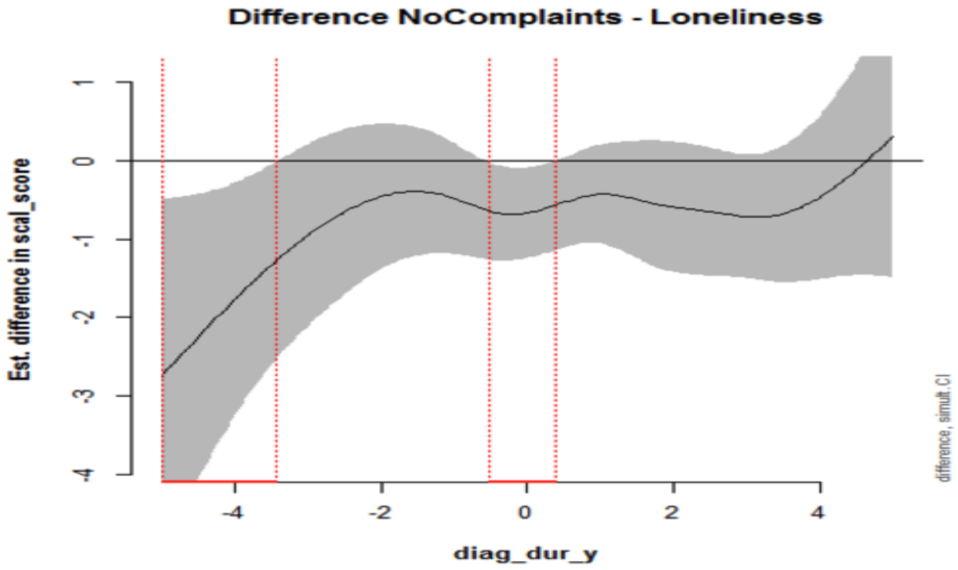


Figure 6.3B

The Predicted Non-Linear Difference Between No Reports and Isolation Reports

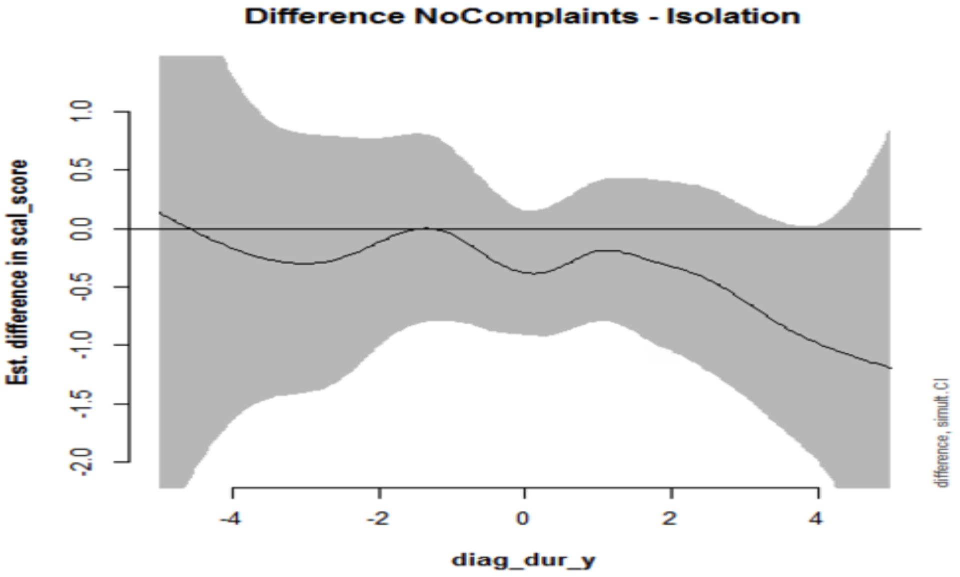


Table 6.2

Model Coefficients for the Parametric Output from a Generalised Additive Multilevel Model Predicting MMSE as a Function of the Effect of Social Connection Reports and Diagnosis Duration Controlling for Age, Sex, Ethnicity and Diagnosis Cause

Factor	Estimate	SE	t-value	p-value
Main Exposures				
Intercept*	**26.27**	**0.33**	**79.05**	**< 0.001**
Diagnosis duration**	**-0.85**	**0.04**	**-21.70**	**< 0.001**
Social isolation	0.29	0.32	0.90	0.371
Loneliness	0.34	0.27	1.29	0.197
Diagnosis duration x Social isolation	0.16	0.16	0.99	0.321
Diagnosis duration x Loneliness	-0.13	0.13	-0.98	0.326

Demographic Factors				
Marital$_{\textbf{Separated/Divorced}}$	**1.01**	**0.39**	**2.60**	**0.009**
Marital$_{\text{Single}}$	0.06	0.35	0.17	0.865
Marital$_{\text{Widowed}}$	0.63	0.36	1.73	0.084
Marital$_{\text{Not known}}$	0.28	0.19	1.49	0.136
Accommodation$_{\textbf{Supported}}$	**-1.55**	**0.28**	**-5.56**	**< 0.001**
Accommodation$_{\text{Other}}$	-1.35	0.96	1.40	0.162
Accommodation$_{\textbf{Not known}}$	**-1.30**	**0.18**	**-7.04**	**< 0.001**
Age	**-0.11**	**0.01**	**-12.56**	**< 0.001**
Sex$_{\textbf{Male}}$	**0.39**	**0.14**	**2.84**	**0.004**
Ethnicity$_{\textbf{Non-White}}$	**-1.70**	**0.55**	**-3.07**	**0.002**
Ethnicity$_{\text{Not known}}$	-0.13	0.18	-0.74	0.462
Diagnostic Factors				
DLB	-0.38	0.49	-0.78	0.437
FTD	1.84	1.24	1.49	0.138
Mixed	-0.39	0.60	-0.66	0.510
VaD	**-1.00**	**0.24**	**-4.08**	**< 0.001**
Other	-0.35	0.84	-0.42	0.671
Unspecified	**-0.37**	**0.14**	**-2.57**	**0.010**

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD patients without any reports of loneliness or social isolation. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

** The diagnosis duration represents the change in estimated coefficient given a one unit increase in time for the reference group. Estimates for other interaction effects, such as diagnosis duration x social isolation, are relative to the diagnosis duration for the reference group.

6.3.4 The Effect of Social Connection Reports on MoCA Trajectories

The results show a significant difference in average MoCA scores between patients with loneliness and social isolation reports in their EHRs and those without such reports. In the case of patients with loneliness reports (Figure 6.4A), MoCA scores were lower throughout the disease (Figure 6.4C). Parametric estimates show the scores of patients with loneliness reports are lower by 1.01 MoCA points at the time of ADRD diagnosis (Table 6.3)

Figure 6.4

Predicted Non-Linear Changes and Differences Between Patients With Social Connection Reports and Those Without

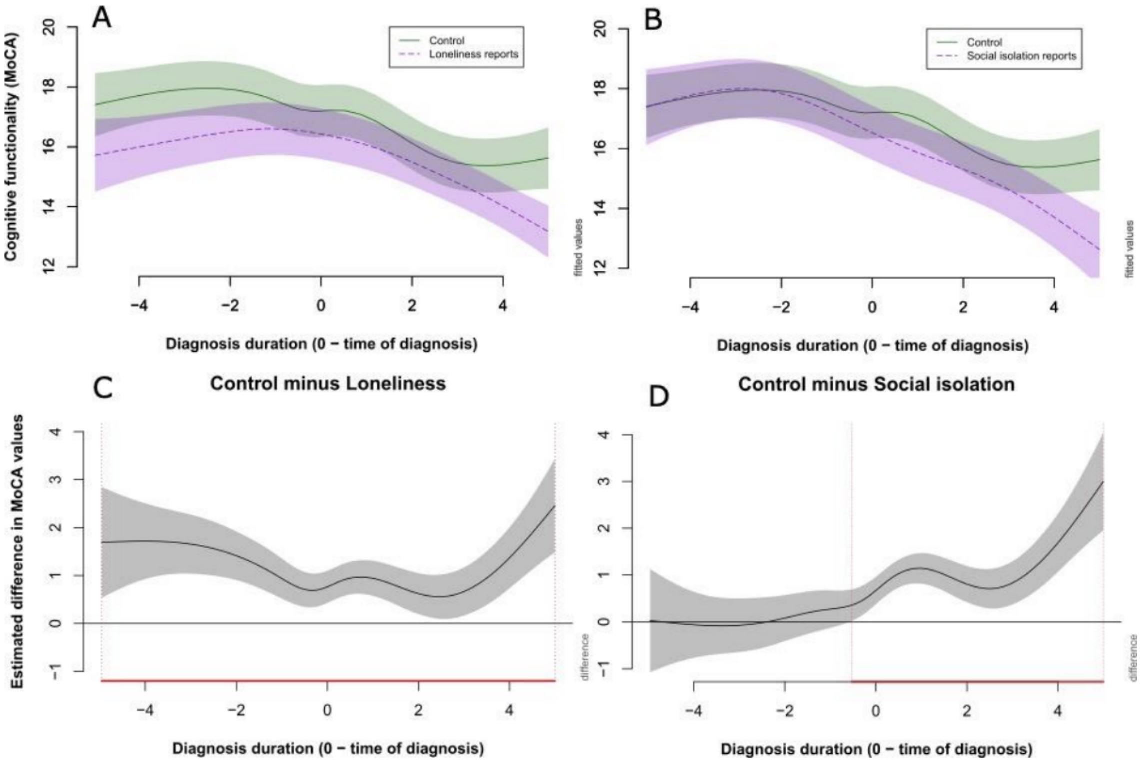


Table 6.3

Model Coefficients for the Parametric Output from a Generalised Additive Multilevel Model Predicting MoCA as a Function of the Effect of Social Connection Reports and Diagnosis Duration Controlling for Age, Sex, Ethnicity and Diagnosis Cause

Factor	Estimate	SE	t-value	p-value
Main Exposures				
Intercept*	**21.33**	**0.39**	**54.71**	**< 0.001**
Diagnosis duration**	**-0.39**	**0.04**	**-9.78**	**< 0.001**
Social isolation	-0.67	0.34	-1.94	0.052
Loneliness	**-1.01**	**0.31**	**-3.23**	**0.001**
Diagnosis duration x Social isolation	-0.13	0.12	-1.10	0.271
Diagnosis duration x Loneliness	-0.01	0.11	-0.11	0.915
Demographic Factors				
Marital$_{\text{Separated/Divorced}}$	0.30	0.46	0.64	0.520
Marital$_{\text{Single}}$	**-1.36**	**0.61**	**-2.22**	**0.027**
Marital$_{\text{Widowed}}$	0.03	0.26	0.13	0.896
Marital$_{\text{Not known}}$	**-0.98**	**0.23**	**-4.30**	**< 0.001**
Accommodation$_{\text{Supported}}$	**-1.54**	**0.28**	**-5.55**	**< 0.001**
Accommodation$_{\text{Other}}$	-1.34	0.84	-1.59	0.112
Accommodation$_{\text{Not known}}$	**0.79**	**0.17**	**4.51**	**< 0.001**
Age	**-0.11**	**0.01**	**-9.78**	**< 0.001**
Sex$_{\text{Male}}$	**0.93**	**0.16**	**5.72**	**< 0.001**
Ethnicity$_{\text{Non-White}}$	-1.19	0.69	-1.72	0.085

Ethnicity$_{\text{Not known}}$	-0.01	0.20	-0.07	0.947
Diagnostic Factors				
DLB	0.15	0.58	0.26	0.794
FTD	-0.79	1.21	-0.65	0.514
Mixed	-0.45	0.59	-0.77	0.439
VaD	**-1.24**	**0.30**	**-4.19**	**< 0.001**
Other	2.18	5.78	0.38	0.706
Unspecified	0.29	0.18	1.65	0.100

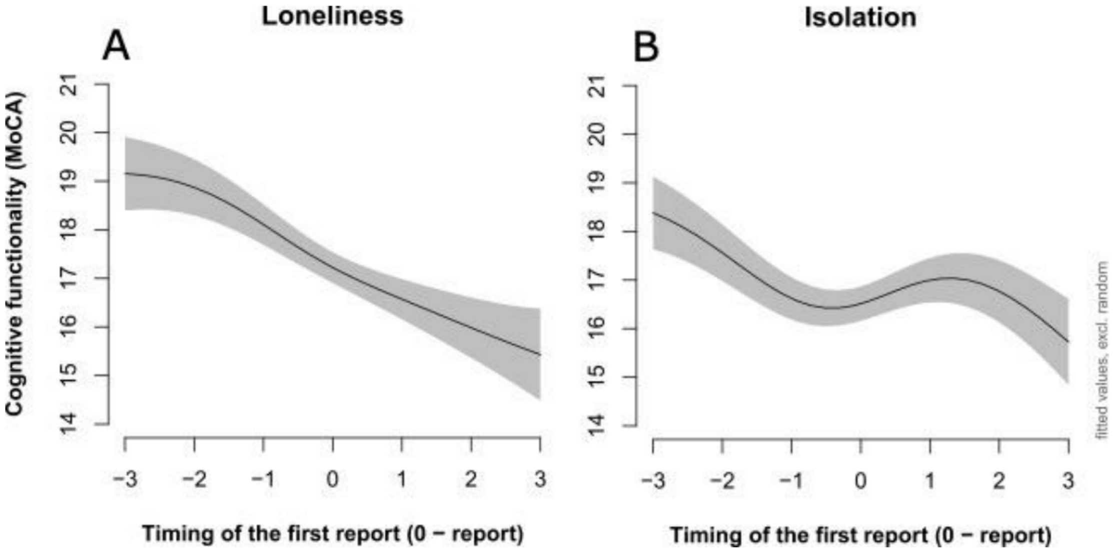
* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD patients without any reports of loneliness or social isolation. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group. ** The diagnosis duration represents the change in estimated coefficient given a one unit increase in time for the reference group. Estimates for other interaction effects, such as diagnosis duration x social isolation, are relative to the diagnosis duration for the reference group.

6.3.5 Cognitive Change After First Report of Social Isolation or Loneliness

The change in MoCA scores after the first social isolation and loneliness report behaves differently between the two groups of patients. In the case of patients reporting loneliness, the cognitive function continues to decline at the same rate as before the report of loneliness (Figure 6.5A). The cognitive function of patients experiencing social isolation, however, improves on average after the first mention of social isolation (Figure 6.4B). Looking at the differences in MoCA scores before and after the reports, results show that MoCA scores are on average higher after the report in the social isolation group (before = 17.32, after = 18.08, t = 2.11, df = 1048.6, p = .034), but not in the loneliness group (before = 17.36, after = 17.08, t = -0.67, df = 770.62, p = .490). Yet, identifying patients with at least one MoCA measure before and after the first report, repeated measures t-test reveal that the MoCA scores decline for both loneliness (before = 17.58, after = 16.62, t = 2.31, df = 85, p = .023) and social isolation (before = 18.03, after = 16.87, df = 115, t = 3.35, p = .001) groups.

Figure 6.5

Changes in MoCA Score After First Social Connection Report



6.4 Discussion

6.4.1 Summary of Findings

This study examined the effect of reported loneliness and social isolation on the rate of cognitive change of patients with an Alzheimer's disease or related disease diagnosis using electronic health records from a retrospective cohort of patients from Oxford Health NHS Foundation Trust. The results showed that, when cognition was assessed using Montreal Cognitive Assessment, patients with evidence of loneliness have, on average, worse cognition throughout their disease course (where negative diagnosis durations represent time before diagnosis, positive durations representing the time after diagnosis, and zero representing the time at which diagnosis occurred). Under the same cognitive measure, patients whose electronic health records have reports of social isolation show comparable cognition, before diagnosis, to patients without such reports. Six months before diagnosis, however, the cognition of socially isolated patients begins to decline at a higher rate, resulting in worse cognition at the point of diagnosis and post-diagnosis. When Mini-Mental State Examination was the measure of cognitive function, results suggested that, unexpectedly, patients with loneliness reports in their electronic health records show, on average, higher cognition scores at the point of diagnosis and during a period between 5 and 4 years before diagnosis. Generalised Additive Multilevel Models did not find any significant difference in patients with social isolation complaints and controls, relative to Mini-Mental State Examination scores, across the disease course.

Beyond these primary findings, parametric estimations consistently reinforced the impact of several demographic control variables. As would be expected, older age was significantly associated with lower cognitive scores at diagnosis (intercept) in both the MMSE and MoCA models. Similarly, being male was associated with higher cognitive scores at diagnosis, in both models, compared to the female reference group. As with the previous studies (Chapters 4 & 6), living in supported accommodation was a consistent predictor of lower cognition compared to living in mainstream housing. Other findings were less consistent, with 'non-white' ethnicity being associated with significantly lower diagnosis scores in the MMSE model but not the MoCA model. As previously discussed in section 5.4.2, the imbalance in sample sizes for ethnicity and likely heterogeneity of the non-white ethnicity group likely contributes to the inconsistency of findings and reduces interpretability. Similar inconsistencies across models in single marital status may highlight different sensitivities of the two cognitive tests and the populations they were used in.

6.4.2 Mechanisms of Social Isolation and Loneliness

The conceptualisation of the two concepts, social isolation and loneliness, likely underlies the estimated differences between the MoCA scores of the three groups of patients. Social isolation represents more of a physical barrier to maintaining social connections or participating in social engagement, while loneliness reflects emotional aspects of this feeling. While modelled separately, the relationship between SI and loneliness is complex and likely to be bidirectional. While some people may have a preference for solitude, others in isolated settings seek greater connection through alternative accommodation (Scocco et al., 2006). Objectively isolated people may be at greater risk for developing subjective feelings of loneliness. Conversely lonely people may experience more social withdrawal, compounding issues with social connection. Studying social connection more holistically may be more beneficial than focussing on the separate components that comprise it (Holt-Lunstad et al., 2021).

This study found that socially isolated patients have stronger rates of cognitive deterioration several months before a dementia diagnosis while being comparable with controls in the preceding period. In the context of a life-changing and stigmatising diagnosis such as dementia, the lack of social contact could prevent patients from receiving needed support, leading to higher rates of cognitive decline. Previous intervention studies have found positive effects on cognition of social activity on cognitive outcomes of ADRD patients in some situations (Fritsch et al., 2014; Lee & Lee, 2020). When reported for the first time, the current findings show that average values of MoCA scores increase for socially isolated patients. This improvement may reflect positive action taken by healthcare and/or social services in response to the report. In contrast, patients who experience loneliness have worse cognition throughout the disease course. Whereas, lonely patients also do not observe any improvement in their cognition after the first report of loneliness, which might be expected given that improvement in feeling of loneliness requires a change in the subjective emotions related to the availability of social networks, psychological wellbeing, life satisfaction, activities, and other psychiatric symptoms (de Jong Gierveld et al., 2006, Perlman and Peplau, 1981).

6.4.3 Additional Interpretation of Differences

The differences between GAMMs and linear multilevel regression, in this case, may reflect a difference between the non-parametric and linear approaches to the models. GAMM may more accurately capture the cognitive changes across the disease course, such as the tendency to see a period of cognitive stability after diagnosis due to changes in care and medication (Vaci et al., 2021). The difference in findings between MoCA and MMSE may reflect differences in cognitive domains captured by the measures. Previous studies have shown that MoCA is more sensitive to MCI and early stages of ADRD, in comparison to MMSE (Pinto et al., 2019). Another explanation could be a reflection of differences in clinical practices over time, as the majority of MMSE measures are from earlier observations, whereas MoCA observations are more recent (see Appendix H).

6.4.4 Strengths and Limitations

This study illustrates the potential of medical records from mental health institutions to provide evidence-based results on the effect of symptoms in dementia diseases. Using large data and advanced statistical modelling, this study shows that social isolation and loneliness can be seen as disease progression factors. Not only is this a novel finding in the domain, contrasting with some previous studies which showed limited effects or their complete absence (see Chapter 2) but we show differing effects of SI and loneliness on the cognitive trajectories of patients with an ADRD diagnosis.

There are, however, several limitations when using large observational datasets. Patients' membership in the group cannot be allocated and can only be controlled for a limited number of factors that could have moderating effects on social isolation and loneliness, such as depression. Lack of control over the allocation of patients and barriers when accessing healthcare may have led to inadequacies regarding diversity, equality and inclusion, which may reduce the wider generalisability of findings. The correlational nature of the data limits the causal interpretation of our findings, and even though we see improvement in cognition after the first report of social isolation, we cannot ascertain what change to patients' social circumstances followed. There are multiple sources of support that patients can receive after social isolation is identified, such as closer family connections, social services provision of care or change to their living conditions (e.g. admittance to residential care). Our interpretation of social isolation relies on a subjective perception from the patient, carer or clinician, rather than an objective measure e.g. of frequency of social contact. Automated and trained NLP model architectures are probabilistic, and even though they achieve high levels of accuracy, they introduce an additional layer of noise to the later data analysis due to high variability in clinical texts. This may be due to grammar or spelling peculiarities, the use of jargon or abbreviations, or establishing temporality within complex cases (Perera et al., 2016).

6.4.5 Clinical Implications

While acknowledging limitations, this study shows that social isolation and loneliness could be seen as disease progression factors for dementia patients, given their effect on cognitive trajectories. These findings could have direct implications for clinical practice providing clinicians with indications of an increased rate of cognitive decline, especially before diagnosis for socially isolated patients. It is hoped that these effects could steer the debate concerning modifiable symptoms that could be used to support the care of patients and outline a research approach that could provide more evidence-based studies of modifiable disease progression factors.

7 General Discussion

7.1 Summary of findings

Factors of social connection have previously been linked to ADRD incidence (Desai et al., 2020; Kuiper et al., 2015; Penninkilampi et al., 2018; Sommerlad et al., 2018, 2019) and cognitive outcomes (Evans et al., 2019; Kuiper et al., 2016; Piolatto et al., 2022). Social isolation has been identified as one of 14 modifiable risk factors for ADRD (Livingston et al., 2017, 2020, 2024). Despite this, the effect of social connection on cognitive trajectories in patients at and following an ADRD diagnosis is relatively understudied. This thesis aimed to provide novel insights into the impact of social connection on the cognition and cognitive trajectories of ADRD patients, utilising data from EHRs of ADRD patients from Oxford Health NHS Foundation Trust. Across multiple models, the findings suggest that accommodation status, that is whether a person is living in mainstream housing or supported accommodation, is a more consistent predictor of cognitive impairment in ADRD patients than marital status, or whether the patient is living alone or cohabiting. This finding was consistent, regardless of which measure of cognition was used. What’s more, the MoCA may be a more capable measure of cognition than the MMSE for detecting changes in cognition in ADRD patients related to social connection. MoCA models found significant negative impacts on cognition of groups associated with worse social connection, such as patients with single marital status, and patients with loneliness or social isolation reports. Collectively, these findings directly contribute to the existing literature by providing insight into ADRD patients’ cognitive trajectories at diagnosis, as well as in the years directly preceding and following diagnosis. Furthermore, these findings demonstrate the feasibility of utilising data from EHRs as a viable method for investigating the impact of lifestyle factors on clinical outcomes.

7.2 Findings in Context

7.2.1 Accommodation Status as a Predictor of Cognitive Trajectories

All three studies found a significant main effect of accommodation status on cognitive intercept scores. The models suggest that patients living in supported accommodation experience significantly lower cognitive scores (MMSE or MoCA) at diagnosis, and that these differences persist throughout the majority of the window of assessed diagnosis duration (the time from diagnosis, with negative times representing time before diagnosis, positive time representing the time after diagnosis, and zero representing the time at which diagnosis occurred). A crucial consideration in interpreting this finding is the potential for reverse causation: patients often transition to supported accommodation precisely due to increasing cognitive or functional needs associated with their ADRD progression, rather than the living situation itself initiating this decline (Harmand et al., 2014). The current studies considered living in supported accommodation to represent an SI (rather than a non-SI) proxy group, due to previously reported associations between living in supported accommodation and perceived social isolation (Nikmat, Hashim, et al., 2015) and reports that living in supported accommodation predicted lower cognitive scores and faster rates of decline (Harmand et al., 2014; Harsányiová & Prokop, 2018; Wilson, McCann, et al., 2007). The studies in this thesis further support these previous findings and demonstrate that the impact of accommodation status on cognition and rates of cognitive change, specifically in ADRD patients, can be assessed retrospectively using data from EHRs.

The current findings that patients categorised as living in a socially isolated accommodation status group experience lower cognitive scores at diagnosis compared to patients categorised as living in a non-isolated group supports the cognitive reserve concept, which posits that increased social connection can offer protection from cognitive impairment (Perry, Roth, et al., 2022). The current finding that rates of decline are similar between patients living in mainstream housing and supported accommodation across linear models could suggest more of an impact on brain reserve (i.e. the capacity of function within the brain capable of being lost before impacts are felt) rather than brain maintenance (i.e. the brain's capability to limit the rate at which negative consequences of brain changes impact function, such as limiting the impact of neurodegeneration on rate of cognitive decline). This would align with the findings of Zhang and colleagues (2022) who report that social connection is associated with both cognitive trajectories and regional grey matter volume. It has been suggested that participation in more diverse roles across social networks could facilitate the neurostimulation that promotes cognitive reserve (Perry, Roth, et al., 2022). Patients living in supported accommodation are unlikely to participate in social networks that are as complex as patients living in mainstream housing. Clinical reports suggest that ADRD patients may struggle to adapt to new surroundings (Wilson, McCann, et al., 2007), taking people away from their existing social network structure, and may also impact their ability to integrate in their new one.

Non-linear analysis reveals a more complex interaction between time and cognition when considering accommodation status as a factor. These models suggest that the difference between cognitive scores of patients living in mainstream housing and supported accommodation are pronounced towards the end of the diagnosis duration window compared to towards the beginning of the diagnosis duration window. Rates of change in the years around diagnosis, however, are more similar. These findings highlight the additional insight non-linear models can attain on changes in cognitive scores over time in ADRD patients. That these findings indicate similar rates of decline around diagnosis between groups could indicate an effect of additional treatment at diagnosis, such as medication prescriptions (Vaci et al., 2021), is similar regardless of accommodation status. It could be the case that patients' move into supported accommodation reflects their need for functional assistance. While this may explain lower levels of cognition for these patients, it would not necessarily explain why they might experience increased rates of change once they have moved into supported accommodation compared to before (Wilson, McCann, et al., 2007). In the current thesis, as accommodation status is measured at the level of the patient, rather than the level of the observation, it is not possible to know when a patient may have moved into supported accommodation, therefore it was not possible to make these sorts of comparisons. Previous studies that have found an increase in rates of cognitive decline amongst people living in supported accommodation have attributed this to difficulties adapting to new environments which may also lead to increased stress, lack of cognitive stimulation, living in a relatively impoverished environment, and/or sedentary lifestyle habits (Harmand et al., 2014; Harsányiová & Prokop, 2018; Wilson, McCann, et al., 2007).

