A biosocial approach to healthy ageing: The interplay between social isolation and inflammation

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Thesis submitted for Doctor of Philosophy (Social Epidemiology)

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2023

Declaration

I, Charlotte Louise Campbell, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed, 28 July 2023

Abstract

Background: An individual's social relationships are consistently shown to be associated with many aspects of health, especially in the context of healthy ageing. Social isolation of older adults is associated with mortality and a range of mental and physical health problems. One possible mechanism implicated in the process of social isolation affecting health is chronic inflammation, a widespread phenomenon in older people that is a known risk factor for a wide range of health conditions.

Methods: Data from the English Longitudinal Study of Ageing (ELSA) was used to explore the associations between social isolation and intrinsic capacity, and whether inflammation was a mediator of this relationship. First, a measure of healthy ageing was operationalised based upon the intrinsic capacity (IC), which refers to capacity in 5 domains of function: cognition, locomotion, sensory, vitality, and psychological. Item response theory was used to generate an IC score in three waves of ELSA spanning 8 years. Latent growth curve models tested the association between social isolation and intrinsic capacity before cross-lagged panel models were used to test the possible mediation effect of inflammation, both using full information maximum likelihood to handle missing data.

Results: The novel IC score was associated with key sociodemographic and health-related covariates and predicted subsequent difficulties with ADLs and IADLs, hospital admission and mortality. Lower social isolation was associated with higher baseline levels of IC but a steeper decline in IC over time. Inflammation was not found to mediate the association between social isolation and IC, but a bidirectional relationship between inflammation and IC was uncovered.

Conclusions: Inflammation is not likely a key mechanism for social isolation to affect healthy ageing. Policy to reduce social isolation may not slow declines in health but could give older adults a better "starting point" and, therefore, more time in better health.

Impact statement

Population ageing is a phenomenon seen in many societies around the world and is a topic of high policy and research interest, with 2020-2030 the UN Decade of Healthy Ageing. The impact of social isolation on older people has become particularly salient in the context and aftermath of the Covid-19 pandemic. Understanding if and how social isolation impacts the health of older people is crucial to the directing of interventions aiming to improve healthy ageing.

In this thesis, I first demonstrate how a new model of healthy ageing, intrinsic capacity, can be operationalised in longitudinal population surveys and how the validity of such models can be assessed, which has a clear impact on future research intending to measure intrinsic capacity. I then show that social isolation has a harmful association with the capacity of older adults in England but that being more socially isolated does not speed up the decline of capacity with increasing age. This is a novel result in the academic literature and could be helpful to inform interventions attempting to prolong the healthy life expectancy of the population. The final analysis in this thesis shows that raised inflammation is probably not the mechanism through which social isolation damages health but highlights the importance of inflammation to the healthy ageing of older adults. This has implications for the academic understanding of social-biological pathways in health, as well as for policies that aim to promote healthy ageing in a population.

Results from this thesis have been presented at the international conferences of the Society for Social Medicine and Population Health (online in 2021 and Exeter in 2022) and the Society for Longitudinal and Lifecourse Studies (online in 2020 and Cleveland, USA, in 2022). The operationalisation of intrinsic capacity outlined in Chapter 4 has also been published in the Journal of Gerontology: Medical Sciences https://doi.org/10.1093/gerona/glac250.

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Acknowledgements

I would first like to thank my supervisors Paola Zaninotto, Dorina Cadar, and Anne McMunn for their support, inspiration, and expertise throughout the past 4+ years. A global pandemic was not what I had planned for the majority of my PhD experience and, although lucky to not have my work hugely changed by lockdowns and working from home, the support from my supervisors was invaluable to getting through the tough months when I could not see the light at the end of the tunnel. Thank you to Paola for your compassion and encouragement, and for keeping me on track when I needed it most.

Thank you to my funders and doctoral programme, the ESRC-BBSRC Soc-B Centre for Doctoral Training in Biosocial Research. You've enabled me to do something I never imagined I could do and introduced me to the most incredible people.

Thank you to all those involved in the English Longitudinal Study of Ageing, from the respondents who give up so much of their time to answer the surveys, to the data managers who prepare and release the data for us to explore. Thank you for the privilege of using this amazing data resource and cementing my belief in these important data infrastructures.

Thank you to my friends and colleagues from the Institute of Epidemiology and Health Care and Soc-B programme at UCL, Manchester, and Essex. You kept me optimistic and excited when Mplus was tearing me down. Particular thanks to my friends from the 7th floor, Megan Arnot, Charis Bridger-Staatz, Luke Kretschmer, Lucy Karwatowska, and Liam Wright, and Matt Jay from further afield. Thank you for your practical help when I don't know the right words or how R works, and all your emotional support at the pub. A special mention goes to Emma Walker. Thank you for being my hype girl, my shoulder to cry on, my office soulmate. I probably couldn't have done this without you.

To my oldest friends Emma Sinclair, Keira Thompson, and Robyn Stanley. You have been my rocks for the majority of my life and it is endlessly comforting knowing that you are always there for me. Thank you for your unwavering belief in me when I didn't have it in myself.

Thank you to my parents, Gill and Paul. Thank you for your unconditional love and support. There aren’t words to express how grateful I am to you for all the opportunities and experiences you have given me. Thank you for always taking me under your wings when I needed it and encouraging me to fly when I wasn’t sure I could. To Andrew, I know we aren’t very soppy, but I am forever impressed and proud of you. I am very lucky to have a little brother I look up to.

And finally, thank you to my Liam. Thank you for encouraging me to apply in the first place and your steady belief that I could do it. Thank you for being strong when I’m faltering. Thank you for being my person.

List of publications

Charlotte L Campbell, MSc, Dorina Cadar, PhD, Anne McMunn, PhD, Paola Zaninotto, PhD, Operationalisation of intrinsic capacity in older people and its association with subsequent disability, hospital admission and mortality: results from ELSA, The Journals of Gerontology: Series A, 2022; glac250, **https://doi.org/10.1093/gerona/glac250**

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    Date: 02/02/2023

    Supervisor/ Senior Author (where appropriate)

    Paola Zaninotto

    Date: 02/02/2023

Chapter 1: Background

1.1 Introduction

As population ageing becomes more commonplace worldwide, it is increasingly important to understand healthy ageing and the factors influencing it. Social influences, such as the quantity or quality of relationships we have with other people, are increasingly thought to be significant factors in maintaining health into older age. The interactions between these social influences and the body's biology are important to explore. This project aims to investigate the association between social relationships, in particular social isolation, and healthy ageing, exploring the role of inflammation within this relationship.

This thesis will first describe and review the relevant literature on healthy ageing, social relationships, and inflammation and introduce a novel model of healthy ageing termed intrinsic capacity (**Chapter 1**). The aims and objectives of the PhD project will then be outlined (**Chapter 2**) and the sample described (**Chapter 3**). The following chapters build upon each other, first defining and testing a novel measure of intrinsic capacity (**Chapter 4**), then expanding this to longitudinal measurement (**Chapter 5**), and then testing the association between social isolation and intrinsic capacity (**Chapter 6**), before finally testing the mediating effect of inflammation on this relationship (**Chapter 7**). Each chapter will describe the data source and sample, present the methods, analysis, and results of each stage of the project, and finally discuss the findings and implications.

1.2 Healthy ageing

From a biological perspective, ageing is characterised by many physical changes which are common but not homogeneous. There is also much heterogeneity among individuals, with some developing many age-related health issues while others live to older ages without any or only minor issues. Many different labels have been generated to conceptualise "ageing well", including successful ageing, productive ageing, active ageing, and healthy ageing. Each of these terms has specific definitions reflecting different concepts; however, it can be difficult to fully disentangle exactly how each of these is measured as the terms are often used interchangeably.

The term 'healthy ageing' has proved the most popular of the ageing well conceptualisations, being the subject in a majority of papers exploring ageing well between 1995-2015 [1]. The term is widespread and appears to have gained popularity due to its lesser emphasis on success versus failure and broader focus than just a particular subset of the population, which is the case with successful ageing, the second most popular term. However, there has not been a seminal model for healthy ageing. The definition and/or measurement of healthy ageing is often specific to a single paper or study, and there is no overall consensus across the literature [2-4].

Most reviews on healthy ageing definitions include studies of successful ageing, highlighting the use of these terms interchangeably. An early model of successful ageing, Cummings and Henry's Disengagement theory [5], proposed that successful ageing was the ability to withdraw from society and detach from the activities of mid-life in preparation for death [6], but successful ageing was also described in a more positive manner by Havighurst's Activity Theory, which defined it as the maintenance of activities and attitudes from mid-life [7]. Later, the MacArthur model of successful ageing proposed by Rowe and Kahn became the most prominent model distinguishing successful ageing with three criteria: a low probability of disease and disease-related disability, high cognitive and physical functional capacity, and an active engagement with life [8, 9]. This model has been modified and expanded to include broader level factors [10]; however, the model still receives criticism for being too narrow and exclusionary to apply to a large majority of older people [10]. Depending on the study and measurements used, there is considerable variation in the proportion of older adults categorised as "successful", with most studies finding the majority of older people not passing the criteria – specifically the absence of disease or chronic conditions [2]. Some have rightly questioned the usefulness and suitability of the expectations of a model that excludes the majority of the older population, especially since many older individuals live long, independent, and quality lives with chronic conditions [11]. The binary nature of successful ageing has also been criticised, with many calling for healthy ageing models to adopt a continuum approach which allows for more information on heterogeneity in ageing trajectories and individual changes in components [12-14].

Indexes for measuring frailty are also sometimes used in literature to identify healthy ageing as the opposing state to frailty. A popular phenotypic approach defines frailty as a clinical syndrome [15] characterised by weight loss, exhaustion, weakness, slow walking speed and low physical activity. However, frailty is also defined as a multi-dimensional construct which includes physical, cognitive, psychological, social and environmental aspects [16-18] and is found to predict adverse outcomes in older people [19]. Frailty indexes can be considered measures of deficit accumulation [20], indicating an individual's risk profile for adverse health outcomes [21].

As there is no firm consensus on healthy ageing definitions or a seminal model to guide conceptualisations, individual studies tend to conceptualise healthy ageing in their own way. Therefore, there have been numerous different models of healthy ageing with a wide range of indicators. There are two citation networks of healthy ageing, with one focusing on the perspectives and experiences of older people with regard to healthy ageing and the other taking the perspective of the researcher or clinician and concentrating on measurements of functioning [4]. The first of these approaches follows criticisms that successful and healthy ageing definitions differ from the lay perspectives of ageing and that they should include more subjective indicators and emphasise wellbeing [6]. The second approach focuses more on measurements of physical, cognitive and mental health measures, with models often not including the absence/presence of disease or chronic conditions as an indicator [3].

In a review of papers measuring healthy ageing, Mount et al. [22] found a diverse range of indicators with some reports using biomarkers of physiological functions such as cardiovascular function, glucose homeostasis, lung function, adiposity, lipid metabolism and inflammation [23], and others using indexes covering a wide range of factors, such as education, financial status, social activities, cardiovascular disease risk, BMI, depression, physical activity and diet [24]. Other indexes of healthy ageing have included, for example, 33 indicators covering physical, cognitive and physiological functions alongside psychological and social well-being [25];

components assessing cognitive function and impairment, disability, psychosocial factors, medication use, physiological measurements and 40 parameters of frailty [26]; and a 52-item health deficit accumulation index encompassing functional impairments, self-rated health, mental health and morbidity/health service use [27]. Although no consensus has been reached on the specific definition and measurement of healthy ageing, there is a general consensus that models should be multi-dimensional, ideally with a mixture of objective and subjective indicators [22].

In an assessment of reviews and meta-analyses on objectively measured biomarkers of healthy ageing, Lara et al. (2013) [28] identified five common domains: physiological and metabolic health, physical capability, cognitive function, social well-being, and psychological well-being. Based on these five domains, the Healthy Ageing Phenotype (HAP) is a relatively new tool being developed to fill the role of a single reliable measure of how someone is ageing [28]. The HAP attempts to capture an individual's ability to be socially engaged and to function independently, physically and cognitively. It is proposed to include a combination of objective and subjective dimensions covering the five domains, and sensorial functions have also been considered [22]. A panel of 26 biomarkers that could be used to build the HAP have been proposed, each measuring particular features of the identified domains [29].

A key consideration for the measurement of health across older age is the issue of age-specificity. Some measurements of health will mean different things for someone in their 60s versus someone in their 90s and may require a different expectation or benchmark of "acceptable" or "healthy". For example, we might expect an individual in their 60s to be able to walk upstairs without resting and be concerned if they could not; however, we would not be so alarmed if someone in their 90s required a little rest. The age-specificity of measures of health and functioning is important for classifying and judging individuals correctly, but also an issue for the usefulness of healthy ageing measures across multiple age ranges. A measure that is very sensitive to changes in health for the oldest old would probably not give much information about the state of health for younger individuals if almost everyone in that lower age range performs well on every indicator, particularly if they are dichotomous indicators. Although this is a big conceptual problem, most discussions of healthy ageing models haven't yet discussed or offered solutions for age-specificity and focus on one model that is applied across older age ranges.

1.2.1 Background and development of intrinsic capacity

The most influential attempt to define healthy ageing has come from the World Health Organisation (WHO). Defined as "the process of developing and maintaining the functional ability that enables well-being in older age", healthy ageing has been the focus of the WHO's work on ageing since 2015, with 2020-2030 deemed the United Nations Decade of Healthy Ageing [30, 31]. This model attempts to move away from deficit-based models, which focus on clinical indicators and treatment of deficits, as well as reactive models, which respond to disease or impairment once it has already manifested. The WHO model aligns more with preventative models of medicine, aiming to use longitudinal models to generate healthy ageing trajectories for individuals, promoting proactive interventions ahead of the manifestation of disease and impairment [32].

There are different distinct elements to healthy ageing within this framework. Functional ability is said to be comprised of the intrinsic capacity of an individual, the environment in which they live, and interactions between the individual and their environment (**Figure 1.1**). Environments include all extrinsic world factors that give context to an individual's life from the micro- to macro-level, such as the built environment, relationships with other people, health and social policies, and attitudes and values. Intrinsic capacity (IC) is defined as the "composite of all the physical and mental capacities of an individual", which itself is determined by interactions between genetics, personal characteristics (e.g., sex, ethnicity, education, occupation) and other health characteristics (e.g., physiological risk factors, diseases, injuries). The development of an operationalised measure of healthy ageing based on the WHO framework has focused on this concept of IC as this is the centre point on which functional ability and healthy ageing depend.

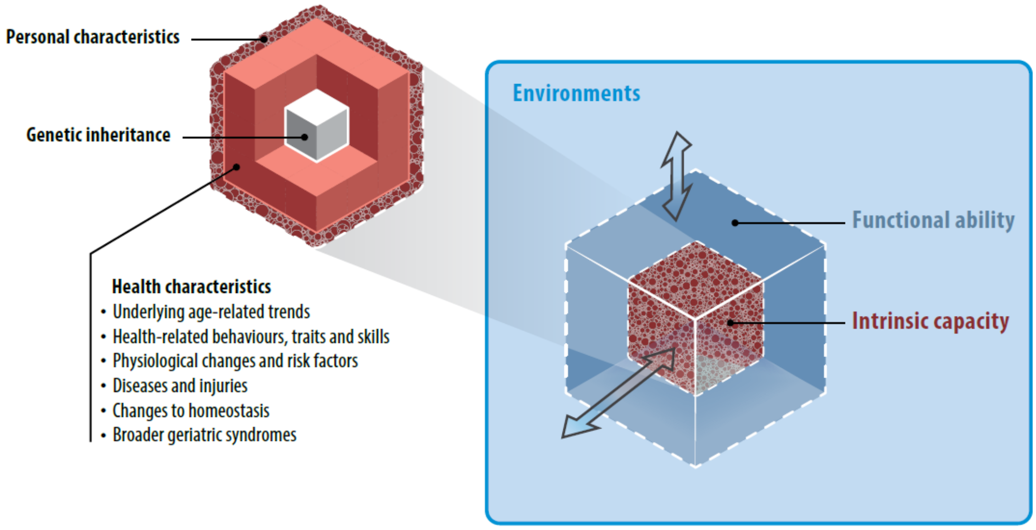

Figure 1.1 Diagram of the healthy ageing framework outlined by the World Health Organisation (WHO) with intrinsic capacity making up a part of functional ability along with an individual's environment and interactions with the environment.

Source: WHO (2015) [30, p.28].

As a measure of capacity, the WHO framework hypothesises different trajectories of IC over time, capturing the heterogeneity of healthy ageing found in prior studies. For example, IC could remain high until the end of life, an event could cause a rapid decline in IC before a period of recovery, or IC could decline steadily until death. Functional ability is thought to follow a trajectory slightly different to IC, as an individual's environment can provide benefits or barriers to functioning beyond an individual's capacity.

The first exploration of IC used cross-sectional data from WHO's Study on Global Ageing and Adult Health (SAGE) in 2016 [33]. An IC score was generated from 16 self-report questions (covering vision, mobility, self-care, cognition, interpersonal activities, pain, sleep, energy, and affect) and objective measures of grip strength, gait speed, and cognitive function (fluency & recall) using factor analysis. Results found a gradual decline in IC with increasing age and a wide range of capabilities across age groups (**Figure 1.2**). This pattern of gradual decline and broad heterogeneity matches with previous measures of healthy ageing and the hypotheses of the WHO framework.

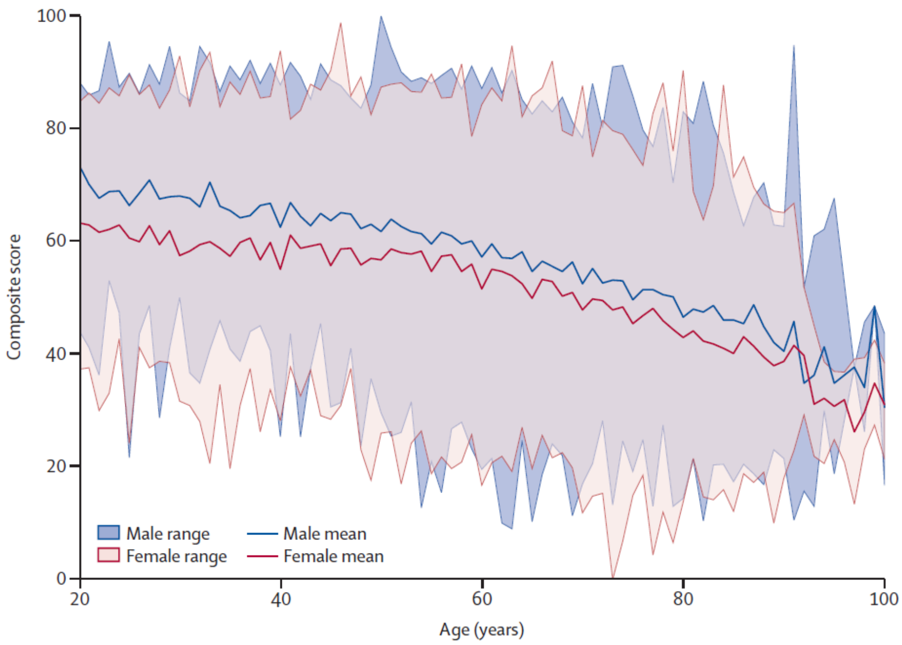

Figure 1.2 Range and mean of the intrinsic capacity score of men and women in SAGE 2007-2010 (wave 1)

Source: Beard et al. (2016) [33, p.2148]

Focusing on the structure of IC, theoretical and empirical work in 2018 defined five domains of IC: cognition, locomotion (mobility and muscular function), sensory (vision and hearing), vitality (balance between energy intake and utilisation) and psychological (mood and capacity for social interaction) (see **Figure 1.3**) [32, 34]. These domains were identified through a non-systematic review which pinpointed the functions that are most strongly linked to the maintenance of health and functional loss [32], as well as through exploratory and confirmatory factor analysis in a background paper for the WHO Clinical Consortium on Healthy Ageing in 2017 by Araujo de Carvalho et al. [34]. The factor analyses used data from the English Longitudinal Study of Ageing (ELSA). First, they ran exploratory factor analysis on a range of objective biomarkers, revealing a seven-factor model with variables clustering into domains termed strength, sensory, hypertension, metabolism, inflammation, cognition, and locomotion (**Figure 1.4, A**). Second-order confirmatory factor analysis found a good fit for a model constrained to five factors and one general factor (**Figure 1.4, B**). Three domains (cognition, locomotion and sensory) were identical to the data-driven model; however, a psychosocial domain was added as this was deemed a key component of IC but was not seen in the exploratory analysis as only objective markers were used. A new vitality domain was a combination of strength, metabolic and endocrine markers that were judged to be components of capacity; markers of blood pressure and inflammation were excluded from this model as they were seen as drivers of change. The IC score generated from both models was found to be associated with subsequent functional loss measured through Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs), with the paper concluding that both data- and theory-driven structures of IC had significant predictive value in relation to functional loss and the theory-driven structure did seem to be primarily supported by the data.

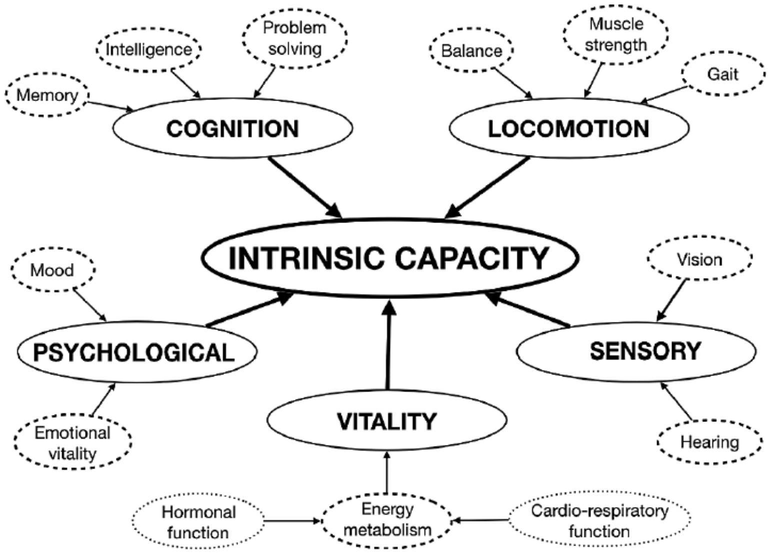

Figure 1.3 The five domains that make up the intrinsic capacity construct. Examples of possible subdomains are also provided (in dashed lines). Source: Cesari et al. (2018) [32, p.1655].