In the current thesis, living status models considering whether a patient was cohabiting, living alone, living in supported accommodation, based on a combination of their marital status and accommodation status, there were no significant differences between patients living alone and cohabiting at diagnosis. Similarly, in linear models there were no significant differences between cohabiting patients and patients living alone in terms of rates of decline. There were also no differences in cognition in non-linear interactions between these two groups across diagnosis duration. In contrast, these same models predicted patients living in supported accommodation had lower cognitive scores at diagnosis that persisted across diagnosis duration. These findings suggest that living in supported accommodation is a strong predictor of cognition, regardless of whether the patient is living alone or cohabiting. Previous research has found an association between living alone and increased ADRD incidence risk, through meta-analysis, attributed to increased social isolation for those living alone (Desai et al., 2020). However, individual studies have reported that people with an ADRD diagnosis living alone have been found to have higher cognitive scores than those cohabiting, which may contribute to their capability to live independently, and have been attributed to social network size and frequency of contact (Clare et al., 2020, 2024; Edwards & Morris, 2007). The finding of the current thesis, that patients living alone and those cohabiting have similar scores across diagnosis may reflect the mixed findings within the literature.

7.2.2 Loneliness and Social Isolation Reports

Study 3 involved the development of a natural language processing model to develop new proxies of both social isolation and loneliness from clinical reports within the EHRs. Non-linear models for the impact of social isolation and loneliness reports on cognitive trajectories revealed a significant impact for both kinds of reports, compared to patients without such reports, when MoCA was the measure of cognition. The models showed overall cognitive scores for patients with loneliness reports were significantly lower throughout the diagnosis duration window. Conversely, patients with social isolation reports had similar initial cognitive scores to patients without reports in the earlier years preceding diagnosis, followed by increased rates of cognitive decline that resulted in statistically lower cognitive scores from 1 year to 6 months before diagnosis, with this difference persisting for the remainder of the diagnosis duration window. These results demonstrate that the approach taken in Study 3 represents a pipeline for using clinical reports to make meaningful predictions regarding patient cognitive outcomes using lifestyle factors. These findings are in line with previous research defining both social isolation and loneliness as predictors of increased incidence risk and worse cognitive outcomes (Kuiper et al., 2015, 2016; Lara et al., 2019). Whereas other studies may equate perceived social isolation as a proxy for loneliness due to its subjective nature, the current findings, due to the difference in the models, suggest that patients are capable of discerning between feelings of loneliness and feelings of isolation in their reports, and that these reports represent distinct experiences. The natural language processing algorithm was trained on examples of social isolation and loneliness that were in line with previously defined concepts and measures (de Jong Gierveld et al., 2006; de Jong Gierveld & van Tilburg, 1999; Lubben, 1988; Russell, 1996).

7.2.3 Mixed Findings Between MMSE and MoCA

Across the different studies conducted as part of this thesis, there was often a difference in model predictions based on whether MMSE or MoCA was the measure of cognitive performance used. Linear models using marital status as a proxy of social isolation and MMSE as the measure of cognition found separated patients (patients who were divorced or separated from their previous partner) had higher cognition at diagnosis compared to other marital status groups. Rates of change, in the same model, were predicted to be similar for all marital status groups except life-long single marital status groups whose rates of decline were predicted to be slower. This finding did not support or, in the case of single patients' rates of decline, directly contradicted previous findings regarding the association of marital status to social isolation and its impact on ADRD incidence, cognition, and other health outcomes (Helmer et al., 1999; Joung et al., 1995; Sommerlad et al., 2018). In a sensitivity analysis, there was a predicted difference between widowed patients and patients with partners, however this was no longer significant after introducing controls, suggesting that this effect was attenuated by their introduction. Age is one plausible factor that could have mediated the effect of widowed marital status, as cognition was shown to experience a significant reduction with each increased year of age across models.

When considering linear models that used marital status as a proxy of social isolation and MoCA as the measure of cognitive function, models revealed contradictory results. In this case, single patients were predicted to have significantly lower cognitive scores at diagnosis compared to all other groups, while rates of decline were similar. This finding is partially in line with previous findings suggesting single and widowed people are more at risk of ADRD incidence (Sommerlad et al., 2018). However, neither linear model of marital status provided robust evidence of its impact on cognitive outcomes. Non-linear model findings mostly mirrored linear findings, with the addition of increased insight into the interaction between diagnosis duration and cognition between the groups. With regards to Study 3, as mentioned in section 7.2.2, MoCA models of loneliness and social isolation reports found significant effects on cognitive trajectories. This was not the case for MMSE models, as they failed to find a significant effect.

It is unclear why the current studies often found divergence in model predictions between MMSE and MoCA, particularly given previous research has identified significant effects with a variety of cognitive measures (see Chapter 2). The current findings may reflect differences in the sensitivity of MMSE and MoCA to detect nuanced cognitive changes in domains impacted or associated with changes in social connection (Pinto et al., 2019). The MMSE primarily assesses general cognitive function, heavily weighting orientation, attention, and memory recall that, while useful for initial screening, the limits its scope, particularly for executive functions and visuospatial skills (Trzepacz et al., 2015; Zadikoff et al., 2008). This may reduce the sensitivity of the MMSE to the subtle yet significant cognitive changes that could be modulated by social isolation or loneliness. In contrast, the MoCA evaluates a broader range of cognitive domains, including executive functions, attention, language, abstract thinking, and visuospatial abilities, which are often implicated in the earliest stages of cognitive decline and are more susceptible to the broader environmental and social factors thought to influence cognitive reserve (Nasreddine et al., 2005; Smith et al., 2007). It could be that the effects of social isolation and loneliness, which may impact brain areas supporting executive function, attention and complex social cognition, are more readily captured by the MoCA's wider cognitive assessment.

Alternatively, or additionally, these findings may reflect a difference in the date at which the measures were taken and recorded. Comparatively more MMSE data were recorded earlier within the cohort sample period, whereas MoCA became more frequently used as data were taken from more recent EHR records (see Appendix H). As these data span years, there may be differences in terms of quality of recorded EHRs, and/or differences in levels of association between marital/accommodation/living statuses and levels of social connection across years. For example, aspects of community relating to social networks may have changed over time, as may the quality and circumstance of care provided in supported accommodation, or modes in which people communicate with others.

7.3 Strengths and Limitations and Future Considerations

This thesis presents several key strengths that enhance its contribution to the understanding of social connection and cognitive trajectories in ADRD patients. Firstly, a major strength lies in the retrospective utilisation of real-world EHRs from a large NHS Trust. This approach offers a powerful methodology for investigating the long-term impact of lifestyle factors on clinical outcomes in a diagnostically meaningful patient cohort. Unlike controlled clinical trials, EHR data reflect routine clinical practice, enhancing the generalisability of findings to real-world healthcare settings. The use of an extensive dataset, encompassing a significant number of cognitive assessments over extended periods, allowed for the rigorous longitudinal modelling of cognitive change.

Secondly, the thesis provides novel findings by focusing on the understudied post-diagnosis period for ADRD patients. While previous research has largely concentrated on social connection as a risk factor for ADRD incidence or its impact on cognition in cognitively healthy older adults, this work directly addresses a critical knowledge gap concerning the influence of social factors on cognitive trajectories once a diagnosis is established. Furthermore, in Study 3, the development and application of an NLP pipeline to extract novel proxies for social isolation and loneliness from free-text clinical notes represents a significant methodological strength. This approach overcomes the limitations of relying solely on structured EHR data, such as marital status or living situation, by capturing more nuanced and subjective aspects of social connection directly from clinicians' observations. The ability to differentiate between reported loneliness and social isolation, as demonstrated by the distinct model predictions, further highlights the utility of this NLP methodology.

Finally, the comprehensive statistical modelling, including both linear and non-linear multilevel models, allowed for a detailed examination of complex cognitive trajectories over time. The insights gained from non-linear modelling, in particular, provided a richer understanding of how social connection proxies interact with cognitive change across the diagnosis duration window, which would not have been apparent from simpler linear approaches.

Despite its strengths, this thesis is subject to several limitations that warrant consideration when interpreting the findings. Reliance on retrospective EHRs introduces inherent challenges. These include: missing data and irregular assessment frequencies, leading to varying amounts of data per patient; a lack of direct measures for key constructs leading to a reliance on proxies and indirect NLP measures; limited data on other confounding factors, such as other modifiable factors related to ADRD incidence and cognition. Overall, this lack of control over the data limits the interpretation of causation that can be made from the data.

A methodological challenge encountered was integration of medication data into the models as a control variable. These data were recorded at the level of the observation and did not consistently align temporally with cognitive assessments. Therefore, it was unclear whether prescribed medications were active or therapeutically effective at the precise time of cognitive measurement. Ultimately, these data were omitted from models conducted as part of this thesis, meaning the potential impact of pharmacological interventions on cognitive trajectories could not be fully accounted for. Additionally, computational resource constraints within the encrypted virtual environment prevented the analysis of more intensive models. Finally, the

NLP pipeline used within this thesis may lack generalisability to trusts outside of Oxford Health NHS Foundation Trust.

Further research could look to involve additional trusts in order to improve generalisability of findings. Prospective approaches could look to measure variables more directly and consistently. Data with more observations from after the onset of the COVID-19 pandemic could consider additional patient comparisons regarding the effect of this period on patients' cognitive outcomes. Incorporating a direct measure of disease progression would allow for direct assessments of the impact of social connection variables on cognitive reserve. Future studies could also consider other modifiable risk factors identified in the Livingston reports (2017, 2020, 2024) and their link to cognitive reserve and cognitive outcomes in ADRD patients.

7.4 Conclusion

While acknowledging limitations, this thesis shows that factors related to social isolation and loneliness have an effect on the cognitive trajectories of ADRD patients. Along with providing a novel contribution to the existing literature, these findings could have implications for clinical practice and patient care by increasing understanding of changes of cognitive trajectories given the factors explored in this thesis.

References

Abbott, K. M., & Pachucki, M. C. (2017). Associations between social network characteristics, cognitive function, and quality of life among residents in a dementia special care unit: A pilot study. *Dementia*, *16*(8), 1004–1019. https://doi.org/10.1177/1471301216630907

AddNeuroMed Consortium, Liu, Y., Julkunen, V., Paajanen, T., Westman, E., Wahlund, L.-O., Aitken, A., Sobow, T., Mecocci, P., Tsolaki, M., Vellas, B., Muehlboeck, S., Spenger, C., Lovestone, S., Simmons, A., & Soininen, H. (2012). Education increases reserve against Alzheimer's disease—Evidence from structural MRI analysis. *Neuroradiology*, *54*(9), 929–938. https://doi.org/10.1007/s00234-012-1005-0

Ahmadi-Abhari, S., Guzman-Castillo, M., Bandosz, P., Shipley, M. J., Muniz-Terrera, G., Singh-Manoux, A., Kivimäki, M., Steptoe, A., Capewell, S., O'Flaherty, M., & Brunner, E. J. (2017). Temporal trend in dementia incidence since 2002 and projections for prevalence in England and Wales to 2040: Modelling study. *BMJ*, j2856. https://doi.org/10.1136/bmj.j2856

Akaike, H. (1974). A new look at the statistical model identification. *IEEE Transactions on Automatic Control*, *19*(6), 716–723. https://doi.org/10.1109/TAC.1974.1100705

Akbaraly, T. N., Portet, F., Fustinoni, S., Dartigues, J.-F., Artero, S., Rouaud, O., Touchon, J., Ritchie, K., & Berr, C. (2009). Leisure activities and the risk of dementia in the elderly: Results from the Three-City Study. *Neurology*, *73*(11), 854–861. https://doi.org/10.1212/WNL.0b013e3181b7849b

Akhter-Khan, S. C., Tao, Q., Ang, T. F. A., Itchapurapu, I. S., Alosco, M. L., Mez, J., Piers, R. J., Steffens, D. C., Au, R., & Qiu, W. Q. (2021). Associations of loneliness with risk of Alzheimer's disease dementia in the Framingham Heart Study. *Alzheimer's & Dementia*, *17*(10), 1619–1627. https://doi.org/10.1002/alz.12327

Aldus, C. F., Arthur, A., Dennington-Price, A., Millac, P., Richmond, P., Dening, T., Fox, C., Matthews, F. E., Robinson, L., Stephan, B. C., Brayne, C., & Savva, G. M. (2020). Undiagnosed dementia in primary care: A record linkage study. *Health Services and Delivery Research*, *8*(20), 1–108. https://doi.org/10.3310/hsdr08200

Alexander, G. E., Furey, M. L., Grady, C. L., Pietrini, P., Brady, D. R., Mentis, M. J., & Schapiro, M. B. (1997). Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: Implications for the cognitive reserve hypothesis. *American Journal of Psychiatry*, *154*(2), 165–172. https://doi.org/10.1176/ajp.154.2.165

Allan, L. M., Rowan, E. N., Firbank, M. J., Thomas, A. J., Parry, S. W., Polvikoski, T. M., O'Brien, J. T., & Kalaria, R. N. (2011). Long term incidence of dementia, predictors of mortality and pathological diagnosis in older stroke survivors. *Brain*, *134*(12), 3716–3727. https://doi.org/10.1093/brain/awr273

Alvares Pereira, G., Silva Nunes, M. V., Alzola, P., & Contador, I. (2022). Cognitive reserve and brain maintenance in aging and dementia: An integrative review. *Applied Neuropsychology: Adult*, *29*(6), 1615–1625. https://doi.org/10.1080/23279095.2021.1872079

Alzheimer's Association. (2014). 2014 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, *10*(2), e47–e92. https://doi.org/10.1016/j.jalz.2014.02.001

Alzheimer's Society. (2025a). *Mild cognitive impairment (MCI)*. https://www.alzheimers.org.uk/about-dementia/types-dementia/mild-cognitive-impairment-mci

Alzheimer's Society. (2025b). *Types of dementia*. https://www.alzheimers.org.uk/about-dementia/types-dementia

Amato, M. P., Razzolini, L., Goretti, B., Stromillo, M. L., Rossi, F., Giorgio, A., Hakiki, B., Giannini, M., Pastò, L., Portaccio, E., & De Stefano, N. (2013). Cognitive reserve and cortical atrophy in multiple sclerosis: A longitudinal study. *Neurology*, *80*(19), 1728–1733. https://doi.org/10.1212/WNL.0b013e3182918c6f

Amieva, H., Le Goff, M., Millet, X., Orgogozo, J. M., Pérès, K., Barberger-Gateau, P., Jacqmin-Gadda, H., & Dartigues, J. F. (2008). Prodromal Alzheimer's disease: Successive emergence of the clinical symptoms. *Annals of Neurology*, *64*(5), 492–498. https://doi.org/10.1002/ana.21509

Amieva, H., Mokri, H., Le Goff, M., Meillon, C., Jacqmin-Gadda, H., Foubert-Samier, A., Orgogozo, J.-M., Stern, Y., & Dartigues, J.-F. (2014). Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: A study of 20 years of cognitive decline. *Brain*, *137*(4), 1167–1175. https://doi.org/10.1093/brain/awu035

Anatürk, M., Kaufmann, T., Cole, J. H., Suri, S., Griffanti, L., Zsoldos, E., Filippini, N., Singh-Manoux, A., Kivimäki, M., Westlye, L. T., Ebmeier, K. P., & de Lange, A.-M. G. (2021). Prediction of brain age and cognitive age: Quantifying brain and cognitive maintenance in aging. *Human Brain Mapping*, *42*(6), 1626–1640. https://doi.org/10.1002/hbm.25316

Andrew, M., & Morava, S. (2021, April 17). *Loneliness won't end when the pandemic ends*. CNN. https://www.cnn.com/2021/04/17/us/loneliness-epidemic-covid-wellness-trnd/index.html

Arai, A., Katsumata, Y., Konno, K., & Tamashiro, H. (2004). Sociodemographic Factors Associated With Incidence of Dementia Among Senior Citizens of a Small Town in Japan. *Care Management Journals*, *5*(3), 159–165. https://doi.org/10.1891/cmaj.2004.5.3.159

Arenaza-Urquijo, E. M., & Vemuri, P. (2018). Resistance vs resilience to Alzheimer disease. *Neurology*, *90*(15), 695–703. https://doi.org/doi:10.1212/WNL.0000000000005303

Arenaza-Urquijo, E. M., & Vemuri, P. (2020). Improving the resistance and resilience framework for aging and dementia studies. *Alzheimer's Research & Therapy*, *12*(1), 41. https://doi.org/10.1186/s13195-020-00609-2

Armstrong, R. A. (2019). Risk factors for Alzheimer's disease. *Folia Neuropathologica*, *57*(2), 87–105. https://doi.org/10.5114/fn.2019.85929

Azevedo, L. V. dos S., Calandri, I. L., Slachevsky, A., Graviotto, H. G., Vieira, M. C. S., Andrade, C. B. de, Rossetti, A. P., Generoso, A. B., Carmona, K. C., Pinto, L. A. C., Sorbara, M., Pinto, A., Guajardo, T., Olavarria, L., Thumala, D., Crivelli, L., Vivas, L., Allegri, R. F., Barbosa, M. T., … Caramelli, P. (2021). Impact of Social Isolation on People with Dementia and Their Family Caregivers. *Journal of Alzheimer's Disease*, *81*(2), 607–617. https://doi.org/10.3233/JAD-201580

Babulal, G. M., Torres, V. L., Acosta, D., Agüero, C., Aguilar-Navarro, S., Amariglio, R., Ussui, J. A., Baena, A., Bocanegra, Y., Brucki, S. M. D., Bustin, J., Cabrera, D. M., Custodio, N., Diaz, M. M., Peñailillo, L. D., Franco, I., Gatchel, J. R., Garza-Naveda, A. P., González Lara, M., … Quiroz, Y. T. (2021). The impact of COVID-19 on the well-being and cognition of older adults living in the United States and Latin America. *EClinicalMedicine*, *35*, 100848. https://doi.org/10.1016/j.eclinm.2021.100848

Bakker, E. D., Van Der Pas, S. L., Zwan, M. D., Gillissen, F., Bouwman, F. H., Scheltens, P., Van Der Flier, W. M., & Van Maurik, I. S. (2023). Steeper memory decline after COVID-19 lockdown measures. *Alzheimer's Research & Therapy*, *15*(1), 81. https://doi.org/10.1186/s13195-023-01226-5

Balouch, S., Rifaat, E., Chen, H. L., & Tabet, N. (2019). Social networks and loneliness in people with Alzheimer's dementia. *International Journal of Geriatric Psychiatry*, *34*(5), 666–673. https://doi.org/10.1002/gps.5065

Barguilla, A., Fernández-Lebrero, A., Estragués-Gázquez, I., García-Escobar, G., Navalpotro-Gómez, I., Manero, R. M., Puente-Periz, V., Roquer, J., & Puig-Pijoan, A. (2020). Effects of COVID-19 Pandemic Confinement in Patients With Cognitive Impairment. *Frontiers in Neurology*, *11*, 589901. https://doi.org/10.3389/fneur.2020.589901

Bartrés-Faz, D., Solé-Padullés, C., Junqué, C., Rami, L., Bosch, B., Bargalló, N., Falcón, C., Sánchez-Valle, R., & Molinuevo, J. L. (2009). Interactions of cognitive reserve with regional brain anatomy and brain function during a working memory task in healthy elders. *Biological Psychology*, *80*(2), 256–259. https://doi.org/10.1016/j.biopsycho.2008.10.005

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*, *67*(1), 1–48. https://doi.org/10.18637/jss.v067.i01

BBC. (2020a, March 31). *Coronavirus: Submarine captain's advice on social isolation*. BBC News. https://www.bbc.co.uk/news/av/uk-england-hampshire-52104076

BBC. (2020b, May 14). *Lockdown with cancer: 'Social isolation is not new to me'*. BBC News. https://www.bbc.co.uk/news/av/uk-scotland-52669409

BBC. (2020c, November 18). *Covid-19: Coping with loneliness in a pandemic*. BBC News. https://www.bbc.co.uk/news/av/uk-england-essex-54938694

BBC. (2021, April 3). *Covid-19 and care homes: 'The light's back on in my mum's eyes'*. BBC News. https://www.bbc.co.uk/news/av/uk-56624249

Behl, C. (2024). In 2024, the amyloid-cascade-hypothesis still remains a working hypothesis, no less but certainly no more. *Frontiers in Aging Neuroscience*, *16*, 1459224. https://doi.org/10.3389/fnagi.2024.1459224

Bennett, D. A., Schneider, J. A., Tang, Y., Arnold, S. E., & Wilson, R. S. (2006). The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: A longitudinal cohort study. *The Lancet Neurology*, *5*(5), 406–412. https://doi.org/10.1016/S1474-4422(06)70417-3

Bennett, I. (2021, March 8). *COVID-19: Families kept apart by pandemic meet as care homes allow visitors again*. Sky News. https://news.sky.com/story/wonderful-feeling-families-separated-by-pandemic-meet-as-care-homes-allow-visitors-12240126

Berkman, L. F., Glass, T., Brissette, I., & Seeman, T. E. (2000). From social integration to health: Durkheim in the new millennium p. *Social Science*.

Bethell, C. (2021, March 15). *'Dad stood at Mum's window every night for a year': Care home visitors – a photo essay*. The Guardian. https://www.theguardian.com/society/2021/mar/15/green-gables-care-home-restarts-family-visits-a-photo-essay

Bickel, H., & Cooper, B. (1994). Incidence and relative risk of dementia in an urban elderly population: Findings of a prospective field study. *Psychological Medicine*, *24*(1), 179–192. https://doi.org/10.1017/S0033291700026945

Bocancea, D. I., van Loenhoud, A. C., Groot, C., Barkhof, F., van der Flier, W. M., & Ossenkoppele, R. (2021). Measuring Resilience and Resistance in Aging and Alzheimer Disease Using Residual Methods: A Systematic Review and Meta-analysis. *Neurology*, *97*(10), 474–488.

Borda, M. G., Brønnick, K. K., Garcia-Cifuentes, E., Jaramillo-Jimenez, A., Reyes-Ortiz, C., Patricio-Baldera, J., Soennesyn, H., Pérez-Zepeda, M. U., Vik-Mo, A. O., & Aarsland, D. (2023). Specific neuropsychiatric symptoms are associated with functional decline trajectories in Alzheimer's disease and Lewy body dementia: A five-year follow-up study. *Frontiers in Medicine*, *10*, 1267060. https://doi.org/10.3389/fmed.2023.1267060

Borelli, W. V., Augustin, M. C., de Oliveira, P. B. F., Reggiani, L. C., Bandeira-de-Mello, R. G., Schumacher-Schuh, A. F., Chaves, M. L. F., & Castilhos, R. M. (2021). Neuropsychiatric Symptoms in Patients with Dementia Associated with Increased Psychological Distress in Caregivers During the COVID-19 Pandemic. *Journal of Alzheimer's Disease*, *80*(4), 1705–1712. https://doi.org/10.3233/JAD-201513

Borkowski, J. G., Benton, A. L., & Spreen, O. (1967). Word fluency and brain damage. *Neuropsychologia*, *5*(2), 135–140. https://doi.org/10.1016/0028-3932(67)90015-2

Borroni, B., Premi, E., Agosti, C., Alberici, A., Garibotto, V., Bellelli, G., Paghera, B., Lucchini, S., Giubbini, R., Perani, D., & Padovani, A. (2009). Revisiting Brain Reserve Hypothesis in Frontotemporal Dementia: Evidence from a Brain Perfusion Study. *Dementia and Geriatric Cognitive Disorders*, *28*(2), 130–135. https://doi.org/10.1159/000235575

Bowlby, J. (1979). The Bowlby-Ainsworth attachment theory. *Behavioral and Brain Sciences*, *2*(4), 637–638. https://doi.org/10.1017/S0140525X00064955

Boyle, P. A., Yang, J., Yu, L., Leurgans, S. E., Capuano, A. W., Schneider, J. A., Wilson, R. S., & Bennett, D. A. (2017). Varied effects of age-related neuropathologies on the trajectory of late life cognitive decline. *Brain*, *140*(3), 804–812. https://doi.org/10.1093/brain/aww341

Braak, E., & Braak, H. (1997). Alzheimer’s disease: Transiently developing dendritic changes in pyramidal cells of sector CA1 of the Ammon’s horn. *Acta Neuropathologica*, *93*(4), 323–325. https://doi.org/10.1007/s004010050622

Buchman, A. S., Yu, L., Wilson, R. S., Lim, A., Dawe, R. J., Gaiteri, C., Leurgans, S. E., Schneider, J. A., & Bennett, D. A. (2019). Physical activity, common brain pathologies, and cognition in community-dwelling older adults. *Neurology*, *92*(8). https://doi.org/10.1212/WNL.0000000000006954

Casaletto, K. B., Renteíıa, M. A., Pa, J., Tom, S. E., Harrati, A., Armstrong, N. M., Rajan, K. B., Mungas, D., Walters, S., Kramer, J., & Zahodne, L. B. (2020). Late-Life Physical and Cognitive Activities Independently Contribute to Brain and Cognitive Resilience. *Journal of Alzheimer’s Disease : JAD*, *74*(1), 363–376. https://doi.org/10.3233/JAD-191114

Casaletto, K. B., Staffaroni, A. M., Wolf, A., Appleby, B., Brushaber, D., Coppola, G., Dickerson, B., Domoto-Reilly, K., Elahi, F. M., Fields, J., Fong, J. C., Forsberg, L., Ghoshal, N., Graff-Radford, N., Grossman, M., Heuer, H. W., Hsiung, G.-Y., Huey, E. D., Irwin, D., … Study, the A. (2020). Active lifestyles moderate clinical outcomes in autosomal dominant frontotemporal degeneration. *Alzheimer’s & Dementia*, *16*(1), 91–105. https://doi.org/10.1002/alz.12001

Casanova, R., Saldana, S., Lutz, M. W., Plassman, B. L., Kuchibhatla, M., & Hayden, K. M. (2020). Investigating Predictors of Cognitive Decline Using Machine Learning. *The Journals of Gerontology: Series B*, *75*(4), 733–742. https://doi.org/10.1093/geronb/gby054

Cavaillès, C., Carrière, I., Wagner, M., Dartigues, J.-F., Berr, C., Dauvilliers, Y., & Jaussent, I. (2022). Trajectories of sleep duration and timing before dementia: A 14-year follow-up study. *Age and Ageing*, *51*(8), afac186. https://doi.org/10.1093/ageing/afac186

Chan, D., Shafto, M., Kievit, R., Matthews, F., Spink, M., Valenzuela, M., & Henson, R. N.

(2018). Lifestyle activities in mid-life contribute to cognitive reserve in late-life, independent of education, occupation, and late-life activities. *Neurobiology of Aging*, *70*, 180–183. https://doi.org/10.1016/j.neurobiolaging.2018.06.012

Chapuis, J., Flaig, A., Grenier-Boley, B., Eysert, F., Pottiez, V., Deloison, G., Vandeputte, A., Ayral, A.-M., Mendes, T., Desai, S., Goate, A. M., Kauwe, J. S. K., Leroux, F., Herledan, A., Demiautte, F., Bauer, C., Checler, F., Petersen, R. C., Blennow, K., … ADGC, Alzheimer's Disease Neuroimaging Initiative. (2017). Genome-wide, high-content siRNA screening identifies the Alzheimer's genetic risk factor FERMT2 as a major modulator of APP metabolism. *Acta Neuropathologica*, *133*(6), 955–966. https://doi.org/10.1007/s00401-016-1652-z

Chen, R., Hu, Z., Wei, L., Ma, Y., Liu, Z., & Copeland, J. R. (2011). Incident Dementia in a Defined Older Chinese Population. *PLoS ONE*, *6*(9), e24817. https://doi.org/10.1371/journal.pone.0024817

Chen, X. R., Shao, Y., & Sadowski, M. J. (2021). Segmented Linear Mixed Model Analysis Reveals Association of the APOEε4 Allele with Faster Rate of Alzheimer's Disease Dementia Progression. *Journal of Alzheimer's Disease*, *82*(3), 921–937. https://doi.org/10.3233/JAD-210434

Chen, X., Zhang, Y., Hou, L., Shen, Y., Li, J., & Dong, B. (2020). Analysis of Risk Factors for Cognitive Dysfunction in Disabled Elderly Patients in Chengdu, China. *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research*, *26*, e923590-1-e923590-8. https://doi.org/10.12659/MSM.923590

Chen, Z.-C., Liu, S., Gan, J., Ma, L., Du, X., Zhu, H., Han, J., Xu, J., Wu, H., Fei, M., Dou, Y., Yang, Y., Deng, P., Wang, X.-D., & Ji, Y. (2021). The Impact of the COVID-19 Pandemic and Lockdown on Mild Cognitive Impairment, Alzheimer's Disease and Dementia With Lewy Bodies in China: A 1-Year Follow-Up Study. *Frontiers in Psychiatry*, *12*, 711658. https://doi.org/10.3389/fpsyt.2021.711658

Chieffi, S., Messina, G., Villano, I., Messina, A., Esposito, M., Monda, V., Valenzano, A., Moscatelli, F., Esposito, T., Carotenuto, M., Viggiano, A., Cibelli, G., & Monda, M.

(2017). Exercise Influence on Hippocampal Function: Possible Involvement of Orexin-A. *Frontiers in Physiology*, *8*. https://doi.org/10.3389/fphys.2017.00085

Chillag, A. (2020, June 23). *They bonded over bagels and lox, then Covid-19 hit. Now this 82-year-old and his millennial friend bond over Zoom*. CNN. https://www.cnn.com/2020/06/23/us/elder-loneliness-covid-19-zoom-volunteers-trnd-iyw/index.html

Chowdhury, S., & Chowdhury, N. S. (2023). Novel anti-amyloid-beta (Aβ) monoclonal antibody lecanemab for Alzheimer's disease: A systematic review. *International Journal of Immunopathology and Pharmacology*, *37*, 03946320231209839. https://doi.org/10.1177/03946320231209839

Ciesielska, N., Sokołowski, R., Mazur, E., Podhorecka, M., Polak-Szabela, A., & Kędziora-Kornatowska, K. (2016). Is the Montreal Cognitive Assessment (MoCA) test better suited than the Mini-Mental State Examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? Meta-analysis. *Psychiatr Pol, 50*(5), 1039-1052.

Clare, L., Gamble, L. D., Martyr, A., Henderson, C., Knapp, M., & Matthews, F. E. (2024). Living Alone With Mild-to-Moderate Dementia Over a Two-Year Period: Longitudinal Findings From the IDEAL Cohort. *The American Journal of Geriatric Psychiatry*, *32*(11), 1309–1321. https://doi.org/10.1016/j.jagp.2024.05.012

Clare, L., Martyr, A., Henderson, C., Gamble, L., Matthews, F. E., Quinn, C., Nelis, S. M., Rusted, J., Thom, J., Knapp, M., Hart, N., & Victor, C. (2020). Living Alone with Mild-To-Moderate Dementia: Findings from the IDEAL Cohort. *Journal of Alzheimer's Disease*, *78*(3), 1207–1216. https://doi.org/10.3233/JAD-200638

Copeland, J. R. M., Dewey, M. E., Davidson, I. A., Saunders, P. A., & Scott, A. (1992). Geriatric Mental State-AGECAT: Prevalence, Incidence and Long-Term Outcome of Dementia and Organic Disorders in the Liverpool Study of Continuing Health in the Community. *Neuroepidemiology*, *11*(Suppl. 1), 84–87. https://doi.org/10.1159/000110996

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., Roses, A. D., Haines, J. L., & Pericak-Vance, M. A. (1993). Gene Dose of Apolipoprotein E Type 4 Allele and the Risk of Alzheimer's Disease in Late Onset Families. *Science*, *261*(5123), 921–923. https://doi.org/10.1126/science.8346443

Costa, L. G., Cole, T. B., Coburn, J., Chang, Y.-C., Dao, K., & Roqué, P. J. (2017). Neurotoxicity of traffic-related air pollution. *NeuroToxicology*, *59*, 133–139. https://doi.org/10.1016/j.neuro.2015.11.008

Daniel Lüdecke, Mattan S. Ben-Shachar, Indrajeet Patil, Philip Waggoner, & Dominique Makowski. (2021). performance: An R Package for Assessment, Comparison and Testing of Statistical Models. *Journal of Open Source Software*, *6*(60), 3139. https://doi.org/10.21105/joss.03139

Davies, C. (2020, July 14). *Coronavirus: 'Social isolation' of new parents during lockdown*. BBC News. https://www.bbc.com/news/uk-wales-53368246

de Jong Gierveld, J., & van Tilburg, T. (1999). *Manual of the Loneliness Scale. Methoden en technieken.* Open Science Framework. https://osf.io/u6gck/

de Jong Gierveld, J., van Tilburg, T., & Dykstra, P. A. (2006). Loneliness and Social Isolation. In Anita L. Vangelisti & Daniel Perlman (Eds.), *The Cambridge Handbook of Personal Relationships* (pp. 485–500). Cambridge University Press.

de Jong-Gierveld, J. (1987). Developing and testing a model of loneliness. *Journal of Personality and Social Psychology*, *53*(1), 119–128.

Defrancesco, M., Schurr, T. A., & Hofer, A. (2024). COVID-19 restrictions promoted the newly occurring loneliness in older people – a prospective study in a memory clinic population. *Frontiers in Psychiatry*, *15*, 1340498. https://doi.org/10.3389/fpsyt.2024.1340498

Dekhtyar, S., Wang, H.-X., Scott, K., Goodman, A., Koupil, I., & Herlitz, A. (2015). A Life-Course Study of Cognitive Reserve in Dementia—From Childhood to Old Age. *The American Journal of Geriatric Psychiatry*, *23*(9), 885–896. https://doi.org/10.1016/j.jagp.2015.02.002

Desai, R., John, A., Stott, J., & Charlesworth, G. (2020). Living alone and risk of dementia: A systematic review and meta-analysis. *Ageing Research Reviews*, *62*, 101122. https://doi.org/10.1016/j.arr.2020.101122

Dobrzyn-Matusiak, D., Marcisz, C., Bak, E., Kulik, H., & Marcisz, E. (2014). Physical and mental health aspects of elderly in social care in Poland. *Clinical Interventions in Aging*, *9*, 1793. https://doi.org/10.2147/CIA.S69741

Dodge, H. H., Buracchio, T. J., Fisher, G. G., Kiyohara, Y., Meguro, K., Tanizaki, Y., & Kaye, J. A. (2012). Trends in the Prevalence of Dementia in Japan. *International Journal of Alzheimer's Disease*, *2012*(1), 956354. https://doi.org/10.1155/2012/956354

Dura-Perez, E., Goodman-Casanova, J. M., Vega-Nuñez, A., Guerrero-Pertiñez, G., Varela-Moreno, E., Garolera, M., Quintana, M., Cuesta-Vargas, A. I., Barnestein-Fonseca, P., Sánchez-Lafuente, C. G., Mayoral-Cleries, F., & Guzman-Parra, J. (2022). The Impact of COVID-19 Confinement on Cognition and Mental Health and Technology Use Among Socially Vulnerable Older People: Retrospective Cohort Study. *Journal of Medical Internet Research*, *24*(2), e30598. https://doi.org/10.2196/30598

Dyer, A. H., Murphy, C., Lawlor, B., Kennelly, S. P., & Study Group, For The Nilvad. (2021). Social networks in mild-to-moderate Alzheimer disease: Longitudinal relationships with dementia severity, cognitive function, and adverse events. *Aging & Mental Health*, *25*(10), 1923–1929. https://doi.org/10.1080/13607863.2020.1745146

Ebly, E. M., Hogan, D. B., & Rockwood, K. (1999). Living Alone with Dementia. *Dement Geriatr Cogn Disord*.

Edwards, D. F., & Morris, J. C. (2007). Alone and confused: Community-residing older African Americans with dementia. *Dementia*, *6*(4), 489–506. https://doi.org/10.1177/1471301207084367

Elman, J. A., Vogel, J. W., Bocancea, D. I., Ossenkoppele, R., van Loenhoud, A. C., Tu, X. M., Kremen, W. S., & the Alzheimer's Disease Neuroimaging Initiative. (2022). Issues and recommendations for the residual approach to quantifying cognitive resilience and reserve. *Alzheimer's Research & Therapy*, *14*(1), 102.

https://doi.org/10.1186/s13195-022-01049-w

Elovainio, M., Lahti, J., Pirinen, M., Pulkki-Råback, L., Malmberg, A., Lipsanen, J., Virtanen, M., Kivimäki, M., & Hakulinen, C. (2020). *Association of social isolation, loneliness, and genetic risk with incidence of dementia: UK Biobank cohort study*. https://doi.org/10.1101/2020.02.25.20027177

Evans, I. E. M., Martyr, A., Collins, R., Brayne, C., & Clare, L. (2019). Social Isolation and Cognitive Function in Later Life: A Systematic Review and Meta-Analysis. *Journal of Alzheimer's Disease*, *70*(s1), S119–S144. https://doi.org/10.3233/JAD-180501

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). *Mini-Mental State Examination*. https://doi.org/10.1037/t07757-000

Franco-Marina, F., García-González, J. J., Wagner-Echeagaray, F., Gallo, J., Ugalde, O., Sánchez-García, S., ... & García-Peña, C. (2010). The Mini-mental State Examination revisited: ceiling and floor effects after score adjustment for educational level in an aging Mexican population. *International Psychogeriatrics, 22*(1), 72-81.

Fratiglioni, L., Paillard-Borg, S., & Winblad, B. (2004). An active and socially integrated lifestyle in late life might protect against dementia. *The Lancet Neurology*, *3*(6), 343–353. https://doi.org/10.1016/S1474-4422(04)00767-7

Fratiglioni, L., Wang, H.-X., Ericsson, K., Maytan, M., & Winblad, B. (2000). Influence of social network on occurrence of dementia: A community-based longitudinal study. *The Lancet*, *355*(9212), 1315–1319. https://doi.org/10.1016/S0140-6736(00)02113-9

Freak-Poli, R., Wagemaker, N., Wang, R., Lysen, T. S., Ikram, M. A., Vernooij, M. W., Dintica, C. S., Vernooij-Dassen, M., Melis, R. J. F., Laukka, E. J., Fratiglioni, L., Xu, W., & Tiemeier, H. (2022). Loneliness, Not Social Support, Is Associated with Cognitive Decline and Dementia Across Two Longitudinal Population-Based Cohorts. *Journal of Alzheimer's Disease*, *85*(1), 295–308. https://doi.org/10.3233/JAD-210330

Friedland, R., Brun, A., & Budinger, T. (1985). PATHOLOGICAL AND POSITRON EMISSION TOMOGRAPHIC CORRELATIONS IN ALZHEIMER'S DISEASE. *The Lancet*, *325*(8422), 228. https://doi.org/10.1016/S0140-6736(85)92074-4

Fritsch, T., McClendon, M. J., Wallendal, M. S., Smyth, K. A., Geldmacher, D. S., Hyde, T. F., & Leo, G. J. (2014). Can a Memory Club Help Maintain Cognitive Function? A Pilot Investigation. *Activities, Adaptation & Aging*, *38*(1), 29–52. https://doi.org/10.1080/01924788.2014.878873

Fuller, T. D., & Tech, V. (2010). Relationship Status, Health, and Health Behavior: An Examination of Cohabiters and Commuters. *Sociological Perspectives*, *53*(2), 221–245. https://doi.org/10.1525/sop.2010.53.2.221

Fyffe, D. C., Mukherjee, S., Barnes, L. L., Manly, J. J., Bennett, D. A., & Crane, P. K. (2011). Explaining Differences in Episodic Memory Performance among Older African Americans and Whites: The Roles of Factors Related to Cognitive Reserve and Test Bias. *Journal of the International Neuropsychological Society*, *17*(4), 625–638. https://doi.org/10.1017/S1355617711000476

Gan, J., Liu, S., Wu, H., Chen, Z., Fei, M., Xu, J., Dou, Y., Wang, X., & Ji, Y. (2021). The Impact of the COVID-19 Pandemic on Alzheimer’s Disease and Other Dementias. *Frontiers in Psychiatry*, *12*, 703481. https://doi.org/10.3389/fpsyt.2021.703481

Gelman, A., & Hill, J. (2006). *Data Analysis Using Regression and Multilevel/Hierarchical Models*. Cambridge University Press. https://doi.org/10.1017/CBO9780511790942

Gligic, L., Kormilitzin, A., Goldberg, P., & Nevado-Holgado, A. (2020). Named entity recognition in electronic health records using transfer learning bootstrapped Neural Networks. *Neural Networks*, *121*, 132–139. https://doi.org/10.1016/j.neunet.2019.08.032

Goodday, S. M., Kormilitzin, A., Vaci, N., Liu, Q., Cipriani, A., Smith, T., & Nevado-Holgado, A. (2020). Maximizing the use of social and behavioural information from secondary care mental health electronic health records. *Journal of Biomedical Informatics*, *107*, 103429. https://doi.org/10.1016/j.jbi.2020.103429

Graham, E. K., James, B. D., Jackson, K. L., Willroth, E. C., Boyle, P., Wilson, R., Bennett, D. A., & Mroczek, D. K. (2021). Associations Between Personality Traits and Cognitive Resilience in Older Adults. *The Journals of Gerontology: Series B*, *76*(1), 6–19. https://doi.org/10.1093/geronb/gbaa135

Habeck, C., Eich, T. S., Gu, Y., & Stern, Y. (2019). Occupational Patterns of Structural Brain Health: Independent Contributions Beyond Education, Gender, Intelligence, and Age. *Frontiers in Human Neuroscience*, *13*, 449. https://doi.org/10.3389/fnhum.2019.00449

Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022). *PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis Campbell Systematic Reviews* (Version 18, e1230) [Computer software].

Hajek, A., & König, H.-H. (2025). Prevalence of loneliness and social isolation among individuals with mild cognitive impairment or dementia: Systematic review and meta-analysis. *BJPsych Open*, *11*(2), e44. https://doi.org/10.1192/bjo.2024.865

Hajek, A., Volkmar, A., & König, H.-H. (2023). Prevalence and correlates of loneliness and social isolation in the oldest old: A systematic review, meta-analysis and meta-regression. *Social Psychiatry and Psychiatric Epidemiology*. https://doi.org/10.1007/s00127-023-02602-0

Hardy, J. A., & Higgins, G. A. (1992). Alzheimer’s Disease: The Amyloid Cascade Hypothesis. *Science*, *256*(5054), 184–185. https://doi.org/10.1126/science.1566067

Harmand, M. G.-C., Meillon, C., Rullier, L., Avila-Funes, J.-A., Bergua, V., Dartigues, J.-F., & Amieva, H. (2014). Cognitive Decline After Entering a Nursing Home: A 22-Year Follow-Up Study of Institutionalized and Noninstitutionalized Elderly People. *Journal of the American Medical Directors Association*, *15*(7), 504–508. https://doi.org/10.1016/j.jamda.2014.02.006

Harris, P., Fernandez Suarez, M., Surace, E., Chrem Mendez, P., Martin, M. E., Clarens, M. F., Tapajoz, F., Campos, J., Sevlever, G., Allegri, R. F., Guinjoan, S., & Russo, M. J. (2015). Cognitive reserve and Aβ1-42 in mild cognitive impairment (Argentina-Alzheimer’s Disease Neuroimaging Initiative). *Neuropsychiatric Disease and Treatment*, 2599. https://doi.org/10.2147/NDT.S84292

Harsányiová, M., & Prokop, P. (2018). Living condition, weight loss and cognitive decline among people with dementia. *Nursing Open*, *5*(3), 275–284. https://doi.org/10.1002/nop2.137

Hawthorne, G. (2006). Measuring social isolation in older adults: development and initial validation of the friendship scale. Social indicators research, 77(3), 521-548.

Hawthorne, G., & Griffith, P. (2000). The friendship scale: Development and properties. West Heidelberg, Victoria, Australia: Centre for Health Program Evaluation.

He, Y. L., Zhang, X. K., & Zhang, M. Y. (2000). Psychosocial risk factors for Alzheimer's disease? *Hong Kong Journal of Psychiatry*, *10*(2), 2.

Helmer, C., Damon, D., Letenneur, L., Fabrigoule, C., Barberger-Gateau, P., Lafont, S., Fuhrer, R., Antonucci, T., Commenges, D., Orgogozo, J. M., & Dartigues, J. F. (1999). Marital status and risk of Alzheimer's disease. *Neurology*, *53*(9), 1953–1953. https://doi.org/10.1212/WNL.53.9.1953

Hippius, H., & Neundörfer, G. (2003). The discovery of Alzheimer's disease. *Dialogues in Clinical Neuroscience*, *5*(1), 101–108. https://doi.org/10.31887/DCNS.2003.5.1/hhippius

Hoffman, J. M., Welsh-Bohmer, K. A., Hanson, M., Crain, B., Hulette, C., Earl, N., & Coleman, R. E. (2000). *FDG PET Imaging in Patients with Pathologically Verified Dementia*.

Holt-Lunstad, J. (2017). The Potential Public Health Relevance of Social Isolation and Loneliness: Prevalence, Epidemiology, and Risk Factors. *Public Policy & Aging Report*, *27*(4), 127–130. https://doi.org/10.1093/ppar/prx030

Holt-Lunstad, J. (2021). Loneliness and social isolation as risk factors: The power of social connection in prevention. *American Journal of Lifestyle Medicine, 15*(5), 567-573.

Holwerda, T. J., Deeg, D. J. H., Beekman, A. T. F., Van Tilburg, T. G., Stek, M. L., Jonker, C., & Schoevers, R. A. (2014). Feelings of loneliness, but not social isolation, predict dementia onset: Results from the Amsterdam Study of the Elderly (AMSTEL). *Journal of Neurology, Neurosurgery & Psychiatry*, *85*(2), 135–142.

https://doi.org/10.1136/jnnp-2012-302755

Honma, A. (1992). Development of a Japanese version of Alzheimer's disease assessment scale (ADAS). Jpn J Geriatr Psychiatry, 3, 647-655.

Hsu, H.-C., & Bai, C.-H. (2022). Individual and environmental factors associated with cognitive function in older people: A longitudinal multilevel analysis. *BMC Geriatrics*, *22*(1), 243. https://doi.org/10.1186/s12877-022-02940-9

Hughes, C. P., Berg, L., Danziger, W., Coben, L. A., & Martin, R. L. (1982). A New Clinical Scale for the Staging of Dementia. *The British Journal of Psychiatry*, *140*(6), 566–572. https://doi.org/10.1192/bjp.140.6.566

Hughes, M. E., Waite, L. J., Hawkley, L. C., & Cacioppo, J. T. (2004). A Short Scale for Measuring Loneliness in Large Surveys: Results From Two Population-Based Studies. *Research on Aging*, *26*(6), 655–672. https://doi.org/10.1177/0164027504268574

Irwin, D. J., Lee, V. M.-Y., & Trojanowski, J. Q. (2013). Parkinson's disease dementia: Convergence of α-synuclein, tau and amyloid-β pathologies. *Nature Reviews Neuroscience*, *14*(9), 626–636. https://doi.org/10.1038/nrn3549

Ito, K., Corrigan, B., Zhao, Q., French, J., Miller, R., Soares, H., Katz, E., Nicholas, T., Billing, B., Anziano, R., & Fullerton, T. (2011). Disease progression model for cognitive deterioration from Alzheimer's Disease Neuroimaging Initiative database. *Alzheimer's & Dementia*, *7*(2), 151–160. https://doi.org/10.1016/j.jalz.2010.03.018

Jacqmin-Gadda, H., Commenges, D., & Dartigues, J.-F. (2006). Random Changepoint Model for Joint Modeling of Cognitive Decline and Dementia. *Biometrics*, *62*(1), 254–260. https://doi.org/10.1111/j.1541-0420.2005.00443.x

Jellinger, K. A. (2010). Should the word 'dementia' be forgotten? *Journal of Cellular and Molecular Medicine*, *14*(10), 2415–2416. https://doi.org/10.1111/j.1582-4934.2010.01159.x

Jerskey, B. A., & Meyers, J. E. (2011). Rey Complex Figure Test. In J. S. Kreutzer, J. DeLuca, & B. Caplan (Eds.), *Encyclopedia of Clinical Neuropsychology* (pp. 2176–

2179). Springer. https://doi.org/10.1007/978-0-387-79948-3_1399

Jia, X., Wang, Z., Huang, F., Su, C., Du, W., Jiang, H., ... & Zhang, B. (2021). A comparison of the Mini-Mental State Examination (MMSE) with the Montreal Cognitive Assessment (MoCA) for mild cognitive impairment screening in Chinese middle-aged and older population: a cross-sectional study. *BMC psychiatry, 21*(1), 485.

Jo, E., Sung, J. E., & Lee, Y. (2021). A Longitudinal Analysis of the Cognitive Function and Related Factors in Older Adults Using a Multilevel Growth Model. *Communication Sciences & Disorders*, *26*(3), 601–615. https://doi.org/10.12963/csd.21829

Johansson, L., Guo, X., Hällström, T., Norton, M. C., Waern, M., Östling, S., Bengtsson, C., & Skoog, I. (2013). Common psychosocial stressors in middle-aged women related to longstanding distress and increased risk of Alzheimer's disease: A 38-year longitudinal population study. *BMJ Open*, *3*(9), e003142. https://doi.org/10.1136/bmjopen-2013-003142

Joo, S. H., Hahn, C. T., & Lee, C. U. (2022). The Impact of the COVID-19 Pandemic and Social Distancing on Cognition of Alzheimer's Disease Patients. *Psychiatry Investigation*, *19*(11), 973–980. https://doi.org/10.30773/pi.2022.0179

Jopling, K., Kennedy, S., & Reeves, R. (2017). *Jo Cox Commission on Loneliness—Combating loneliness one conversation at a time: A call to action*. The Jo Cox Foundation. https://www.ageuk.org.uk/siteassets/documents/reports-and-publications/reports-and-briefings/active-communities/rb_dec17_jocox_commission_finalreport.pdf

Joung, I. M., Stronks, K., Mheen, H. van de, & Mackenbach, J. P. (1995). Health behaviours explain part of the differences in self reported health associated with partner/marital status in The Netherlands. *Journal of Epidemiology & Community Health*, *49*(5), 482–488. https://doi.org/10.1136/jech.49.5.482

Kabir, Md. T., Uddin, Md. S., Setu, J. R., Ashraf, G. M., Bin-Jumah, M. N., & Abdel-Daim, M. M. (2020). Exploring the Role of PSEN Mutations in the Pathogenesis of Alzheimer's Disease. *Neurotoxicity Research*, *38*(4), 833–849. https://doi.org/10.1007/s12640-

020-00232-x

Kanazawa, T., Uchihara, T., Takahashi, A., Nakamura, A., Orimo, S., & Mizusawa, H. (2008). Three-layered structure shared between Lewy bodies and lewy neurites-three-dimensional reconstruction of triple-labeled sections. *Brain Pathology (Zurich, Switzerland)*, *18*(3), 415–422. https://doi.org/10.1111/j.1750-3639.2008.00140.x

Karp, A., Andel, R., Parker, M. G., Wang, H.-X., Winblad, B., & Fratiglioni, L. (2009). Mentally Stimulating Activities at Work During Midlife and Dementia Risk After Age 75: Follow-Up Study From the Kungsholmen Project. *The American Journal of Geriatric Psychiatry*, *17*(3), 227–236. https://doi.org/10.1097/JGP.0b013e318190b691

Katzman, R., Aronson, M., Fuld, P., Kawas, C., Brown, T., Morgenstern, H., Frishman, W., Gidez, L., Eder, H., & Ooi, W. L. (1989). Development of dementing illnesses in an 80-year-old volunteer cohort. *Annals of Neurology*, *25*(4), 317–324. https://doi.org/10.1002/ana.410250402

Katzman, R., & Saitoh, T. (1991). Advances in Alzheimer’s disease. *The FASEB Journal*, *5*(3), 278–286. https://doi.org/10.1096/fasebj.5.3.2001787

Khan, A., Kalaria, R. N., Corbett, A., & Ballard, C. (2016). Update on Vascular Dementia. *Journal of Geriatric Psychiatry and Neurology*, *29*(5), 281–301. https://doi.org/10.1177/0891988716654987

Kim, Y., Kong, M., & Lee, C. (2013). Association of intronic sequence variant in the gene encoding spleen tyrosine kinase with susceptibility to vascular dementia. *The World Journal of Biological Psychiatry*, *14*(3), 220–226. https://doi.org/10.3109/15622975.2011.559272

Kleemeier, R. W. (1962). Intellectual changes in the senium. *Proceedings of the American Statistical Association*, *1*(2), 181–190.