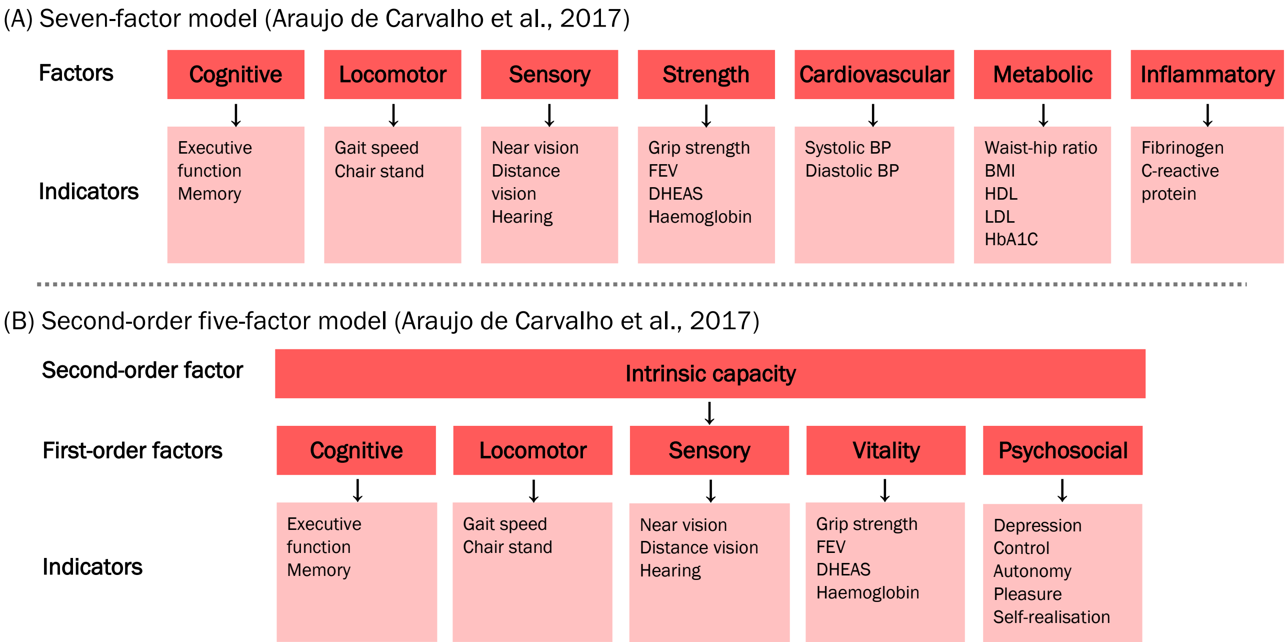

Figure 1.4 The two models of intrinsic capacity generated by Araujo de Carvalho et al. (2017) [34].

Figure A displays the seven-factor model generated by exploratory factor analysis. Figure B shows the second-order five-factor model generated through confirmatory factor analysis. The indicators used are shown under their respective domain.

With this five-domain structure, IC is a multidimensional measure of physical, cognitive, and mental health which matches with previous models of healthy ageing, including the HAP. IC also shares some overlap with measures of frailty, with some proposing that the concepts are "two sides of the same coin", with IC representing an individual's reserves and frailty, the deficits associated with ageing [21]. However, the IC models generated in the Araujo de Carvalho et al. report are constrained by the data available. It was argued that all objective biomarkers that were measured in wave 4 of ELSA were included in the exploratory analysis, but there are tests of functioning and other biomarkers excluded. These include balance tests, other tests of cognitive function (orientation, prospective memory, fluid intelligence, letter cancellation, numerical ability), and other biomarkers (triglycerides, mean corpuscular haemoglobin, ferritin, white blood cell count, fasting lipids, glucose, and glycated haemoglobin). Although some of these biomarkers may not have been relevant to IC, it is still incorrect to argue that all available biomarkers were assessed for their contribution to IC. Additionally, the explored biomarkers were ultimately limited to those that were chosen to be measured as part of the ELSA survey. Thus, as the ELSA data do not include all indicators of health and capacity that have ever been identified, this IC model may be missing some elements that are not objectively measured in ELSA, such as gut health and bone density, for example. Another criticism of the model generation methods is that there has not been discussion regarding whether or how these factor-analysis-generated models might be used longitudinally to build a trajectory of IC for an individual, a key element of the IC model and strategy. Additionally, although the capacity for social interaction was identified as a potential element of the psychological domain and the factor analysis revealed a domain termed psychosocial, the IC model generated did not include explicit measures of social functioning. The IC concept as a whole also does not include more subjective experiences of ageing that have been highlighted in reviews and studies on lay perspectives of healthy ageing [2, 6, 22]. However, as a measure of the capacities intrinsic to an individual, it perhaps makes sense that IC does not include extrinsic factors such as social functioning and subjective experiences of ageing. It could be argued that these more extrinsic factors could be included in the wider definition of healthy ageing in the WHO framework but that they do not reflect the intrinsic capacities of an individual. Although more psychosocial elements of ageing are important, it is still beneficial to have a measure of intrinsic factors more explicitly based on health domains in order to generate risk profiles and prevent functional decline.

The WHO also undertook work to identify the components of capacity within each domain and the specific indicators that could be used in a measure of IC. In 2018, the WHO Clinical Consortium on Healthy Ageing working groups outlined components of each domain that could capture declines in IC over different trajectories and be measured comparably across levels of capacity [35]. Multiple components were found for each domain, the most being 12 for vitality (**Table 1.1**). Additional results were reported from a series of rapid systematic reviews on the validity and reliability of screening and diagnostic instruments for consideration in an IC assessment tool [36]. A particular scale was identified as the recommended measurement for each condition:

Mini Nutritional Assessment (MNA) [37] for malnutrition, Mini-Mental State Examination (MMSE) [38] for cognitive impairment, Geriatric Depression Scale (GDS) [39] for depressive symptoms, Short Physical Performance Battery (SPPB) [40] for mobility impairment, visual acuity test cards and portable eye examination kits for visual impairment, and the whispered voice test for hearing impairment. However, the paper found limitations to the assessed studies, including challenges in interpreting the outcomes of the tests due to selective reporting of cut-off scores and gaps in evidence assessing screening tools for subsyndromal conditions (for example, mild cognitive impairment).

Table 1.1 The IC domains and their proposed measurable components, adapted from WHO (2018) [35].

Domain	Components	
Cognition	• Memory • Verbal fluency • Letter cancellation	• Digit span • Financial literacy • Alternative uses test
Locomotion	• Muscle performance (power, strength, fatigue) • Bone health • Balance	• Walking (capacity, speed, exhaustion) • Self-reported outcomes (particularly pain, self-perception of mobility)
Sensory	• Vision	• Hearing
Vitality	• Fatigue, exhaustion, motivation, or endurance • Psychological resilience • Lung function • Haemoglobin • Weight loss/gain or obesity	• Metabolic balance • Sleep • Inflammation • Sexual function • Muscle function (grip specifically) • Oral health
Psychological	• Mood • Life satisfaction • Anxiety • Self-esteem • Sleep • Agency	• Coping/self-efficacy • Loneliness • Distress • Personality traits • Fatigue

1.2.2 Models of intrinsic capacity

Since the original development of IC, researchers have begun to use IC as a measure of healthy ageing.

A literature search was carried out using publication alerts and keyword searches (see **Appendix 1.1.1**) for papers using a measure of IC as a predictor or outcome or using a model of healthy ageing based on the concept of IC. The five-domain structure of IC outlined by Cesari et al. [32]

was used as a comparison model; however, the exact structure and the number of domains or indicators used to represent IC in the models were not constrained. Results from the literature search are displayed in **Appendix 1.2** in a table showing each models' authors, the data for which the model was derived, the domains measured, and the method for generating a total IC score, where possible.

The following discussion is focused on how IC was measured in these previous studies. Models are presented in **Appendix 1.2** in chronological order of publication, and each was given a model number in this order; these model numbers are used to reference the individual models in this section. Some models of IC were used across multiple papers, in which case the model was counted once and assigned one model number, and all associated papers were shown in the row for that model in **Appendix 1.2**. In this section, paper citations for the IC models are referenced as normal with square brackets in the text.

A total of 47 unique models/measurements of IC were identified in 57 papers. A majority of 36 of the models used pre-existing datasets (models 1-3, 5-14, 16-20, 24, 27-30, 32-36, 38-44, 47), 6 recruited a sample specifically for the paper/project (models 15, 21, 25, 26, 37, 45) and 5 were conceptual or proposed models of IC assessment (models 4, 22, 23, 46).

A key conceptual model to highlight was defined by the WHO [41] as part of their Integrated care for older people (ICOPE) initiative (model 4). This model was a proposed screening tool for IC to be used in self-assessments or by community health workers, with the idea that any deficits identified in the screening would then be further assessed by a health-care professional in primary care. The ICOPE screening tool covered the five domains of IC with 9 tests: 3-word recall and orientation in time and space (cognition), chair rise test (locomotion), weight loss and appetite loss (vitality), self-reported vision impairments and hearing tests (sensory), and self-reported depressive symptoms (psychological). Each of these tests was either passed or failed, with a "fail" triggering further assessment. Since the screening tool was developed for primary care assessment, it focuses on quick assessment using simple indicators, whereas most other models of IC, not aimed at primary care assessment, focus on a complete evaluation of IC with in-depth indicators of each domain. Nevertheless, the ICOPE screening tool, or an adaptation of it, has been applied in research settings using different existing datasets (model 14 [42], model 15 [43], model 24 [44], model 26 [45], model 29 [46], model 37 [47], model 39 [48], model 43 [49], and model 45 [50]) as well as included in protocols for future studies measuring IC (model 4 [51], model 22 [52], model 23 [53]).

Domains

The five-domain structure of IC laid out by Cesari et al. in 2018 [32] was followed by 34 models, while 4 models measured 4 domains, 3 measured 3 domains, 2 measured 2 domains, 2 measured 1 domain, and 2 models measured none of Cesari's domains. The most commonly measured domains were locomotion and vitality, which were included in 41 models each, while the cognition and psychological domains were measured in 40 models each. The sensory domain was measured in 34 models, with those not including the domain mainly reporting a lack of sensory measurements in the chosen datasets. Five models used some indicators that did not fall under the five Cesari-defined domains and so were categorised under "other" in **Appendix 1.2.** Two models only used "other" indicators and did not include or identify the five Cesari-defined domains. Model 28 by Gómez, Oscorio-Garciá, Panesso, and Curcio [54] defined IC with nine multidimensional indicators but did not reference or mention domains and used IC as a general term for the collection of indicators, so the indicators were not categorised into domains. Model 11 by Stephens et al. [55] used the number of chronic health conditions as a proxy of IC, referencing one of the earlier models by Beard et al. [56] (model 7), which found that health conditions were correlated with IC.

Two models were defined as a measure of healthy ageing based on indicators of both IC and functional ability (models 8 and 12). The layout of the indicators amongst the domains was not specified in the papers, but manual categorisation of the indicators revealed that they covered the five domains of IC along with the additional indicators of functional ability. The two models that measured only one domain both focused on the vitality domain – one explored an operational definition of vitality (model 10), and one considered an absence of deficits in multiple domains (measured with a frailty index) as vitality (model 18). Cheong et al. [57] (model 42) specifically tested how different combinations and numbers of domains affected their IC model's ability to predict mortality and found that a 3-domain index including locomotion, sensory, and vitality domains performed as well as a 4- or 5-domain index, indicating that these may be the key domains driving IC, although this has not been explored in more detail.

Total intrinsic capacity score

With regards to a total IC score, 28 models generated a total score using various methods. The most common technique was the summing of domain scores or impairments used in 12 models (models 6, 15, 16, 21, 22,24, 26, 29, 44-46). Eight models extracted a factor score representing IC using data consolidation methods, including confirmatory factor analysis (CFA) (models 7, 8, 20, 25, 27), principal component analysis (models 17 and 42), and item response theory (IRT) (models 12 and 41). Five models used z-scores to calculate an IC score by taking an average of domain-specific z-scores (models 5, 13, 19, 32, 38). One model used a pooled odds ratio to generate a total IC score (model 2), and another took a mean of the domain-specific scores (model 33).

Sum scores were the most common total IC scores and the most straightforward method to generate a summary score from the IC domains. Additionally, although some of the domain-specific scores were generated using quantiles, sum scores are the least reliant on the distribution of the data and, therefore, may be more useful if comparing across time or populations. However, across the IC models, different numbers of domains were measured, and varying methods were used to combine the individual indicators of each domain into a domain-specific score prior to being summed into the total IC score, making sum scores from different models not directly comparable. In addition, this simple sum method doesn't allow for weighting the score dependent on the contribution of each domain to the overall IC.

In comparison, the factor scores extracted from data-driven methods like CFA and IRT consider the individual indicator or item loadings onto the latent factor and essentially produce a weighted score. This is important as the studies using these methods for IC do find different loadings for different items, indicating some are contributing more to the IC factor than others [56, 58, 59], but this has not been explored in enough detail to recommend a specific weighting. Nevertheless, due to these methods' reliance on the data used to create the initial model, making comparisons across time points and populations is more complex and requires measurement invariance and validity testing for each additional group.

Longitudinal modelling of intrinsic capacity

Of the 47 models, 5 were purely theoretical or planned for IC measurement and so were not modelled in data (models 4, 22, 23, 31, and 46). Of those that were modelled in data, 32 were generated cross-sectionally, 7 longitudinally (models 5, 13, 25, 33, 39, 41, and 47), and 3 both cross-sectionally and longitudinally (models 12, 19, and 38). When modelled longitudinally, results found that IC tended to decline over time but with substantial heterogeneity between people [60, 61] (models 25 and 33). The decline in IC was found to be more pronounced in those with low-grade inflammation [62] (model 5) and those who were "socially frail", defined as those who fulfilled at least two of the following criteria: lived alone, required financial support, did not participate in social activities, and had irregular contact with others [63] (model 19). In particular, declines in performance in the locomotion and psychological domains were found to be significantly associated with increased healthcare costs [48] (model 39) and mortality risk [64] (model 38). On the other hand, IC scores were shown to be improved by resistance training exercise [65] (model 13) and healthy diet interventions [66] (model 47), but only in the short term (4 months – 1 year). Using model 12, Moreno-Agostino et al. [67] modelled trajectories of their healthy ageing index using growth mixture modelling to identify three latent classes: stable low, stable high, and fast decline. In model 41, Salinas-Rodriguez et al. [68] also used growth mixture modelling and identified three classes: steeply declining (low baseline and steep decline), slightly declining (medium baseline and slight decline), and moderately increasing (high baseline and slight increase). These trajectory groups follow the pattern that is observed in all measures of healthy ageing and is ultimately why healthy ageing exists as a field of study – some individuals experience very little health declines with increasing age whereas others experience sharp declines in health and functioning.

Comparison with other healthy ageing models

Two models were compared explicitly against other indicators of health to assess the validity of IC. Daskalopoulou et al. (2019) [58] compared their healthy ageing index with self-rated health, finding a significant association between the general factor of healthy ageing and the self-rated health measure, demonstrating some evidence of validity. Zhao et al. [69] found that impairment in IC domains predicted the incidence of disability measured with activities of daily living (ADLs) more than a disease-based approach (number of chronic diseases) over a 1-year follow-up, showing how a capacity-based approach is more useful in this scenario.

Predictive validity

The predictive validity of IC was tested for 15 models out of the 47 identified in the literature review. In the first paper to do so, Beard et al. (2019), including collaborators from the WHO [56], tested the predictive value of their IC model (model 7 in **Appendix 1.2**) for subsequent functional ability. Using data from ELSA, IC and multi-morbidity were measured in wave 4 (2008-9), and limitations experienced with ADLs and instrumental activities of daily living (IADLs) were measured 5 years later. The total IC score was produced from the bifactor model generated through CFA. Results found that both IC and multi-morbidity were found to independently predict incident loss of ADLs, but IC alone predicted loss of IADLs. This is probably because IADLs are higher-level tasks requiring more complex cognitive processing compared to ADLs. Reduced capacity for this more complex cognition is captured in IC but not by multi-morbidity, as the reduction in cognitive processing is likely sub-clinical and not enough to result in a diagnosis of cognitive impairment.

This association between IC and ADLs and IADLs disability was repeated by Beard et al. [70] in a sample of older Chinese adults using a bifactor CFA model of IC (model 27). Also, using factor scores extracted from a bifactor CFA model (model 8), Daskalopoulou et al. [59] found their healthy ageing index (including measures of IC and functional ability) predicted mortality and incident care dependence in a population-based study of ageing and dementia in Latin America, finding that those with lower healthy ageing scores were more at risk of care dependence and death in the following 3-5 years. Similarly, factor scores from a bifactor CFA model of IC in a Hong Kong osteoporosis study (model 20) were found to predict incident IADL limitations after 7 years [71] and incident frailty after 4 years [72], while factor scores extracted using principal components analysis in a Singaporean population-based sample (model 42) was found to predict 9-year all-cause mortality [57]. All this evidence indicates that IC factors scores show a good predictive validity for mortality which has also been replicated using IC scores generated with different methods.

Using the different data-driven methods of IRT to generate factor scores, Sanchez-Niubo et al. (model 12) tested the predictive validity of their healthy ageing (IC and functional ability) index in a sample of almost 344,000 individuals aged over 18 from 16 studies covering 38 countries [73]. They found that their index showed concurrent validity by corresponding well with sociodemographic and health factors, convergent validity by relating to healthy life expectancy and GDP within each country, and predictive validity by predicting mortality over a maximum of 20-year follow-up.

Predictive validity has also been tested in models that used averages over domains to generate an IC score. In a small sample of 481 adults aged 65 and over with sarcopenia [64], an IC score generated as an average of domain-specific z-scores (model 38) was found to be associated with mortality, with one standard deviation increase in IC associated with a 49% decrease in the risk of mortality. A weighted mean of IC domain scores was also found to be associated with 4-year all-cause mortality in a sample of 839 Taiwanese adults aged ≥50 years (model 43) [49]. Using an unweighted means of IC domain scores (model 33), Stolz et al. [61] found a 1-point reduction in IC associated with a 7% increase in the risk of ADL disability, 6% increase in the risk of nursing home admission, and 5% increase in mortality in a sample of 754 American adults taking part in a health plan.

IC scores that represent a sum of domain scores or impairments have also been checked for predictive validity. In 329 Chinese adults aged ≥60 years who were temporary inpatients in hospitals, Zeng et al. [74] found that higher IC scores were associated with decreased risk of 1-

year incident ADLs and IADLs limitations and mortality after adjustment for demographic factors, education, and chronic diseases (model 21). Similarly, Gonzalez-Bautista et al. [44] found that an increased total score, reflecting a higher number of impairments in IC domains, was associated with a higher risk of 5-year incident frailty and ADLs and IADLs disability in 759 adults aged 70-89 who were taking part in a nutrition and cognition clinical trial (model 24). In a sample of almost 9,500 Taiwanese adults aged ≥50 years requiring long-term care, Chen, Liu and Chang [75] summed binary domain-specific scores (1=good performance in that domain) and found lower IC scores to be associated with earlier onset of severe ADLs disability.

Finally, the predictive value of individual IC domains, without a total IC score, was explored in 3 models. Charles et al. [76] found that poor function in the locomotion and vitality domains predicted 3-year mortality and falls in a small sample of Belgian nursing home residents (model 9). In a large sample of 13-16,000 adults aged ≥65 years in South and Central America, India and China (model 30), Prince et al. [77] found that impairments in one or more domains of IC were strongly and independently predictive of incident care dependence and mortality. Focusing on particular domains in a sample of 756 community-dwelling Chinese adults aged ≥60 years, Yu et al. [47] found that impairments in cognition, locomotion, sensory and psychological domains were predictive of incident disability, visual impairment was predictive of falls, cognitive and locomotion impairments were predictive of emergency hospital visits, and poor locomotion was predictive of poor quality of life.

The consistent finding that IC can predict negative health outcomes, such as disability and mortality, suggests that IC is a relevant and useful measure of healthy ageing. The particular association with incident loss of functional ability, e.g., ADLs and IADLs disability, demonstrates that IC could indicate changes in capacity, perhaps upstream of loss in everyday functioning in older people. This supports the WHO framework of IC forming part of functional ability and therefore underlying more everyday-relevant functions and activities rather than directly reflecting them. Nevertheless, much of the testing of the predictive validity of IC has been carried out in specific and/or small samples, so further exploration in community-dwelling population-representative samples would bolster this evidence.

Indicators and domains of intrinsic capacity

Across the studies, there was a mixture of different types of indicators, with the majority of models using a mix of objective tests, validated scales, and self-report measures. The most common self-reported domain was sensory, with 20 models using at least one self-reported question on vision or hearing. Two models used both participant and informant-derived indicators, with informant answers contributing to the cognitive and sensory domains and functional ability indicators in one model (8) and “other” indicators in the other (30).

Cognition

Forty-one models measured various domains of cognition, with the most common indicators being tests of memory (e.g., word recall), orientation in time and space, and verbal fluency (e.g., animal naming). The most used validated scale for measuring cognition was the Mini-Mental State Exam (MMSE) [78, 79] which includes tests of memory, executive function, orientation and attention and has been identified as the recommended instrument to measure cognition in IC [36]. The full or modified scale was used in 13 models, while elements from the MMSE were used in a further 3 models. Other validated scales used in the models included the Community Screening Instrument for Dementia, the Short Portable Mental Status Questionnaire, the Montreal Cognitive Assessment, and the Abbreviated Mental Test. The number of cognitive indicators in each paper varied, meaning some models of IC contained more comprehensive cognition assessments, but almost all the IC models that included cognition measured the key cognitive component of memory.