Kormilitzin, A., Vaci, N., Liu, Q., & Nevado-Holgado, A. (2021). Med7: A transferable clinical natural language processing model for electronic health records. *Artificial Intelligence in Medicine*, *118*, 102086. https://doi.org/10.1016/j.artmed.2021.102086

Krause, N., & Rook, K. S. (2003). Negative Interaction in Late Life: Issues in the Stability and Generalizability of Conflict Across Relationships. *The Journals of Gerontology: Series B*, *58*(2), P88–P99. https://doi.org/10.1093/geronb/58.2.P88

Kremen, W. S., Elman, J. A., Panizzon, M. S., Eglit, G. M. L., Sanderson-Cimino, M., Williams, M. E., Lyons, M. J., & Franz, C. E. (2022). Cognitive Reserve and Related Constructs: A Unified Framework Across Cognitive and Brain Dimensions of Aging. *Frontiers in Aging Neuroscience*, *14*. https://doi.org/10.3389/fnagi.2022.834765

Kröger, E., Andel, R., Lindsay, J., Benounissa, Z., Verreault, R., & Laurin, D. (2008). Is Complexity of Work Associated with Risk of Dementia?: The Canadian Study of Health and Aging. *American Journal of Epidemiology*, *167*(7), 820–830. https://doi.org/10.1093/aje/kwm382

Kuiper, J. S., Zuidersma, M., Oude Voshaar, R. C., Zuidema, S. U., van den Heuvel, E. R., Stolk, R. P., & Smidt, N. (2015). Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. *Ageing Research Reviews*, *22*, 39–57. https://doi.org/10.1016/j.arr.2015.04.006

Kuiper, J. S., Zuidersma, M., Zuidema, S. U., Burgerhof, J. G., Stolk, R. P., Oude Voshaar, R. C., & Smidt, N. (2016). Social relationships and cognitive decline: A systematic review and meta-analysis of longitudinal cohort studies. *International Journal of Epidemiology*, *45*(4), 1169–1206. https://doi.org/10.1093/ije/dyw089

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. B. (2017). lmerTest Package: Tests in Linear Mixed Effects Models. *Journal of Statistical Software*, *82*(13), 1–26. https://doi.org/10.18637/jss.v082.i13

Laininger, L., Dietzel, N., Graessel, E., Prokosch, H.-U., & Kolominsky-Rabas, P. L. (2024). Impact of social network composition on cognitive decline: Digital Dementia Registry Bavaria (digiDEM Bayern). *PLOS ONE*, *19*(7), e0306447. https://doi.org/10.1371/journal.pone.0306447

Lampinen, J., Conradsson, M., Nyqvist, F., Olofsson, B., Gustafson, Y., Nilsson, I., & Littbrand, H. (2022). Loneliness among very old people with and without dementia:

Prevalence and associated factors in a representative sample. *European Journal of Ageing*, *19*(4), 1441–1453. https://doi.org/10.1007/s10433-022-00729-8

Landsteiner, I., Pinheiro, J. A., Leles Vieira de Souza, B., Setti Frizon, D. M., Federighi Baisi Chagas, E., & Marques Payão, S. L. (2025). Effect of COVID-19 Related Social Isolation on Cognitive Decline in Neurocognitive Disorder Patients: A Systematic Review and Meta-Analysis. *Neurology India*, *73*(1), 10. https://doi.org/10.4103/neurol-india.Neurol-India-D-24-00337

Lao, P., Young, C. B., Ezeh, C., Lacayo, B., Seblova, D., Andrews, R. M., Gibbons, L., Kraal, A. Z., Turney, I., Deters, K. D., Dotson, V., Manly, J. J., Barnes, L. L., & Zahodne, L. B. (2024). Loneliness, cerebrovascular and Alzheimer’s disease pathology, and cognition. *Alzheimer’s & Dementia*, *20*(10), 7113–7123. https://doi.org/10.1002/alz.14196

Lara, E., Martín-María, N., De la Torre-Luque, A., Koyanagi, A., Vancampfort, D., Izquierdo, A., & Miret, M. (2019). Does loneliness contribute to mild cognitive impairment and dementia? A systematic review and meta-analysis of longitudinal studies. *Ageing Research Reviews*, *52*, 7–16. https://doi.org/10.1016/j.arr.2019.03.002

Lazzari, C., & Rabottini, M. (2022). COVID-19, loneliness, social isolation and risk of dementia in older people: A systematic review and meta-analysis of the relevant literature. *International Journal of Psychiatry in Clinical Practice*, *26*(2), 196–207. https://doi.org/10.1080/13651501.2021.1959616

Leduc, V., Jasmin-Bélanger, S., & Poirier, J. (2010). APOE and cholesterol homeostasis in Alzheimer’s disease. *Trends in Molecular Medicine*, *16*(10), 469–477. https://doi.org/10.1016/j.molmed.2010.07.008

Lee, J., & Lee, A. Y. (2020). Home-Visiting Cognitive Intervention for the Community-Dwelling Elderly Living Alone. *Dementia and Neurocognitive Disorders*, *19*(2), 65–73. https://doi.org/10.12779/dnd.2020.19.2.65

Lee, T. W., Yim, E., Cho, E., & Chung, J. (2014). Cognitive Function, Behavioral Problems, and Physical Function in Long-Term Care Insurance Beneficiaries with Dementia in

South Korea: Comparison of Home Care and Institutional Care Services. *Journal of the American Geriatrics Society*, *62*(8), 1467–1475. https://doi.org/10.1111/jgs.12944

Lehmann, S. W., Black, B. S., Shore, A., Kasper, J., & Rabins, P. V. (2010). Living alone with dementia: Lack of awareness adds to functional and cognitive vulnerabilities. *International Psychogeriatrics*, *22*(5), 778–784. https://doi.org/10.1017/S1041610209991529

Lehtisalo, J., Palmer, K., Mangialasche, F., Solomon, A., Kivipelto, M., & Ngandu, T. (2021). Changes in Lifestyle, Behaviors, and Risk Factors for Cognitive Impairment in Older Persons During the First Wave of the Coronavirus Disease 2019 Pandemic in Finland: Results From the FINGER Study. *Frontiers in Psychiatry*, *12*, 624125. https://doi.org/10.3389/fpsyt.2021.624125

Lessig, S., Nie, D., Xu, R., & Corey-Bloom, J. (2012). Changes on brief cognitive instruments over time in Parkinson's disease. *Movement Disorders, 27*(9), 1125-1128.

LeVasseur, A. L. (2021). Effects of social isolation on a long-term care resident with dementia and depression during the COVID-19 pandemic. *Geriatric Nursing*, *42*(3), 780–781. https://doi.org/10.1016/j.gerinurse.2021.04.007

Li, Q., Zhang, Q., Zhang, S., Du, M., Wang, X., Hu, S., & Li, L. (2022). Relationship between frailty and cognitive decline in Chinese older patients with Alzheimer’s disease: The mediating role of social contact. *Geriatric Nursing*, *43*, 175–181. https://doi.org/10.1016/j.gerinurse.2021.11.019

Liu, Q., Vaci, N., Koychev, I., Kormilitzin, A., Li, Z., Cipriani, A., & Nevado-Holgado, A. (2022). Personalised treatment for cognitive impairment in dementia: Development and validation of an artificial intelligence model. *BMC Medicine*, *20*(1), 45. https://doi.org/10.1186/s12916-022-02250-2

Livingston, G., Huntley, J., Liu, K. Y., Costafreda, S. G., Selbæk, G., Alladi, S., Ames, D., Banerjee, S., Burns, A., Brayne, C., Fox, N. C., Ferri, C. P., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson, E. B., Nakasujja, N., Rockwood, K., … Mukadam,

N. (2024). Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *The Lancet*, *404*(10452), 572–628. https://doi.org/10.1016/S0140-6736(24)01296-0

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S. G., Dias, A., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson, E. B., Ogunniyi, A., … Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*, *396*(10248), 413–446. https://doi.org/10.1016/S0140-6736(20)30367-6

Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., Ballard, C., Banerjee, S., Burns, A., Cohen-Mansfield, J., Cooper, C., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Larson, E. B., Ritchie, K., Rockwood, K., Sampson, E. L., … Mukadam, N. (2017). Dementia prevention, intervention, and care. *The Lancet Commissions*, *390*, 2673–2734. http://dx.doi.org/10.1016/ S0140-6736(17)31363-6

Lobo, A., LóPez-Antón, R., De-La-CÁmara, C., Quintanilla, M. Á., Campayo, A., Saz, P., & Zarademp Workgroup. (2008). Non-cognitive psychopathological symptoms associated with incident mild cognitive impairment and dementia, alzheimer's type. *Neurotoxicity Research*, *14*(2–3), 263–272. https://doi.org/10.1007/BF03033815

Long, J. D. (2011). *Longitudinal Data Analysis for the Behavioral Sciences Using R*. SAGE Publications.

Lopez, O. L., Becker, J. T., Kaufer, D. I., Hamilton, R. L., Sweet, R. A., Klunk, W., & DeKosky, S. T. (2002). Research Evaluation and Prospective Diagnosis of Dementia With Lewy Bodies. *Archives of Neurology*, *59*(1), 43–46. https://doi.org/10.1001/archneur.59.1.43

Lubben, J. E. (1988). Assessing social networks among elderly populations. *Family and Community Health*, *11*(3), 42–52.

Lüdecke, D., Waggoner, P., & Makowski, D. (2019). insight: A Unified Interface to Access Information from Model Objects in R. *Journal of Open Source Software*, *4*(38), 1412.

https://doi.org/doi:10.21105/joss.01412.

Maggio, M. G., De Domenico, C., Manuli, A., Latella, D., Marra, A., La Rosa, G., Portaro, S., & Calabrò, R. S. (2023). Alzheimer cafè: Toward bridging the gap between cure and care in patients with dementia. *International Journal of Neuroscience*, *133*(9), 1024–1030. https://doi.org/10.1080/00207454.2022.2040024

Manca, R., De Marco, M., Colston, A., Raymont, V., Amin, J., Davies, R., Kumar, P., Russell, G., Blackburn, D. J., & Venneri, A. (2022). The Impact of Social Isolation Due to COVID-19 on Symptom Progression in People With Dementia: Findings of the SOLITUDE Study. *Frontiers in Psychiatry*, *13*, 877595. https://doi.org/10.3389/fpsyt.2022.877595

Manca, R., De Marco, M., & Venneri, A. (2020). The Impact of COVID-19 Infection and Enforced Prolonged Social Isolation on Neuropsychiatric Symptoms in Older Adults With and Without Dementia: A Review. *Frontiers in Psychiatry*, *11*. https://doi.org/10.3389/fpsyt.2020.585540

Martins, C. A. R., Oulhaj, A., de Jager, C. A., & Williams, J. H. (2005). APOE alleles predict the rate of cognitive decline in Alzheimer disease. *Neurology*, *65*(12), 1888–1893. https://doi.org/10.1212/01.wnl.0000188871.74093.12

Masurkar, A. V. (2018). Towards a Circuit-Level Understanding of Hippocampal CA1 Dysfunction in Alzheimer's Disease Across Anatomical Axes. *Journal of Alzheimer's Disease & Parkinsonism*, *08*(01). https://doi.org/10.4172/2161-0460.1000412

Matthews, F. E., Arthur, A., Barnes, L. E., Bond, J., Jagger, C., Robinson, L., & Brayne, C. (2013). A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: Results of the Cognitive Function and Ageing Study I and II. *The Lancet*, *382*(9902), 1405–1412. https://doi.org/10.1016/S0140-6736(13)61570-6

McGeer, E. G., McGeer, P. L., Harrop, R., Akiyama, H., & Kamo, H. (1990). Correlations of regional postmortem enzyme activities with premortem local glucose metabolic rates in alzheimer's disease. *Journal of Neuroscience Research*, *27*(4), 612–619.

https://doi.org/10.1002/jnr.490270422

McGeer, E. G., Peppard, R. P., McGeer, P. L., Tuokko, H., Crockett, D., Parks, R., Akiyama, H., Calne, D. B., Beattie, B. L., & Harrop, R. (1990). ^{18} Fluorodeoxyglucose Positron Emission Tomography Studies in Presumed Alzheimer Cases, Including 13 Serial Scans. *Canadian Journal of Neurological Sciences / Journal Canadien Des Sciences Neurologiques*, *17*(1), 1–11. https://doi.org/10.1017/S0317167100029930

McGeer, P. L., Kamo, H., Harrop, R., Li, D. K., Tuokko, H., McGeer, E. G., Adam, M. J., Ammann, W., Beattie, B. L., & Calne, D. B. (1986). Positron emission tomography in patients with clinically diagnosed Alzheimer's disease. *CMAJ: Canadian Medical Association Journal*, *134*(6), 597–607.

McGeer, P. L., Kamo, H., Harrop, R., McGeer, E. G., Martin, W. R. W., Pate, B. D., & Li, D. K. B. (1986). Comparison of PET, MRI, and CT with pathology in a proven case of Alzheimer's disease. *Neurology*, *36*(12), 1569–1569. https://doi.org/10.1212/WNL.36.12.1569

McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J.-P., Weintraub, D., Aarsland, D., Galvin, J., Attems, J., Ballard, C. G., Bayston, A., Beach, T. G., Blanc, F., Bohnen, N., Bonanni, L., Bras, J., Brundin, P., Burn, D., Chen-Plotkin, A., … Kosaka, K. (2017). Diagnosis and management of dementia with Lewy bodies. *Neurology*, *89*(1), 88–100. https://doi.org/10.1212/WNL.0000000000004058

Meng, X., & D'Arcy, C. (2012). Education and Dementia in the Context of the Cognitive Reserve Hypothesis: A Systematic Review with Meta-Analyses and Qualitative Analyses. *PLoS ONE*, *7*(6), e38268. https://doi.org/10.1371/journal.pone.0038268

Mielke, R., Schröder, R., Fink, G. R., Kessler, J., Herholz, K., & Heiss, W.-D. (1996). Regional cerebral glucose metabolism and postmortem pathology in Alzheimer's disease. *Acta Neuropathologica*, *91*(2), 174–179. https://doi.org/10.1007/s004010050410

Mintun, M. A., Lo, A. C., Evans, C. D., Wessels, A. M., Ardayfio, P. A., Andersen, S. W., Shcherbinin, S., Sparks, J., Sims, J. R., Brys, M., Apostolova, L. G., Salloway, S. P.,

& Skovronsky, D. M. (2021). Donanemab in Early Alzheimer’s Disease. *New England Journal of Medicine*, *384*(18), 1691–1704. https://doi.org/10.1056/NEJMoa2100708

Missotten, P., Thomas, P., Squelard, G., Di Notte, D., Fontaine, O., Paquay, L., De Lepeleire, J., Buntinx, F., & Ylieff, M. (2009). Impact of Place of Residence on Relationship Between Quality of Life and Cognitive Decline in Dementia. *Alzheimer Disease & Associated Disorders*, *23*(4), 395–400. https://doi.org/10.1097/WAD.0b013e3181b4cf48

Mohammadian, F., Rezaee, M., Kalantar, A., Mohebbi, N., & Motamed, M. (2022). Relationship Between Psychological Impacts of COVID-19 and Loneliness in Patients With Dementia: A Cross-Sectional Study From Iran. *Frontiers in Psychiatry*, *13*, 814676. https://doi.org/10.3389/fpsyt.2022.814676

Morris, J. C., Heyman, A., Mohs, R. C., Hughes, J. P., van Belle, G., Fillenbaum, G., Mellits, E. D., & Clark, C. (1989). The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer’s disease. *Neurology*, *39*(9), 1159–1165. https://doi.org/10.1212/wnl.39.9.1159

Moss, A., & England, R. (2021, May 3). *Covid: Lockdown loneliness could leave people ‘stuck’, charity warns*. BBC News. https://www.bbc.com/news/uk-england-56808885

Murdoch, T. B., & Detsky, A. S. (2013). The Inevitable Application of Big Data to Health Care. *JAMA*, *309*(13), 1351. https://doi.org/10.1001/jama.2013.393

Myers, J. A. C., Stafford, T., Koychev, I., Perneczky, R., Bandmann, O., Vaci, N. (2025). Loneliness, social isolation and effects on cognitive decline in patients with dementia: A retrospective cohort study suing natural language processing. *Alzheimer’s & Dementia: Diagnosis, Assessment & Disease Monitoring, 17*(3). e70149

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-

5415.2005.53221.x

National Health Service. (2024, January 3). *Causes of dementia*. Nhs.Uk. https://www.nhs.uk/conditions/dementia/about-dementia/causes/

National Institute for Health and Care Excellence. (2015). *Dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset* (pp. 1–53). National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ng16/resources/dementia-disability-and-frailty-in-later-life-midlife-approaches-to-delay-or-prevent-onset-pdf-1837274790085

Negash, S., Wilson, R. S., Leurgans, S. E., Wolk, D. A., Schneider, J. A., Buchman, A. S., Bennett, D. A., & Arnold, Steven. E. (2013). Resilient Brain Aging: Characterization of Discordance between Alzheimer’s Disease Pathology and Cognition. *Current Alzheimer Research*, *10*(8), 844–851.

Nervi, A., Reitz, C., Tang, M.-X., Santana, V., Piriz, A., Reyes, D., Lantigua, R., Medrano, M., Jiménez-Velázquez, I. Z., Lee, J. H., & Mayeux, R. (2011). Familial Aggregation of Dementia With Lewy Bodies. *Archives of Neurology*, *68*(1). https://doi.org/10.1001/archneurol.2010.319

Newsom, J., Nishishiba, M., Morgan, D., & Rook, K. (2003). The Relative Importance of Three Domains of Positive and Negative Social Exchanges: A Longitudinal Model With Comparable Measures. *Psychology and Aging*, *18*, 746–754. https://doi.org/10.1037/0882-7974.18.4.746

NICE. (2024, October 23). *New Alzheimer’s treatment donanemab does not currently demonstrate value for the NHS says NICE*. NICE Website: The National Institute for Health and Care Excellence; NICE. https://www.nice.org.uk/news/articles/new-alzheimer-s-treatment-donanemab-does-not-currently-demonstrate-value-for-the-nhs-says-nice

Nikmat, A. W., Hashim, N. A., Omar, S. A., & Razali, S. (2015). Depression and loneliness/social isolation among patients with cognitive impairment in nursing home. *Nursing Home ASEAN Journal of Psychiatry*, *16*(2).

Nikmat, A. W., Hawthorne, G., & Al-Mashoor, S. H. (2015). The comparison of quality of life among people with mild dementia in nursing home and home care—A preliminary report. *Dementia*, *14*(1), 114–125. https://doi.org/10.1177/1471301213494509

Noone, P. (2015). Addenbrooke's Cognitive Examination-III. *Occupational Medicine*, *65*(5), 418–420. https://doi.org/10.1093/occmed/kqv041

Norton, M. C., Piercy, K. W., Rabins, P. V., Green, R. C., Breitner, J. C. S., Ostbye, T., Corcoran, C., Welsh-Bohmer, K. A., Lyketsos, C. G., & Tschanz, J. T. (2009). Caregiver-Recipient Closeness and Symptom Progression in Alzheimer Disease. The Cache County Dementia Progression Study. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *64B*(5), 560–568. https://doi.org/10.1093/geronb/gbp052

Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K., & Brayne, C. (2014). Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *The Lancet Neurology*, *13*(8), 788–794. https://doi.org/10.1016/S1474-4422(14)70136-X

Norton, S., Matthews, F. E., & Brayne, C. (2013). A commentary on studies presenting projections of the future prevalence of dementia. *BMC Public Health*, *13*(1), 5. https://doi.org/10.1186/1471-2458-13-1

Nouraeinejad, A. (2022). Brain fog as a Long-term Sequela of COVID-19. *SN Comprehensive Clinical Medicine*, *5*(1), 9. https://doi.org/10.1007/s42399-022-01352-5

Nunnari, D., De Cola, M. C., Costa, A., Rifici, C., Bramanti, P., & Marino, S. (2016). Exploring cognitive reserve in multiple sclerosis: New findings from a cross-sectional study. *Journal of Clinical and Experimental Neuropsychology*, *38*(10), 1158–1167. https://doi.org/10.1080/13803395.2016.1200538

Office for Health Improvement and Disparities. (2022, February 22). *Dementia: Applying All Our Health*. Guidance - Dementia: Applying All Our Health. https://www.gov.uk/government/publications/dementia-applying-all-our-health/dementia-applying-all-our-health

Outeiro, T. F., Koss, D. J., Erskine, D., Walker, L., Kurzawa-Akanbi, M., Burn, D., Donaghy, P., Morris, C., Taylor, J.-P., Thomas, A., Attems, J., & McKeith, I. (2019). Dementia with Lewy bodies: An update and outlook. *Molecular Neurodegeneration*, *14*(1). https://doi.org/10.1186/s13024-019-0306-8

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). *Rayyan* [Computer software]. https://www.rayyan.ai/

Oxford Health NHS Foundation Trust (2024). *Oxford Health in Numbers 2023/24*. https://www.oxfordhealth.nhs.uk/wp-content/uploads/2017/04/104817_Oxford_Health_In_Numbers_Report_ACCESSIBLE_Final_v2.pdf

Pagliari, C., Detmer, D., & Singleton, P. (2007). *Potential of electronic personal health records*. https://doi.org/10.1136/bmj.39279.482963.AD

Paillard-Borg, S., Fratiglioni, L., Winblad, B., & Wang, H.-X. (2009). Leisure Activities in Late Life in Relation to Dementia Risk: Principal Component Analysis. *Dementia and Geriatric Cognitive Disorders*, *28*, 136–144. https://doi.org/10.1159/000235576

Panegyres, P. K., & Chen, H. Y. (2013). Differences between early and late onset Alzheimer's disease. *American Journal of Neurodegenerative Disease, 2*(4), 300.

Patterson, C. (2018). *World Alzheimer Report 2018—The state of the art of dementia research: New frontiers*. Alzheimer's Disease International.

Pendlebury, S. T., Markwick, A., De Jager, C. A., Zamboni, G., Wilcock, G. K., & Rothwell, P. M. (2012). Differences in cognitive profile between TIA, stroke and elderly memory research subjects: a comparison of the MMSE and MoCA. *Cerebrovascular diseases, 34*(1), 48-54.

Pendlebury, S. T., & Rothwell, P. M. (2009). Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: A systematic review and meta-analysis. *The Lancet Neurology*, *8*(11), 1006–1018. https://doi.org/10.1016/S1474-4422(09)70236-4

Penninkilampi, R., Casey, A.-N., Singh, M. F., & Brodaty, H. (2018). The Association between Social Engagement, Loneliness, and Risk of Dementia: A Systematic Review and Meta-Analysis. *Journal of Alzheimer's Disease*, *66*(4), 1619–1633. https://doi.org/10.3233/JAD-180439

Perach, R., Read, S., Hicks, B., Harris, P. R., Rusted, J., Brayne, C., Dangoor, M., Miles, E., Dixon, J., Robinson, L., Thomas, A., Banerjee, S., & for the DETERMIND Team. (2023). Predictors of loneliness during the Covid-19 pandemic in people with dementia and their carers in England: Findings from the DETERMIND-C19 study. *Aging & Mental Health*, *27*(3), 521–532. https://doi.org/10.1080/13607863.2022.2080179

Perera, G., Broadbent, M., Callard, F., Chang, C. K., Downs, J., Dutta, R., ... & Stewart, R. (2016). Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) case register: current status and recent enhancement of an electronic mental health record-derived data resource. *BMJ Open, 6*(3), e008721.

Pereiro, A. X., Dosil-Díaz, C., Mouriz-Corbelle, R., Pereira-Rodríguez, S., Nieto-Vieites, A., Pinazo-Hernandis, S., Pinazo-Clapés, C., & Facal, D. (2021). Impact of the COVID-19 Lockdown on a Long-Term Care Facility: The Role of Social Contact. *Brain Sciences*, *11*(8), 986. https://doi.org/10.3390/brainsci11080986

Perissinotto, C., Holt-Lunstad, J., Periyakoil, V. S., & Covinsky, K. (2019). A Practical Approach to Assessing and Mitigating Loneliness and Isolation in Older Adults. *Journal of the American Geriatrics Society*, *67*(4), 657–662. https://doi.org/10.1111/jgs.15746

Perlman, D., & Peplau, L. A. (1981). Toward a Social Psychology of Loneliness. In R. Duck & R. Gilmour (Eds.), *Personal Relationships in Disorder* (pp. 31–56). Academic Press.

Perneczky, R., Wagenpfeil, S., Lunetta, K. L., Cupples, L. A., Green, R. C., DeCarli, C., Farrer, L. A., & Kurz, A. (2009). Education Attenuates the Effect of Medial Temporal

Lobe Atrophy on Cognitive Function in Alzheimer's Disease: The MIRAGE Study. *Journal of Alzheimer's Disease : JAD*, *17*(4), 855–862. https://doi.org/10.3233/JAD-2009-1117

Perry, B. L., McConnell, W. R., Coleman, M. E., Roth, A. R., Peng, S., & Apostolova, L. G. (2022). Why the cognitive "fountain of youth" may be upstream: Pathways to dementia risk and resilience through social connectedness. *Alzheimer's & Dementia*, *18*(5), 934–941. https://doi.org/10.1002/alz.12443

Perry, B. L., McConnell, W. R., Peng, S., Roth, A. R., Coleman, M., Manchella, M., Roessler, M., Francis, H., Sheean, H., & Apostolova, L. A. (2022). Social Networks and Cognitive Function: An Evaluation of Social Bridging and Bonding Mechanisms. *The Gerontologist*, *62*(6), 865–875. https://doi.org/10.1093/geront/gnab112

Perry, B. L., Roth, A. R., Peng, S., Risacher, S. L., Saykin, A. J., & Apostolova, L. G. (2022). Social Networks and Cognitive Reserve: Network Structure Moderates the Association Between Amygdalar Volume and Cognitive Outcomes. *The Journals of Gerontology: Series B*, *77*(8), 1490–1500. https://doi.org/10.1093/geronb/gbab192

Peters, R., Ee, N., Peters, J., Booth, A., Mudway, I., & Anstey, K. J. (2019). Air Pollution and Dementia: A Systematic Review. *Journal of Alzheimer's Disease*, *70*(s1), S145–S163. https://doi.org/10.3233/JAD-180631

Pezzotti, P., Scalmana, S., Mastromattei, A., Di Lallo, D., & the 'Progetto Alzheimer' Working Group. (2008). The accuracy of the MMSE in detecting cognitive impairment when administered by general practitioners: A prospective observational study. *BMC Family Practice*, *9*(1), 29. https://doi.org/10.1186/1471-2296-9-29

Piolatto, M., Bianchi, F., Rota, M., Marengoni, A., Akbaritabar, A., & Squazzoni, F. (2022). The effect of social relationships on cognitive decline in older adults: An updated systematic review and meta-analysis of longitudinal cohort studies. *BMC Public Health*, *22*(1), 278. https://doi.org/10.1186/s12889-022-12567-5

Prommas, P., Lwin, K. S., Chen, Y. C., Hyakutake, M., Ghaznavi, C., Sakamoto, H., Miyata, H., & Nomura, S. (2023). The impact of social isolation from COVID-19-related public health measures on cognitive function and mental health among older adults: A systematic review and meta-analysis. *Ageing Research Reviews*, *85*, 101839. https://doi.org/10.1016/j.arr.2022.101839

Rafnsson, S. B., Orrell, M., d'Orsi, E., Hogervorst, E., & Steptoe, A. (2020). Loneliness, Social Integration, and Incident Dementia Over 6 Years: Prospective Findings From the English Longitudinal Study of Ageing. *The Journals of Gerontology: Series B*, *75*(1), 114–124. https://doi.org/10.1093/geronb/gbx087

Rashad, A., Rasool, A., Shaheryar, M., Sarfraz, A., Sarfraz, Z., Robles-Velasco, K., & Cherrez-Ojeda, I. (2023). Donanemab for Alzheimer's Disease: A Systematic Review of Clinical Trials. *Healthcare*, *11*(1), Article 1. https://doi.org/10.3390/healthcare11010032

Rawtaer, I., Gao, Q., Nyunt, M. S. Z., Feng, L., Chong, M. S., Lim, W. S., Lee, T.-S., Yap, P., Yap, K. B., Ng, T. P., & Anstey, K. (2017). Psychosocial Risk and Protective Factors and Incident Mild Cognitive Impairment and Dementia in Community Dwelling Elderly: Findings from the Singapore Longitudinal Ageing Study. *Journal of Alzheimer's Disease*, *57*(2), 603–611. https://doi.org/10.3233/JAD-160862

Reed, B. R., Dowling, M., Tomaszewski Farias, S., Sonnen, J., Strauss, M., Schneider, J. A., Bennett, D. A., & Mungas, D. (2011). Cognitive Activities During Adulthood Are More Important than Education in Building Reserve. *Journal of the International Neuropsychological Society*, *17*(4), 615–624. https://doi.org/10.1017/S1355617711000014

Rey, A. (1958). *L'examen clinique en psychologie. [The clinical examination in psychology.]* (p. 222). Presses Universitaries De France.

Riegel, K. F., & Riegel, R. M. (1972). Development, drop, and death. *Developmental Psychology*, *6*(2), 306–319. https://doi.org/10.1037/h0032104

Roalf, D. R., Moberg, P. J., Xie, S. X., Wolk, D. A., Moelter, S. T., & Arnold, S. E. (2013). Comparative accuracies of two common screening instruments for classification of Alzheimer's disease, mild cognitive impairment, and healthy aging. *Alzheimer's &*

Dementia, *9*(5), 529–537. https://doi.org/10.1016/j.jalz.2012.10.001

Robinson, D. M., & Keating, G. M. (2006). Memantine. *Drugs*, *66*(11), 1515–1534. https://doi.org/10.2165/00003495-200666110-00015

Rodriguez, F. S., Pabst, A., Luck, T., König, H.-H., Angermeyer, M. C., Witte, A. V., Villringer, A., & Riedel-Heller, S. G. (2018). Social Network Types in Old Age and Incident Dementia. *Journal of Geriatric Psychiatry and Neurology*, *31*(4), 163–170. https://doi.org/10.1177/0891988718781041

Röhr, S., Löbner, M., Gühne, U., Heser, K., Kleineidam, L., Pentzek, M., Fuchs, A., Eisele, M., Kaduszkiewicz, H., König, H.-H., Brettschneider, C., Wiese, B., Mamone, S., Weyerer, S., Werle, J., Bickel, H., Weeg, D., Maier, W., Scherer, M., … Riedel-Heller, S. G. (2020). Changes in Social Network Size Are Associated With Cognitive Changes in the Oldest-Old. *Frontiers in Psychiatry*, *11*, 330. https://doi.org/10.3389/fpsyt.2020.00330

Rosen, W. G., Mohs, R. C., & Davis, K. L. (1984). A new rating scale for Alzheimer's disease. *The American Journal of Psychiatry*, *141*(11), 1356–1364. https://doi.org/10.1176/ajp.141.11.1356

Rothman, S. M., & Mattson, M. P. (2010). Adverse Stress, Hippocampal Networks, and Alzheimer's Disease. *NeuroMolecular Medicine*, *12*(1), 56–70. https://doi.org/10.1007/s12017-009-8107-9

Rouillard, M., Audiffren, M., Albinet, C., Ali Bahri, M., Garraux, G., & Collette, F. (2017). Contribution of four lifelong factors of cognitive reserve on late cognition in normal aging and Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology*, *39*(2), 142–162. https://doi.org/10.1080/13803395.2016.1207755

RStudio Team. (2020). *RStudio: Integrated Development for R* (Version 1.3.1093) [Computer software]. R Studio PBC. http://www.rstudio.com/

Russell, D. W. (1996). UCLA Loneliness Scale (Version 3): Reliability, Validity, and Factor Structure. *Journal of Personality Assessment*, *66*(1), 20. https://doi.org/10.1207/s15327752jpa6601_2

Saito, T., Murata, C., Saito, M., Takeda, T., & Kondo, K. (2018). Influence of social relationship domains and their combinations on incident dementia: A prospective cohort study. *J Epidemiol Community Health*, *72*(1), 7–12. https://doi.org/10.1136/jech-2017-209811

Saliba, D., Buchanan, J., Edelen, M. O., Streim, J., Ouslander, J., Berlowitz, D., & Chodosh, J. (2012). MDS 3.0: Brief interview for mental status. *Journal of the American Medical Directors Association*, *13*(7), 611–617. https://doi.org/10.1016/j.jamda.2012.06.004

Salinas, J., Beiser, A. S., Samra, J. K., O'Donnell, A., DeCarli, C. S., Gonzales, M. M., Aparicio, H. J., & Seshadri, S. (2022). Association of Loneliness With 10-Year Dementia Risk and Early Markers of Vulnerability for Neurocognitive Decline. *Neurology*, *98*(13). https://doi.org/10.1212/WNL.0000000000200039

Sánchez-Valdeón, L., Bello-Corral, L., Mayo-Iscar, A., Fernández-Lázaro, D., & Seco-Calvo, J. (2023). Impact of discontinuing non-pharmacological interventions on cognitive impairment in dementia patients by COVID-19 lockdown. A pilot observational, longitudinal, retrospective study carried out in an adult day center in Spain during the COVID-19 pandemic. *Frontiers in Medicine*, *10*, 1204151. https://doi.org/10.3389/fmed.2023.1204151

Sanyaolu, A., Okorie, C., Marinkovic, A., Patidar, R., Younis, K., Desai, P., Hosein, Z., Padda, I., Mangat, J., & Altaf, M. (2020). Comorbidity and its Impact on Patients with COVID-19. *SN Comprehensive Clinical Medicine*, *2*(8), 1069–1076. https://doi.org/10.1007/s42399-020-00363-4

Saunders, A. M., Strittmatter, W. J., Schmechel, D., St. George-Hyslop, P. H., Pericak-Vance, M. A., Joo, S. H., Rosi, B. L., Gusella, J. F., Crapper-MacLachlan, D. R., Alberts, M. J., Hulette, C., Crain, B., Goldgaber, D., & Roses, A. D. (1993). Association of apolipoprotein E allele ϵ4 with late-onset familial and sporadic Alzheimer's disease. *Neurology*, *43*(8), 1467–1467. https://doi.org/10.1212/WNL.43.8.1467

Scarmeas, N., & Stern, Y. (2003). Cognitive Reserve and Lifestyle. *Journal of Clinical and Experimental Neuropsychology*, *25*(5), 625–633. https://doi.org/10.1076/jcen.25.5.625.14576

Scarmeas, N., Zarahn, E., Anderson, K. E., Habeck, C. G., Hilton, J., Flynn, J., Marder, K. S., Bell, K. L., Sackeim, H. A., Van Heertum, R. L., Moeller, J. R., & Stern, Y. (2003). Association of Life Activities With Cerebral Blood Flow in Alzheimer Disease: Implications for the Cognitive Reserve Hypothesis. *Archives of Neurology*, *60*(3), 359–365. https://doi.org/10.1001/archneur.60.3.359

Sclan, S. G., & Reisberg, B. (1992). Functional assessment staging (FAST) in Alzheimer's disease: reliability, validity, and ordinality. International psychogeriatrics, 4(3), 55-69.

Scheff, T. J. (2007). A Concept of Social Integration. *Philosophical Psychology*, *20*(5), 579–593. https://doi.org/10.1080/09515080701549314

Schmidt, H., Freudenberger, P., Seiler, S., & Schmidt, R. (2012). Genetics of subcortical vascular dementia. *Experimental Gerontology*, *47*(11), 873–877. https://doi.org/10.1016/j.exger.2012.06.003

Schneider, J. A., Arvanitakis, Z., Bang, W., & Bennett, D. A. (2007). Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*, *69*(24), 2197–2204. https://doi.org/10.1212/01.wnl.0000271090.28148.24

Schwarz, G. (1978). Estimating the Dimension of a Model. *The Annals of Statistics*, *6*(2), 461–464. https://doi.org/10.1214/aos/1176344136

Scocco, P., Rapattoni, M., & Fantoni, G. (2006). Nursing home institutionalization: A source of eustress or distress for the elderly? *International Journal of Geriatric Psychiatry*, *21*(3), 281–287. https://doi.org/10.1002/gps.1453

Selkoe, D. J. (2024). The advent of Alzheimer treatments will change the trajectory of human aging. *Nature Aging*, *4*(4), 453–463. https://doi.org/10.1038/s43587-024-00611-5

Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer’s disease at 25 years. *EMBO Molecular Medicine*, *8*(6), 595–608. https://doi.org/10.15252/emmm.201606210

Seltzer, B. (2005). Donepezil: A review. *Expert Opinion on Drug Metabolism & Toxicology*, *1*(3), 527–536. https://doi.org/10.1517/17425255.1.3.527

Seltzer, B. (2007). Donepezil: An update. *Expert Opinion on Pharmacotherapy*, *8*(7), 1011–1023. https://doi.org/10.1517/14656566.8.7.1011

Senior, M., Burghart, M., Yu, R., Kormilitzin, A., Liu, Q., Vaci, N., Nevado-Holgado, A., Pandit, S., Zlodre, J., & Fazel, S. (2020). Identifying Predictors of Suicide in Severe Mental Illness: A Feasibility Study of a Clinical Prediction Rule (Ox ford M ental I llness and S uicide Tool or OxMIS). *Frontiers in Psychiatry*, *11*, 268.

Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological Alterations in Alzheimer Disease. *Cold Spring Harbor Perspectives in Medicine*, *1*(1), a006189. https://doi.org/10.1101/cshperspect.a006189

Shen, C., Rolls, E. T., Cheng, W., Kang, J., Dong, G., Xie, C., Zhao, X.-M., Sahakian, B. J., & Feng, J. (2022). Associations of Social Isolation and Loneliness With Later Dementia. *Neurology*, *99*(2). https://doi.org/10.1212/WNL.0000000000200583

Sheppard, O., & Coleman, M. (2020). Alzheimer's Disease: Etiology, Neuropathology and Pathogenesis. *Exon Publications*, 1–21. https://doi.org/10.36255/exonpublications.alzheimersdisease.2020.ch1

Shibata, M., Ohara, T., Hosoi, M., Hata, J., Yoshida, D., Hirabayashi, N., Morisaki, Y., Nakazawa, T., Mihara, A., Nagata, T., Oishi, E., Anno, K., Sudo, N., & Ninomiya, T. (2021). Emotional Loneliness Is Associated With a Risk of Dementia in a General Japanese Older Population: The Hisayama Study. *The Journals of Gerontology: Series B*, *76*(9), 1756–1766. https://doi.org/10.1093/geronb/gbaa196

Siqueira, G. S., Hagemann, P. D. M., Coelho, D. D. S., Santos, F. H. D., & Bertolucci, P. H. (2019). Can MoCA and MMSE be interchangeable cognitive screening tools? A systematic review. *The Gerontologist, 59*(6), e743-e763.

Smith, E. E. (2017). Clinical presentations and epidemiology of vascular dementia. *Clinical Science*, *131*(11), 1059–1068. https://doi.org/10.1042/CS20160607

Smith, G. E., Kokmen, E., & O'Brien, P. C. (2000). Risk Factors for Nursing Home

Placement in a Population-Based Dementia Cohort. *Journal of the American Geriatrics Society*, *48*(5), 519–525. https://doi.org/10.1111/j.1532-5415.2000.tb04998.x

Smith, M. L., Steinman, L. E., & Casey, E. A. (2020). Combatting Social Isolation Among Older Adults in a Time of Physical Distancing: The COVID-19 Social Connectivity Paradox. *Frontiers in Public Health*, *8*. https://doi.org/10.3389/fpubh.2020.00403

Smith, T., Gildeh, N., & Holmes, C. (2007). The Montreal Cognitive Assessment: validity and utility in a memory clinic setting. *The Canadian Journal of Psychiatry, 52*(5), 329-332.

Snitz, B. E., Chang, Y., Tudorascu, D. L., Lopez, O. L., Lopresti, B. J., DeKosky, S. T., Carlson, M. C., Cohen, A. D., Kamboh, M. I., Aizenstein, H. J., Klunk, W. E., & Kuller, L. H. (2020). Predicting resistance to amyloid-beta deposition and cognitive resilience in the oldest-old. *Neurology*, *95*(8). https://doi.org/10.1212/WNL.0000000000010239

Sommerlad, A., Ruegger, J., Singh-Manoux, A., Lewis, G., & Livingston, G. (2018). Marriage and risk of dementia: Systematic review and meta-analysis of observational studies. *Journal of Neurology, Neurosurgery & Psychiatry*, *89*(3), 231–238. https://doi.org/10.1136/jnnp-2017-316274

Sommerlad, A., Sabia, S., Singh-Manoux, A., Lewis, G., & Livingston, G. (2019). Association of social contact with dementia and cognition: 28-year follow-up of the Whitehall II cohort study. *PLOS Medicine*, *16*(8), e1002862. https://doi.org/10.1371/journal.pmed.1002862

Song, S., Stern, Y., & Gu, Y. (2022). Modifiable lifestyle factors and cognitive reserve: A systematic review of current evidence. *Ageing Research Reviews*, *74*, 101551. https://doi.org/10.1016/j.arr.2021.101551

Sørensen, Ø., Fjell, A. M., & Walhovd, K. B. (2023). Longitudinal Modeling of Age-Dependent Latent Traits with Generalized Additive Latent and Mixed Models. *Psychometrika*, *88*(2), 456–486. https://doi.org/10.1007/s11336-023-09910-z

Sörman, D. E., Rönnlund, M., Sundström, A., Adolfsson, R., & Nilsson, L.-G. (2015). Social relationships and risk of dementia: A population-based study. *International Psychogeriatrics*, *27*(8), 1391–1399. https://doi.org/10.1017/S1041610215000319

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, *8*(3), 448–460. https://doi.org/10.1017/S1355617702813248

Stern, Y., Albert, M., Barnes, C. A., Cabeza, R., Pascual-Leone, A., & Rapp, P. R. (2023). A framework for concepts of reserve and resilience in aging. *Neurobiology of Aging*, *124*, 100–103. https://doi.org/10.1016/j.neurobiolaging.2022.10.015

Stern, Y., Alexander, G. E., Prohovnik, I., & Mayeux, R. (1992). Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. *Annals of Neurology*, *32*(3), 371–375. https://doi.org/10.1002/ana.410320311

Stern, Y., Arenaza-Urquijo, E. M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., Ewers, M., Franzmeier, N., Kempermann, G., Kremen, W. S., Okonkwo, O., Scarmeas, N., Soldan, A., Udeh-Momoh, C., Valenzuela, M., Vemuri, P., Vuoksimaa, E., & and the Reserve, Resilience and Protective Factors PIA Empirical Definitions and Conceptual Frameworks Workgroup. (2020). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's & Dementia*, *16*(9), 1305–1311. https://doi.org/10.1016/j.jalz.2018.07.219

Storey, A. (2018). *Living longer—How our population is changing and why it matters* (pp. 1–53). Office for National Statistics.

Sumowski, J. F., Rocca, M. A., Leavitt, V. M., Riccitelli, G., Comi, G., DeLuca, J., & Filippi, M. (2013). Brain reserve and cognitive reserve in multiple sclerosis: What you've got and how you use it. *Neurology*, *80*(24), 2186–2193. https://doi.org/10.1212/WNL.0b013e318296e98b

Sumowski, J. F., Wylie, G. R., Gonnella, A., Chiaravalloti, N., & DeLuca, J. (2010). Premorbid cognitive leisure independently contributes to cognitive reserve in multiple sclerosis. *Neurology*, *75*(16), 1428–1431. https://doi.org/10.1212/WNL.0b013e3181f881a6

Sun, W., Matsuoka, T., Oba, H., & Narumoto, J. (2021). Importance of loneliness in behavioral and psychological symptoms of dementia. *International Journal of Geriatric Psychiatry*, *36*(4), 540–546. https://doi.org/10.1002/gps.5450

Sundström, A., Adolfsson, A. N., Nordin, M., & Adolfsson, R. (2020). Loneliness Increases the Risk of All-Cause Dementia and Alzheimer's Disease. *The Journals of Gerontology: Series B*, *75*(5), 919–926. https://doi.org/10.1093/geronb/gbz139

Sutin, A. R., Stephan, Y., Luchetti, M., & Terracciano, A. (2020). Loneliness and Risk of Dementia. *The Journals of Gerontology: Series B*, *75*(7), 1414–1422. https://doi.org/10.1093/geronb/gby112

Sutton, E., Catling, J., Segaert, K., & van Zanten, J. V. (2022). Cognitive Health Worries, Reduced Physical Activity and Fewer Social Interactions Negatively Impact Psychological Wellbeing in Older Adults During the COVID-19 Pandemic. *Frontiers in Psychology*, *13*. https://doi.org/10.3389/fpsyg.2022.823089

Te Boekhorst, S., Depla, M. F. I. A., De Lange, J., Pot, A. M., & Eefsting, J. A. (2009). The effects of group living homes on older people with dementia: A comparison with traditional nursing home care. *International Journal of Geriatric Psychiatry*, *24*(9), 970–978. https://doi.org/10.1002/gps.2205

Terrera, G. M., Minett, T., Brayne, C., & Matthews, F. E. (2014). Education associated with a delayed onset of terminal decline. *Age and Ageing*, *43*(1), 26–31. https://doi.org/10.1093/ageing/aft150

Tondo, G., Sarasso, B., Serra, P., Tesser, F., & Comi, C. (2021). The Impact of the COVID-19 Pandemic on the Cognition of People with Dementia. *International Journal of Environmental Research and Public Health*, *18*(8), 4285. https://doi.org/10.3390/ijerph18084285

Topiwala, A., Allan, C. L., Valkanova, V., Zsoldos, E., Filippini, N., Sexton, C., Mahmood, A., Fooks, P., Singh-Manoux, A., Mackay, C. E., Kivimäki, M., & Ebmeier, K. P. (2017). Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: Longitudinal cohort study. *BMJ*, j2353.

https://doi.org/10.1136/bmj.j2353

Trachtenberg, D. I., & Trojanowski, J. Q. (2008). Dementia: A Word to Be Forgotten. *Archives of Neurology*, *65*(5), 593–595. https://doi.org/10.1001/archneur.65.5.593

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., … Straus, S. E. (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Annals of Internal Medicine*, *169*(7), 467–473. https://doi.org/10.7326/M18-0850

Trzepacz, P. T., Hochstetler, H., Wang, S., Walker, B., Saykin, A. J., & Alzheimer's Disease Neuroimaging Initiative. (2015). Relationship between the Montreal Cognitive Assessment and Mini-mental State Examination for assessment of mild cognitive impairment in older adults. *BMC geriatrics, 15*(1), 107.

Tsatali, M., Moraitou, D., Boza, E. S., & Tsolaki, M. (2023). Cognition and Functionality Were Not Affected Due to the COVID-19 Pandemic in People with Mild Cognitive Impairment and AD Dementia Attending Digital Non-Pharmacologic Interventions. *Brain Sciences*, *13*(7), 1044. https://doi.org/10.3390/brainsci13071044

Tsatali, M., Moraitou, D., Poptsi, E., Sia, E., Agogiatou, C., Gialaouzidis, M., Tabakis, I.-M., Avdikou, K., Bakoglidou, E., Batsila, G., Bekiaridis-Moschou, D., Chatziroumpi, O., Diamantidou, A., Gavra, A., Kouroundi, E., Liapi, D., Markou, N., Ouzouni, F., Papasozomenou, C., … Tsolaki, M. (2021). Are There Any Cognitive and Behavioral Changes Potentially Related to Quarantine Due to the COVID-19 Pandemic in People with Mild Cognitive Impairment and AD Dementia? A Longitudinal Study. *Brain Sciences*, *11*(9), Article 9. https://doi.org/10.3390/brainsci11091165

Tuokko, H., MacCourt, P., & Heath, Y. (1999). Home alone with dementia. *Aging & Mental Health*, *3*(1), 21–27. https://doi.org/10.1080/13607869956406

Vaci, N., Koychev, I., Kim, C.-H., Kormilitzin, A., Liu, Q., Lucas, C., Dehghan, A., Nenadic, G., & Nevado-Holgado, A. (2021). Real-world effectiveness, its predictors and onset of action of cholinesterase inhibitors and memantine in dementia: Retrospective health record study. *The British Journal of Psychiatry*, *218*(5), 261–267. https://doi.org/10.1192/bjp.2020.136

Vaci, N., Liu, Q., Kormilitzin, A., Crescenzo, F. D., Kurtulmus, A., Harvey, J., O’Dell, B., Innocent, S., Tomlinson, A., Cipriani, A., & Nevado-Holgado, A. (2020). Natural language processing for structuring clinical text data on depression using UK-CRIS. *BMJ Ment Health*, *23*(1), 21–26. https://doi.org/10.1136/ebmental-2019-300134

van der Lee, S. J., Teunissen, C. E., Pool, R., Shipley, M. J., Teumer, A., Chouraki, V., Melo van Lent, D., Tynkkynen, J., Fischer, K., Hernesniemi, J., Haller, T., Singh-Manoux, A., Verhoeven, A., Willemsen, G., de Leeuw, F. A., Wagner, H., van Dongen, J., Hertel, J., Budde, K., … van Duijn, C. M. (2018). Circulating metabolites and general cognitive ability and dementia: Evidence from 11 cohort studies. *Alzheimer’s & Dementia*, *14*(6), 707–722. https://doi.org/10.1016/j.jalz.2017.11.012

Van Dyck, C. H., Swanson, C. J., Aisen, P., Bateman, R. J., Chen, C., Gee, M., Kanekiyo, M., Li, D., Reyderman, L., Cohen, S., Froelich, L., Katayama, S., Sabbagh, M., Vellas, B., Watson, D., Dhadda, S., Irizarry, M., Kramer, L. D., & Iwatsubo, T. (2023). Lecanemab in Early Alzheimer’s Disease. *New England Journal of Medicine*, *388*(1), 9–21. https://doi.org/10.1056/NEJMoa2212948

van Rij, J., Wieling, M., Baayen, R. H., & van Rijn, H. (2022). *itsadug: Interpreting Time Series and Autocorrelated Data Using GAMMs.* (Version 2.4.1) [Computer software].

Victor, C. R., Rippon, I., Nelis, S. M., Martyr, A., Litherland, R., Pickett, J., Hart, N., Henley, J., Matthews, F., Clare, L., & Team, I. programme. (2020). Prevalence and determinants of loneliness in people living with dementia: Findings from the IDEAL programme. *International Journal of Geriatric Psychiatry*, *35*(8), 851–858. https://doi.org/10.1002/gps.5305

Wagner, M., Grodstein, F., Proust-Lima, C., & Samieri, C. (2020). Long-Term Trajectories of Body Weight, Diet, and Physical Activity From Midlife Through Late Life and Subsequent Cognitive Decline in Women. *American Journal of Epidemiology*, *189*(4), 305–313. https://doi.org/10.1093/aje/kwz262

Wagner, M., Hedeker, D. R., Wang, T., Muniz-Terrera, G., & Capuano, A. W. (2024). *A comparison of mixed-models for the analysis of non-linear longitudinal data: Application to late-life cognitive trajectories* (arXiv:2402.07806). arXiv. http://arxiv.org/abs/2402.07806

Wagner, M., Wilson, R. S., Leurgans, S. E., Boyle, P. A., Bennett, D. A., Grodstein, F., & Capuano, A. W. (2022). Quantifying longitudinal cognitive resilience to Alzheimer’s disease and other neuropathologies. *Alzheimer’s & Dementia*, *18*(11), 2252–2261. https://doi.org/10.1002/alz.12576

Walker, Z., Jaros, E., Walker, R. W. H., Lee, L., Costa, D. C., Livingston, G., Ince, P. G., Perry, R., McKeith, I., & Katona, C. L. E. (2007). Dementia with Lewy bodies: A comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy. *Journal of Neurology, Neurosurgery & Psychiatry*, *78*(11), 1176–1181. https://doi.org/10.1136/jnnp.2006.110122

Walker, Z., Possin, K. L., Boeve, B. F., & Aarsland, D. (2015). Lewy body dementias. *The Lancet*, *386*(10004), 1683–1697. https://doi.org/10.1016/S0140-6736(15)00462-6

Wang, C. S. M., Pai, M. C., Chen, P. L., Hou, N. T., Chien, P. F., & Huang, Y. C. (2013). Montreal Cognitive Assessment and Mini-Mental State Examination performance in patients with mild-to-moderate dementia with Lewy bodies, Alzheimer's disease, and normal participants in Taiwan. *International psychogeriatrics, 25*(11), 1839-1848.

Ward, A., Caro, J. J., Kelley, H., Eggleston, A., & Molloy, W. (2002). Describing cognitive decline of patients at the mild or moderate stages of Alzheimer's disease using the Standardized MMSE. *International Psychogeriatrics, 14*(3), 249-258.

Wattmo, C., Minthon, L., & Wallin, Å. K. (2016). Mild versus moderate stages of Alzheimer's disease: three-year outcomes in a routine clinical setting of cholinesterase inhibitor therapy. *Alzheimer's Research & Therapy, 8(1)*, 7.

Wechsler, D. (1945). *Wechsler memory scale*. Psychological Corporation.