Locomotion

The locomotion domain was measured in 43 models of IC. The most common indicator used was the Short Physical Performance Battery (SPPB), which had been identified as the recommended tool to measure mobility impairment by the WHO Clinical Consortium [36]. The SPPB measures lower extremity function and includes tests of standing balance, walking speed, and chair rising, covering key components of locomotion identified by the WHO [35]. The full SPPB was used in 11 models, and a further 4 models used the three elements but did not call it the SPPB. Another 12 models used the chair rise test, and 11 used walking speed as separate indicators, not as part of the SPPB. Other validated measures or tests used as indicators of locomotion were the Tinetti Performance Orientated Mobility Assessment (POMA) [80] (models 21 and 34) and the Timed Up-and-Go test (TUG) [81] (models 3, 42 and 47). The POMA assesses sitting and standing balance and gait in older adults with 16 items in the most common version (although there are other variations) [82] and attempts to replicate moves required during normal daily activities. The TUG involves standing from a chair, walking 3 metres and back, and sitting back down in the chair, with the time in seconds to complete the task recorded. A commonly used cut-off indicating an increased risk of falls is 13.5 seconds, although this ranges from >10 to ≥33 seconds in the literature [83]. The SPPB, POMA, and TUG all assess key areas of physical mobility (balance, walking, sitting and rising), albeit in different depths, but there are some limitations to consider. The SPPB and POMA both use an ordinal scale to score participants, with points for completing the tasks; this means they can be subject to ceiling effects when assessing higher-functioning older adults, which means the full spectrum of functioning is not captured. Additionally, all three measures would be affected by an individual's cognitive state. It is commonly found that those with cognitive impairment take longer or are not able to complete the tasks [84], highlighting the difficulty of isolating the physical and cognitive domains for assessment.

Three models used grip strength as an indicator of locomotion. This is interesting as grip strength, in particular, was highlighted as a measurable component of the vitality domain (**Table 1.1**), while general muscle performance was identified as a measurable component of locomotion. This perhaps highlights the difficulty with defining the vitality domain as well as the overlap between the domains, with muscle performance indicating an individual's ability to be mobile as well as their nutrition and metabolic status.

Three models used the Activities of Daily Living (ADLs) and/or Instrumental Activities of Daily Living (IADLs) or other measures of mobility that are relevant to functional ability. Functional ability is theorised to be an outcome of IC and was not included as a key component of locomotion; however, some use these measures as indicators of capacity in the locomotion domain - this highlights the potential difficulty in disentangling indicators and outcomes of IC and the need for clear guidance on indicators.

Sensory

Thirty-four models included measurement of the sensory domain, mainly with self-reported vision and self-reported hearing which were used in 27 models. Seven models included tests of hearing, including the whisper test, audiometry, and the Weber and Rinne tuning fork tests. Eight models used eye charts (where letters or symbols are displayed in varying sizes on a chart to assess the clarity of vision), and one model used the Frisby stereo test (a test of depth perception using symbols printed on plastic plates of varying thickness) [85]. Although objective measures of vision and hearing have been recommended as tools to measure this domain, the lack of objective tests across the models highlights the fact that many observational studies do not have data on these tests and tend to rely on self-reported problems with these senses.

Vitality

The vitality domain was measured in 43 models with a range of indicators, which is not surprising considering this domain has the highest number of identified components [35]. The most common single indicator used in 17 models was grip strength, which has been identified as a key component of vitality and considered a marker of various underlying systems, including brain health, nutrition, immune function, and hormone status in older people [86-88]. Thirty-two models used indicators related to nutrition, such as appetite loss (9 models), weight loss (12 models), or body mass index (BMI, 6 models) and 11 used the Mini Nutritional Assessment (MNA), which was the WHO-recommended tool for measuring malnutrition [35]. Seven models measured lung function, including tests of forced vital capacity, forced expiratory volume, peak flow, VO2 peak (peak oxygen consumption), and 4 measured feelings of energy – both highlighted as components of vitality.

One model by Masciocchi et al. (model 10) explored the definition of vitality, looking at physical vitality and mental vitality and compared their prediction of functional ability and hospitalisations among a sample of 541 French nursing home residents [89]. Physical vitality was assessed with grip strength, while mental vitality used three questions from the Geriatric Depression Scale (GDS) involving feeling satisfied with life, feeling that life is empty, and feeling full of energy. High physical vitality was found to predict fewer functional limitations, measured with ADLs, and lower mortality rates; however, high mental vitality predicted increased functional limitations in ADLs in the whole sample but not in a sub-sample excluding those with a diagnosis of dementia or depression. This result was posited to be due to the GDS questions not adequately capturing the mental vitality of those with a diagnosis of dementia and depression. High combined physical and mental vitality predicted a reduction in hospitalisation risk. It is interesting to consider different definitions of vitality, but it is unclear whether the premise of mental vitality follows the theoretical underpinnings of the vitality domain. It was posited more as a reflection of biological energy balance than a psychological domain by Cesari et al. (2018) [32], although psychological resilience was identified as a possible component of vitality by the WHO Clinical Consortium [35]. Nevertheless, it is important to consider the overlap between mental vitality and the psychological domain. When measuring mental vitality, Masciocchi et al. (2019) used three items from the GDS, which has been identified as a recommended tool to measure depressive symptoms under the psychological domain. Therefore, it is probably the case that the capacities under mental vitality are captured in the psychological domain, and the vitality domain should focus on the physical components of energy balance and nutrition.

Psychological

Forty models measured components of the psychological domain. The most common indicator was depressive symptoms, measured using the GDS [39] in 17 models, the Center for Epidemiologic Studies Depression (CES-D) scale [90] in 7 models, and with an explicit question on depressive symptoms in 6 models. The GDS and CES-D are common screening scales with excellent properties for screening depression in older adults [91]. Other less frequently used measures capturing depressive symptoms were the Composite International Diagnostic Interview

[92, 93], the Cornell Scale for Depression in Dementia [94], and the EuroQoL-5D [95]. Four models included indicators relating to sleep, and one model used items from the EuroQol-5D instrument for measuring health-related quality of life.

One model included social participation, and another included psychological support from relatives as indicators of psychological function. However, these social influences have not been identified as components of the psychological domain and, as extrinsic factors, could be considered more as an indicator of functional ability or an environmental influence in the WHO framework than an element of IC. There were various identified components of the psychological domain that were not tested in any model; however, the literature consensus appears to be that mood, specifically depression, is the key element of the domain to measure. Sleep was also included in some models and is identified as a component of the domain, but it could be argued that sleep is not only an indicator of psychological wellbeing as it is linked to many physical and mental states [96], such as chronic illness [97], frailty [98], cognition [99], mental health [100] and mortality [101].

1.2.3 Summary

This review found that IC has been operationalised in many different ways, with no two papers using the exact same indicators to measure domains and a mixture of methods used to generate a summary score. This reflects the current lack of an operationalised definition of IC for research and ambiguity around the same components and structure of the concept.

Development work has led to IC being composed of five main domains covering cognition, mobility, vision and hearing, psychological wellbeing, and energy balance. This five-domain structure identified theoretically was followed by the majority of IC models in the literature, with those not including certain domains normally due to missing information in datasets. One paper found that a 3-domain structure with just the locomotion, sensory and vitality domains performed just as well at predicting mortality as 5- and 4-domain models, which suggests that these domains are potentially the key elements of IC to measure for this outcome. However, this has not been explored further, and the idea of IC capturing capacity in all aspects of an individual and giving a holistic impression of capacity aligns with the overall goal of the WHO healthy ageing strategy. This ensures all dimensions of capacity that are very important for individuals' wellbeing and to healthcare systems are captured, e.g., cognition and psychological wellbeing.

Different types of indicators are used across the domains, and indicators of cognition, mobility and vitality were often measured with objective measures or tests of function, while vision and hearing and psychological wellbeing tended to rely on self-reported questions and scales.

Currently, there is no recommended method to generate a summary IC score when using existing data, leading to a wide range of methods seen in the literature. There is also a discrepancy between the operationalised measures of IC being published by the WHO, the organisation that originally proposed and defined the concept. The ICOPE screening tool developed by the WHO is composed of simple pass/fail tests focusing on key conditions within each domain [41]. Beard et al. and WHO collaborators' IC model generated with existing data and used to predict health outcomes has a wider range of indicators and used factor analysis to develop a more complex model demonstrating the structure of the concept and generating summary scores [56]. Due to the nature of using existing data, it is impossible to define a model that can be applied on all occasions, thus leaving some flexibility in the indicators may be helpful; however, adding clarity to the definition of each domain of IC and the exact components that should be captured would allow the literature to become more consistent.

Although the models of IC varied in indicators and methods used, there was consistency in the predictive validity of IC, with all papers that tested this finding that IC significantly predicted health outcomes for older people. The most common finding was that IC predicted functional limitations (measured with ADLs and IADLs) and mortality, with those with poorer total or domain-specific IC more likely to experience functional limitations and have a higher risk of death in the following years. This overall association between IC and health outcomes is key to the IC measure being a useful measure of healthy ageing that can indicate those who may require intervention to prevent declines in capacity. However, whether interventions targeted based on IC status can prevent capacity decline has not yet been tested, and all of the predictive validity tests have been carried out in observational data at a population, rather than individual, level, so the utility of IC to identify individuals is still unclear.

In creating IC, the WHO aimed to take a step away from disease- and impairment-based models of healthy ageing towards function-based models. This can be seen in the fact that very few models of IC include an illness or chronic condition diagnosis as an indicator; however, it is misguided to think IC is not in some way focusing on impairment and decline. IC plays a part in a strategy to prevent declines in functioning with age, and in order to do this, it should indicate a decline or impairment, as seen with the ICOPE screening tool. Therefore, there will always be a "negative" aspect to measuring healthy ageing, and the shift towards function-based models is more aimed at changing attitudes and stigma surrounding ageing as opposed to changing all the measurements of ageing in practice.

When measuring healthy ageing and especially creating policy, it is important to consider that indicators and scoring systems may not be relevant in or adapt to countries with different cultures and political systems [102]. The papers included in the current review measured IC in many individual countries around the world, but when investigating IC across countries and cultures, it will be important to consider the cultural sensitivity and validity of the measure in order to make valid interpretations and comparisons.

1.3 Social relationships as a determinant of healthy ageing

Many factors have been found to influence and predict healthy ageing in older adults, ranging from individual biology to sociocultural influences. Lifestyle factors and health behaviours are found to impact healthy ageing outcomes; the common factors implicated are smoking [103], alcohol consumption [104], physical activity [105-107], unhealthy diet, and higher body mass index [108, 109]. There are also known inequalities in healthy ageing outcomes, with individuals with the most advantage having markedly better health outcomes than those with lower advantages [25, 110, 111].

Social factors, such as social relationships and activities, are sometimes included as components of healthy ageing [24, 112] but are too considered a determinant of health and mortality, with the increased understanding that the social and biographical context of ageing is intertwined with biological processes and medical outcomes [113]. Large amounts of evidence have indicated that less social integration, poor quality social relationships, isolation and loneliness are related to a greater risk of all-cause mortality [114-120] and adverse healthy ageing outcomes [121].

1.3.1 Defining social relationships

There are many terms and definitions used to describe different aspects of social relationships and interactions, the most common being networks, support, participation, and engagement. In a seminal paper, Berkman et al. (2000) [118] outlined definitions for these terms, which are now commonly used.

Social networks and participating in activities are considered structural aspects of social relationships, meaning they describe the quantitative aspects and structure of social relationships [122]. Networks are described as the web of social relationships surrounding an individual and specifically encompass features such as density, duration, dispersion, and homogeneity of relationships. Network size is commonly assessed by asking about the number of known or close people, sometimes by a particular category, to understand network composition [123].

Social activities, also termed social participation or engagement, include meeting friends, attending events and volunteering, and are generally assessed with questions covering what type of activity and how often, where and with whom the activity takes place [124].

Social support represents functional aspects of relationships, such as provision and receipt of information (informational support), help with tangible needs (instrumental support), love, care and sympathy (emotional support) and advice with decisions (appraisal support) [118, 125]. Various indexes and scales for measuring social support have been developed, covering aspects such as the type of social support experienced (e.g., “I get help around the house”, “I get love and affection”) and satisfaction with the support that is available [126, 127].

The concepts of social isolation and loneliness are often used in the literature concerning the associations between social relationships and health in order to explore the effects of a lack of relationships. Social isolation is an objective measure of an absence of relationships related to small network size, little diversity and low frequency of contact, and represents the structural aspect of missing relationships [128]. On the other hand, representing the lack of functional aspects, loneliness is a subjective measure of negative feelings about missing relationships based on the perceived quality of social support and the extent to which social needs are met by others [128-130]. These measures are similar but can occur independently of each other; it is possible for an individual to be socially isolated without feeling lonely, and vice versa, or both isolated and lonely. Loneliness is driven by individual and cultural norms and expectations of what constitutes an optimal quantity or quality of social relationships, as an individual’s subjective evaluation of their situation will revolve around comparisons with these believed norms. The types of relationships that determine loneliness and social isolation are generally marital or partner relationships, relationships with family, relationships with non-relatives, e.g. friends, colleagues and other people partaking in social activities, and the size and overall composition of an individual’s network, with a more extensive and heterogeneous network, the more likely social desires are fulfilled [131].

1.3.2 Social relationships and healthy ageing

A large body of evidence has focused on social relationships and individual health outcomes, such as cognitive function, cardiovascular health, or mortality. These generally find a positive association on health with increased social participation [121, 132-135], larger social networks [136, 137], and more social support from others [129, 138-143] and a negative health impact of social isolation and loneliness [144-152]. In a meta-analytic review of studies testing the association between social relationships and mortality, Holt-Lunstad, Smith and Layton [153] found an average effect size of OR=1.5, indicating a 50% increased likelihood of survival for those with stronger social relationships (i.e., more social support, lower feelings of loneliness, larger social networks). This effect was comparable to other well-established risk factors for mortality, such as smoking and alcohol consumption, and was larger than the influence of risk factors, such as physical inactivity and obesity.

A smaller evidence base has investigated social relationships and multi-dimensional measures of healthy ageing, on which this section will focus, and very few have used IC. A literature search was carried out to capture papers that explored the association between social relationships and specifically multi-dimensional measures of healthy ageing. This search included publication alerts and keyword searches (see **Appendix 1.1.2**) as well as direct searches for papers assessing social relationships and intrinsic capacity, in particular. Papers were considered if they included a health outcome that measured ≥3 of the following dimensions: physiology or physical health, physical capability/function, cognition, psychological wellbeing, sensory function, and social functioning. These dimensions loosely followed those identified as part of IC, but also included elements of functional ability and social functioning that would not be strictly included in IC but have been included in other measures of healthy ageing [22]. A total of 14 papers were identified that fit the criteria at the time of the search; these are discussed in the following sections organised by the outcome they used.

Successful ageing

Nine of the papers identified used a measure of successful ageing as the multi-dimensional health outcome. Higher participation in social and leisure activities was found to be associated with an increased likelihood of successful ageing in a sample of Taiwanese octogenarians [154], where successful ageing was defined as being free of dependency with ADLs, without depressive symptoms, without cognitive impairment, and able to give social support to others. In another study of the oldest-old adults aged 95-108 years in Hong Kong, those living with family and friends and who had fewer barriers to social activities were more likely to have a higher score on a successful ageing index [155]. The index was comprised of 8 indicators: self-reported current health, ADLs, the Mini-Mental State Exam, the short version of the Geriatric Depression Scale, frequency of social engagement, family emotional support, perceived economic status of the household, and financial security. Both these studies found that more social participation and interaction were associated with better successful ageing for the oldest old; however, they also both included social functioning in their measure of successful ageing, so these results may not be surprising. To fully investigate the association between social relationships and healthy ageing, it would be more informative not to have social relationships as both a predictor and component of healthy ageing. Nevertheless, these results were supported by another study of older adults aged ≥65 years in Shanghai, where more frequent participation in social activities and being married were associated with a higher likelihood of successful ageing. Those deemed to have achieved successful ageing had an MMSE score at least 4 points above the educational-specific cut-off (those with a higher level of education had a higher cut-off), few difficulties with ADLs, a good to excellent self-reported mood, and no physical disabilities, so did not include a measure of social functioning. This gives some support to the results seen in the oldest-old; however, the studies in Hong Kong and Shanghai reported unadjusted or least-adjusted (only age and sex as covariates) associations and correlations, so more robust methods are needed to increase confidence in the results.

With regards to social support, positive effects of social support on multi-dimensional successful ageing have been seen across different populations, including Chinese nursing home residents aged ≥60 [156], community-dwelling Australians aged >60 [157], New Jersey (USA) residents aged 50-74 [158], and community-dwelling Chinese aged ≥65 [159]. All four of these studies used indicators of physical health in their successful ageing measure (including chronic conditions and self-reported physical health) [156-159], three included functional ability (e.g., ADLs and IADLs) [156, 158, 159], three included the MMSE to measure cognition [156, 157, 159], three measured psychological health (including mental health scales, life satisfaction, and diagnosed mental health conditions) [156, 157, 159], two included measures of social functioning (frequency of participation in social activities) [156, 159], and one included a subjective rating of successful ageing [158].

Conversely, in a longitudinal study of Australian residents aged ≥70 years, elements of social connectedness (marital status, the number of individuals living in the household, number of relatives visited monthly, number of friends visited without an invitation and number of hours of social activity) were not found to predict successful ageing after a median of 11.7 years follow-up [160]. In this study, successful ageing was based on the absence of chronic health conditions, the absence of major difficulties with physical functioning, and the absence of psychological distress. Comparing this result with the number of studies that find a positive association between social support and successful ageing indicates that the quality of the relationships (support) may be more important for successful ageing than the quantity (connectedness). However, the studies focusing on social support were mostly cross-sectional, whereas this study was longitudinal, so it may also be that the relationship between social relationships and successful ageing is seen at one-time point and does not extend so much over time. More longitudinal studies would be needed to understand the temporality of this relationship.

Health-related quality of life

As an indicator of an individual's overall health status, health-related quality of life (HRQL) has also been used to assess healthy ageing in older people across multiple domains, including physical health, physical functioning, and psychological health. As a measure focusing on the quality of life, the measures are mostly self-reported feelings and beliefs about health and ability, as opposed to objective tests.

In a cross-sectional study of Spanish adults aged ≥65, HRQL (measured with ratings of overall health, pain, mobility, self-care, daily activities, and mood) was found to be higher among those who engaged in cognitively stimulating and group social activities, had lower social isolation, increased social support and high social trust, and rated their social life as satisfactory [161]. HRQL measured in the same way was also found to be lower among older English adults who were deemed socially isolated (those with less than weekly direct contact with friends and relatives) compared to the HRQL in age-matched UK population norms [162]. In this cross-sectional study, social isolation was independently related to self-reported health and HRQL, even when adjusted for depression, physical comorbidity, age, gender, living alone, employment status, and accommodation type. However, as a cross-sectional study, the direction of this relationship could not be entirely ascertained.

Also using HRQL, Kim and Lee [163] found that increased social support from significant others and friends was associated with lower physical health and higher mental health scores on the 12-item Short-Form Health Survey in a cross-sectional study of community-dwelling South Koreans aged ≥65 years. The negative association between physical health scores (physical function, physical limitations, pain, general health, and vitality) and social support was an unusual result that goes against previous findings. It was suggested that as half of the sample had lived alone for approximately 20 years or more with chronic conditions, these individuals had developed the skills to manage their health problems without depending on significant others and perhaps rely more on social services and care providers for assistance with daily functions. Therefore, social support may not be related to or important for physical health in these individuals. However, this could also be culturally specific to South Korea, where these care services are commonly provided. Additionally, as a cross-sectional study, it is not possible to unpick the direction and temporality of this relationship; it may be that those with poorer physical health seek out or receive more social support.

Frailty indexes

Finally, one study identified in the search used a multi-dimensional frailty index to assess the association between sociodemographic and lifestyle factors and 2-year frailty transitions in a sample of Chinese older adults aged ≥60 years [164]. The index included 36 indicators covering the presence of chronic diseases, difficulties with ADLs, physical and neurological signs (urinary incontinence, impaired hearing, irregular gait pattern, difficulty doing up buttons, a change in writing, voice weakening, and facial change), and cognitive and mental symptoms (self-reported memory problems, orientation in time, dyscalculia, frequent repeating, impaired judgement, difficulty in operating a remote control, and loss of interest). An index score was calculated per person as the number of deficits over the total number of indicators; the resulting scores were then categorised into robust (very few deficits), prefrail (some deficits), and frail (more deficits). The results showed that more frequent interactions with neighbours and participation in various social activities predicted a lower risk of those who were prefrail at baseline becoming frail after 2 years and a higher chance of improving to robust from a prefrail state. These results show that, when taking a deficit-based approach to measuring health in older adults, more frequent social interactions and participation shows a positive association with health for those with some deficits but not for those with more deficits, who could be considered frail. This could indicate that there could be a cut-off to health status, beyond which these social relationship elements do not have such a positive impact; however, this would need investigating in further studies.

Intrinsic capacity

Two studies so far have explored the relationship between social factors and IC. Huang et al. (2021) [63] measured IC over 3 years using five domains and generated a total score using the average of domain z-scores (**Appendix 1.2**, model 19) and tested whether social frailty was associated with IC. They used Bunt et al.'s definition, which characterised social frailty as a lack of general resources (resources that are beneficial in an indirect way for fulfilling social needs, e.g., education or income), reduced social behaviour and activities, insufficient social resources, and compromised fulfilment of social needs [165]. Following this definition, using data from the Nagoya Longitudinal Study for Healthy Elderly, social frailty was measured with 4 indicators – the need for financial support, living alone, participation in social activities, and regular contact with others – and resulting scores were categorised into social robustness, social prefrailty, and social frailty. Results found that the IC scores of those in the social prefrailty and social frailty groups declined more over three years than the socially robust group, especially in the cognition, psychological, and vitality domains; socially prefrail/frail men also showed a greater reduction in the psychological and cognition domains than women.

In a more recent study, Leung et al. (2022) [50] found that IC was positively associated with social engagement in a cross-sectional analysis. In a recruited sample of 304 community-dwelling older adults living in Hong Kong, IC was measured in five domains with validated tests

(**Appendix 1.2**, model 45), each with a cut-off indicating impairment, and a total IC score was generated by summing the scores across tests and domains – a higher score indicated better IC. Social engagement was assessed with the frequency of engagement with leisure activities, hobbies, work, volunteering, supporting family, education, or spiritual activities, with the categories inactive, less active, and active. A structural equation model found a significant positive relationship between IC and social engagement, and a mediating role of IC was found between age and social engagement, indicating that age's influence on social engagement depends somewhat on the individual's IC. It is feasible that an individual's capacity across the IC domains would influence their ability to be engaged with different social activities, as impairments in IC domains would make it more difficult to access or enjoy social activities. However, being a cross-sectional study, it is difficult to make conclusions about the direction of any associations, and it may be the case that the association between IC and social engagement is potentially bidirectional.

1.3.3 Summary

Although a couple of studies have begun to explore the relationship between IC and social relationships and activities, the associations between social isolation and IC, specifically, is yet to be explored.

In analyses using other multi-dimensional measures of healthy ageing, a positive association between a higher quantity and quality of social relationships and better health is generally seen, although more robust methods and longitudinal analyses would strengthen the evidence base.

Studies focusing on successful ageing found that more frequent participation in social activities and more social interactions through living arrangements or partnerships were associated with more "success" in older and oldest-old populations in Asia. However, a more robust methodology is needed to further support these results. Additionally, in cross-sectional studies, social support has been shown to be positively associated with successful ageing in populations of older adults from around the world, but a longitudinal analysis showed that this effect might not extend over time.

Similarly, HRQL measures, which focus on perceptions of health and ability, were found to be higher among those with more frequent social participation and more social support and lower among those who were socially isolated. Nevertheless, these studies were again mostly cross-sectional, and the HRQL outcome is quite different from other healthy ageing measures as it focuses on perceptions and not performance. Finally, a study utilising a frailty index found that social participation was beneficial for those with prefrailty but not frailty, indicating that there may be a health status cut-off beyond which positive social relationship factors may not stabilise or improve health.

In summary, much of the current evidence on the association between social relationships and multi-dimensional healthy ageing is cross-sectional, thus, there is a need to expand on these results in longitudinal data, which will help explain cause-and-effect and the temporal order of the relationship. Additionally, a lot of the previous studies explored the associations between a range of predictors and the healthy ageing outcome and did not use more complex analyses than multiple regression. As such, more investigation targeted at specific social relationships as predictors using more sophisticated methods would be another way to improve understanding.

In the current literature, it is also difficult to compare results across studies as most measure social relationships and healthy ageing in a different way, even if they use the same underlying concepts, such as successful ageing or social support. It is also hard to compare these measures against IC as they often involve indicators that would not be included in IC, such as functional ability, chronic conditions, and social functioning. In future research, it will also be important to disentangle social relationships from the health outcome when exploring social relationships as a predictor to get truly informative results and understand cause and effect.

1.4 Inflammation as a mechanism

As social relationships have been found to affect healthy ageing, it is important to explore the reasons and mechanisms for this association. As well as defining terms, Berkman et al. [118] laid out a framework by which social relationships could influence health, suggesting a cascading model from societal level factors to psycho-biological processes. According to this model, elements at the social-structural level shape the structure and characteristics of social networks, which in turn facilitate engagement in social activities and access to social support. These psychosocial mechanisms then influence health through various pathways such as healthy behaviours, psychological states and traits, and direct physiological pathways like the immune and stress systems. For example, the hypothalamic-pituitary-adrenal (HPA) axis is a hormonal response system that is activated by stressful events and ultimately results in cortisol being excreted from the adrenal gland [166]. Cortisol has many important roles in the body, but when there is inadequate or excessive amounts, it can become harmful [166, 167]. There are also other hormone axes (the sympathetic-adrenal-medullary and hypothalamic-pituitary-ovarian) and pituitary hormones, as well as interactions between the brain and immune system through neuro-immune pathways, that respond to stress by secreting substances that bind to white blood cells, influencing and directing immune responses [168].

These stress processes are a direct way for social relationships to affect health. Social isolation is shown to increase stress and vascular resistance, slow wound healing and promote poor sleep in young adults [169], and seems to affect multiple organ systems, particularly the cardiovascular, neuroendocrine and cognitive systems [170]. It is hypothesised that humans have an instinctive need to belong and when this is not satisfied, an internal response system is activated to prevent potential adverse outcomes, but this response is taxing on physiological systems and can have deleterious effects [171]. Nevertheless, social relationships can also illicit beneficial physiological processes. Supportive interactions with others are found to benefit immune, endocrine and cardiovascular functions and reduce allostatic load – a marker of physiological wear and tear [167, 172, 173]. The beneficial effects of social relationships can be seen across the life course, with supportive childhood environments promoting the healthy development of physiological systems [174] and social support in adulthood shown to reduce physiological responses such as cardiovascular reactivity to both anticipated and existing stressors [175].

A specific physiologic pathway identified in the Berkman et al. model is immune system function, a key element of which is inflammation. Inflammation is a normal part of the body's defence system and involves communication molecules, termed cytokines, which can promote inflammation as a generalised response to attack a foreign invader, e.g., bacteria or virus, or clear away damaged tissue [168]. Inflammation in response to infection or damage to tissues normally lasts for a short amount of time (days) and is termed acute inflammation [176]. Of more interest to research in ageing is chronic inflammation, which is long-term (lasting months to years) and systemic, thus not localised to a site of infection or trauma [177]. Chronic inflammation is commonly measured in epidemiological and ageing studies using biomarkers present in the blood; the most frequent markers used are C-reactive protein (CRP), fibrinogen and interleukin-6 (IL-6) [178]. Chronic inflammation is widespread in older people, with some referring to this phenomenon as "inflammageing" [179]. It is a known risk factor for cardiovascular and other chronic diseases, frailty, limitations in activities of daily living, impaired balance and walking speed, depression, and dementia [180-183].

1.4.1 Inflammation and social relationships

As suggested by the Berkman et al. framework, inflammatory processes can be influenced by social relationships. In a meta-analysis, social support and social integration were found to be significantly related to lower levels of inflammatory markers, indicating that inflammation is one important mechanism linking these social factors to the development of disease [184]. Positive social support from family, friends, and spouse was found to moderately protect against inflammation; however, the negative associations on inflammation from strained relationships were more robust than those from positive support [185].

Social isolation and loneliness have both been found to be associated with higher levels of fibrinogen generally and in response to stress [186-188], indicating that isolation and loneliness are psychological experiences with adverse effects on biological stress systems. Social isolation, in particular, has been found to be significantly associated with higher levels of IL-6 and CRP in older adults taking part in the US National Health and Aging Trends Study, even after adjusting for age, gender, race/ethnicity, income, tobacco use, BMI, and chronic conditions [189]. In a systematic review and meta-analysis of the association between loneliness and social isolation with inflammation, loneliness was found to be associated with IL-6 in fully-adjusted analyses, while isolation was associated with CRP and fibrinogen in least-adjusted analyses but not when key confounders had been accounted for [190]. The meta-analysis concluded that social isolation and loneliness could be associated with inflammatory markers; however, there were large amounts of heterogeneity found in the included studies' theory and methods which makes interpreting the overall picture difficult. It was highlighted that robust methodologies are needed to further understand the complex relationship between these social factors and inflammation.

The meta-analysis also highlighted a possible effect of sex on the relationship between isolation and CRP and fibrinogen. Studies from the USA and UK have previously found differences in the association between social isolation and inflammation between men and women, with most associations only significant for men. In the MacArthur Successful Ageing Study in the US, men who were in the lower quartiles of a social network score and therefore deemed more socially isolated were over twice as likely to have elevated fibrinogen [191] and elevated CRP and IL6 [192] compared to those in the highest quartile. No significant associations between social isolation and inflammatory markers were found for women. This result was repeated in another US study, the Third National Health and Nutrition Examination Survey, where social integration was found to be significantly associated with elevated CRP in men aged ≥60 years and women aged 20-59 years when adjusted for only age and ethnicity, but this significant association remained only for men when fully adjusted for sociodemographic and health-related covariates [193]. Similar results have been found in ELSA, where a significant association between isolation and CRP was not found in women [194], and the onset of loneliness was only associated with increased CRP and fibrinogen in men [195]. The reason for this sex difference is not fully understood. One potential explanation is that there are differences in qualitative elements of social relationships between men and women that were not captured in the measures of social isolation, which focused on quantitative elements. For example, in the MacArthur Successful Aging study, a social network score was created from six indicators focusing on quantitative elements: the presence of a spouse, number of close relatives and friends, and frequency of participation in religious services, activities and clubs. This didn't capture whether the social relationships in question were supportive or burdensome, or if the respondent was the care-receiver or care-giver in the relationship, with women more likely to report negative relationships and caregiving than men [191-193]. However, the same sex difference has also been seen with measures of loneliness that do capture more subjective feelings about relationships, so the difference may not be fully down to differences in these qualitative elements of the relationships. It could also be differences in the biologic pathways between isolation and inflammatory marker as there have also been sex differences reported for the relationship between the environment and other biological markers, such as blood pressure [194, 196] and neuroendocrine reactivity [197].

The observed sex differences highlight how the connection between inflammation and social relationships is not straightforward, and it may also be dependent on the type of social interaction. Social support from friends was found to be more impactful than that from family or neighbours, indicating that support from experientially similar people (friends) may be different from the perhaps obligatory support from family or neighbours [198, 199]. Additionally, structural and functional aspects of social support are differentially associated with biomarkers of inflammation, with structural elements related to lower IL-6 and functional aspects related to CRP; there may also be effects of age and gender on this relationship [200]. It is also possible that the association is moderated by other factors. The association between perceived social support and inflammation was found to be moderated by self-esteem, with social support predicting levels of CRP for those with higher self-esteem but not low [201].

1.4.2 Inflammation and intrinsic capacity

Inflammation was originally proposed as a possible indicator of IC, as part of the vitality domain [35] or as a separate domain [34]. However, although inflammation appeared as a domain in the initial data-driven factor analysis model by Araujo de Carvalho et al. [34], inflammation and blood pressure were removed from the later theory-driven model as they were deemed to be drivers of change rather than indicators, but it is still unclear whether inflammation is a direct cause or a biomarker of biological ageing [179]. There may also be a bidirectional relationship between inflammation and IC, with those with higher IC being able to develop anti-inflammageing mechanisms and counterbalance detrimental age-related processes [202].

In the first study to explore IC and inflammatory biomarkers, Giudici et al. [62] measured IC in 1,516 participants of the Multidomain Alzheimer Preventive Trial (MAPT) aged ≥70 years and tested whether chronic inflammation was associated with impairments in IC. The MAPT study is a prospective observational study set up to investigate the efficacy of omega-3 supplementation and intervention in preventing cognitive decline over 3 years; all participants did not have dementia but suffered from memory complaints, limitations with at least one instrumental ADL or slow walking speed. IC was measured on five occasions over the 5-year follow-up (baseline, 6, 12, 24, 36, 48 and 60 months) in four domains: cognition, locomotion, vitality and psychological (**Appendix 1.2**). The inflammatory biomarker CRP was measured from blood at baseline, 6 months, and 12 months follow-up, with chronic inflammation defined as having at least two consecutively high CRP readings (3-10mg/L). Another marker of potential inflammation, homocysteine, was measured at baseline only, with hyperhomocysteinemia defined as having homocysteine concentrations >15μg/L. Total and domain-specific IC scores were found to decrease over follow-up in those with and without chronic inflammation, but this decrease was more pronounced in those with chronic inflammation in unadjusted analyses; however, this result did not reach statistical significance in analyses adjusted for age, sex, education, BMI, MAPT group and time interaction. The same pattern of results was observed for homocysteine, except decreases in handgrip strength remained significantly worse in the hyperhomocysteinemia groups in the adjusted analyses. In those with both chronic inflammation and hyperhomocysteinemia, marked declines in total IC score were found in comparison to the groups with normal biomarker values, and significant impairment in psychological domain scores remained in adjusted analyses.

In a subsequent study of 283 adults aged 60-97 years from China, Ma et al. [203] found that individuals with low IC, measured with the ICOPE screening tool, had higher levels of CRP but did not show differences in white blood cells or fibrinogen when compared to those with higher IC.

Similarly, in a sample of 130 Chinese adults taking part in the Cardiovascular Health, Cognition and Aging Study, Ma et al. [204] also found that higher concentrations of tumour necrosis factor receptor 1 (TNF-R1, a pro-inflammatory cytokine [205]), were associated with lower IC but found no association between IC and IL-6, insulin-like growth factor-1 (IGF-1, a hormone implicated in inflammatory processes [206]), and vaspin (an anti-inflammatory protein [207]). In the most recent study to assess IC and inflammatory markers, Meng et al. [49] found that high IL-6, high E-selectin, low serum albumin, and low folate – all biomarkers of inflammation and endothelial (lining of blood vessels) function – were associated with low IC in their sample of 839 individuals aged ≥50 years in the Social Environment and Biomarkers of Aging Study in Taiwan. However, they did not find significant differences in CRP or fibrinogen between those with low and high IC.

As inflammatory biomarkers are associated with many adverse outcomes in older age, it is not surprising that they are implicated in reduced IC. However, the current evidence gives a mixed picture of the relationship between inflammatory markers and IC, with different biomarkers implicated in different studies. This may be due to the complex relationship between inflammation and the expression of capacity but may also be due to methodological issues – most of the samples testing these associations have been relatively small or specialist samples that are not necessarily representative of the general population – thus more evidence of the link between inflammatory biomarkers and IC is required.

It is interesting that adjustment for sociodemographic factors accounted for the difference in IC between chronic and non-chronic inflammation seen by Giudici et al., indicating that these factors may be more important for IC than inflammation. Within the paper, there is a discussion of certain behaviours that could elevate inflammation, such as smoking, obesity, sedentary lifestyle, and diet, and how biomarker concentrations could be the outcome of these influencing factors; it will also be informative to explore the social factors that may be influencing levels of inflammation and whether this then influences subsequent levels of IC, following the cascade model of social influence on biology and health.

1.4.3 Social relationships, inflammation, and healthy ageing

A wide range of evidence has supported the association between missing or poor-quality social relationships and poorer health, the link between social relationships and inflammation, and the link between inflammation and health outcomes. However, there is less evidence exploring the entire pathway with inflammation as a mediator between social relationships and health, and none looking specifically at healthy ageing or IC as the health outcome.

Penwell and Larkin [208] reviewed the literature linking social support and inflammation in the context of cardiovascular disease and cancer patients. They followed the requirements for mediation set out by Baron and Kenny [209], which specify the demonstration of three relationships between a predictor, mediator and outcome: social support is associated with disease outcomes, inflammation of associated with disease outcomes, and social support is associated with inflammation; mediation is supported if all (or most) of the variance in the relationship between social support and disease outcomes is explained by inflammation. The review results gave tentative support to a link between the quality of social relationships and inflammation with several well-designed studies finding social support predictive of levels of inflammation, but it was deemed premature to conclude that inflammation is the mechanism between social support and health.

A couple of studies have explored the mediating role of inflammation explicitly. Boen et al. [210] found that, among cancer patients, higher levels of satisfaction with social support were associated with lower levels of the inflammatory markers CRP, IL-6 and TNF-alpha, and these inflammatory markers were positively associated with mortality risk. Formal mediation tests found that CRP and IL-6 accounted for a large amount of the association between social support and mortality risk, but these tests were limited by low power. Yang et al. [211] similarly found evidence for the mediating effects of inflammation on the relationship between social isolation and all-cause and disease-specific mortality, with inflammation accounting for 12-24% of the associations. They concluded that with all other factors remaining equal, inflammation in individuals with social isolation greatly increases the likelihood of mortality.

1.5 Summary

Healthy ageing has been conceptualised and operationalised in multiple ways. Since 2015, there has been a concerted effort by the WHO to define a framework to direct proactive interventions to prevent manifestations of disease and impairment, part of which involves operationalising IC as an indicator of healthy ageing. The development work and research using IC have outlined five domains of capacity that should be captured in the measure: cognitive health, locomotion/mobility, sensory function, vitality/energy balance, and psychological/mental health. Different conceptualisations of IC have been shown to predict functional ability, mortality, and other health outcomes, which is an important step to assure the validity of a new conceptualisation, although not all models of IC have had their validity checked in this manner.

IC is becoming more established as a valuable tool to measure healthy ageing in a way that overcomes some of the weaknesses of previously established deficit-based models. It is able to capture the main dimensions relevant to health in older age and currently maintains flexibility in the indicators used. This is a positive and negative outcome of the lack of an operationalised definition, as it allows for a range of studies with different indicators to measure IC, but it means that the comparison of IC across different studies and populations is more difficult if the conceptualisation and measurement of IC are different. There are some standard tools and types of indicators used across the growing research, but, at present, there is no consensus on the method to generate an IC score, with a range of simple to more complex methods used in the literature. There is also less exploration of the trajectories of IC, even though this is a central element of the WHO framework for IC.

There is a broad evidence base regarding the positive impact of numerous good-quality social relationships and the detrimental impact of poor-quality or a lack of relationships on many health outcomes covering cognitive health, physical function, disease risk and mortality. There is emerging evidence suggesting inflammation could be a possible mechanism for this effect. While there is a wealth of information on social relationships and individual health outcomes, there is less evidence of the association between social relationships, particularly social isolation, and multi-dimensional measures of healthy ageing. Social support and participation have been associated with successful ageing, health-related quality of life and frailty indexes cross-sectionally in multiple populations of older adults around the world. However, the association over time and for social isolation, specifically, are less well evidenced.

Inflammation has been identified as a possible mechanism through which social relationships impact health, and evidence has found an association between social relationships and inflammation, with more frequent contact and supportive social relationships related to lower inflammation and vice versa. Inflammation has been theorised to be linked with IC, at first as an indicator but more as an underlying driver of IC. Different biomarkers of inflammation have been linked to IC, with increased inflammation generally seen in those with low IC. Still, the evidence is mixed and limited by small and specialist samples. As it is associated with social relationships and IC, inflammation is a candidate for a mediating role between these two factors, but there is limited evidence of this relationship.

As a relatively new model of healthy ageing, there has been increasing use of IC in literature, but it has not yet been used to explore the effects of both social relationships and inflammation on healthy ageing. This is an important area of research since the IC model forms a central part of the healthy ageing policy and intervention frameworks being rolled out worldwide. There is also a little exploration of the entire cascade pathway from social relationships to health, with inflammation as a mediator, especially with regard to healthy ageing and social isolation.

Raised inflammation is a notable candidate in the process of biological ageing. However, it is important to understand its involvement in the whole cascade from an individual's everyday life to their health if time and resources will be spent on targeting inflammation in a health intervention. Similarly, increasing the number of social interactions is a goal of social prescribing interventions to improve health, so understanding how social relationships affect health is key to being able to direct these interventions to communities and populations who would benefit the most. Finding that social relationships impact health through inflammation would mean that interventions could focus on social factors upstream of inflammation and avoid the use of direct interventions, such as drugs which would come with side effects and ultimately not address the underlying problem.

Therefore, the current project aims to investigate the association between social isolation and healthy ageing, measured by a multi-dimensional measure of intrinsic capacity, and explore the mediating effect of inflammation on this relationship in parts and as a full cascade model.

Chapter 2: Research aim, objectives, and hypotheses

2.1 Research aim

The overall aim of this thesis is to investigate the association between social isolation and intrinsic capacity (IC) in older adults in England and assess whether inflammation is a mediator of this relationship.

2.2 Objectives and hypotheses

2.2.1 Objective 1

To operationalise IC as a measure of healthy ageing (across multiple time points) in an observational study of ageing. This will involve checking the validity of the model of IC by testing whether it is associated with adverse health and functional outcomes, which are theorised to be downstream of IC, and testing the associations between sociodemographic and other health-related factors and IC. The generation of the score longitudinally will also require testing of the score's measurement invariance over time.

Hypotheses

1) The IC score is negatively associated with adverse health and functional outcomes such as functional impairment, hospital admissions, and mortality.
2) The IC score is associated with key sociodemographic factors, such as age, sex, and socioeconomic position, and health-related factors, such as subjective health ratings. Higher IC scores will be associated with younger, more socioeconomically advantaged, and "healthier" individuals.

2.2.2 Objective 2

To examine the association between social isolation and IC and whether social isolation predicts IC over time.

Hypotheses

1) High social isolation is associated with a lower (worse) IC score, cross-sectionally and over time.
2) Those with low social isolation will experience less decline in IC scores over time than those with high isolation.

2.2.3 Objective 3

To test the direct and indirect associations between social isolation and IC through inflammation.

Hypotheses

1) Inflammation predicts IC, with those with raised inflammation experiencing lower IC scores at baseline and larger declines in IC scores over time.
2) Social isolation is associated with inflammation, with those with high social isolation more likely to experience raised inflammation.
3) The association between social isolation and IC will be partially mediated by inflammation.

2.3 Conceptual model

The conceptual model that provides a general framework for this research is depicted in **Figure 2.1** . The far-right side of the diagram includes a reference to the WHO's framework for healthy ageing, which specifies that IC determines functional ability, along with other environmental factors. The model describes a pathway for social isolation to influence IC: directly and through stress and inflammation. The pathways investigated in this research have been highlighted with black arrows. In the indirect path through inflammation, it is expected that social isolation influences stress processes and the maintenance and repair systems of the body. This, in turn, affects the level of inflammation, which then impacts IC; this is the main pathway that will be investigated in this research. The model also highlights some key outcomes of IC – functional ability, which is outlined by the WHO model, as well as hospital admissions and mortality – which will be investigated in this research in order to test the validity of the IC measure. The pathway(s) displayed in the figure sets out a temporal order for each stage, but this order may not be that simple in reality – for example, changes in the level of inflammation may occur at the same time as changes in stress, not necessarily only afterwards. There may also be more complex relationships between the outcomes specified in the figure, for example, functional ability itself probably determines hospital admission and mortality. This project will not test the temporal order within this framework precisely as it will not measure stress and the maintenance of physiological systems directly and will not explore the relationship between outcomes.

There are other pathways included in the conceptual model which are beyond the scope of this thesis, for example, those involving health behaviours, genetic predisposition, and other social, cultural, and demographic factors. Regarding health behaviours, it is assumed that the level of an individual's social isolation influences the lifestyle behaviours they adopt, which in turn impact IC; this pathway will not be directly tested in this research but will be important when considering adjustment for covariates. There are some other factors identified in the model that will not be possible to measure or adjust for; for example, genetics will play in role in predisposing individuals to a certain level of inflammation, as well as functional performance and health outcomes as captured by the various domains of IC.