Wechsler, D. (2012). *Wechsler Adult Intelligence Scale—Fourth Edition* [Dataset].

https://doi.org/10.1037/t15169-000

Wenger, G. C., Davies, R., Shahtahmasebi, S., & Scott, A. (1996). Social Isolation and Loneliness in Old Age: Review and Model Refinement. *Ageing & Society*, *16*(3), 333–358. https://doi.org/10.1017/S0144686X00003457

Wilkosz, P. A., Seltman, H. J., Devlin, B., Weamer, E. A., Lopez, O. L., DeKosky, S. T., & Sweet, R. A. (2010). Trajectories of cognitive decline in Alzheimer's disease. *International Psychogeriatrics*, *22*(2), 281–290. https://doi.org/10.1017/S1041610209991001

Williams-Gray, C. H., Mason, S. L., Evans, J. R., Foltynie, T., Brayne, C., Robbins, T. W., & Barker, R. A. (2013). The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *Journal of Neurology, Neurosurgery & Psychiatry*, *84*(11), 1258–1264. https://doi.org/10.1136/jnnp-2013-305277

Wilson, R. S., Boyle, P. A., James, B. D., Leurgans, S. E., Buchman, A. S., & Bennett, D. A. (2015). Negative Social Interactions and Risk of Mild Cognitive Impairment in Old Age. *Neuropsychology*, *29*(4), 561–570. https://doi.org/10.1037/neu0000154

Wilson, R. S., Krueger, K. R., Arnold, S. E., Schneider, J. A., Kelly, J. F., Barnes, L. L., Tang, Y., & Bennett, D. A. (2007). Loneliness and Risk of Alzheimer Disease. *Archives of General Psychiatry*, *64*(2), 234–240. https://doi.org/10.1001/archpsyc.64.2.234

Wilson, R. S., McCann, J. J., Li, Y., Aggarwal, N. T., Gilley, D. W., & Evans, D. A. (2007). Nursing Home Placement, Day Care Use, and Cognitive Decline in Alzheimer's Disease. *American Journal of Psychiatry*, *164*(6), 910–915. https://doi.org/10.1176/ajp.2007.164.6.910

Wilson, R. S., Wang, T., Yu, L., Bennett, D. A., & Boyle, P. A. (2020). Normative Cognitive Decline in Old Age. *Annals of Neurology*, *87*(6), 816–829. https://doi.org/10.1002/ana.25711

Wilson, R. S., Yu, L., Leurgans, S. E., Bennett, D. A., & Boyle, P. A. (2020). Proportion of cognitive loss attributable to terminal decline. *Neurology*, *94*(1).

https://doi.org/10.1212/WNL.0000000000008671

Wood, S. N. (2017). *Generalized Additive Models: An Introduction with R, Second Edition* (2nd ed.). Chapman and Hall/CRC. https://doi.org/10.1201/9781315370279

Wood, S. N., Goude, Y., & Shaw, S. (2015). Generalized Additive Models for Large Data Sets. *Journal of the Royal Statistical Society Series C: Applied Statistics*, *64*(1), 139–155. https://doi.org/10.1111/rssc.12068

World Health Organization. (2023a). *Dementia*. https://www.who.int/news-room/fact-sheets/detail/dementia

World Health Organization. (2023b, November 15). *WHO launches commission to foster social connection*. World Health Organisation. https://www.who.int/news/item/15-11-2023-who-launches-commission-to-foster-social-connection

World Health Organization. (2024, January 15). *WHO Commission on Social Connection*. World Health Organisation. https://www.who.int/groups/commission-on-social-connection

Wu, Y.-T., Beiser, A. S., Breteler, M. M. B., Fratiglioni, L., Helmer, C., Hendrie, H. C., Honda, H., Ikram, M. A., Langa, K. M., Lobo, A., Matthews, F. E., Ohara, T., Pérès, K., Qiu, C., Seshadri, S., Sjölund, B.-M., Skoog, I., & Brayne, C. (2017). The changing prevalence and incidence of dementia over time—Current evidence. *Nature Reviews Neurology*, *13*(6), 327–339. https://doi.org/10.1038/nrneurol.2017.63

Yao, T., Sweeney, E., Nagorski, J., Shulman, J. M., & Allen, G. I. (2020). Quantifying cognitive resilience in Alzheimer's Disease: The Alzheimer's Disease Cognitive Resilience Score. *PLOS ONE*, *15*(11), e0241707. https://doi.org/10.1371/journal.pone.0241707

Yu, R., Chau, P. H., McGhee, S. M., Cheung, W. L., Chan, K. C., Cheung, S. H., & Woo, J. (2012). Trends in Prevalence and Mortality of Dementia in Elderly Hong Kong Population: Projections, Disease Burden, and Implications for Long-Term Care. *International Journal of Alzheimer's Disease*, *2012*(1), 406852. https://doi.org/10.1155/2012/406852

Zadikoff, C., Fox, S. H., Tang-Wai, D. F., Thomsen, T., & de Bie, R. M. A. (2008). A comparison of the Mini Mental State Exam to the Montreal Cognitive Assessment in identifying cognitive deficits in Parkinson's disease. *Movement Disorders, 23*(2), 297—299. DOI: 10.1002/mds.21837

Zhang, Y., Tatewaki, Y., Liu, Y., Tomita, N., Nagasaka, T., Muranaka, M., Yamamoto, S., Takano, Y., Nakase, T., Mutoh, T., & Taki, Y. (2022). Perceived social isolation is correlated with brain structure and cognitive trajectory in Alzheimer's disease. *GeroScience*, *44*(3), 1563–1574. https://doi.org/10.1007/s11357-022-00584-6

Zhou, Z., Wang, P., & Fang, Y. (2018). Loneliness and the risk of dementia among older Chinese adults: Gender differences. *Aging & Mental Health*, *22*(4), 519–525. https://doi.org/10.1080/13607863.2016.1277976

Appendices

Appendix A

Remaining Scoping Review Search Terms

Table A

Search Terms for Databases Not Already Given in Main Text

Database	Search Terms
Scopus	(TITLE-ABS-KEY ("social* isolat*" OR "lonel*" OR "social connect*") AND TITLE-ABS-KEY ("cognitive decline" OR "cognition" OR "cognitive impairment") AND TITLE-ABS-KEY ("dementia" OR "alzheimer*" OR "AD" OR "FTD") AND NOT TITLE ("parkinson*" OR "down* syndrome" OR "mouse" OR "rat" OR "rodent" OR "animal" OR "dog"))
PsycINFO	1. Social isolation 2. Loneliness 3. Social interaction 4. Cognitive impairment 5. Cognition 6. Dementia 7. Alzheimer’s disease 8. 1 or 2 or 3 9. 4 or 5 10. 6 or 7 11. 8 and 9 and 10
PubMed	(((social* isolat* OR lonel* OR social connect*) AND (cognitive decline OR cognition OR cognitive impairment)) AND (dementia OR alzheimer* OR AD OR FTD)) NOT (parkinson* OR down* syndrome OR mouse OR mice OR rat OR animal OR rodent* OR dog)

Note. The * is used to represent any sequence of characters.

Appendix B

Example Screening Tools for Full Text Articles

Figure B1

A Blank Screening Tool

Article reference:

Inclusion	**Exclusion**
● People with dementia or related disease diagnosis, not including MCI or premorbid condition	● No dementia or related disease diagnosis, including MCI or premorbid condition, or studies focusing on dementia caregivers, or animal model study
● Studies investigating the association/effects of social connection (e.g. loneliness/social isolation) on cognition	● Studies investigating the effects of social connection on quality of life, depression, hearing loss or other condition, without cognition or as risk factor only
● Studies using a validated measure of cognition, e.g. MMSE/MoCA	● No validated measure of cognition
● At least one measure of social connection	● No measure of social connection
● Reports impact/relationship of cognition vs social connection	● Does not report the impact/relationship of cognition vs social connection
● Published, peer-reviewed articles, conference proceedings or editorial pieces printed or translated into English	● Unpublished manuscripts, grey literature, or published articles (etc.) where English translation is not available

Figure B2

An Example of an Eligible Study

Article reference: Abbot & Pachucki (2017). Associations between social network characteristics, cognitive function, and quality of life among residents in a dementia special care unit: A pilot study.

Inclusion	Exclusion
- People with dementia or related disease diagnosis, not including MCI or premorbid condition	- No dementia or related disease diagnosis, including MCI or premorbid condition, or studies focusing on dementia caregivers, or animal model study
- Studies investigating the association/effects of social connection (e.g. loneliness/social isolation) on cognition	- Studies investigating the effects of social connection on quality of life, depression, hearing loss or other condition, without cognition or as risk factor only
- Studies using a validated measure of cognition, e.g. MMSE/MoCA	- No validated measure of cognition
- At least one measure of social connection	- No measure of social connection
- Reports impact/relationship of cognition vs social connection	- Does not report the impact/relationship of cognition vs social connection
- Published, peer-reviewed articles, conference proceedings or editorial pieces printed or translated into English	- Unpublished manuscripts, grey literature, or published articles (etc.) where English translation is not available

Note. Only studies meeting all eligibility criteria were included in the final scoping review

Figure B3

An Example of an Ineligible Study

Article reference: Almeida et al. (2021). Short-Term Impact of Social Distancing Measures During the COVID-19 Pandemic on Cognitive Function and Health Perception of Brazilian Older Adults: A Pre-Post Study

Inclusion	**Exclusion**
● People with dementia or related disease diagnosis, not including MCI or premorbid condition	● No dementia or related disease diagnosis, including MCI or premorbid condition, or studies focusing on dementia caregivers, or animal model study
● Studies investigating the association/effects of social connection (e.g. loneliness/social isolation) on cognition	● Studies investigating the effects of social connection on quality of life, depression, hearing loss or other condition, without cognition or as risk factor only
● Studies using a validated measure of cognition, e.g. MMSE/MoCA	● No validated measure of cognition
● At least one measure of social connection	● No measure of social connection
● Reports impact/relationship of cognition vs social connection	● Does not report the impact/relationship of cognition vs social connection
● Published, peer-reviewed articles, conference proceedings or editorial pieces printed or translated into English	● Unpublished manuscripts, grey literature, or published articles (etc.) where English translation is not available

Note. Once a study met at least one exclusion criterion, it was deemed no longer necessary to continue the screening process and the study was rejected for inclusion in the scoping review.

Appendix C

Scoping Review: Studies Identified for Inclusion

Table C

Studies Identified for Inclusion at the Database Search and at the Citation Search

Database Search			
Author(s)	Year	Title	Journal, volume (issue)
Abbott & Pachucki	2017	Associations between social network characteristics, cognitive function, and quality of life among residents in a dementia special care unit: A pilot study	Dementia, 16(8)
Azevedo, Calandri, Slachevsky, et al.	2021	Impact of social isolation on people with dementia and their family caregivers	Journal of Alzheimer's Disease, 81(2)
Balouch, Rifaat, Chen, et al.	2019	Social networks and loneliness in people with Alzheimer's dementia	International Journal of Geriatric Psychiatry, 34(5)
Barguilla, Fernández-Lebrero, Estragués-Gázquez, et al.	2020	Effects of COVID-19 pandemic confinement in patients with cognitive impairment	Frontiers in Neurology, 11
Borelli, Augustin, de Oliveira, et al.	2021	Neuropsychiatric symptoms in patients with dementia associated with increased psychological distress in caregivers during the COVID-19 pandemic	Journal of Alzheimer's Disease, 80(4)
Chen, Liu, Gan, et al.	2021	The impact of the COVID-19 pandemic and lockdown on mild cognitive impairment, Alzheimer's disease and dementia with Lewy bodies in China: a 1-year follow-up study	Frontiers in Psychiatry, 12
Clare, Martyr, Henderson, et al.	2020	Living alone with mild-to-moderate dementia: Findings from the IDEAL Cohort	Journal of Alzheimer's Disease, 78(3)
Dobrzyn-Matusiak, Marcisz, Bak, et al.	2014	Physical and mental health aspects of elderly in social care in Poland	Clinical Interventions in Aging, 9

Dura-Perez, Goodman-Casanova, Vega-Nuñez, et al.	2022	The impact of COVID-19 confinement on cognition and mental health and technology use among socially vulnerable older people: Retrospective cohort study	Journal of Medical Internet Research, 24(2)
Edwards & Morris	2007	Alone and confused: Community-residing older African Americans with dementia	Dementia, 6(4)
Fritsch, McClendon, Wallendal, et al.	2014	Can a memory club help maintain cognitive function? A pilot investigation	Activities, Adaptation & Aging, 38(1)
Harsányiová & Prokop	2018	Living condition, weight loss and cognitive decline among people with dementia	Nursing Open, 5(3)
Lee & Lee	2020	Home-visiting cognitive intervention for the community-dwelling elderly living alone	Dementia and Neurocognitive Disorders, 19(2)
LeVasseur	2021	Effects of social isolation on a long-term care resident with dementia and depression during the COVID-19 pandemic	Geriatric Nursing, 42(3)
Maggio, De Domenico, Manuli, et al.	2023	Alzheimer cafè: toward bridging the gap between cure and care in patients with dementia	International Journal of Neuroscience, 133(9)
Mohammadian, Rezaee, Kalantar, et al.	2022	Relationship between psychological impacts of COVID-19 and loneliness in patients with dementia: A cross-sectional study from Iran	Frontiers in Psychiatry, 13
Nikmat, Hawthorne & Al-Mashoor	2015	The comparison of quality of life among people with mild dementia in nursing home and home care—a preliminary report	Dementia, 14(1)
Norton, Piercy, Rabins, et al.	2009	Caregiver-recipient closeness and symptom progression in Alzheimer disease. The Cache County dementia progression study	The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 64B(5)
Pereiro, Dosil-Díaz, Mouriz-Corbelle, et al.	2021	Impact of the COVID-19 lockdown on a long-term care facility: The role of social contact	Brain Sciences, 11(8)

Perry, McConnell, Coleman, et al.	2022	Why the cognitive “fountain of youth” may be upstream: Pathways to dementia risk and resilience through social connectedness	Alzheimer's & Dementia, 18(5)
Perry, Roth, Peng, et al.,	2022	Social networks and cognitive reserve: Network structure moderates the association between amygdalar volume and cognitive outcomes	The Journals of Gerontology: Series B. 77(8)
Tondo, Sarasso, Serra, et al.	2021	The impact of the COVID-19 pandemic on the cognition of people with dementia	International Journal of Environmental Research and Public Health, 18(8)
Tsatali, Moraitou, Poptsi, et al.	2021	Are there any cognitive and behavioral changes potentially related to quarantine due to the COVID-19 pandemic in people with mild cognitive impairment and AD dementia? A longitudinal study	Brain Sciences, 11(9)
Victor, Rippon, Nelis, et al.	2020	Prevalence and determinants of loneliness in people living with dementia: Findings from the IDEAL programme	International Journal of Geriatric Psychiatry, 35(8)
Zhang, Tatewaki, Liu, et al.	2022	Perceived social isolation is correlated with brain structure and cognitive trajectory in Alzheimer’s disease	GeroScience, 44(3)

Citation Search

Author(s)	Year	Title	Journal, volume (issue)
Bakker, Van Der Pas, Zwan, et al.	2023	Steeper memory decline after COVID-19 lockdown measures	Alzheimer's Research & Therapy, 15(1)
Bennett, Schneider, Tang, et al.	2006	The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: A longitudinal cohort study	The Lancet Neurology, 5(5)
Clare, Gamble, Martyr, et al.	2024	Living alone with mild-to-moderate dementia over a two-year period: Longitudinal findings from the IDEAL cohort	The American Journal of Geriatric Psychiatry, 32(11)

Defrancesco, Schurr & Hofer	2024	COVID-19 restrictions promoted the newly occurring loneliness in older people – a prospective study in a memory clinic population	Frontiers in Psychiatry, 15
Dyer, Murphy, Lawlor, et al.	2021	Social networks in mild-to-moderate Alzheimer disease: Longitudinal relationships with dementia severity, cognitive function, and adverse events	Aging & Mental Health, 25(10)
Ebly, Hogan & Rockwood	1999	Living alone with dementia	Dementia and Geriatric Cognitive Disorders, 10
Gan, Liu, Wu, et al.	2021	The impact of the COVID-19 pandemic on Alzheimer's disease and other dementias	Frontiers in Psychiatry, 12
Joo, Hahn & Lee	2022	The impact of the COVID-19 pandemic and social distancing on cognition of Alzheimer’s disease patients	Psychiatry Investigation, 19(11)
Laininger, Dietzel, Graessel, et al.	2024	Impact of social network composition on cognitive decline: Digital Dementia Registry Bavaria (digiDEM Bayern)	PLOS ONE, 19(7)
Lampinen, Conradsson, Nyqvist, et al.	2022	Loneliness among very old people with and without dementia: Prevalence and associated factors in a representative sample	European Journal of Ageing, 19(4)
Lao, Young, Ezeh, et al.	2024	Loneliness, cerebrovascular and Alzheimer's disease pathology, and cognition	Alzheimer's & Dementia, 20(10)
Lee, Yim, Cho & Chung	2014	Cognitive function, behavioral problems, and physical function in long-term care insurance beneficiaries with dementia in South Korea: Comparison of home care and institutional care services	Journal of the American Geriatrics Society, 62(8)
Lehmann, Black, Shore, et al.	2010	Living alone with dementia: lack of awareness adds to functional and cognitive vulnerabilities	International Psychogeriatrics, 22(5)
Li, Zhang, Zhang, et al.	2022	Relationship between frailty and cognitive decline in Chinese older patients with Alzheimer's	Geriatric Nursing, 43

		disease: The mediating role of social contact	
Manca, De Marco, Colston, et al.	2022	The impact of social isolation due to COVID-19 on symptom progression in people with dementia: Findings of the SOLITUDE study	Frontiers in Psychiatry, 13
Missotten, Thomas, Squelard, et al.	2009	Impact of place of residence on relationship between quality of life and cognitive decline in dementia	Alzheimer Disease & Associated Disorders, 23(4)
Perach, Read, Hicks, et al.	2023	Predictors of loneliness during the Covid-19 pandemic in people with dementia and their carers in England: findings from the DETERMIND-C19 study	Aging & Mental Health, 27(3)
Perry, McConnell, Peng	2022	Social networks and cognitive function: An evaluation of social bridging and bonding mechanisms	The Gerontologist, 62(2)
Sánchez-Valdeón, Bello-Corral, Mayo-Iscar, et al.	2023	Impact of discontinuing non-pharmacological interventions on cognitive impairment in dementia patients by COVID-19 lockdown. A pilot observational, longitudinal, retrospective study carried out in an adult day center in Spain during the COVID-19 pandemic	Frontiers in Medicine, 10
Te Boekhorst, Depla, De Lange, et al.	2009	The effects of group living homes on older people with dementia: A comparison with traditional nursing home care	International Journal of Geriatric Psychiatry, 24(9)
Tsatali, Moraitou, Boza, et al.	2023	Cognition and functionality were not affected due to the COVID-19 pandemic in people with mild cognitive impairment and AD dementia attending digital non-pharmacologic interventions	Brain Sciences, 13(7)
Tuokko, MacCourt & Heath	1999	Home alone with dementia	Aging & Mental Health, 3(1)

Appendix D
Study 1: Model Equations for Multilevel Linear Regressions

Equation D1 represents cognition, as measured by MMSE, as a function of the interaction between diagnosis duration and marital status plus control variables, with terms for random intercepts and random slopes, as well as variance at the level of patient and observation.

Equation D2 represents cognition, as measured by MMSE, as a function of the interaction between diagnosis duration and accommodation status plus control variables, with terms for random intercepts and random slopes, as well as variance at the level of patient and observation.

Equation D3 represents cognition, as measured by MMSE, as a function of the interaction between diagnosis duration and living status plus control variables, with terms for random intercepts and random slopes, as well as variance at the level of patient and observation.

Equation D4 represents cognition, as measured by MoCA, as a function of the interaction between diagnosis duration and marital status plus control variables, with terms for random intercepts and random slopes, as well as variance at the level of patient and observation.

Equation D5 represents cognition, as measured by MoCA, as a function of the interaction between diagnosis duration and accommodation status plus control variables, with terms for random intercepts and random slopes, as well as variance at the level of patient and observation.

Equation D6 represents cognition, as measured by MoCA, as a function of the interaction between diagnosis duration and living status plus control variables, with terms for random intercepts and random slopes, as well as variance at the level of patient and observation.

Equation D7 represents the random effect model structures application to all random slope random intercept models.

$$Y^{\text{Cognition(MMSE)}}{}_{jt} = \beta_0 + \beta_{0j} + (\beta_1 + \beta_{1j})X1^{\text{Diagnosis duration}}{}_{jt} * X2^{\text{SI proxy(marital status)}}{}_{j} + X3^{\text{Age}}{}_{j} + X4^{\text{Ethnicity}}{}_{j} + X5^{\text{Sex}}{}_{j} + X6^{\text{Diagnosis}}{}_{j} + \varepsilon_{jt} \quad \text{(D1)}$$

$$Y^{Cognition(MMSE)}{}_{jt} = \beta_0 + \beta_{0j} + (\beta_1 + \beta_{1j})X1^{Diagnosis\ duration}{}_{jt} * X2^{SI\ proxy(accommodation\ status)}{}_{j} + X3^{Age}{}_{j} + X4^{Ethnicity}{}_{j} + X5^{Sex}{}_{j} + X6^{Diagnosis}{}_{j} + \varepsilon_{jt} \tag{D2}$$

$$Y^{Cognition(MMSE)}{}_{jt} = \beta_0 + \beta_{0j} + (\beta_1 + \beta_{1j})X1^{Diagnosis\ duration}{}_{jt} * X2^{SI\ proxy(living\ status)}{}_{j} + X3^{Age}{}_{j} + X4^{Ethnicity}{}_{j} + X5^{Sex}{}_{j} + X6^{Diagnosis}{}_{j} + \varepsilon_{jt} \tag{D3}$$

$$Y^{Cognition(MoCA)}{}_{jt} = \beta_0 + \beta_{0j} + (\beta_1 + \beta_{1j})X1^{Diagnosis\ duration}{}_{jt} * X2^{SI\ proxy(marital\ status)}{}_{j} + X3^{Age}{}_{j} + X4^{Ethnicity}{}_{j} + X5^{Sex}{}_{j} + X6^{Diagnosis}{}_{j} + \varepsilon_{jt} \tag{D4}$$

$$Y^{Cognition(MoCA)}{}_{jt} = \beta_0 + \beta_{0j} + (\beta_1 + \beta_{1j})X1^{Diagnosis\ duration}{}_{jt} * X2^{SI\ proxy(accommodation\ status)}{}_{j} + X3^{Age}{}_{j} + X4^{Ethnicity}{}_{j} + X5^{Sex}{}_{j} + X6^{Diagnosis}{}_{j} + \varepsilon_{jt} \tag{D5}$$

$$Y^{Cognition(MoCA)}{}_{jt} = \beta_0 + \beta_{0j} + (\beta_1 + \beta_{1j})X1^{Diagnosis\ duration}{}_{jt} * X2^{SI\ proxy(living\ status)}{}_{j} + X3^{Age}{}_{j} + X4^{Ethnicity}{}_{j} + X5^{Sex}{}_{j} + X6^{Diagnosis}{}_{j} + \varepsilon_{jt} \tag{D6}$$

$$\begin{gathered} \beta_{0j} \sim N(0, \sigma^2{}_{Jint.}) \\ \beta_{1j} \sim N(0, \sigma^2{}_{Jslope}) \\ \varepsilon_{jt} \sim N(0, \sigma^2{}_{E}) \end{gathered} \tag{D7}$$

Appendix E
Study 1: Unconstrained Model Estimates – Marital Status

Factor	Estimate	Standard Error	df	t-value	p-value
MMSE					
Intercept*†	**21.97**	**0.12**	**4036**	**190.20**	**< 0.001**
Diagnosis duration**	**-1.08**	**0.05**	**1247**	**-20.07**	**< 0.001**
Separated / Divorced†	**1.40**	**0.39**	**4143**	**3.57**	**< 0.001**
Single‡	-0.18	0.35	4187	-0.51	0.608
Widowed‡	**-0.50**	**0.18**	**4085**	**-2.82**	**0.005**
Diagnosis duration x Separated	0.21	0.18	1345	1.16	0.245
Diagnosis duration x Single	**0.43**	**0.16**	**1536**	**2.59**	**0.001**
Diagnosis duration x Widowed	0.17	0.09	1399	1.32	0.188
MoCA					
Intercept*†	**19.04**	**0.16**	**2125**	**121.97**	**< 0.001**
Diagnosis duration**	**-0.58**	**0.07**	**423**	**-8.81**	**< 0.001**
Separated / Divorced†	0.17	0.46	2194	0.36	0.719

Single[‡]	**-1.37**	**0.63**	**2090**	**-2.17**	**0.030**
Widowed[‡]	**-1.05**	**0.25**	**2159**	**-4.12**	**< 0.001**
Diagnosis duration x Separated	0.23	0.21	482	1.09	0.275
Diagnosis duration x Single	0.30	0.30	612	1.00	0.317
Diagnosis duration x Widowed	-0.03	0.12	475	-0.24	0.815

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD patients with partners. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

** The diagnosis duration represents the change in estimated coefficient given a one unit increase in time for the reference group. Estimates for other interaction effects, such as diagnosis duration x single, are relative to the diagnosis duration for the reference group.

[†] Considered to be a non-socially isolated category

[‡] Considered to be a socially isolated category

Appendix F
Study 1: Unconstrained Model Estimates – Accommodation Status

Factor	Estimate	Standard Error	df	t-value	p-value
MMSE					
Intercept*†	**23.21**	**0.15**	**1589**	**155.34**	**< 0.001**
Diagnosis duration**	**-0.72**	**0.07**	**536**	**-10.99**	**< 0.001**
Supported accommodation‡	**-1.76**	**0.25**	**1539**	**-6.99**	**< 0.001**
Clinical‡	**-2.61**	**1.11**	**1659**	**-2.35**	**0.019**
No fixed abode‡	0.48	1.39	1682	0.34	0.731
Diagnosis duration x supported accommodation	-0.04	0.11	528	-0.33	0.744
Diagnosis duration x clinical	-0.53	0.53	666	-1.01	0.313
Diagnosis duration x no fixed abode	-0.82	0.53	391	-1.55	0.121
MoCA					
Intercept*†	**18.03**	**0.12**	**2387**	**145.73**	**< 0.001**

Diagnosis duration**	**-0.61**	**0.06**	**437**	**-10.72**	**< 0.001**
Supported accommodation‡	**-1.95**	**0.27**	**2377**	**-7.20**	**< 0.001**
Clinical‡	**2.54**	**1.25**	**2346**	**-2.03**	**0.043**
No fixed abode‡	-0.53	1.14	2417	-0.47	0.639
Incarceration‡	**-11.58**	**5.42**	**2748**	**-2.14**	**0.033**
Diagnosis duration x supported accommodation	-0.09	0.12	492	-0.71	0.478
Diagnosis duration x clinical	0.61	0.46	337	1.32	0.189
Diagnosis duration x no fixed abode	-0.65	0.55	628	-1.19	0.235
Diagnosis duration x incarceration	-9.81	6.33	2491	-1.55	0.122

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD patients with living in mainstream housing. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

** The diagnosis duration represents the change in estimated coefficient given a one unit increase in time for the reference group. Estimates for other interaction effects, such as diagnosis duration x supported accommodation, are relative to the diagnosis duration for the reference group.