Regarding social isolation, the model assumes that an individual's degree of isolation is influenced by social, cultural, and demographic factors, such as financial wealth, occupation, cultural norms, and expectations, as well as individual factors, such as personality traits, values, and interests. It is assumed that these factors can generate conditions that are conducive to more or less connection and interaction with others, e.g., higher wealth may allow greater access to certain social groups and activities, some cultural norms may encourage more social interaction, or certain personality traits may mean individuals do or do not seek out lots of social contacts. In the conceptual model, these factors are also proposed to directly influence stress, health behaviours, and IC; this pathway is beyond the scope of this thesis but some of these factors will be included as covariates in the analyses.

There is a feedback loop within this particular framework, presented with the dashed arrows. It is assumed that an individual's functional ability will impact upon their social isolation, health behaviours, and broader social, cultural, demographic, and individual factors; for example, an individual's functional ability will determine what social activities they can participate in, the wealth they can accrue, or the amount of exercise they can perform. This will also not be directly assessed in this thesis but is considered in the conceptualisation of the wider model beyond the main pathway being measured.

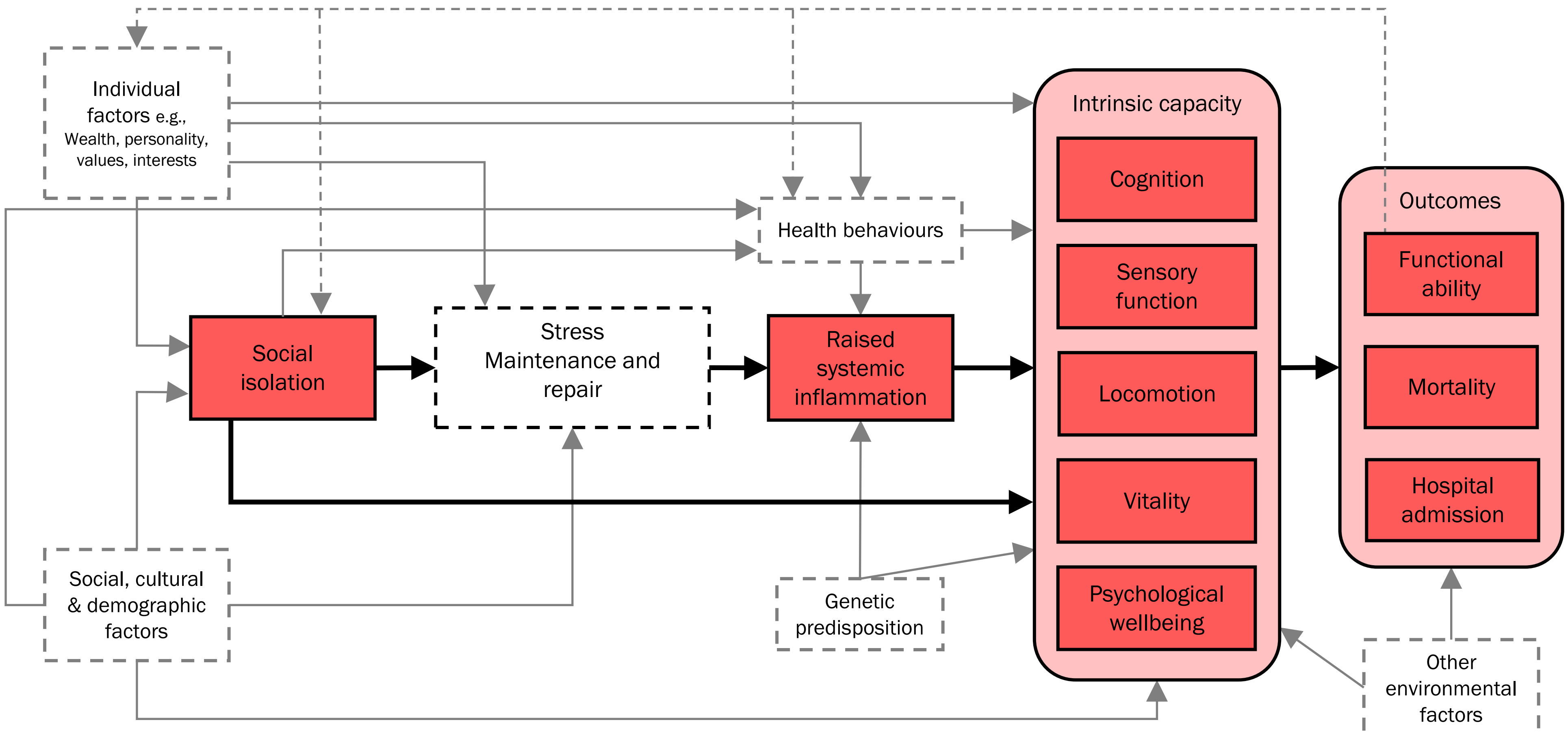

Figure 2.1 Diagram of the conceptual framework for this research.

Arrows indicate influence but not total causation. The bold lines and coloured boxes represent the main pathway being explored in this research; dashed boxes represent factors not being directly measured/focused on; however, some factors will be included in analyses as covariates.

Chapter 3: Sample

3.1 Study description

The English Longitudinal Study of Ageing (ELSA) [212] is a large, ongoing, nationally representative prospective cohort study of men and women aged ≥50 years living in England. ELSA was established in 2002, using objective and subjective measures to assess the causes and consequences of health-related outcomes. The original sample consisted of people born before 1 March 1952, drawn from private English households participating in the Health Survey for England in 1998, 1999, or 2001 [168]. The sample was selected through multistage stratified probability sampling, which first selected postcode sectors and then household addresses. Since 2002, there have been 9 waves of data collection biennially. The sample has been refreshed at waves 3, 4, 6, 7 and 9 with participants selected from the Healthy Survey for England. The same eligibility criteria for new participants has been used since wave 1, with the exception of the range of year of birth which changes to include those aged ≥50 years at each refreshment [213]. All ELSA participants provided informed consent prior to the study, and ethical approval was granted by the London Multi-Centre Research Ethics Committee. Data are made available through the UK Data Service.

3.1.1 Interviews and nurse visits

In every wave, interviews are carried out face-to-face with an interviewer using computer-assisted interviewing (CAPI) alongside self-completion questionnaires filled out with pen and paper. In waves 2, 4, 6 and 8/9, nurses also conducted a follow-up visit to perform various physical examinations and collect a range of biological measures. All core members who completed the main interview themselves (not by proxy) were eligible for a nurse visit, and consent was given separately. In waves 8 and 9, the participants were split, with half receiving the nurse visit in wave 8 and the other half in wave 9; these waves were combined for the purpose of this study.

ELSA also interviews some partners of those recruited as part of the target sample (core members), some of whom are aged <50 years. In this study, only core members or ELSA were included.

3.2 Sample selection

This section will describe the ELSA sample that was eligible for the generation of an intrinsic capacity score. The precise sample used in each analysis in further chapters may be different due to missing data or exclusions due to other reasons, such as death. The sampling process can be seen in the flowchart in **Figure 3.1**.

As objective measures of performance are important to capture IC in a well-rounded manner, the main waves of interest for the generation of intrinsic capacity are the waves of ELSA, including a nurse visit: waves 2, 4, 6, and 8/9. Wave 2 was used as the baseline for this study.

In wave 2, a total of 9,432 respondents were interviewed between June 2004 and July 2005; two were excluded at this point due to errors (age decreasing over time and an interview after the reported date of death). Of the remaining respondents, 8,778 were core members, while 652 were partners and were excluded from this study. Of the core members, 7,665 consented to a nurse visit which took place in a separate visit after the main interview between July 2004 and August 2005.

Within each nurse visit, ELSA also included an age limit of ≥60 years for some performance tests [214], so those aged under 60 were also excluded. This left a sample of 5,343 in wave 2 who were eligible for the generation of an intrinsic capacity score and formed the baseline sample for this thesis. Throughout this thesis, the precise sample and missing data on the analysis variables for each analysis will be outlined in the methods section of each separate chapter.

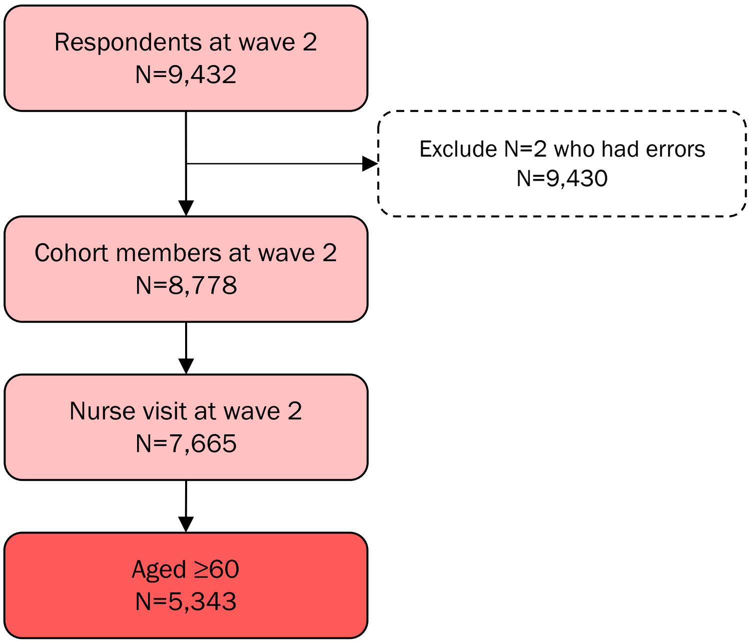

Figure 3.1 Flowchart showing the sample selection process at baseline (Wave 2).

3.3 Covariates

A common set of covariates will be used throughout the different sections of this research project to control for potential confounders. These will cover key demographic, socioeconomic and health-related factors that are known to be associated with social isolation, inflammation, and/or health in older age.

3.3.1 Age

Chronological age is inextricably linked to healthy ageing. Although the health experiences of individuals as they age are heterogenous, generally, with increasing age, the gradual accumulation of molecular and cellular damage at the biological level leads to a decrease in physiological reserves, an increased risk of chronic diseases, and a decline in capacity [30]. The biological changes with age also impact inflammatory processes throughout the body, with chronic inflammation increasingly seen with older age [179]. Therefore, chronological age will be very closely linked to an individual's IC and their level of inflammation. Age is also associated with isolation. Many of the changes experienced with increasing age can impact how connected an individual is with other people, for example, the loss of a spouse, children and family members moving away, or a reduction in mobility, and it has been found that levels of isolation generally increase over the life course [215]. Age in the ELSA data is measured with the chronological age of the respondent in years on the date of the interview; those aged ≥90 years are top-coded at 90 years.

3.3.2 Sex

Sex is important to include as a covariate as there may be differences in health, inflammation, and social isolation between men and women. Women tend to live longer than men but also experience worse health in older age on average [216], and differences in immune function [217] and inflammation have also been observed between sexes [191-195]. The level of social isolation has also been found to differ between men and women, with results indicating that men tend to be more isolated over the life course than women [215]. In ELSA, sex is ascertained by asking the respondent if they are “Male” or “Female” at each wave.

3.3.3 Marital status

Marital status is a key demographic and social variable to include as a covariate due to its known links to health in older age, although the very close relationship between marital status and social isolation makes its use as a covariate a little more complex.

Marital status is found to be associated with health outcomes in older adults, including disability and mortality [218]; however, there are different patterns seen in men versus women. For example, married men have a lower risk of adverse outcomes than unmarried men, particularly those widowed or divorced, but this difference is smaller or not seen for women [219, 220]. It is also important to distinguish between unmarried groups as they can show different health patterns [221]. For example, while being a widow(er) is associated with poorer health, single women are more likely to have better health outcomes than married women, and those who were never married may have better health outcomes than those who were previously married [218].

Marital status is clearly linked to social isolation as having a spouse or partner provides a key social contact. Not being married may also have a knock-on effect on wider social networks; for example, a married individual may gain contacts and social activities through their partner, or on the other hand, a single individual may partake in more social activities with friends or their community in order the get social interaction in the absence of a spouse. However, it is important to consider whether marital status is included in or too close to measures of social isolation when using it as a covariate (this will be discussed further in **Section 6.2.1**).

A marital status variable was derived in ELSA at baseline and further waves from a question asking the respondent their current legal marital status at the time of the interview. Four categories were generated: “Never married”, “Married”, “Separated/Divorced”, and “Widowed”. The categories included those who reported being previously in a civil partnership.

3.3.4 Highest educational qualification

Inequalities in health outcomes are seen between people with different levels of education, with those with less formal education often experiencing worse health [222]. Particularly with regards to healthy ageing, lower levels of education are associated with lower baseline levels of healthy ageing in older adults from around the world [223]. An individual’s level of education may also impact their social behaviours and whether they experience social isolation. A study of German adults found that the more disadvantaged a person with regard to education and other socioeconomic factors, the more likely they were to be socially isolated, and this effect was more pronounced with increasing age [224]. The causal pathways between education and health or social isolation are not fully known and are likely complex and varied with many indirect pathways.

In ELSA, individuals are asked about the highest educational qualification that they have obtained, covering different types of qualifications available in England, such as General Certificate of Education (GCE), Ordinary and Advanced levels (O and A-Levels), National Vocational Qualifications (NVQs), and Certificate of Secondary Education (CSE). The variable was recoded into four categories: “Degree” (NVQ4/NVQ5/Degree or higher), “A-Level” (Higher

Education below Degree-level, NVQ3/GCE A-Level or equivalent), “O-Level or Other qualification” (NVQ2/GCE O-Level or equivalent, NVQ1/CSE or equivalent, Foreign/other qualifications), and “No qualifications”.

3.3.5 Total net wealth

As another measure of socioeconomic position, wealth is similar to education in that it is associated with both healthy ageing and social isolation. Wealthier individuals tend to experience better health and healthy ageing [223, 225] as well as less social isolation [224]. Wealth is a more accurate measure of financial circumstances in later life than income. Many older people are retired and/or receiving an income that does not reflect their financial resources from other sources, such as savings or housing.

Wealth is measured in varying ways in the ELSA data, with variables including different elements of wealth, e.g., savings, investments, and property. For this study, the variable used represented total net wealth at the benefit unit level (a single adult or a couple living as married and any dependent children) and included the sum of savings, investments, physical wealth, and housing wealth after the financial debt had been subtracted. The variable was derived and split into quartiles by ELSA and available in the downloaded data. Quartiles were used instead of the continuous variable as continuous values of wealth showed positive skew with a small number of people with a large amount of wealth.

3.3.6 Employment status

Employment status is important to include as a covariate as an individual’s occupation can impact their health through mechanisms such as health behaviours and stress processes, and also their level of social isolation through exposure to other people. The type of occupation a person carries out is important for health; however, in the ELSA sample, a large number of the sample participants are no longer working due to retirement or other age-associated reasons, so it is more appropriate to measure the employment status as opposed to occupation type. Employment status for this sample is linked closely to health, with those with poorer health more likely to cease working, and socioeconomic position, with those working past state pension age tending to be the most advantaged individuals [226].

In each wave of ELSA, the respondents were asked what best described their employment status at the time of the interview from a range of 7 options. These were condensed into 4 categories for this study: “Retired/Semi-retired”, “Employed” (including self-employed), “Permanently unable to work” (due to sickness or disability), “Looking after home or family or unemployed”. The group of respondents who were retired/semi-retired or permanently unable to work for health reasons were kept separate from the other non-working group as they were all deemed to have had quite different employment and health experiences.

3.3.7 Alcohol consumption

Alcohol consumption is an important health behaviour to account for in this study’s analyses as it has been found to have a complex relationship with healthy ageing, social isolation, and inflammation. Moderate alcohol is often found to have beneficial effects on the health of older people. In a meta-analysis of longitudinal studies, light to moderate alcohol consumption was found to be beneficial to healthy ageing, compared to those who never drank, but the overall findings were judged to be ambiguous and could be influenced by the measurement of alcohol and unmeasured confounders [227]. The relationship between alcohol and social isolation is also mixed. Some cross-sectional studies report an association between greater isolation from others and heavy drinking or alcohol abuse in American adults [228, 229], while in a study using ELSA data, no association was found between social isolation and daily alcohol consumption over a 10-year period [230]. Others also propose a quadratic relationship, with those most and least isolated potentially consuming more alcohol than those in the middle of the scale [231]. A similar U-shaped relationship is seen between alcohol consumption and markers of systemic inflammation, with non-drinkers and heavy drinkers showing high inflammatory marker concentrations [232]. Moderate drinking of red wine, in particular, has been seen to potentially have anti-inflammatory effects [233, 234], although the existence of health benefits with any level of alcohol consumption has recently been disputed [235].

Alcohol consumption has been assessed in ELSA at every wave by asking respondents how often they have had an alcoholic drink of any kind over the previous 12 months, with the categories “Almost every day”, “Five or six days a week”, “Three or four days a week”, “Once or twice a week”, “Once or twice a month”, “Once every couple of months”, “Once or twice a year”, and “Not at all in the last 12 months”. For the purposes of this study, these were reduced to two categories “Five or more times per week” and “Less than five times per week”.

3.3.8 Smoking status

Consistent evidence shows the detrimental effect of smoking on health and health in older age [236, 237]. A meta-analysis of longitudinal studies found that being a non-smoker or an ex-smoker considerably increases the odds of healthy ageing, with those who have never smoked having double the odds of healthy ageing compared to current smokers and 30% more odds than ex-smokers [227]. Social isolation has been linked to smoking behaviour in ELSA, with those, particularly men, who are more isolated, being more likely to smoke [194]. In the same study, smokers were also found to have higher levels of inflammatory markers, which has been backed up by other population-based studies finding low-grade systemic inflammation in those who smoke [238], making controlling for smoking particularly important when investigating inflammation.

Smoking in ELSA was captured by a variable derived by the Institute of Fiscal Studies, which was based on 8 ELSA variables asking whether the respondent has ever smoked and used information from past and present waves. The derivation process is outlined in the ELSA documentation. The categories were “Never smoked”, “Ex-smoker”, and “Current smoker”.

3.3.9 Physical activity

Evidence shows that taking part in regular physical activity is beneficial for a wide range of health outcomes for older people, including reducing the risks of major diseases, falls, and cognitive impairments [239]. Physical activity is also related to social isolation, with sports and physical activities being one-way older people can connect with others, with studies finding positive effects of physical activity on social isolation [240]. However, the direction of causation is not clear, and it may be bidirectional, with more physical activity leading to less social isolation or more social isolation leading to withdrawal and less physical activity [241]. The relationship between physical activity and inflammation has also been explored. Strenuous physical activity is shown to promote a short-term inflammatory response with raised inflammatory biomarkers but in the long term, regular physical activity demonstrates an anti-inflammatory effect [242, 243]. Adipose tissue (body fat) is a production site for many inflammatory markers and, as such, the reduction of adipose tissue through exercise is one way that physical activity may lower inflammation [244], although independent effects of physical activity on inflammatory biomarkers have been found [242] so there must be other mechanisms involved. Other mechanisms that have been implicated include regular physical activity reducing the cytokines released by other tissues such as muscle, blood vessel cells, and blood cells, as well as improving blood vessel function and insulin sensitivity [243].

Obesity is associated with chronic low-grade inflammation, so it is hypothesised that physical activity may reduce inflammation, although it is not known whether any anti-inflammatory effects would be directly caused by the level of exercise itself or the body composition changes associated with it

Physical activity was measured in ELSA using a derived variable based on the level of physical activity from a respondent's occupation and recreational activities. The survey questions included a description of the type of work carried out in the respondent's main job and whether they participate in sports or activities with different energy levels. The full derivation process is outlined in the ELSA documentation. The resulting variable had the categories: "Sedentary", "Low", "Moderate", and "High".

3.3.10 Number of health conditions

The number of health conditions has previously been used in measures of healthy ageing, particularly successful ageing [8, 9]. The incidence of many diseases increases with age, but there is heterogeneity among individuals about the type and quantity of disease diagnoses in later life [30, 245]; therefore, health conditions are an indicator that can distinguish "successful" and “usual” ageing. However, health conditions have been removed as indicators of healthy ageing in more recent conceptualisations, including that by the WHO, as a diagnosis of a disease does not give much information about the impact that condition has on the individual’s life and might be well-managed and not impact the individual’s functioning [30, 246].

Therefore, it was decided to include the number of health conditions as a covariate to explore the utility of an IC score over that of the number of health conditions. Health conditions may also be associated with social isolation and inflammation in a different way from IC, so it is useful to account for this.

As part of the ELSA interview, respondents are asked about any new health conditions they have been diagnosed with since the last wave and whether they confirm any diagnoses from previous waves. The variable used in this study was a count of all diagnosed conditions from a set list of 18 conditions based on any disclosures of a new diagnosis at that wave and disclosures at previous waves. The conditions included are Alzheimer’s disease, angina, arrhythmia, arthritis, asthma, cancer, chronic lung disease, coronary heart failure, dementia, diabetes, heart murmur, high blood pressure, high cholesterol, myocardial infarction, osteoporosis, Parkinson’s disease, psychiatric problems, and stroke.

3.3.11 Self-rated health

Self-rated health is a general measure of subjective health that is very commonly used in surveys. It is normally assessed with one question asking respondents to rate their health on a scale, but due to the vagueness of the question, respondents may interpret and base their ratings on different things, making it very subjective and diverse [247]. Self-rated health was chosen as a covariate for the same reasons as the number of health conditions – to explore IC as a measure of healthy ageing above other measures of health that may not capture the entire picture.

In ELSA, self-rated health is assessed with one question asking the respondent to judge their health as “Excellent”, “Very good”, “Good”, “Fair” or “Poor”.

Chapter 4: Operationalising intrinsic capacity

4.1 Introduction

The literature review in **Chapter 1** identified 47 models of IC that have been generated, with most based upon the five domain structure outlined by Cesari et al. [32]: cognition, locomotion (mobility and muscular function), sensory (vision and hearing), vitality (energy balance and nutrition), and psychological mood. Although there is no consensus on a standard index of IC [42, 248], the indicators used generally capture this five-domain structure. As well as differences in the indicators used to measure IC, there is also no agreement on generating a total score of IC, with many models only producing domain-specific scores [42].

In an early model of IC using data from ELSA, Beard et al. [56] used confirmatory factor analysis (CFA) to generate a bifactor model of IC and extract a score for the general IC factor (**Appendix 1.2**, model 7). Item-response theory (IRT) is another data-driven method used to assess latent factors in a similar way to CFA [249] and has been used by two existing models of IC (**Appendix 1.2**, models 12 and 41). IRT is increasingly used in a wide range of disciplines [250] and has applications in patient-reported outcomes and clinical assessment [251, 252]. The IRT method links item responses to a latent trait, assuming that the respondent's natural position on the latent trait influences their probability of a certain response category on the item. IRT can provide information about how the included items capture information across the range of a latent construct and how well the scale operates at all levels of the latent trait [250]. As a data-driven method, IRT suffers from some of the same limitations of CFA but its focus on items means it is more suited to examining individual item characteristics or estimating scores for respondents, while CFA is more appropriate when focusing on the structural makeup of a scale.

A 2-parameter IRT model was successfully employed by Sanchez-Niubo et al. (2020) and the Ageing Trajectories of Health-Longitudinal Opportunities and Synergies (ATHLOS) project to generate a healthy ageing index, including measures of functional ability and IC [73]. The ATHLOS project has produced a harmonised dataset of 17 international cohorts relating to health and ageing across 38 countries [253]: 10/66 Dementia Research Group Population-based Cohort Study, the Australian Longitudinal Study of Aging (ALSA), the ATTICA study, the China Health and Retirement Longitudinal Study (CHARLS), Collaborative Research on Ageing in Europe (COURAGE), the English Longitudinal Study of Ageing (ELSA), the Study on Cardiovascular Health, Nutrition and Frailty in Older Adults in Spain (ENRICA), the Health, Alcohol and Psychosocial factors in Eastern Europe Study (HAPIEE), the Health 2000-2011 survey (H2000/11), the Health and Retirement Survey (HRS), the Japanese Study of Aging and Retirement (JSTAR), the Korean Longitudinal Study of Ageing (KLOSA), the Mexican Health and Aging Study (MHAS), WHO Study on Global Ageing and Health (SAGE), the Survey of Health, Ageing and Retirement in Europe (SHARE), the Irish Longitudinal Study of Ageing (TILDA), and the Uppsala Birth Cohort Multigenerational Study (UBCOS).

In 2020, Sanchez-Niubo et al. used 16 cohorts to generate a healthy ageing index (**Appendix 1.2**, model 12), including all the studies listed above apart from the ATTICA study and UBCOS and instead including the Longitudinal Aging Study in India (LASI). A list of 41 items (healthy ageing index indicators), which were each harmonised in at least three studies, was agreed and each item was dichotomised based on the presence or absence of difficulties. Using a 2-parameter IRT model, the probability of a certain response to an item was modelled as a function of the item discrimination and difficulty, as well as a person parameter, which was completed using full information maximum likelihood (FIML) to account for missing data. A score for each individual's latent factor (healthy ageing) was estimated using expected a-posteriori estimation and then standardised across the sample to a mean of 0 and standard deviation of 1. This healthy ageing score was then found to correspond well with functional health status and was also a predictor of mortality.

IRT was also used by Salinas- Rodríguez, González-Bautista, Rivera-Almaraz and Manrique-Espinoza [68] to create a model of IC (**Appendix 1.2**, model 41) in three waves of the WHO SAGE in Mexico (2009, 2014, and 2017). They estimated a graded response model where the item (IC indicator) responses were categorical, ordered, and defined in terms of cumulative probabilities. They then extracted a factor score for the latent trait of IC, which was transformed into a scale from 0-100, with better scores indicating better IC. Using growth mixture modelling on the resulting IC scores, three classes of IC trajectory were identified – low baseline IC with a steep decline, medium baseline IC with a slight decline, and high baseline IC with moderate increase – and those with the increasing trajectory were found to have a higher quality of life and fewer limitations in activity and daily-life participation.

So far, IRT has seen limited application to the generation of IC and has yet to be applied to ELSA for a measure of only IC.

4.1.1 Chapter objectives

This chapter explores **Objective 1**: To operationalise IC as a measure of healthy ageing in an observational study of ageing and test whether this model of IC is associated with adverse health outcomes and key sociodemographic factors.

Therefore, the aim of this chapter is to operationalise IC (using the WHO definition) in one wave of ELSA using IRT methodology. This model is intended to be simple enough to be replicated in other studies of ageing and to allow for the possibility of modelling IC over time. The predictive validity of the measure will be assessed through its association with subsequent functional ability, hospital admissions and mortality. The validity will also be evaluated by testing that the well-validated associations between sociodemographic and health-related factors and IC are replicated with this IC measure. This work in this chapter has been published in Campbell, Cadar, McMunn and Zaninotto (2022) [254], but the writing in this section has been adapted from and expanded on that included in the published article.

Hypotheses

1) The IC score is negatively associated with adverse health and functional outcomes such as functional impairment, hospital admissions, and mortality.
2) The IC score is associated with key sociodemographic factors, such as age, sex, and socioeconomic position, and health-related factors, such as subjective health ratings. Higher IC scores will be associated with younger, more socioeconomically advantaged, and "healthier" individuals.

4.2 Methods

4.2.1 Sample

Wave 2 (2004-5) was taken as the baseline for this analysis, as performance assessments included in the nurse visit allowed for the generation of intrinsic capacity. Of those with a nurse visit, 5,343 members aged ≥60 were eligible for a walking speed test and so were used as the analytical sample for generating an intrinsic capacity score. A description of the sample based on the covariates can be found in **Table 4.3**, and the full sample selection flowchart can be seen in **Figure 4.1** after the discussion of the covariates.

4.2.2 Intrinsic capacity

This section will discuss the selected indicators for each domain of IC, covering the theoretical justification but also any constraints on this decision from the ELSA data. As the aim of this model of IC is to indicate the risk of functional ability decline and adverse outcomes, each indicator's relationship with these outcomes will be highlighted. Each indicator will be dichotomised into "No difficulty" and "Difficulty", with the latter representing performance at a level shown to indicate risk of adverse outcomes, where such specific cut-off is possible. A summary of the indicators and their cut-offs can be found in **Table 4.1,** and the waves of ELSA that they have been measured in are displayed in **Table 4.2.**

Cognition

In the development of IC [35], six components of the cognition domain that could be assessed were identified: memory, verbal fluency, letter cancellation, digit span, financial literacy, and the alternative uses test. A commonly used indicator of the cognitive domain in previous models of IC was the Mini-Mental State Examination (MMSE) [38], which is the most well-known cognitive screen in the world [255] and was the recommended tool to assess the cognition domain by the WHO's rapid systematic reviews of screening tools [36]. However, the final WHO ICOPE screening tool assesses cognition with two tests of memory (a three-word list learning test and orientation in time and space), which are simpler, quicker and cheaper than a comprehensive cognitive assessment when carried out in the field [35].

When measuring cognition in the context of ageing, the focus is placed on the fluid elements of intelligence (memory, executive function, processing speed) as these seem to be affected more by the ageing process in comparison to crystallised elements (general knowledge, vocabulary, number skills) which tend to endure with age [256]. Fluid mental abilities are also considered necessary for carrying out everyday activities, living independently and leading a fulfilling life [257]. Although executive function and processing speed are fluid abilities, data on these abilities are not available in ELSA at wave 6 and therefore impede the inclusion of many of these cognition tests. Nevertheless, given the importance of memory in age-related cognitive impairment, a focus on memory ability is not out of place and enables comparisons across waves. Memory is also very commonly assessed in other studies of ageing thus the opportunities for comparison across studies are also still high.

At all waves of ELSA (**Table 4.2**), memory has been assessed with a word-list learning task with immediate and delayed recall. Ten words are presented verbally, and the participant recalls as many words as they can immediately and after a short delay. Word learning is included in the IC screening tool with a list of 3 words, but typically 10+ words are used in observational studies of ageing [258, 259]. Wordlist learning has been found to be predictive of functioning [260, 261], cognitive impairment [262] and decline [263]; however, there are no accepted cut-offs for word-list learning that indicate a current or increased risk of cognitive impairment; therefore a tertile method was used, with the lowest tertile indicating poor performance and categorised as "Difficulty".

Orientation in time is a simple but effective test of memory and forms part of the MMSE assessment [38], with poor orientation being significantly associated with a decline in global MMSE score over time in elderly individuals aged >85 years of age [264]. In ELSA, orientation in time is assessed with the identification of the weekday, day of the month, month, and year at every wave (Table 4.2). The failure criterion in the IC screening tool is any mistake in the orientation questions. This corresponds to research finding very low rates of temporal disorientation in older adults (aged >50) [265]; most errors are made when identifying the day of the month, and these increase with age [266]. Therefore, a cut-off for "No difficulty" on the orientation questions was set at no incorrect answers.

Locomotion

The WHO Clinical Consortium recommended the Short Physical Performance Battery (SPPB) [40] as an appropriate marker for risk stratification for mobility impairment in the locomotion domain [36]. The SPPB consists of tests of standing balance, chair rises and walking speed, each given a score of 0-4, resulting in a total SPPB score ranging from 0-12 [40]. Score on the SPPB has been found to be associated with many health outcomes in older people, including subsequent functional ability [267], risk of mobility impairment [268, 269], falls [270] and mortality [271]. The SPPB and its components were the most popular assessments of locomotion in other models of IC, being used in 38 models (Appendix 1.2). Some also used estimates of functional ability (ADLs/IADLs) and prevalence of falls or sarcopenia, although these could be considered the outcomes that IC is aiming to predict as opposed to indicators.

All the components of SPPB have been measured in ELSA but are only evaluated in those aged ≥60 years. Walking speed has been assessed as part of the main survey at every wave (Table 4.2) and is measured as the time taken to walk 2.44 metres (8 feet), which corresponds with the SPPB protocol [40]. Walking aids are allowed, but the assistance of another person is not.

Walking speed has been associated with frailty [272], mortality [273], disability, cognitive impairment, institutionalisation and falls [274] and has been proposed as a vital indicator of survival [273]. When compared to four other components of the frailty phenotype (weight loss, exhaustion, low grip strength and low physical activity), slow walking speed was found to be the most informative component and seemed to be the key indicator of frailty [275]. Some set the cut-off indicating slow walking speed and subsequent risk of adverse outcomes, at <1 m/s [273, 276]; others, including the European consensus on sarcopenia, establish a cut-off at <0.8 m/s [274, 277], which was used in this study.

Three tests of standing balance and chair rises have been assessed in those aged ≥60 years in ELSA at the nurse waves 2, 4 and 6, but were not included in waves 8 and 9. The balance tests evaluate the ability to hold three separate stands for 10 seconds each: side-by-side (feet together side by side), semi-tandem (the side of one heel touching the big toe of the other foot), and full tandem (the heel of one foot touching the toes of the other foot). In ELSA, the test begins with the simplest test (side-by-side) and then progresses to the more difficult tasks if the participant completes the simpler task. In the original SPPB specification, the test begins with the semi-tandem task and those unable to complete this task move onto the side-by-side test, while those able to complete the task move onto the tandem test [40]. The three trials of balance are considered hierarchical in difficulty and scored 0-4: 0 if unable to complete the side-by-side or semi-tandem tests; 1 if the side-by-side is completed, but the semi-tandem is failed; 2 if the semi-tandem is completed, but the full tandem is failed (held for less than 2 seconds); 3 if the semi-tandem is completed, but the full tandem is only held for 3-9 seconds; 4 if the semi-tandem is completed and the full tandem is held for 10 seconds. The distribution of scores on the SPPB balance test tends to show ceiling effects, with a majority of people being able to pass the full tandem test, even at older ages [40, 278-280]. With this in mind, the cut-off used to indicate “no difficulty” was set as the successful completion of all the stances.

The chair rise element of the SPPB assesses the time taken to complete five rises from a chair without using assistance from arms, with the maximum time limit set at 1 minute. In assessments of the predictive value of the SPPB and its components, poor chair rise performance (defined as rises completed in ≥16.7 seconds) predicted the risk of injurious falls, while the total SPPB score did not [281]. The cut-off of 16.7 seconds is based on the lowest quartile of chair rise performance from original explorations of the SPPB [40, 269]; this cut-off was used in the current model.

Measures of lower and upper mobility have been assessed in ELSA at every wave. Mobility impairments in older people are associated with falls, loss of independence, institutionalisation, and mortality [282-285]. Although measures of mobility could be argued to be functional ability, as opposed to IC, the measures of mobility in ELSA were judged to be more explicitly mobility and locomotion based than measures of functional ability like ADLs and IADLs and allow for a comprehensive assessment of an individual's locomotion capacity in their upper and lower body. Lower mobility was assessed in ELSA with self-reported difficulties with walking 100 yards, sitting for two hours, getting up from a chair after a long period of sitting, climbing several flights of stairs without resting, and stooping/kneeling/crouching. Upper mobility was assessed with self-reported difficulties with reaching/extending arms above shoulder level, pulling or pushing large objects, lifting/carrying weights over 10 pounds (~4.5kg), and picking up a 5-pence coin from a table. For both mobility items, a rating of "No difficulty" was set as reporting no problems.

Sensory

Vision and hearing were identified as components of the sensory domain in the development of IC [32, 35]. The whispered voice test (WVT) [286] was identified as the recommended screening tool for hearing impairment in the IC screening tool [36]; however, both the WVT and perceived hearing loss appeared to be nearly as accurate as more detailed hearing loss questionnaires and audiometric devices. In ELSA, an objective hearing assessment test took place only in wave 8, but self-rated hearing (using a hearing aid if one is usually worn) was measured at every wave (**Table 4.2**) with the ratings excellent, very good, good, fair, or poor. A poor self-rated hearing has been found to be associated with poor self-rated health and depressive symptoms [287], reduced functional ability [288] and frailty [289]; thus, while objective measures are not available, perceived hearing appears to be a good predictor of later health outcomes.

Objective measures, such as the Portable Eye Examination Kit [290] and visual acuity test cards, were recommended by the WHO's review for the measurement of vision impairment [36]. However, no objective test of eyesight has been carried out in ELSA, which has instead collected self-rated eyesight using glasses or contact lenses, if these are usually worn, at each wave with the same scale as hearing (excellent to poor). Similarly to hearing, self-rated eyesight is associated with self-rated health and depressive symptoms [287], frailty [291], functional ability, social activities, hospital admissions, and mortality [292].

As both hearing and eyesight were judged on the same five-point scale, the same cut-off was used. A rating of excellent, very good or good was categorised as "No difficulty", while fair or poor (or legally blind) was categorised as "Difficulty".

Vitality

In the initial identification of the five domains of IC, vitality was defined as the balance between energy intake and expenditure and focused on the body functions devoted to metabolising dietary intake [32]. Vitality is seen as different from the other domains in the respect that it represents elements of biological systems that underlie capacity, compared to the other domains, which are overt expressions of capacity [56].

As more apparent manifestations of energy balance, diet and malnutrition are often referenced or measured under vitality. Indicators of malnutrition such as nutrition status, weight loss and BMI have been used in 32 operationalised models of IC's vitality domain (**Appendix 1.2**), with BMI (body weight in kilograms divided by squared height in metres) a widely available measure used to classify body mass in population-based studies [293]. Although nutrition is not an indicator of capacity, malnutrition (specifically underweight) is associated with mortality and adverse clinical outcomes in older people [294, 295], and it has been identified as a target for intervention when preventing functional decline [296]. On the other hand, overnutrition resulting in overweight and obesity is known to increase the risk of a large number of conditions, including diabetes, arthritis, respiratory conditions, and dementia [297, 298]. However, meta-analyses have demonstrated that the threshold value of BMI indicating an increased risk of mortality and morbidity is higher in older adults at > 30kg/m^2 [299]; therefore, it is suggested that intervention efforts to reduce the risk of adverse outcomes from overnutrition in older adults should focus on obese individuals. An additional consideration when using BMI to define weight characteristics is that BMI is a poor measure of body fat mass as it cannot capture the distribution of fat mass around the body or distinguish between fat mass and muscle mass, all of which are important factors with different effects on health and patterns of change across age [293]. In ELSA, BMI is derived from height and weight measured during the nurse visits in every other wave (Table 4.2). Considering the higher BMI threshold value in older adults and the caveats with using BMI as a measurement, a cut-off for the "No difficulty" category was set at the more extreme ends of BMI values: <18.5 (indicating underweight) and ≥30 (indicating obesity).

Combining BMI and measures of waist circumference can reduce some of the limitations of BMI. Waist circumference is a better marker of abdominal adiposity, which is particularly detrimental to health and is strongly associated with all-cause and cardiovascular mortality [300-302]. It is recommended to use both BMI and waist circumference when identifying obesity, as both measures together are much more effective than BMI alone [303]. Waist circumference was measured as part of the nurse visit in waves 2, 4, and 6 of ELSA. "No difficulty" for waist circumference was based on the International Diabetes Federation guidance for European men and women and set at <94cm for men and <80cm for women [304].

The most common indicator of vitality in previous models of IC was grip strength, which was included in 17 models, either alone or in combination with other indicators (Appendix 1.2). Grip strength is a marker of muscle strength in the upper extremities and is the most frequently used tool to assess muscle function for clinical purposes [86]. Some propose that grip strength can be considered a marker of nutrition due to muscle function's close relationship with diet, protein intake, and body mass, with reduced muscle function being an outcome of malnutrition [86]. Others suggest grip strength could serve as a broader vital sign of health due to its strong prediction of important health outcomes [305], including increased risk of mortality, functional limitations, disability and more extended hospital stays [86, 305]; it may even be an indicator of neurological function and brain health [88]. Grip strength has also been linked to every other domain of IC except hearing impairment [79], demonstrating the idea that indicators of vitality could be more reflective of systems underlying capacity than of capacity itself.

In ELSA, grip strength is measured during the nurse visit, with three measurements obtained for each hand using a Smedley dynamometer; in the current model, the maximum value (from either the dominant or non-dominant hand) is taken for each individual. Cut-offs were based on values defining low grip strength and sarcopenia that were identified by the European Working Group on Sarcopenia in Older People: <30kg for men and <20kg for women [277].

Psychological wellbeing

The psychological domain included the Center for Epidemiological Studies Depression scale (CES-D) [90] and the Satisfaction with Life Scale (SWLS) [306]. "No difficulty" was defined as a score of <4 on the CES-D, indicating no depressive symptoms [307], and ≥20 on the SWLS, indicating slight to extreme satisfaction [306].

A range of different measurable components was proposed for the psychological domain in the initial development of IC: mood, life satisfaction, anxiety, self-esteem, sleep, agency, coping/self-efficacy, loneliness, distress, personality traits and fatigue [35]. The Geriatric Depression Scale (GDS) [39] and the Center for Epidemiological Studies Depression scale (CES-D) scale [90] were the most common instruments used to measure the psychological domain in previous models of IC. The GDS was also found to be the most frequently used and examined tool in the WHO's review of screening tools and was the recommended instrument for measuring depressive symptoms [36].

Depressive symptoms in ELSA are assessed at every wave with the 8-item CES-D depression scale (Table 4.2), which was found to be a valid and reliable instrument for measuring depression in older adults [308]. Each item asks whether the participant has experienced a specified feeling much of the time during the past week, scoring 1 for yes and 0 for no. The items cover feeling depressed, feeling that everything was an effort, having restless sleep, happiness, loneliness, enjoyment of life, sadness, and feelings of not being able to get going. Positive items referencing enjoyment with life and feeling happy are reversed, and all responses are summed into a total score ranging from 0-8. A cut-off of a score ≥4 is commonly used to indicate depressive symptoms and is found to be equivalent to the 16-symptom cut-off used in the validated 20-item CES-D scale [307]; this cut-off was used in the current model.

The IC screening tool and other previous IC models illustrate the focus on depressive symptoms and, thus, the mental health element of the psychological domain. It would be useful to broaden this to include broader aspects of wellbeing, such as subjective wellbeing, which is defined as an individual's evaluations of their life [309], which would capture another component of IC as outlined by the WHO Clinical Consortium [35]. Subjective wellbeing includes three elements: life satisfaction, which refers to cognitive and global evaluations of one's life as a whole [310], and positive and negative affect, which refers to the emotional aspects of the construct [306].

Life satisfaction has been assessed in ELSA using the Satisfaction with Life Scale (SWLS) [306] in every wave since wave 2 (Table 4.2). The SWLS measures global life satisfaction and includes five statements which are rated on a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree); the scores from each item are summed to generate a total score ranging from 5 to 35 [306]. A score of 20 represents the neutral point on the scale, with below this indicating slight to extreme dissatisfaction and above indicating slight to extreme satisfaction [311]. There is little evidence exploring the use of a cut-off in the SWLS and the risk of adverse health outcomes; however, it has been shown that general dissatisfaction with life is related to poor mental and physical health [312]. In line with this, the cut-off for the SWLS for the "No difficulty" category was set at ≥20 points.

Table 4.1 Intrinsic capacity indicators, cut-offs, and proportions in each category or missing at baseline (wave 2) in the IC eligible sample (N=5,343).

Results for underlying items, e.g., individual mobility tests, can be viewed in Appendix 4.1.

Table adapted from Campbell et al. (2022, Suppl. eTable 1) [254]

Variable	"No difficulty"		"Difficulty"		Missing
Word recall (20 words, immediate & delayed recall)	Top 2 tertiles	3,275 61.3%	Bottom tertile	2,051 38.4%	17 0.3%
Orientation (day of the week, day, month, year)	All questions correct	4,104 76.8%	≥1 incorrect answer	1,227 23.0%	12 0.2%
Balance (side-by-side, semi-tandem and full tandem tests)	Score of 4	3,614 67.6%	Score > 4	1,681 31.5%	48 0.9%
Chair rise test	5 rises within 16.7s	3,708 69.4%	5 rises in >16.7s	568 10.6%	1,067 20.0%
Walking speed	≥0.8 m/s	2,870 53.7%	<0.8 m/s	2,015 37.7%	458 8.6%
Upper mobility: self-reported difficulties with 4 actions	No difficulties	3,368 63.0%	≥1 difficulties	1,974 37.0%	1 0.0%
Lower mobility: self-reported difficulties with 6 actions	No difficulties	2,025 37.9%	≥1 difficulties	3,317 62.1%	1 0.0%
Self-reported eyesight	Rated good-excellent	4,519 84.6%	Rated fair-poor	824 15.4%	0 0%
Self-reported hearing	Rated good-excellent	4,015 75.2%	Rated fair-poor	1,328 24.9%	0 0%
Grip strength	≥30kg (men) or ≥20kg (women)	4,003 74.9%	<30kg (men) or <20kg (women)	1,247 23.3%	93 1.7%
Body Mass Index	≥18.5 and <30	3,536 66.2%	<18.5 or ≥30	1,447 27.1%	360 6.7%
Waist circumference	<94cm (men) or <80cm (women)	1,083 20.3%	≥94cm (men) or ≥80cm (women)	4,053 75.9%	207 3.9%
Center for Epidemiology Studies – Depression scale	Score < 4	4,476 83.8%	Score ≥ 4	802 15.0%	65 1.2%
Satisfaction With Life Scale	Score ≥ 20	4,109 76.9%	Score < 20	705 13.2%	529 9.9%

* Reaching/extending arms above shoulder level, pulling or pushing large objects, lifting/carrying weights over 10 pounds (~4.5kg), and picking up a 5-pence coin from a table. ** Walking 100 yards, sitting for two

hours, getting up from a chair after a long period of sitting, climbing several flights of stairs without resting, and stooping/kneeling/crouching.