† Considered to be a non-socially isolated category

‡ Considered to be a socially isolated category

Appendix G

Study 1: Unconstrained Model Estimates – Living Status

Factor	Estimate	Standard Error	df	t-value	p-value
MMSE					
Intercept*†	**23.73**	**0.23**	**1161**	**104.80**	**< 0.001**
Diagnosis duration**	**-0.78**	**0.09**	**412**	**-8.49**	**< 0.001**
Alone‡	-0.23	0.41	1229	-0.55	0.579
Supported accommodation‡	**-2.28**	**0.30**	**1164**	**-7.50**	**< 0.001**
Clinical‡	**-3.13**	**1.12**	**1274**	**-2.78**	**0.006**
No fixed abode‡	-0.04	1.41	1295	-0.03	.977
Diagnosis duration x alone	0.19	0.18	452	1.06	0.289
Diagnosis duration x supported accommodation	0.02	0.13	434	0.16	0.867
Diagnosis duration x clinical	-0.47	0.53	581	-0.89	0.374
Diagnosis duration x no fixed abode	-0.77	0.53	345	-1.44	0.152

MoCA					
Intercept*†	**18.82**	**0.19**	**1607**	**96.76**	**< 0.001**
Diagnosis duration**	**-0.63**	**0.08**	**289**	**-7.57**	**< 0.001**
Alone‡	**-0.72**	**0.34**	**1623**	**-2.14**	**0.033**
Supported accommodation‡	**-2.74**	**0.31**	**1605**	**-8.92**	**< 0.001**
Clinical‡	**-3.32**	**1.24**	**1583**	**-2.68**	**0.007**
No fixed abode‡	-1.32	1.13	1633	-1.17	0.242
Incarceration‡	**-12.36**	**5.33**	**1860**	**-2.32**	**0.021**
Diagnosis duration x alone	0.08	0.16	359	0.48	0.631
Diagnosis duration x supported accommodation	-0.07	0.14	331	-0.48	0.630
Diagnosis duration x clinical	0.63	0.46	238	1.37	0.173
Diagnosis duration x no fixed abode	-0.64	0.55	443	-1.18	0.239
Diagnosis x incarceration	-9.79	6.25	1668	-1.57	0.117

* The Intercept represents the estimated coefficients, when time is equal to zero, for the reference group, female, White, AD, patients assumed to be cohabiting. Estimates for other main exposures, demographic factors, and diagnosis factors, are relative to the reference group.

** The diagnosis duration represents the change in estimated coefficient given a one unit increase in time for the reference group. Estimates for other interaction effects, such as diagnosis duration x alone, are relative to the diagnosis duration for the reference group.

[†] Considered to be a non-socially isolated category

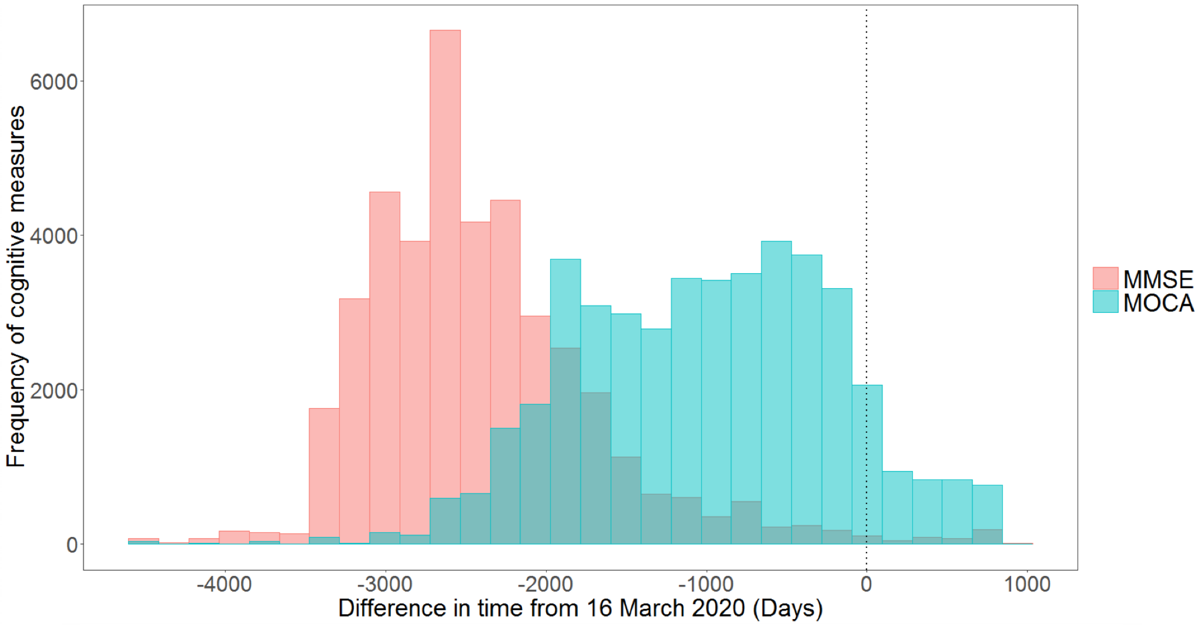
[‡] Considered to be a socially isolated category

Appendix H

Frequency of MMSE and MoCA Use Across Cohort

Figure H

Frequency of MMSE and MoCA Use Across Cohort



Note. Dates are in relation to the first COVID-19 related lockdown in March 2020

Appendix I

Myers, J. A. C., Stafford, T., Koychev, I., Perneczky, R., Bandmann, O., Vaci, N. (2025). Loneliness, social isolation and effects on cognitive decline in patients with dementia: A retrospective cohort study suing natural language processing. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 17*(3). e70149

Received: 6 February 2025 | Revised: 28 April 2025 | Accepted: 29 June 2025

DOI: 10.1002/dad2.70149

Alzheimer's & Dementia
Diagnosis, Assessment
& Disease Monitoring

RESEARCH ARTICLE

Loneliness, social isolation, and effects on cognitive decline in patients with dementia: A retrospective cohort study using natural language processing

James A. C. Myers[1,2,3,4] | **Tom Stafford**[1,2] | **Ivan Koychev**[3,5] | **Robert Perneczky**[2,6,7,8,9,10] | **Oliver Bandmann**[2,6] | **Nemanja Vaci**[1,2,3,4]

[1] School of Psychology, University of Sheffield, ICOSS, Sheffield, UK

[2] Division of Neuroscience, University of Sheffield, Western Bank, Sheffield, UK

[3] Oxford Health NHS Foundation Trust, Warneford Hospital, Headington, UK

[4] Doncaster and South Humber NHS Foundation Trust, Doncaster, UK

[5] Department of Psychiatry, Warneford Hospital, University of Oxford, Headington, UK

[6] School of Medicine and Population Health, University of Sheffield, Sheffield, UK

[7] Department of Psychiatry and Psychotherapy, LMU Hospital, Munich, Germany

[8] German Center for Neurodegenerative Diseases (DZNE), Munich, Germany

[9] Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

[10] School of Public Health, Imperial College London, Ageing Epidemiology Research Unit (AGE), London, UK

Correspondence
Nemanja Vaci, School of Psychology, University of Sheffield, ICOSS, 219 Portobello, Sheffield S1 4DP, UK.
Email: n.vaci@sheffield.ac.uk

Funding information
Akrivia Health; MRC, NIHR Oxford Health Biomedical Research Facility; Novo Nordisk; NIHR Oxford Biomedical Research Centre, Grant/Award Number: NIHR203316

Abstract

INTRODUCTION: The study aimed to compare cognitive trajectories between patients with reports of social isolation and loneliness and those without.

METHODS: Reports of social isolation, loneliness, and Montreal Cognitive Assessment (MoCA) scores were extracted from dementia patients' medical records using natural language processing models and analyzed using mixed-effects models.

RESULTS: Lonely patients ($n = 382$), compared to controls ($n = 3912$), showed an average MoCA score that was 0.83 points lower at diagnosis ($P = 0.008$) and throughout the disease. Socially isolated patients ($n = 523$) experienced a 0.21 MoCA point per year faster rate of cognitive decline in the 6 months before diagnosis ($P = 0.029$), but were comparable to controls before this period. This led to average MoCA scores that were 0.69 MoCA points lower at diagnosis ($P = 0.011$).

DISCUSSION: Lower cognitive levels in lonely and socially isolated patients suggest that these factors may contribute to dementia progression.

KEYWORDS
cognitive decline, electronic health records, loneliness, natural language processing, social isolation

Highlights

- Developed Natural Language Processing model to detect social isolation and loneliness in electronic health records.
- Patients with loneliness reports have lower Montreal Cognitive Assessment (MoCA) scores than other patients.
- Social isolation was related to the faster decline in MoCA scores before diagnosis.
- Social isolation and loneliness are promising targets for slowing cognitive decline.

1 | INTRODUCTION

Social isolation (SI) and loneliness are recognized as priority public health problems,[1] showing impact on physical and mental health,[2–7] with effects on mortality comparable to smoking and obesity.[8] Population attributable fraction, a measure that combines relative risk and prevalence of social isolation in a population, estimates that low social contact in older people explains up to 4% of the risk for dementia development.[9–12] While much of the research has focused on SI and loneliness as risk factors for dementia,[13] these factors may also manifest as symptoms of the disease itself,[14] particularly in its early stages. In this study, we examine how SI and loneliness, when reported in the presymptomatic or symptomatic stage of dementia, influence the cognition of patients and the progression of the disease.

SI and loneliness are related but distinct concepts. SI is operationalized as an objective lack of social and support networks, while loneliness is seen as a negative, subjective feeling resulting from the discrepancy between desired and actualized social connections and closeness to other people.[1] Participation in wider social network structures is associated with higher global cognitive function and moderates the association between cognitive functioning and amygdala volume, an indicator of neuropathological progression in Alzheimer's disease (AD), in cognitively normal people as well as patients with mild cognitive impairment (MCI) and early-stage AD.[15,16] These findings support the idea that SI influences cognitive reserve by moderating cognitive function despite indicators of AD neuropathology.[17,18] Feelings of loneliness have been shown to predict dementia onset[19] and are associated with higher amyloid burden[7] in cognitively normal people, as well as with higher rates of cognitive decline[20,21] in patients with MCI, but not in participants with the diagnosis of AD.[22,23]

Despite these studies, findings for the effect of SI and loneliness on cognitive trajectories are mixed.[24,25] The main challenge in reliably estimating the impact of SI and loneliness symptoms on the cognitive function of dementia patients lies in the need for large-scale longitudinal data,[26] which is essential to capture the progressive nature of the disease.

In this study, we used electronic health records (EHRs) to investigate the effect of SI and loneliness reports on the cognitive trajectories of patients with a dementia diagnosis. Using textual records of patient–care provider interaction, we identify documents that discuss patients' reports about SI and loneliness, and combine them with longitudinal measures of cognitive functionality. Using data from $>$ 4800 patients, we estimate the cognitive trajectories of patients with reports of social isolation and loneliness and compare them to trajectories of patients without such reports, while testing cognitive changes after the first social isolation or loneliness reports. Given previous findings on the effect of SI and loneliness on the risk of dementia,[9,12,20] we expected that perceived SI and loneliness would be associated with more severe cognitive decline throughout the disease.

RESEARCH IN CONTEXT

1. **Systematic review**: We searched Web of Science and PubMed on June 4, 2024, for titles with terms (lonel* OR 'social* isolat*') AND (cognit*) AND (dementia OR 'Alzheimer* disease') and publication reference lists. Search findings included studies on the risk factors for the development of dementia, with some studies investigating the effects of loneliness in mild cognitive impairment and early stages of Alzheimer's disease. These are cited in the text.
2. **Interpretation**: Results illustrate different impacts of loneliness and social isolation on patients' cognition; patients with loneliness reports have lower cognitive trajectories across the disease, while patients with social isolation reports start declining faster several months before the diagnosis.
3. **Future directions**: The article proposes different mechanisms of loneliness and social isolation and their effects on the cognitive functionality of dementia patients. The findings of loneliness and social isolation, as factors that influence disease progression, provide clinicians with indications of an increased rate of cognitive decline, especially before diagnosis in the case of socially isolated patients.

2 | METHODS

2.1 | Study design

The study followed a retrospective cohort design defined through the extraction of information from EHRs, collected by Oxford Health National Health Service (NHS) Foundation Trust in the UK. The data are accessible through the UK-CRIS system, maintained by Akrivia Health (https://akriviahealth.com/). The system allows access to structured information, for example, demographic information and diagnosis codes, as well as unstructured textual information, such as clinical records. These documents collect free-text information on the history of mental disorders under treatment, relevant cognitive assessments, and any other clinically relevant discussions between services and support that went on throughout the treatment.

2.2 | Cohort information

Our cohort included data from all patients with a diagnosis of AD or other forms of dementia (International Classification of Diseases [ICD] codes: F00–F00.9, F01, F02, F03, G30, but excluding F06.7 as MCI is rarely followed up in a memory clinic). The full cohort included 34,469 patients who collectively contributed 6,388,715 medical documents from March 6, 2008, to June 25, 2022. To use the information that resides in rich clinical texts, we developed natural language processing (NLP) models that extracted information on cognitive health assessments in dementia and reports of loneliness and SI made by patients, caregivers, and clinical staff.

2.3 | Cognitive outcomes

The main analysis used the Montreal Cognitive Assessment (MoCA)[27] measure, while in supporting information we report analysis using Mini-Mental State Examination (MMSE)[28] scores. Both measures are widely used tools for assessing cognitive function, particularly in patients with dementia. MoCA detects mild cognitive impairments and early-stage dementia through its heavier emphasis on frontal and parietal function,[29] while MMSE, even though not as sensitive as MoCA, captures moderate to severe cognitive impairment. Both measures are frequently used in clinical practice and research.[30] MoCA scores below the cut-off point of 26 points are taken as suggestive of MCI, below 17 as suggestive of moderate impairment, and under 10 as suggestive of severe cognitive impairment. The minimum clinically important difference, the smallest change in the outcome that patients would find significant, is reported to be between 0.01 and 2 points, depending on the severity of the disease.[31]

2.4 | Procedure

We used structured and unstructured data from EHRs in this study. The unstructured data covered all textual records for the defined patient cohort, while structured data included information about the sex, ethnicity, and date of birth of patients, their marital and accommodation status, and ICD-10 codes for dementia and depression diagnosis (F32.0 to F34.1). To extract information about the cognition of patients, we used the previously published NLP model[32] (for previous work on methodological considerations and description of the mental health EHR data, see Kormilitzin et al.,[33] Senior et al.,[34] Gooddday et al.,[35] Li et al.,[36] and Vaci et al.[37]).

2.5 | NLP model for reports of SI and loneliness

A novel NLP model was developed for the SI and loneliness reports. The model was implemented in Python and processed textual records for reports of SI and loneliness in two stages: pattern matching and a classification stage. In the pattern matching stage, we used a statistical model for word processing from the Spacy library to identify words that describe SI and loneliness. This allowed us to find all documents, including expressions such as “loneliness,” “social isolation,” “living alone,” and so on. In the classification stage, we used sentence transformer models from Huggingface's Spacy-Setfit library to process and classify sentences with SI and loneliness mentions. Sentence transformers[38] are types of neural network models that produce numerical representations of sentence- and paragraph-level linguistic content. This vector space encodes semantic relationships, allowing us to identify and categorize semantically similar sentences. We trained sentence transformers to classify sentences with reports of SI and loneliness into four different categories: (1) SI, (2) loneliness, (3) non-informative isolation, and (4) non-informative sentences.

TABLE 1 Example of sentences that express the social isolation and loneliness of patients and used categorization when training the natural language processing model.

Sentence	Categorization
“Is very lonely—lost husband and more recently best friend.”	Loneliness
“Lonely and unfriended.”	Loneliness
“Reports feeling lonely but is not trying to change this.”	Loneliness
“Patient would wish to go out as remains isolated at home.”	Social isolation
“Social isolation, lives in 2nd floor flat, can manage stairs.”	Social isolation
“Due to XXX impairments and symptoms, she has gradually isolated from others."	Social isolation
“On the morning of the event was feeling isolated.”	Non-informative isolation
“Alone in the tv lounge as wanting some peace.”	Non-informative isolation
“has suffered an isolated fall.”	Non-informative isolation
“XXX will be discharged back to your care.”	Non-informative sentence
“Complained feeling dizzy.”	Non-informative sentence
“Had a lovely day.”	Non-informative sentence

Reports that mention lack of social contact, living alone, and being away from family, or that mention barriers in receiving support from family, were used as an indication of social isolation.[3] Loneliness was operationalized as consisting of reports on emotional aspects of feeling lonely and suffering due to the lack of social connections.[39] The non-informative isolation category included reports of temporary and physical isolation (e.g., “isolated fall” or “isolating in the TV room”), while the non-informative sentences category covered all incorrectly included sentences from the pattern matching stage forwarded to the sentence classification stage (see Table 1 for examples of sentences and NLP categories).

The full model was trained on a randomly selected subset of 11,000 medical documents from the corpus. The terms for the pattern matching stage were derived from a combination of the UCLA Loneliness Scale[40] and linguistic phrases observed in the training set, specifically those referring to reports of SI and loneliness. Sentences identified by the pattern matching in the training data were then used to train the classifiers.

2.6 | NLP accuracy

To evaluate the model's performance in identifying reports of SI and loneliness, we conducted a manual annotation process using an unseen sample of 5000 documents. The annotation was performed independently by the first and last authors. In instances of disagreement, the annotations were discussed collaboratively, and a consensus was reached to ensure consistent labeling.

The annotated data served as the ground truth for evaluating the model's classification performance. Standard classifier performance metrics were used, including sensitivity, specificity, and balanced or F1 accuracy. Across four different categories, the NLP model achieved an average F1 accuracy of 0.74, reaching 0.83 accuracy for SI sentences (sensitivity: 0.73 and specificity: 0.93) and 0.91 accuracy for sentences reporting loneliness (sensitivity: 0.88 and specificity: 0.95). Full Python and R code, detailed measure of model performance, and sensitivity analysis are reported in Supplemental Materials Folder.

Once trained, the NLP models were deployed on the data from the full cohort, effectively processing $>$ 6 million medical records. To focus on the symptomatic interpretation of SI and loneliness, we only considered reports that were made 5 years before or after the initial dementia diagnosis. Our data indicate that most of these reports occur several months before and at the time of diagnosis, and that there was a substantial increase in both types of reports during the first year of the COVID-19 pandemic.

2.7 | Participants

The final data used in this study combined patients with measures of cognitive performance, as measured by MoCA scores, clinical diagnosis information, and loneliness or SI reports, consisting of 4817 patients with 9298 observations. The patient flow chart in Figure 1 outlines the procedure used to derive the sample. Our procedure identified 382 patients (851 observations) with loneliness reports and 523 patients (1185 observations) with SI reports compared to the 3912 patients without such mentions, which were defined as a control group in our study (see Table 2 for a split between the groups on main variables). As the retrospective cohort data were collated from EHRs, diversity, equality, and inclusion could not be directly addressed during data collation.

2.8 | Statistical analysis

The data were analyzed using a combination of generalized additive mixed-effect modeling (GAMMs)[41] and linear mixed-effect modeling (LME).[42] GAMM is a non-parametric data-driven method that estimates a non-linear relationship between predictors of interest and outcome variables. Using this model, we estimated and visualized average changes in cognitive function throughout the disease and tested how trajectories differed between patients who reported loneliness and SI compared to the control group of patients without such reports in their EHRs. To investigate the parametric effects of individual predictors on the slope of cognitive decline, we used LME.

The primary outcome in the analysis was cognitive function, as measured by MoCA and MMSE tests, while we tested the effect of SI and loneliness, and controlled for the effects of age, type of dementia, sex, marital status, accommodation status, and whether patients had a diagnosis of depression in their medical history. In the case of missing information for marital and accommodation status, these patients were included in the analysis under "Missing" categories, while models without these predictors or cases with missing data are reported in the sensitivity analysis. The random by-patient intercept effects were adjusted in all models, which allowed intercepts to vary for each patient.[32] The adjustment of the random-effect structure allowed us to model repeated measures of cognitive scores and guarded us against overfitting of the model. Specifically, the random structure in GAMM and LME models enables us to weigh intra-individual changes over time and inter-individual differences, allowing us to estimate cognitive trajectories over time. Patients with multiple observations provide more information about the rate and direction of change, while those with fewer observations provide more information about the variability at the group level. In addition to modeling how SI and loneliness are associated with the cognitive ability of patients throughout their disease, we also explored the rate of cognitive change after patients' first reports of loneliness and SI.

The sensitivity analysis included looking at reports of SI and loneliness in shorter time windows around the diagnosis date, different methods for dealing with missing observations in predictor variables, and MMSE score analysis. We also report analysis focusing on patients with both sets of reports, SI and loneliness, in their EHRs. Compared to the other three groups, these patients are seen four times more frequently by the health and social services but have fewer measures of cognition, potentially indicating a more complex disease phenotype.

2.9 | Ethical approvals

We state that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Declaration of Helsinki of 1975, as revised in 2008. The study was approved by the local UK-CRIS oversight committees and the University of Sheffield Ethics Application Review Board (ID: 045869). Individual patient consent was not required for the use of anonymized data. The R and Python code used to analyze the data and develop NLP models is reported in Supporting Materials.

3 | RESULTS

The full cohort consisted of 4817 dementia patients with a mean age of 80.79 years, of whom 57% ($n = 2765$) were female and 26% ($n = 1{,}240$)

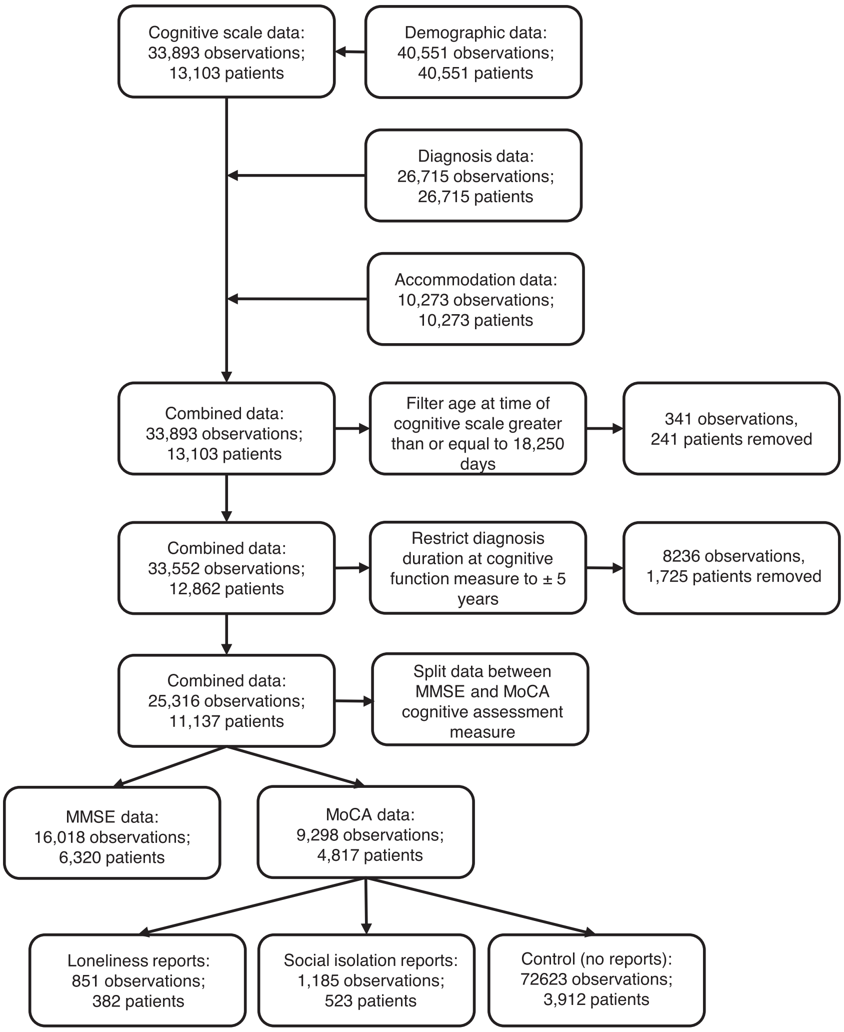


FIGURE 1 Patient flow chart illustrating sample derivation. MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

were married. Of these, 8% ($n = 382$) reported loneliness, 11% ($n = 523$) reported social isolation, and 81% ($n = 3912$) had no reports of either. Patients with loneliness were more likely to be women (75%) and widowed (26%), while those with SI were older (mean age 81.71 years). Controls had the highest percentage of married individuals (27%) and fewer cases of depression (4%). Table 2 reports full descriptive statistics for all variables of interest.

3.1 | The effect of loneliness and SI on cognitive trajectories

The results show a significant difference in average MoCA scores between patients with loneliness and SI reports in their EHRs, and those without such reports. In the case of patients with loneliness reports, MoCA scores (see Figure 2A) were lower throughout the disease, as illustrated by Figure 2C. When estimated using LME, we see that the scores of patients who reported being lonely are lower by 0.83 MoCA points at the time of dementia diagnosis (see Table 3).

Patients with SI reports have comparable MoCA scores to control patients before being diagnosed. Approximately 6 months before diagnosis, the slope of MoCA changes for SI patients, becomes more severe, and they start declining faster than control patients (see Figure 2B and 2D). This pattern is illustrated in the parametric model in which the reference group of patients with no loneliness or SI reports shows an average decline of –0.38 MoCA points per year ($P < 0.001$), whereas the significant interaction between SI reports and slope of diagnosis duration shows SI patients decline faster by a further –0.21 MoCA points per year relative to controls ($P = 0.029$). The interaction

TABLE 2 Descriptive statistics for variables of interest (mean and SD for quantitative variables and percentage and number of cases for categorical variables).