Table 4.2 The waves of ELSA in which each indicator has been measured.

Indicator	1	2*	3	4*	5	6*	7	8*	9*
Cognition									
Word list learning	✓	✓	✓	✓	✓	✓	✓	✓	✓
Orientation in time	✓	✓	✓	✓	✓	✓	✓	✓	✓
Locomotion									
Balance		✓		✓		✓			
Chair rise test		✓		✓		✓			
Walking speed	✓	✓	✓	✓	✓	✓	✓	✓	✓
Upper mobility		✓	✓	✓	✓	✓	✓	✓	✓
Lower mobility		✓	✓	✓	✓	✓	✓	✓	✓
Sensory									
Self-rated eyesight	✓	✓	✓	✓	✓	✓	✓	✓	✓
Self-rated hearing	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vitality									
Grip strength		✓		✓		✓		✓	✓
BMI		✓		✓		✓		✓	✓
Waist circumference		✓		✓		✓			
Psychological wellbeing									
Center for Epidemiological Studies - Depression scale	✓	✓	✓	✓	✓	✓	✓	✓	✓
Satisfaction with Life Scale		✓	✓	✓	✓	✓	✓	✓	✓

* indicates a wave including a nurse visit; in waves 8 and 9; in waves 8 and 9, the nurse visits were split with half the participants having a nurse visit in wave 8 and the other half in wave 9.

Intrinsic capacity in ELSA

It was decided to generate IC in waves 2, 4, and 6 of ELSA as these waves contained a nurse visit and thus measured the key locomotion indicators, balance and chair rise, and the vitality indicators grip strength, BMI, and waist circumference. It was decided not to use waves 8 and 9 due to the lack of balance, chair rise, and waist circumference measurements in these waves and to focus on a richer measurement of IC at three waves than a sparser measurement at 4 waves (as waves 8 and 9 would have to be combined due to the sample being split for the nurse visit).

4.2.3 Outcome measures in ELSA

Subsequent functional ability was measured by difficulties with activities of daily living (ADLs) and instrumental activities of daily living (IADLs) at wave 4 (2008-9) and at wave 6 (2012-13). ADLs include difficulties with dressing, walking across a room, bathing or showering, eating or cutting up food, getting in and out of bed, and using the toilet. IADLs include difficulties with using a map, preparing a hot meal, grocery shopping, making telephone calls, taking medications, doing house or garden work, and managing money. In waves 4-9 of ELSA, two extra IADLs – recognising when in danger and communication – were measured, but these were not included in this study. A total number of difficulties was calculated for ADLs and IADLs separately, with scores ranging from 0-6 and 0-7, respectively, at each wave. Mortality and first hospital admission were calculated from the respondent's wave 2 interview covering the period 2004 to 2018. Mortality up to April 2018 was determined from linked mortality register data. Hospital admissions up to January 2018 were gathered using electronic health records and linked to ELSA survey members. The sample selection for this analysis, including the sample size for each outcome can be seen in **Figure 4.1**.

4.2.4 Covariates

Covariates measured at baseline (wave 2) included age, sex, marital status, highest educational qualification, total net wealth, occupation, alcohol consumption, smoking, level of physical activity, number of health conditions, and self-rated health. The proportion of the sample in each covariate category can be found in **Table 4.3** and the sample selection, including those excluded due to missing covariates, can be seen in **Figure 4.1**.

Table 4.3 Description of the sample (N=5,343) used for the generation of IC at baseline (wave 2)

Covariate	Categories	N	Mean (SD) / Proportion (%)
Sex	Male	2,388	44.69%
	Female	2,955	55.31%
Age		5,343	71.26 (8.20)
Marital status	Married	3,347	62.64%
	Never married	244	4.57%
	Separated/Divorced	444	8.31%
	Widowed	1,307	24.46%
	Missing	*1*	*0.02%*
Education	Degree	537	10.05%
	A-Level	869	16.26%
	O-Level or other	1,591	29.78%
	None	2,346	43.91%
Wealth quintile	1 - Lowest	964	18.04%
	2	1,055	19.75%
	3	1,077	20.16%
	4	1,084	20.29%
	5 - Highest	1,109	20.76%
	Missing	*54*	*1.01%*
Employment status	Retired/Semi-retired	3,946	73.85%
	Employed	647	12.11%
	Permanently unable to work	172	3.22%
	Looking after home or family or unemployed	567	10.61%
	Missing	*11*	*0.21%*
Current smoker	Never smoked	1,925	36.03%
	Ex-smoker	2,757	51.6%
	Current smoker	657	12.3%
	Missing	*4*	*0.07%*
Alcohol consumption	5+ days a week	1,111	20.79%
	<5 days a week	3,609	67.55%
	Missing	*623*	*11.66%*
Physical activity	Sedentary	392	7.34%
	Low	1,455	27.23%
	Moderate	2,649	49.58%
	High	844	15.80%
	Missing	*3*	*0.06%*
Health conditions †	Mean (SD)	5,343	1.17 (1.24)
	0	1,966	36.8%
	1	1,668	31.22%
	2	966	18.08%
	3	449	8.40%
	4	200	3.74%
	5	57	1.07%
	6	33	0.62%
	7	3	0.06%
	8	1	0.02%
Self-rated health	Excellent	591	11.06%
	Very good	1,397	26.15%
	Good	1,768	33.09%
	Fair	1,177	22.03%
	Poor	405	7.58%
	Missing	*5*	*0.09%*

† Count of diagnosed conditions: Alzheimer's disease, angina, arrhythmia, arthritis, asthma, cancer, chronic lung disease, coronary heart failure, dementia, diabetes, heart murmur, high blood pressure, high cholesterol, myocardial infarction, osteoporosis, Parkinson's disease, psychiatric problems, stroke.

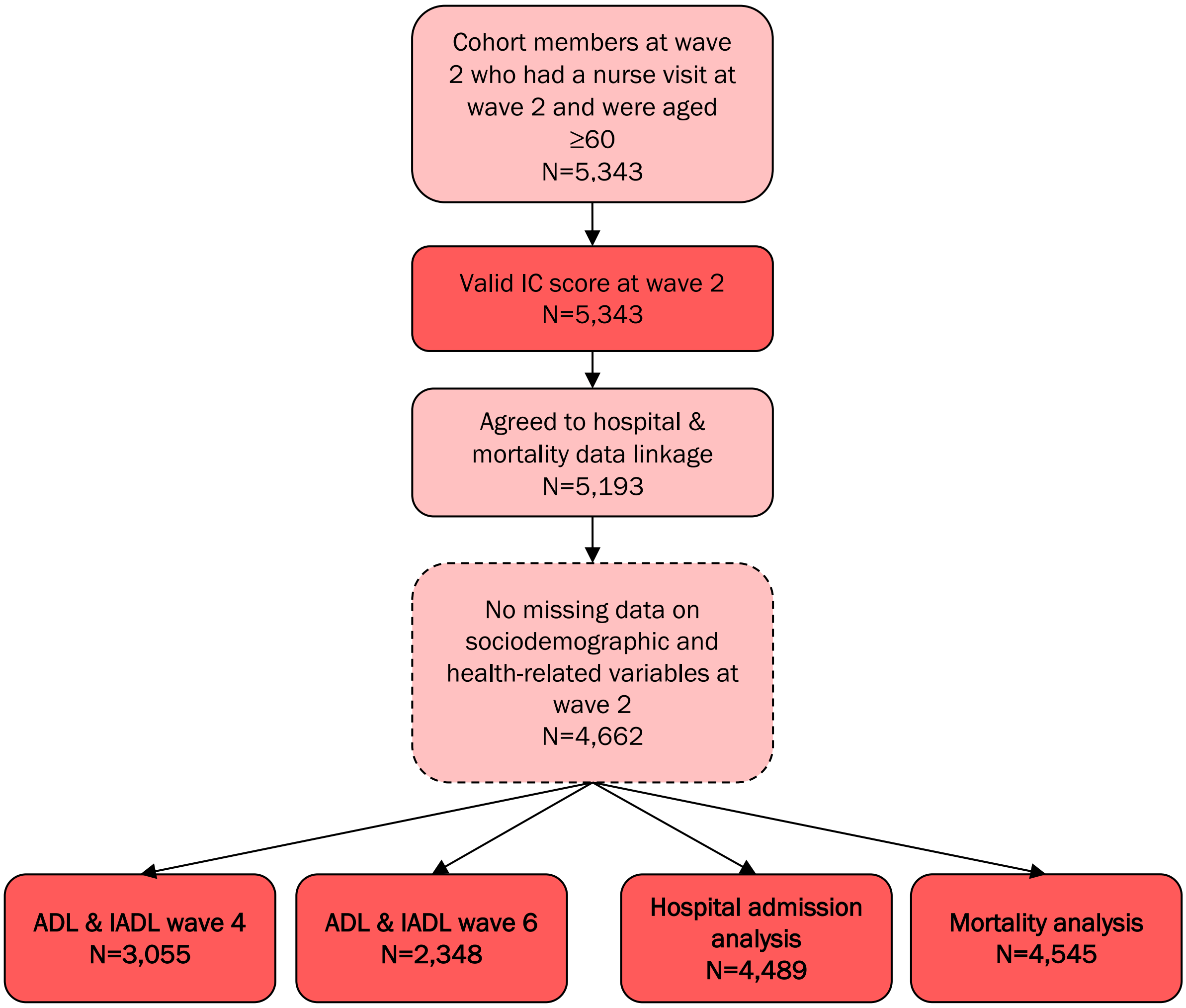

Figure 4.1 Flowchart showing the sample selection process for the predictive validity analysis of intrinsic capacity in wave 2 of ELSA.

4.3 Statistical Analysis

The method for generating the IC score was based on the IRT model used by Sanchez-Niubo et al. for their healthy ageing index in the ATHLOS consortium studies [73]. The IC score was generated using a two-parameter logistic item response theory (IRT) model where the probability of experiencing “no difficulty” on an indicator was modelled as a function of two item parameters (discrimination and difficulty) and a person parameter.

The item parameters can be best understood with a visualisation called an item characteristic curve (ICC), such as in **Figure 4.2**, where the range of the trait level (theta) is plotted against the range of probability of endorsing a certain response. The discrimination parameter is a gauge of measurement precision and refers to the item’s ability to discriminate against people with similar levels of the underlying trait [313]. It is also called the slope parameter as it determines the slope of the ICC, as demonstrated by Items A and C in **Figure 4.2,** which have the same difficulty but different discrimination. For items with high discrimination, a small change in the trait level results in big changes in the probability of a certain response, for example, Item C in **Figure 4.2**. The difficulty parameter refers to the difficulty of achieving a 0.5 probability of a response for an item given an individual’s latent trait level [313]; the more difficult it is for an individual to achieve a 50% chance of the response (e.g., a correct answer), the higher the level on latent trait needed to achieve the response. Some have suggested the term ‘location parameter’ as more relevant for health research, as an item’s difficulty determines the ICC position along the theta range; this can be seen with Items A and B in **Figure 4.2**. which both have the same discrimination (slope) but different difficulties.

The IRT framework has some key assumptions about the items and data: unidimensionality, local independence, monotonicity, and item invariance [314]. The assumption of unidimensionality means that the observed responses on items reflect a single underlying trait, i.e., they have just one thing in common. It is possible to carry out multidimensional IRT models, but the current analysis specified a unidimensional model. Local independence assumes that, conditional on the latent trait, responses to the items are statistically independent of each other. The assumption of monotonicity means that the probability of endorsing (correctly answering) an item increases as an individual’s latent trait level increases. Item invariance means that estimated item parameters are constant across different populations, so an item is measuring the latent trait in the same way across populations; this assumption is tested in the following chapter (**Chapter 5**).

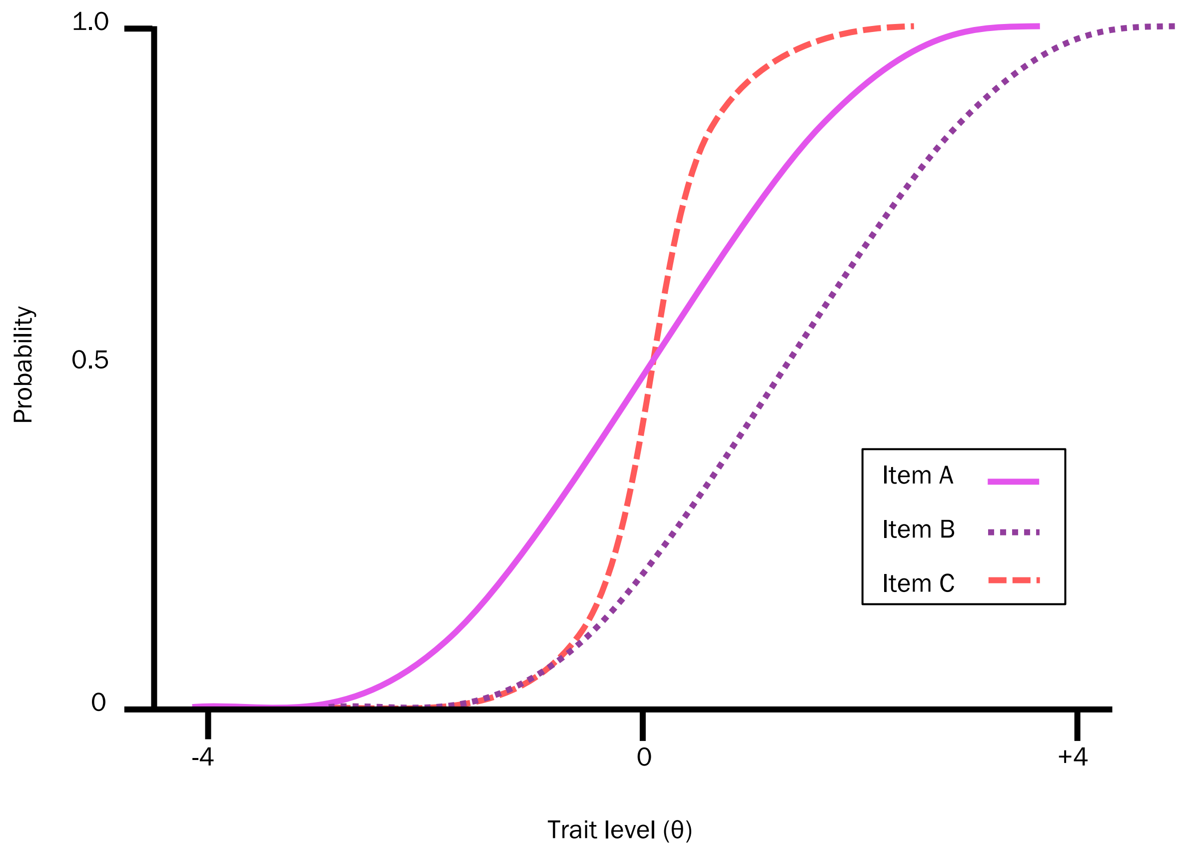

Figure 4.2 Diagram of example item characteristic curves (ICCs) demonstrating different discrimination and difficulty parameters.

Items A and B have the same discrimination (slope) but different difficulty (location). Items A and C have the same difficulty (location) but different discrimination (slope). Source: Figure adapted from diagrams by Cook (2013) [315].

Estimation of the latent trait score followed the common two-stage approach [316]. In the first stage, full information maximum likelihood (FIML) was used to estimate the item and person parameters, which allowed for the parameters to be estimated even when item responses were missing. FIML uses all available data to calculate the parameter estimates, so does not exclude cases based in missing data (like listwise deletion) or impute values for missing values (like multiple imputation). In the second stage, expected a posteriori (EAP) estimation was used to calculate an IC score for each individual. EAP estimation is based on Bayesian statistical principles. It calculates an expected value of the latent trait score (IC score) using a posterior probability distribution of the latent trait scores, which is a predicted distribution of scores for a specific individual based on their response pattern and the estimated model parameters (which were calculated in the first stage with FIML).

The IRT model fit was assessed with the Root Mean Square Error of Approximation (RMSEA), the Comparative Fit Index (CFI), and the Tucker-Lewis index (TLI). To assess the model fit, missing values on the IC indicators were imputed 10 times based on the latent trait value and item parameters of the estimated IRT model; the average model fit statistic from the imputations was reported. The resulting factor scores from the IRT model were extracted and standardised to have a mean of 50 and a standard deviation of 10.

Linear regression was then used to test the association between the IC scores and sociodemographic and health-related variables at wave 2 (2004). Logistic regression models were performed to test the association between IC scores at baseline and the presence of difficulties with ADLs or IADLs at wave 4 (4 years from baseline) and at wave 6 (8 years from baseline). Cox proportional hazard models with hazard ratios (HR) were performed to test the association between the IC scores and mortality during the 14-year follow-up. Competing-risk regression analysis with subdistribution hazard ratios (SHR) was used for the association between IC scores and hospital admission, using a version of the Fine and Gray method [317]. A competing risk is an event that may occur during the follow-up instead of the event – in this case, death was considered as the potential competing risk to hospital admission. In a sensitivity analysis, Cox proportional hazard models were used to explore if there was a difference to the competing-risk analysis. Survival times were measured from the wave 2 interview date to the adverse incident. For study members with no hospital admissions or death, the follow-up time was the end of the mortality/hospital information period (April and January 2018, respectively).

IC was generated in 5,343 individuals, but consent for data linkage with hospital and mortality records was given by 5,193 individuals (**Figure 4.1**). Of these, a total of 4,537 had no missing data on covariates at baseline and thus were used as the base sample for analyses in this chapter. A total of 3,337 individuals also had information on ADLs and IADLs at wave 4, while 2,645 had this information at wave 6. Among the 4,537 individuals in the main sample, 4,481 were included in the competing risk analysis as they experienced admission to hospital or death following their wave 2 interview or reached the censoring point.

All analyses were carried out in Stata SE v16.1, and R. The R package *mirt* [318] was used to generate the item response theory model. R syntax shared by Sanchez-Niubo et al. [73] was used as a template for the IRT model.

4.4 Results

An intrinsic capacity score was generated for 5,343 cohort members, Of these, 67.7% had no missing data on any of the individual IC indicators, 19.8% were missing one indicator, 7.4% were missing two, and 5.1% were missing three or more. The IRT model converged successfully with a good fit (RMSEA = 0.06, TLI = 0.90, CFI = 0.91) (**Table 4.4**). The item parameters (**Table 4.5**) revealed that locomotion items had the highest discrimination, meaning they could identify individuals at different levels of the latent trait range the best, while orientation and waist circumference had the lowest discrimination. Orientation was found to have the lowest difficulty, while waist circumference had the highest, meaning that a low level of IC (the latent trait) was required to answer all the orientation questions correctly, while a high level of IC was required to have a waist circumference under the cut-off (<94cm for men and <80cm for women). The IC factor scores ranged from 20.8 to 66.7, with a mean of 50.00 (SD 10), and were left-skewed.

Table 4.4 Fit statistics for the item response theory model in wave 2.

Fit statistics from the 10 imputed models and the average are shown.

	RMSEA	TLI	CFI
1	0.055	0.896	0.912

2	0.055	0.896	0.912
3	0.056	0.893	0.910
4	0.055	0.895	0.911
5	0.056	0.896	0.912
6	0.056	0.896	0.912
7	0.055	0.896	0.912
8	0.055	0.896	0.912
9	0.056	0.893	0.909
10	0.056	0.894	0.910
Average	**0.056**	**0.895**	**0.911**

RMSEA = Root Mean Square Error Approximation; TLI = Tucker-Lewis Index; CFI = Comparative Fit Index

Table 4.5 Parameter estimates for the intrinsic capacity indicators from the item response theory model in wave 2

Table adapted from Campbell et al. (2022, Suppl. eTable 3) [254]

Domain	Indicator	Parameters (Standard Error)	
		Discrimination	Difficulty
Cognition	Word recall	0.690 (0.040)	-0.748 (0.058)
	Orientation	0.373 (0.040)	-3.336 (0.347)
Locomotion	Chair rises	1.432 (0.088)	-1.478 (0.075)
	Balance test	1.325 (0.058)	-0.759 (0.036)
	Walking speed	1.826 (0.082)	-0.235 (0.025)
	Lower mobility	1.956 (0.090)	0.412 (0.025)
	Upper mobility	2.255 (0.100)	-0.417 (0.023)
Sensory	Eyesight	1.071 (0.058)	-1.915 (0.084)
	Hearing	0.576 (0.041)	-2.059 (0.141)
Vitality	Grip strength	1.469 (0.066)	-1.077 (0.041)
	BMI	0.462 (0.041)	-1.967 (0.178)
	Waist circumference	0.323 (0.043)	4.210 (0.544)
Psychological wellbeing	CES-D	1.182 (0.062)	-1.802 (0.074)
	Satisfaction With Life Scale	0.854 (0.057)	-2.280 (0.134)

Of the 5,343 respondents with a valid IC score at wave 2, 4,662 were included in the analysis with sociodemographic and health-related factors; 55% were female, and the mean age was 70.8 years (SD 7.94). In this reduced sample, the mean IC score was 50.69 (SD 9.79) and ranged from 20.8 to 66.7. In the fully adjusted linear regression model, a significant association was found between IC scores and most covariates (**Figure 4.3** for standardised coefficients, **Appendix 4.2** for unstandardised coefficients and unadjusted results). Lower IC scores were associated with older age (B=-0.32, 95% CI -0.35– -0.29), women (B=-2.89, 95% CI -3.28– -2.43), those in lower wealth quintiles (lowest quintile B=-3.13, 95% CI -3.85– -2.42), not being in employment (retired B=-0.87, 95% CI -1.49– -0.25), lower physical activity levels (sedentary B=-

5.19, 95% CI -6.08– -4.29), more health conditions (B=-0.37, 95% CI -0.54– -0.21), and lower self-ratings of health (poor B=-12.45, 95% CI -13.47– -11.44).