Variables	Whole cohort	Controls (no reports)	Patients with loneliness reports	Patients with social isolation reports
Number of cases	4817	3912	382	523
MoCA score	18.15 (5.86)	18.33 (5.86)	17.66 (5.60)	17.27 (5.92)
Age	80.68 (7.20)	80.84 (7.08)	79.04 (6.86)	81.71 (7.91)
Sex (% women)	2765 (57%)	2162 (55%)	288 (75%)	315 (60%)
Number of observations per patient	1.93 (1.37)	1.85 (1.21)	2.26 (1.70)	2.22 (1.78)
Number of cases with:				
1 observation	2931	2522	183	226
2 observations	952	736	93	123
3 observations	384	282	33	69
4 and more	550	372	73	105
Ethnicity:				
White	2610 (54%)	2075 (53%)	221 (57%)	314 (60%)
Other	59 (1.2%)	45 (1.1%)	7 (1.5%)	7 (1.3%)
Missing	2148 (45%)	1792 (45%)	154 (40%)	202 (38%)
Marital status:				
Married	1240 (26%)	1065 (27%)	48 (12%)	127 (24%)
Divorced	145 (3.0%)	104 (2.7%)	19 (5.0%)	22 (4.2%)
Single	78 (1.6%)	60 (1.5%)	7 (1.8%)	11 (2.1%)
Widowed	735 (15%)	542 (13%)	100 (26%)	93 (17%)
Missing	2619 (54%)	2141 (54%)	208 (54%)	270 (51%)
Diagnosis type:				
AD	2266 (47%)	1864 (47%)	166 (43%)	236 (45%)
Lewy body	86 (1.8%)	67 (1.7%)	10 (2.6%)	9 (1.7%)
Other	153 (3.2%)	138 (3.5%)	6 (1.6%)	9 (1.7%)
Unspecified	1591 (33%)	1260 (32%)	143 (37%)	188 (35%)
Vascular	388 (8.1%)	314 (8.0%)	25 (6.5%)	49 (9.4%)
Missing	333 (6.9%)	269 (6.9%)	32 (8.4%)	32 (6.1%)
Accommodation:				
Mainstream housing	1765 (37%)	1364 (34%)	171 (44%)	230 (43%)
Supported accommodation	461 (10%)	302 (7%)	70 (18%)	89 (17%)
Missing	2550 (53%)	2219 (56%)	137 (35%)	194 (37%)
Depression:				
Mild	75 (1.6%)	57 (1.5%)	7 (1.8%)	11 (2.1%)
Moderate	147 (3.1%)	81 (2.1%)	22 (5%)	44 (8.4%)
Severe	32 (0.66%)	15 (0.38%)	7 (1.8%)	10 (1.9%)
Severe with psychotic episode	40 (0.83%)	15 (0.38%)	5 (1.3%)	20 (3.8%)
Other	40 (0.83%)	23 (0.59%)	5 (1.3%)	12 (2.3%)
Without depression	4483 (93%)	3721 (95%)	336 (87%)	426 (81%)

Note: Categories with a less than five observations were either excluded from the analysis or grouped with similar concepts (e.g., F33.0, F33.1, F33.2 placed in the "Other" category); ICD-10 codes for depression were used as ever-depressed variable.
Abbreviations: AD, Alzheimer's disease; ICD, International Classification of Diseases; MoCA, Montreal Cognitive Assessment; SD, standard deviation.

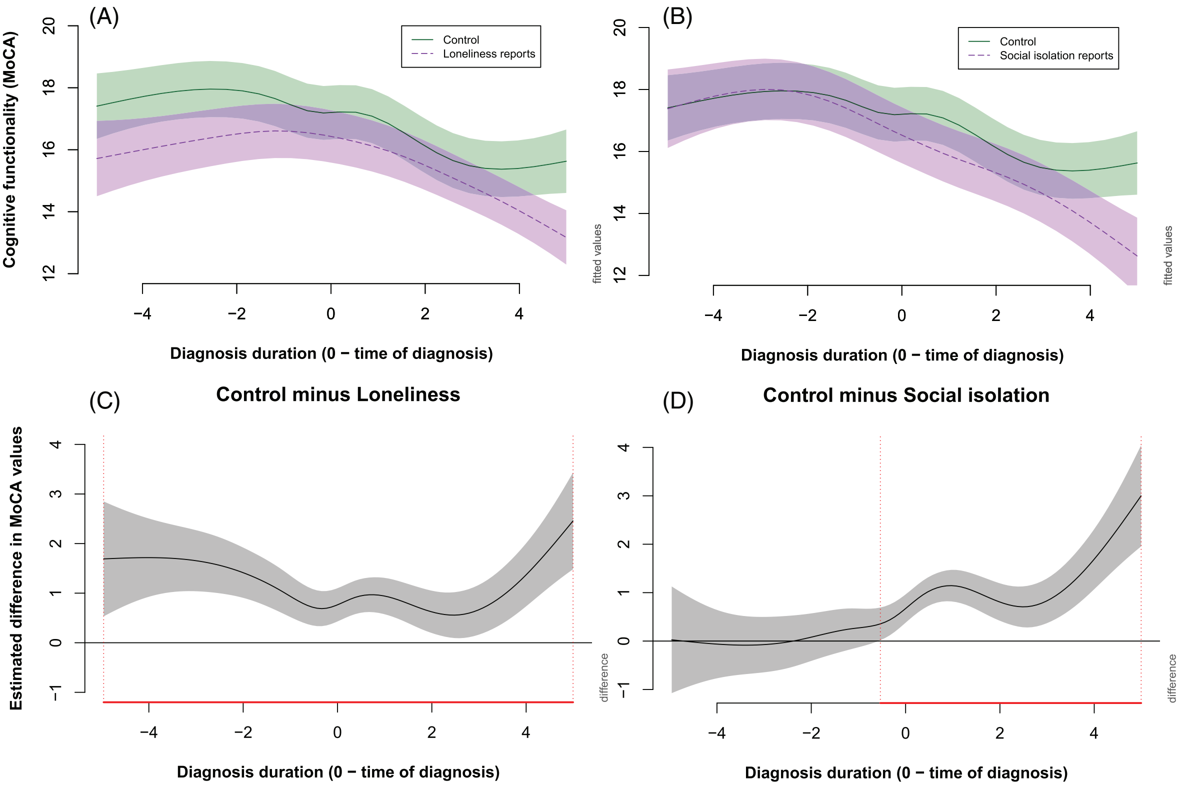


FIGURE 2 The effect of loneliness and social isolation on the non-linear changes in cognition as measured by MoCA. A, Cognitive trajectories of the control group (full green line) and patients with loneliness reports (purple dashed line). B, Cognitive trajectories of the control group (full green line) and patients with social isolation reports (purple dashed line). C, Differences in the cognitive functionality between the two groups (average difference in MoCA scores between the control group and loneliness group), where disease periods estimated as statistically different are highlighted by the red line. D, Differences in the cognitive functionality between the two groups (average difference in MoCA scores between the control group and social isolation group), where disease periods estimated as statistically different are highlighted by the red line. MoCA, Montreal Cognitive Assessment.

between loneliness reports and diagnosis duration was not significant, suggesting rates of decline were similar to those of patients with no SI or loneliness reports (see Table 3).

3.2 | Cognitive change after the first report of SI or loneliness

The change in MoCA scores after the first SI and loneliness report behaves differently between the two groups of patients. In the case of patients reporting loneliness, the cognitive function continues to decline at the same rate as before the report of loneliness (see Figure 3A). The cognitive function of patients experiencing SI improves on average after the first mention of SI (see Figure 3B). Looking at differences in MoCA scores, before and after the reports, results show that MoCA scores are on average higher after the report in the SI group (before = 17.32 vs. after = 18.08, $t = 2.11$, df = 1048.6, $P = 0.034$), but not in the loneliness group (before = 17.36 vs. after = 17.08, $t = -0.67$, df = 770.62, $P = 0.49$). However, when we identify patients with at least one MoCA measure before and after the first report and calculate repeated measure t tests, we see that both groups of patients decline in their MoCA scores (loneliness reports: before = 17.58 vs. after = 16.62, $t = 2.31$, df = 85, $P = 0.023$ and SI reports: before = 18.03 vs. after = 16.87, df = 115, $t = 3.35$, $P = 0.001$).

4 | DISCUSSION

The effect of SI on the risk of dementia development is well established.[9,15] Still, the status of SI and loneliness when presented in presymptomatic and symptomatic stages of the disease and their effect on the progression of the disease is less explored.

We examined the effect of reported SI and loneliness on the rate of cognitive change of patients with dementia using EHRs from a UK NHS mental health trust. We showed that patients with evidence of loneliness have worse cognition throughout their disease course.

TABLE 3 Linear mixed-effect model coefficients.

	Estimate	Standard error	df	*t* value	*P* value
Main exposures					
Intercept[a]	**26.41**	**1.02**	**4463**	**25.78**	**<0.001**
Diagnosis duration[b]	**−0.38**	**0.04**	**7991**	**−8.71**	**<0.001**
Social isolation	**−0.69**	**0.27**	**4438**	**−2.53**	**0.011**
Loneliness	**−0.83**	**0.31**	**4381**	**−2.64**	**0.008**
Diagnosis duration x social isolation	**−0.21**	**0.10**	**7062**	**−2.18**	**0.029**
Diagnosis duration x loneliness	0.01	0.11	7495	0.14	0.885
Demographic factors					
Male	**1.07**	**0.17**	**4377**	**6.15**	**0.001**
Accommodation status					
Supported	**−1.65**	**0.30**	**4213**	**5.53**	**<0.001**
Other	−1.40	0.88	4269	1.59	0.110
Missing	**0.67**	**0.18**	**4391**	**3.64**	**<0.001**
Clinical factors					
Depressed[c]	**2.10**	**0.33**	**4214**	**6.28**	**<0.001**
Diagnosis type					
Lewy body	−0.07	0.60	4190	−0.12	0.903
Other[d]	−0.65	0.46	4334	−0.14	0.158
Unspecified	0.15	0.18	4422	0.85	0.390
Vascular	**−1.47**	**0.30**	**4440**	**−4.82**	**<0.001**
Missing	**−1.20**	**0.49**	**4445**	**−2.43**	**0.016**

Abbreviations: AD, Alzheimer's disease; ICD, International Classification of Diseases; SI, social isolation.

[a] Reference group has no complaints of SI or loneliness, is female, living in mainstream housing, not depressed, with a diagnosis of AD.

[b] Diagnosis duration indicates the change in estimated score per year of disease progression.

[c] The depressed variable represents patients who were ever depressed based on ICD-10 codes.

[d] The type of dementia labeled "Other" consisted of cases with fronto-temporal dementia, mixed Alzheimer's and vascular dementia, and primary psychiatric disorders, while "Other accommodation" included clinical, no fixed abode, and incarcerated.

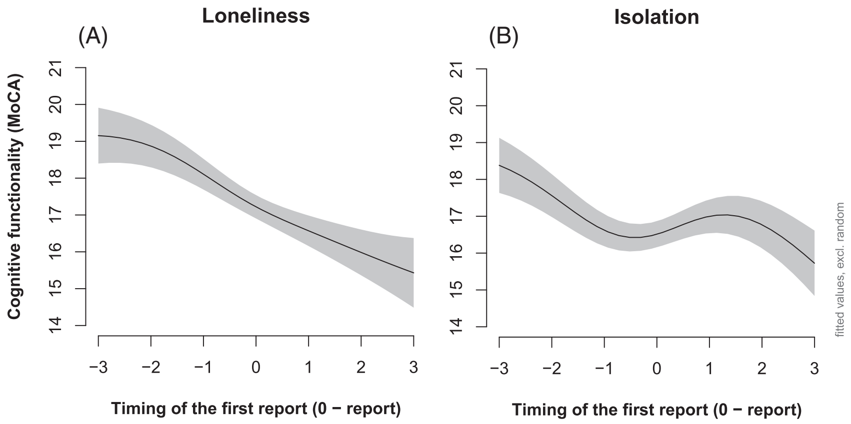


FIGURE 3 The non-linear cognitive change, as measured by MoCA, before and after the first report for loneliness and social isolation group. A, Cognitive trajectories of patients with report(s) of loneliness. B, Cognitive trajectories of patients with report(s) of social isolation. MoCA, Montreal Cognitive Assessment.

Patients whose EHRs mention SI have comparable cognition, before diagnosis, to patients without mentions of such symptoms. However, 6 months before being diagnosed, the cognitive ability of socially isolated patients starts declining at a higher rate, resulting in worse cognition at the point of dementia diagnosis and later in the disease course.

4.1 | Mechanisms of SI and loneliness

The conceptualization of the two concepts, SI and loneliness, likely underlies the estimated differences between the three groups of patients in our study.[1] SI represents more of a physical barrier to receiving social support and/or maintaining social connections, while loneliness reflects emotional aspects of this feeling. We found that socially isolated patients have stronger rates of cognitive deterioration several months before a dementia diagnosis while being comparable to controls in the preceding period. In the context of a life-changing and stigmatizing diagnosis such as dementia, the lack of social contact prevents patients from receiving needed support, and their cognition declines at higher rates.[43] When reported for the first time, we show that average values of MoCA scores increase for this subgroup of patients. This improvement may reflect positive action taken by health-care and/or social services in response to the report. In contrast, patients who experience loneliness have worse cognition throughout the disease course. Such results indicate that loneliness might be an intermediary for depressive symptomatology or might be caused by common origins.[44–46] This interpretation is also supported by the demographic differences split by group, where we see that patients with reports of SI and loneliness also have higher rates of ICD-10 codes for depression. These patients also do not observe any improvement in their cognition after the first report of loneliness, which might be expected given that improvement in feelings of loneliness requires a change in the availability of social networks, psychological well-being, life satisfaction, activities, and other psychiatric symptoms.[47]

4.2 | Strengths and limitations

Our study illustrates the potential of medical records from mental health institutions to provide evidence-based results on the effect of symptoms in dementia diseases.[9,48] Using large data and advanced statistical modeling, our study shows that SI can be seen as a disease progression factor. Not only is this a novel finding in the domain, contrasting with some previous studies which showed limited effects or their complete absence[20,22,23] but we show differing effects of SI and loneliness on the cognitive trajectories of patients with dementia.

There are several limitations when using large observational datasets.[49] We cannot allocate patients' membership in the group and can only control for a limited number of factors that could have moderating effects on SI and loneliness, such as depression. Lack of control over the allocation of patients and barriers when accessing health care may have led to inadequacies regarding diversity, equality, and inclusion, which may reduce the wider generalizability of findings. Similarly, patients with SI or loneliness reports recorded considerably before diagnosis may be a sign of additional health-care needs and could additionally limit the generalizability of findings. The correlational nature of the data limits the causal interpretation of our findings, and even though we see improvement in cognition after the first report of SI, we cannot ascertain what change in patients' social circumstances followed. There are multiple sources of support that patients can receive after SI is identified, such as closer family connections, social services provision of care, or a change to their living conditions (e.g., admittance to residential care). Our interpretation of SI relies on a subjective perception from the patient, caregiver, or clinician, rather than an objective measure, for example, of frequency of social contact. Automated and trained NLP model architectures are probabilistic, and even though they achieve high levels of accuracy, they introduce an additional layer of noise to the later data analysis.[50]

4.3 | Clinical implications

While acknowledging limitations, we show that SI and loneliness could be seen as a disease progression factor for dementia patients, given their effect on cognitive trajectories, even before a formal diagnosis. This means patients experiencing SI or loneliness might benefit from closer monitoring of their cognitive health. While cognitive decline is expected in dementia, the rate of decline can have significant impacts on both patient care and quality of life. By recognizing SI and loneliness as potential factors influencing the speed of decline, these findings could have direct implications for clinical practice, such as identifying potential avenues for intervention, informing treatment strategies, and strengthening the rationale for social prescribing. We hope that these effects could steer the debate concerning modifiable symptoms, as part of a holistic assessment, that could be used to support the care of patients and outline a research approach that could provide us with more evidence-based studies of modifiable disease progression factors.

AUTHOR CONTRIBUTIONS

James A. C. Myers and Nemanja Vaci were granted access to the electronic health records. Nemanja Vaci developed natural language processing models, and James A. C. Myers supported their training and evaluation. James A. C. Myers cleaned and processed extracted data, James A. C. Myers and Nemanja Vaci jointly analyzed data, and all authors worked on the interpretation of the results. Ivan Koychev, Robert Perneczky, and Oliver Bandmann supervised the clinical interpretation of the findings, while Tom Stafford supervised analytical procedures. James A. C. Myers and Nemanja Vaci wrote the manuscript, and all authors revised and reviewed the manuscript. Nemanja Vaci, as the corresponding author, had final responsibility for the decision to submit the manuscript.

ACKNOWLEDGMENT

We acknowledge the work and support of the Oxford Research Informatics Team, Tanya Smith (Head of Research Informatics), Adam Pill and Suzanne Fisher (CRIS Academic Support and Information Analyst), Suzanne Fisher (Research Informatics Systems Analysts), and Lulu Kane (Research Informatics Administrator). Matthew Bladen's contribution to preparing the article for publication is greatly appreciated. The interpretation and conclusions contained in this report are those of the authors alone. The views expressed are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. This study was supported by CRIS Powered by Akrivia Health, using data, systems and support from the NIHR Oxford Health Biomedical Research Centre (NIHR203316) Research Informatics Team. IK is funded through MRC, NIHR Oxford Health Biomedical Research Facility and an investigator-initiated grant by Novo Nordisk.

CONFLICT OF INTEREST STATEMENT

Ivan Koychev is a paid medical advisor to Five Lives, a digital healthcare company developing a platform for addressing preventable risk factors for dementia in ageing adults. All other authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Informed consent was not required for the study as we use anonymized patients' electronic health records. The data were accessed and analyzed in accordance with applicable legal and ethical guidelines to ensure the privacy and confidentiality of all subjects.

DATA AVAILABILITY STATEMENT

The source data for this work is owned by Oxford Health NHS Foundation Trust using anonymized patient records via CRIS Powered by Akrivia Health. The data cannot be made publicly available but can be accessed with permissions from Oxford Health NHS Foundation Trust for UK NHS staff and UK academics within a secure firewall, in the same manner as the authors.

REFERENCES

1. World Health Organization. Social isolation and loneliness among older people: advocacy brief. World Health Organization; 2021:1-17.
2. Evans IE, Martyr A, Collins R, et al., Social isolation and cognitive function in later life: a systematic review and meta-analysis. *J Alzheimers Dis*. 2019;70(s1):S119–S144.
3. Smith KJ, Victor C. Typologies of loneliness, living alone and social isolation, and their associations with physical and mental health. *Ageing Soc*. 2019;39(8):1709–1730.
4. Zhou J, Tang R, Wang X, Li X, Heianza Y, Qi L. Improvement of social isolation and loneliness and excess mortality risk in people with obesity. *JAMA Netw Open*. 2024;7(1):e2352824–e2352824.
5. Lyu C, Siu K, Xu I, Osman I, Zhong J. Social isolation changes and long-term outcomes among older adults. *JAMA Netw Open*. 2024;7(7):e2424519–e2424519.
6. Gerlach LB, Solway ES, Malani PN. Social isolation and loneliness in older adults. *JAMA*. 2024.
7. Donovan NJ, Okereke OI, Vannini P, et al. Association of higher cortical amyloid burden with loneliness in cognitively normal older adults. *JAMA Psychiatry*. 2016;73(12):1230–1237.
8. Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. *Perspect Psychol Sci*. 2015;10(2):227–237.
9. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413–446.
10. Kelly ME, Duff H, Kelly S, et al. The impact of social activities, social networks, social support and social relationships on the cognitive functioning of healthy older adults: a systematic review. *Syst. Rev*. 2017;6(1):1–18.
11. Penninkilampi R, Casey A-N, Singh MF, Brodaty H. The association between social engagement, loneliness, and risk of dementia: a systematic review and meta-analysis. *J Alzheimers Dis*. 2018;66(4):1619–1633.
12. Sommerlad A, Sabia S, Singh-Manoux A, Lewis G, Livingston G. Association of social contact with dementia and cognition: 28-year follow-up of the Whitehall II cohort study. *PLoS Med*. 2019;16(8):e1002862.
13. Lara E, Martín-María N, De la Torre-Luque A, et al. Does loneliness contribute to mild cognitive impairment and dementia? A systematic review and meta-analysis of longitudinal studies. *Ageing Res. Rev*. 2019;52:7–16.
14. Victor CR. Is loneliness a cause or consequence of dementia? A public health analysis of the literature. *Front Psychol*. 2021;11:612771.
15. Perry BL, Roth AR, Peng S, Risacher SL, Saykin AJ, Apostolova LG. Social networks and cognitive reserve: network structure moderates the association between amygdalar volume and cognitive outcomes. *J Gerontol B Psychol Sci Soc Sci*. 2022;77(8):1490–1500.
16. Bennett DA, Schneider JA, Tang Y, Arnold SE, Wilson RS. The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. *Lancet Neurol*. 2006;5(5):406–412.
17. Mathys H, Peng Z, Boix CA, et al. Single-cell atlas reveals correlates of high cognitive function, dementia, and resilience to Alzheimer's disease pathology. *Cell*. 2023;186(20):4365–4385. e27.
18. Stern Y, Albert M, Barnes CA, Cabeza R, Pascual-Leone A, Rapp PR. A framework for concepts of reserve and resilience in aging. *Neurobiol Aging*. 2023;124:100–103.
19. Holwerda TJ, Deeg DJ, Beekman AT, et al. Feelings of loneliness, but not social isolation, predict dementia onset: results from the Amsterdam Study of the Elderly (AMSTEL). *J Neurol Neurosurg Psychiatry*. 2014;85(2):135–142.
20. Zhang Y, Tatewaki Y, Liu Y, et al. Perceived social isolation is correlated with brain structure and cognitive trajectory in Alzheimer's disease. *GeroScience*. 2022;44(3):1563–1574.
21. Freak-Poli R, Wagemaker N, Wang R, et al. Loneliness, not social support, is associated with cognitive decline and dementia across two longitudinal population-based cohorts. *J Alzheimers Dis*. 2022;85(1):295–308.
22. Sun W, Matsuoka T, Oba H, Narumoto J. Importance of loneliness in behavioral and psychological symptoms of dementia. *Int. J. Geriatr. Psychiatry*. 2021;36(4):540–546.
23. Victor CR, Rippon I, Nelis SM, et al. Prevalence and determinants of loneliness in people living with dementia: findings from the IDEAL programme. *Int. J. Geriatr. Psychiatry*. 2020;35(8):851–858.
24. Joyce J, Ryan J, Owen A, et al. Social isolation, social support, and loneliness and their relationship with cognitive health and dementia. *Int. J. Geriatr. Psychiatry*. 2022;37(1).
25. Boss L, Kang D-H, Branson S. Loneliness and cognitive function in the older adult: a systematic review. *Int Psychogeriatr*. 2015;27(4):541–553.
26. Janssen O, Vos SJ, García-Negredo G, et al. Real-world evidence in Alzheimer's disease: the ROADMAP Data Cube. *Alzheimers Dement*. 2020;16(3):461–471.

27. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695–699.
28. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res*. 1975;12(3):189–198.
29. Pinto TC, Machado L, Bulgacov TM, et al. Is the Montreal Cognitive Assessment (MoCA) screening superior to the Mini-Mental State Examination (MMSE) in the detection of mild cognitive impairment (MCI) and Alzheimer's Disease (AD) in the elderly?. *Int Psychogeriatr*. 2019;31(4):491–504.
30. National Institute for Health and Care Excellence. Dementia: assessment, management and support for people living with dementia and their carers (NICE Guideline NG97). National Institute for Health and Care Excellence; 2018.
31. Stojanovic M, Mikula C, John S, Kiselica A. Clinical importance in Alzheimer's disease: effects of anchor agreement and disease severity. *Aging Clin Exp Res*. 2024;36(1):5.
32. Vaci N, Koychev I, Kim C-H, et al. Real-world effectiveness, its predictors and onset of action of cholinesterase inhibitors and memantine in dementia: retrospective health record study. *Br J Psychiatry*. 2021;218(5):261–267.
33. Kormilitzin A, Vaci N, Liu Q, Nevado-Holgado A. Med7: a transferable clinical natural language processing model for electronic health records. *Artif Intell Med*. 2021;118:102086.
34. Senior M, Burghart M, Yu R, et al. Identifying predictors of suicide in severe mental illness: a feasibility study of a clinical prediction rule (Ox ford M ental I llness and S uicide Tool or OxMIS). *Front Psychiatry*. 2020;11:268.
35. Goodday SM, Kormilitzin A, Vaci N, et al. Maximizing the use of social and behavioural information from secondary care mental health electronic health records. *J Biomed Inform*. 2020;107:103429.
36. Li Z, Kormilitzin A, Fernandes M, et al. Validation of UK Biobank data for mental health outcomes: a pilot study using secondary care electronic health records. *Int J Med Inform*. 2022;160:104704.
37. Vaci N, Liu Q, Kormilitzin A, et al. Natural language processing for structuring clinical text data on depression using UK-CRIS. *BMJ Ment Health*. 2020;23(1):21–26.
38. Tunstall L, Reimers N, Jo UES, et al. Efficient few-shot learning without prompts. *arXiv preprint arXiv:220911055*. 2022;2209:11055
39. De Jong-Gierveld J, van Tilburg TG. A 6-item scale for overall, emotional, and social loneliness: confirmatory tests on survey data. *Res. Aging*. 2006;28(5):582–598.
40. Russell DW. UCLA Loneliness Scale (Version 3): reliability, validity, and factor structure. *J. Pers. Assess*. 1996;66(1):20–40.
41. van Rij J, Vaci N, Wurm LH, Feldman LB. *Alternative Quantitative Methods in Psycholinguistics: Implications For Theory and Design*. Word Knowledge Word Usage; 2020:83.
42. Pinheiro JC, Bates DM. Linear mixed-effects models: basic concepts and examples. *Mixed-effects models in S and S-Plus*. 2000:3–56.
43. Murata C, Saito T, Saito M, Kondo K. The association between social support and incident dementia: a 10-year follow-up study in Japan. *Int. J. Environ. Res. Public Health*. 2019;16(2):239.
44. Erzen E, Çikrikci Ö. The effect of loneliness on depression: a meta-analysis. *Int. J. Soc. Psychiatry*. 2018;64(5):427–435.
45. Weeks DG, Michela JL, Peplau LA, Bragg ME. Relation between loneliness and depression: a structural equation analysis. *J Pers Soc Psychol*. 1980;39(6):1238.
46. Shen C, Rolls ET, Cheng W, et al. Associations of social isolation and loneliness with later dementia. *Neurology*. 2022;99(2):e164–e175.
47. Åkerlind I, Hörnquist JO. Stability and change in feelings of loneliness: a two-year prospective longitudinal study of advanced alcohol abusers. *Scand. J. Psychol*. 1989;30(2):102–112. doi:10.1111/j.1467-9450.1989.tb01073.x
48. Oliver D, Arribas M, Perry BI, et al. Using electronic health records to facilitate precision psychiatry. *Biol Psychiatry*. 2024;96(7):532–542.
49. Meystre SM, Savova GK, Kipper-Schuler KC, Hurdle JF. Extracting information from textual documents in the electronic health record: a review of recent research. *Yearb Med Inform*. 2008;17(01):128–144.
50. Perera S, Sheth A, Thirunarayan K, Nair S, Shah N Challenges in understanding clinical notes: why NLP engines fall short and where background knowledge can help. presented at: Proceedings of the 2013 international workshop on Data management & analytics for healthcare; 2013; California, USA.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Myers JAC, Stafford T, Koychev I, Perneczky R, Bandmann O, Vaci N. Loneliness, social isolation, and effects on cognitive decline in patients with dementia: A retrospective cohort study using natural language processing. *Alzheimer's Dement*. 2025;17:e70149. https://doi.org/10.1002/dad2.70149