Baseline IC score was significantly negatively associated with experiencing one or more difficulties with ADLs and IADLs at wave 4 and wave 6 when adjusting for previous difficulties with ADL/IADLs and covariates (**Figure 4.4**). Those with a higher IC score at baseline were 7-9% less likely to experience difficulties with ADLs and IADLs 4 and 8 years later. See **Appendix 4.3** for full results.

Among the 4,545 individuals in the analytical sample for mortality, 40.2% died within the follow-up period. The mean survival time was 11.03 years. Higher IC scores were significantly associated with a lower risk of mortality (**Figure 4.4**), with a one-unit increase in IC score decreasing the probability of death within 14 years by 2% (HR=0.98, 95% CI 0.98–0.99) in the fully adjusted analysis. See **Appendix 4.4** for full results.

For the 4,489 individuals in the hospital admission sample, the follow-up time between the interview and the first admission or competing event ranged between 0.08-13.55 years, with a mean of 3.85 years for those who were admitted to the hospital, 6.64 years for those who died, and 13.17 years for those who experienced neither event. By the end of the follow-up period, 3,784 admissions to the hospital were recorded, and 184 deaths were considered a competing event. Competing risk analysis revealed that a higher IC score was associated with a reduced risk of hospital admission, even when adjusted for covariates (**Figure 4.4**). In fully-adjusted analyses, a one-unit increase in IC score was associated with a 1% reduction (SHR=0.99, 95% CI 0.98-0.99) in the probability of hospital admission within 14 years. See **Appendix 4.4** for full results. Sensitivity analyses using Cox proportional hazard models revealed similar patterns (**Appendix 4.5**).

When the IC score is split into quartiles, as in **Figure 4.5** and **Figure 4.6**, those scoring in the lowest quartile of IC were at the most risk of death and hospital admission, with those scoring in the highest quartile at the least risk. Full results of the mortality and hospital admission analyses by IC quartile can be found in **Appendix 4.4.**

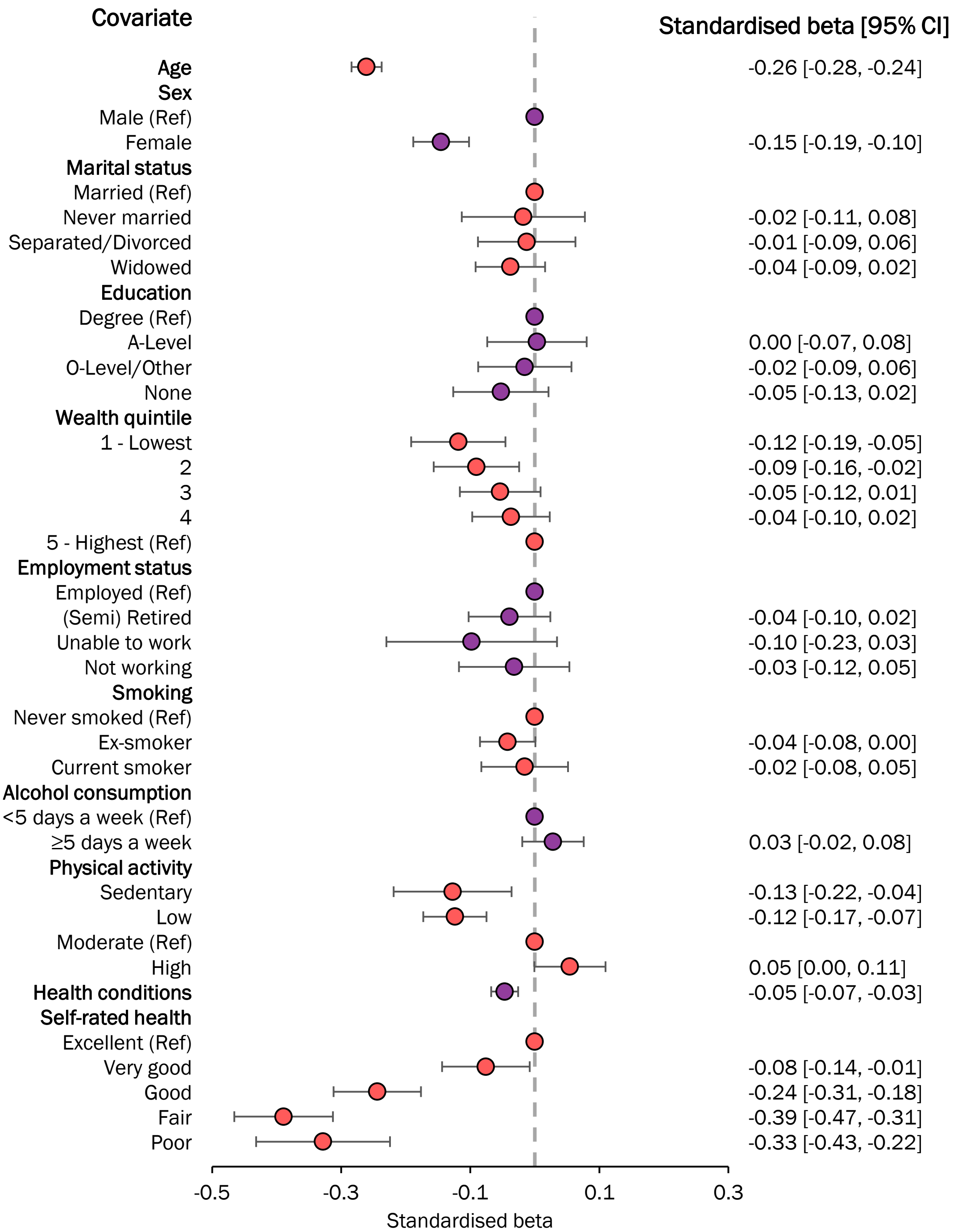

Figure 4.3 Forest plot for the fully-adjusted linear regression between intrinsic capacity scores and sociodemographic and health-related covariates at baseline (N=4,662). Standardised beta coefficients are presented; all variables are mutually adjusted for each other. Figure adapted from Campbell et al. (2022, Figure 1) [254].

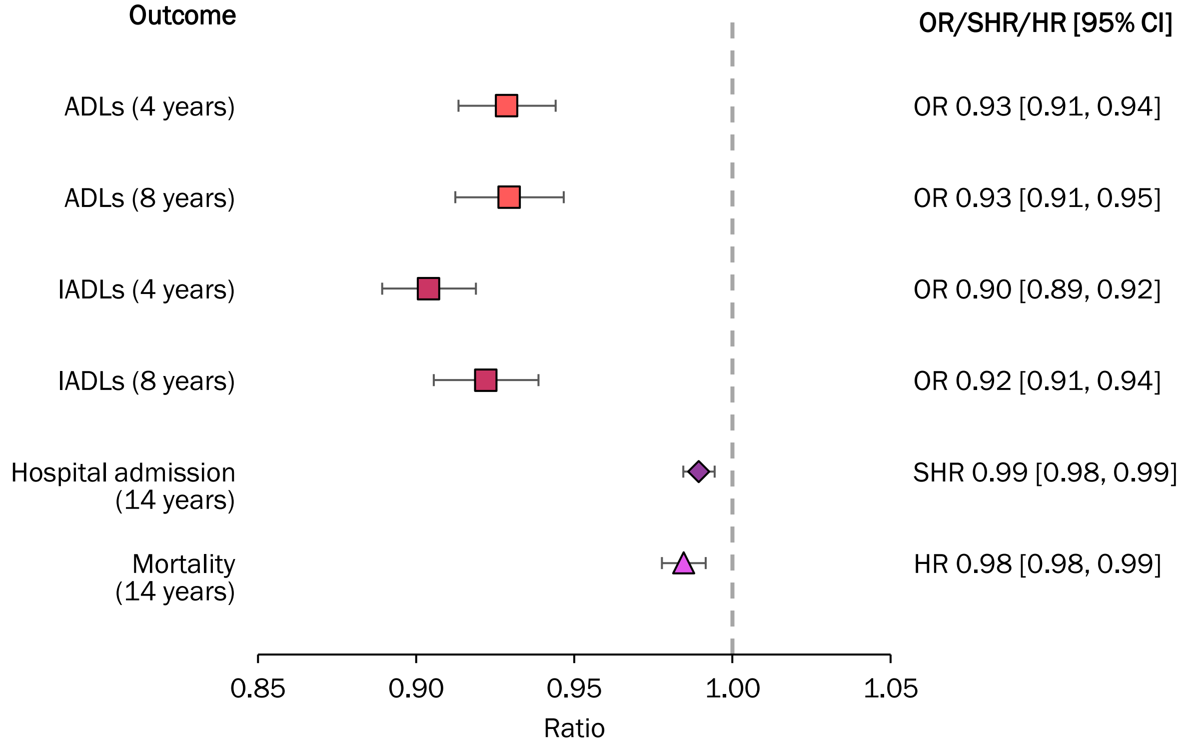

Figure 4.4 Forest plot for the association between baseline intrinsic capacity scores and future outcomes: ADLs and IADLs at 4 years later (N=3,055) and 8 years later (N=2,348), and hospital admission (N=4,489) and mortality (N=4,545) during the 14 years follow-up.

Odds ratio (OR, ■), subhazard ratio (SHR, ♦) or hazard ratio (HR, ▲) are presented depending on the analysis. Figure adapted from Campbell et al. (2022, Figure 2) [254]

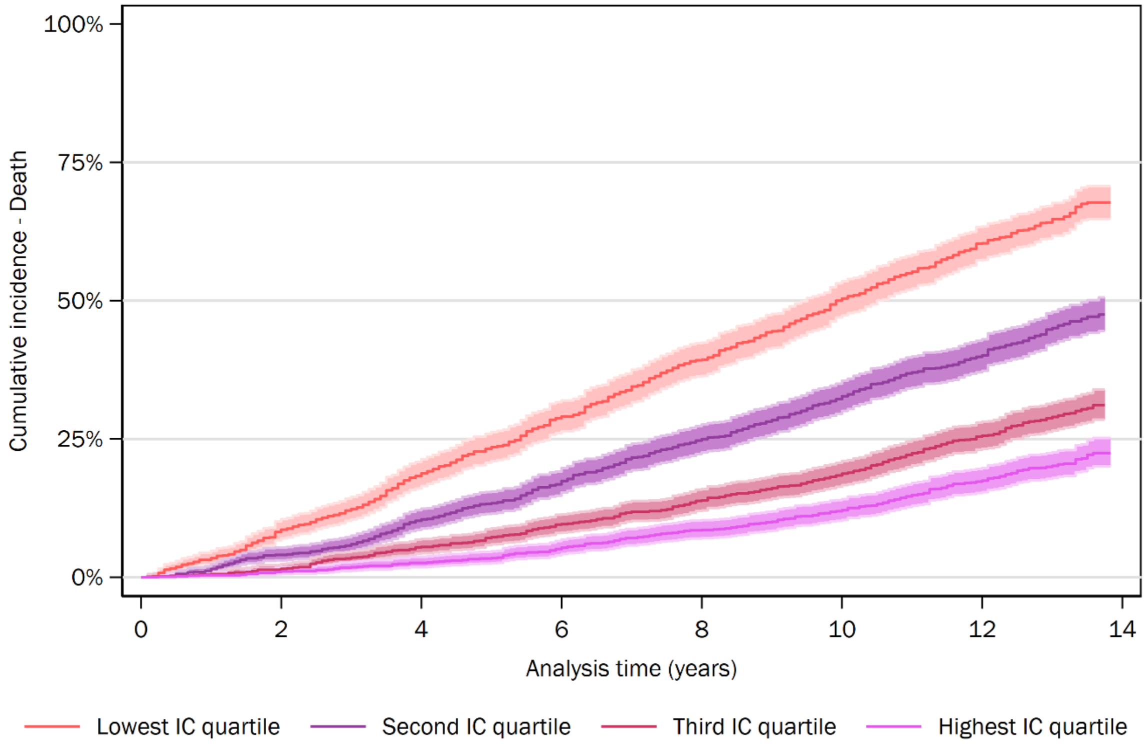

Figure 4.5 Cumulative incidence of death over the 14-year follow-up by quartile of IC score

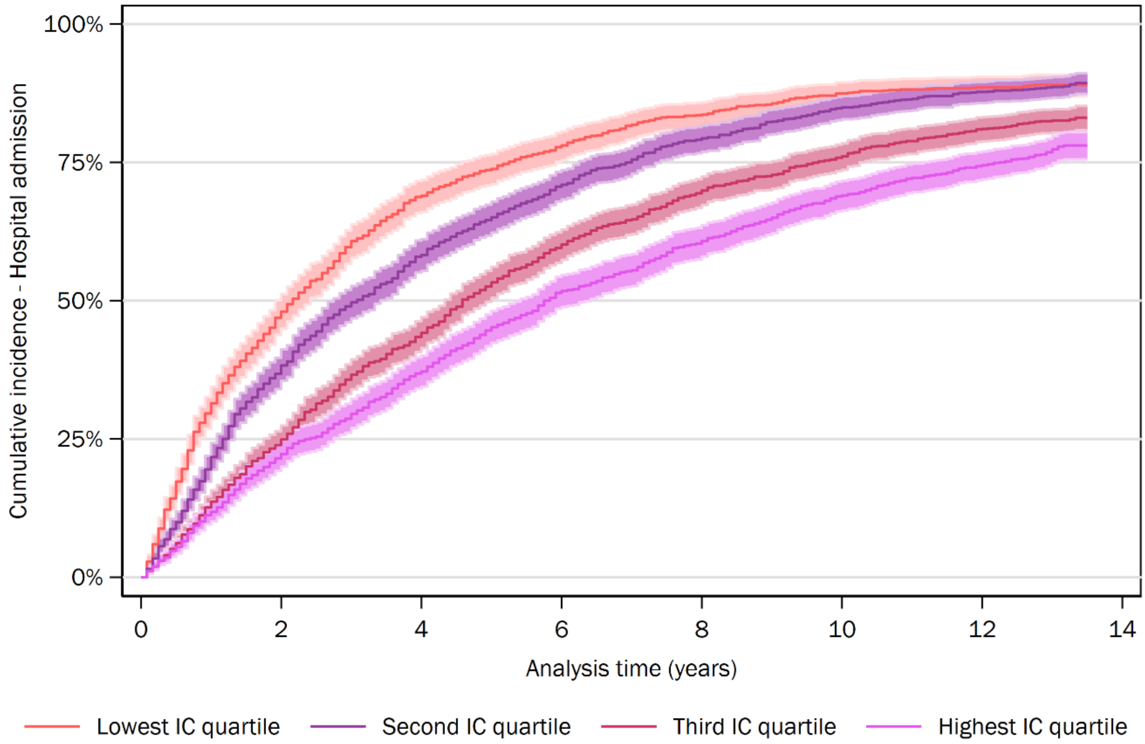

Figure 4.6 Cumulative incidence of hospital admission over the 14-year follow-up by quartile of IC score

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4.5 Discussion

The WHO model has laid out a framework for measuring healthy ageing revolving around the concept of IC. Following this model, this study computed an IC score in a representative sample of adults aged ≥60 years from private households in England. This model, based on 14 indicators and an item response theory model, showed a good fit to the data, and the IC score was associated with sociodemographic and health-related factors. This supported the second hypothesis of this chapter that the IC score would be associated with key sociodemographic factors, such as age, sex, and socioeconomic position, and health-related factors, such as subjective health ratings. Results supported the hypothesis that higher IC scores would be associated with younger, more socioeconomically advantaged, and healthier individuals.

Importantly, the IC score was found to significantly predict subsequent functional ability, hospital admission and mortality over a period of up to 14 years, even when adjusted for other health conditions. This supports the first hypothesis of the chapter, which stated that the IC score would be negatively associated with adverse health and functional outcomes, and demonstrates the score's utility as a measure of risk for future adverse outcomes in older people, potentially above that indicated by health conditions. However, although statistically significant, the magnitude of the associations to health outcomes was modest, so the exact clinical relevance of the IC score still requires exploring in more depth.

The finding that the IC score has the predictive ability for objective health outcomes is consistent with previous similar studies. The ATHLOS consortium found their healthy ageing index, also generated with an IRT model, was associated with sociodemographic and health factors as well as predicted mortality, although the magnitude of this prediction was not tested [73]. A study of community-dwelling older adults aged ≥70 years in the USA found a one-unit reduction in IC score was associated with a 7% increased risk for ADL disability, as well as a 6% increased risk for nursing home admission and 5% increased risk of mortality over 21 years [61]. This is an equivalent increase in the risk of ADL disability to this study but a slightly larger effect for mortality than found in this data (2%). A larger effect for mortality was also described by Loquet et al. [64], who found a 49% decrease in mortality risk with a unit increase in their composite IC score, generated as an average of four domain-specific z-scores in a Belgian sample of community-dwelling participants. They also found the locomotion and psychological domains, in particular, were associated with reduced mortality risk of 55% and 44%, respectively. These variations in the magnitude of the effect may be due to differences between the samples used, with the American and Belgian samples (n=754 and n=481, respectively) being substantially smaller than the ELSA sample, as well as the American participants all taking part in a health plan and Belgian participants recruited mainly from an outpatient clinic and so potentially more health conscious. It could also be due to variations in the IC score used. Both papers generated their score by calculating a score for each domain and then taking an average of the domain-specific scores for total IC, although Stolz et al. [61] did compare this to factors scores generated through confirmatory factor analysis and found a high correlation between the two, this may be another reason for different results to this study as one unit of IC might reflect a different amount of capacity.

With regards to hospital admission, Yu et al. focused on individual domains of IC and found the cognition and locomotion domains were predictive of visits to emergency departments in a Chinese community-dwelling sample aged ≥60 years but did not find any domains associated with incident hospitalisation in a one-year follow-up [47]. They found a large increase in odds for emergency department visits with cognitive impairment based on the Short Portable Mental Status Questionnaire (167% increase) and limited mobility measured with the chair rise test (322% increase), which are substantially larger than the magnitude of the effect found in this study. Nevertheless, visits to the emergency department are a different outcome to hospital admissions, as shown in this study, with admissions often reflecting a more serious or ongoing problem that requires more medical intervention. The Yu et al. study also has other methodological differences from the current study, with a smaller sample (N=756) as well as IC measured as individual domain scores based on one indicator binarised to impaired or not impaired. These differences make it difficult to directly compare the results, but it is clear from the current and previous studies that IC, measured using different methods, can predict objective health outcomes in populations around the world, with the cognition and locomotion domains potentially being of key importance, although more evidence would be needed to untangle this relationship.

A key potential difference between the current study and others assessing objective health outcomes is that the mortality and hospital admission information in ELSA is obtained through data linkage for all those who consented to the linkage. This means that ELSA has information on these outcomes even for people who may have later dropped out of the study due to poor health or any other reason, and thus may capture information from people who may not have been included in other studies.

The range of IC models and indicators in the current literature measuring IC with existing data or research studies provides some evidence that the general domains of IC are the important aspect when measuring IC to explore patterns in a population, as opposed to particular tests or indicators. From this study, the item discrimination parameters identified all the locomotion domain indicators and the vitality domain indicator of grip strength as having the highest discrimination and, thus, best-mapped individuals along the IC trait continuum. The locomotion domain has been identified in previous research as a predictor of hospital visits as well as mortality, with cognition and psychological domains also showing significant associations with adverse outcomes, suggesting these may be key domains to focus on if all domains cannot be measured. However, differences between the domains were not explicitly tested in this study, with the focus being on testing a total measure of IC that captured the domains of IC and measured all the physical and mental capacities of an individual, as per the WHO framework.

The main strengths of this analysis include the use of a large nationally representative survey of community-dwelling older adults in England. The ELSA data linkage to health and mortality records allows for objective health outcomes to be examined, with the longitudinal nature of the data meaning an almost 20-year follow-up, which is longer than most other studies of IC's predictive value. The ELSA survey data also provides rich and comprehensive information on the variables of interest and key covariates.

However, there are limitations to this analysis. ELSA only represents community-dwelling older adults in England; therefore, different results might be found among those in long-term hospital or nursing home care. Concerning the IC score, the dichotomous indicators are sensitive to the cut-offs; thus, choosing different cut-offs may lead to different results. There are also some limitations to the IC indicators. Hearing and vision measurements would be more accurate if assessed with objective tests as opposed to self-reported function. The same could be said for indicators of mobility; however, the inclusion of objective tests of physical function (balance, walking speed, chair rises and grip strength) in addition to the self-reports of mobility mean that physical function was assessed in a more comprehensive manner. Concerning the cognition domain, it would have also been preferable to have a global index of cognitive capacity that captures functioning in fluid elements of cognition, such as memory, executive function, processing speed, as well as crystallised elements, such as general knowledge and vocabulary, in order to capture a comprehensive screenshot of the individual's cognition at that time.

4.6 Conclusion

To conclude, this analysis finds a novel IRT model of intrinsic capacity to be significantly associated with subsequent functional ability, hospital admissions and mortality, even when adjusted for socioeconomic and health-related covariates. These results suggest that IC can effectively predict adverse outcomes and potentially identify individuals at risk of functional decline, hospitalisation, and death. This has implications for the measurement and monitoring of overall health across multiple domains in older people and the targeting of interventions ahead of potential adverse health outcomes, supporting the WHO's focus on IC to promote healthy ageing and reduce disability and care dependence.

Chapter 5: Longitudinal analyses of intrinsic capacity

5.1 Introduction

In the previous chapter, an intrinsic capacity (IC) score was generated using an item response theory (IRT) model in Wave 2 of the English Longitudinal Study of Ageing (ELSA). This chapter will expand the generation of an IC score to multiple waves of ELSA and test the measurement invariance of the score over the three time points.

Longitudinal assessment of IC is central to the WHO healthy ageing framework, as measuring IC over time allows for monitoring of any decreases in capacity, and interventions can be targeted prior to a major decline in physical or cognitive function and/or quality of life. To date, only a minority of IC models have been explored longitudinally, but most find that, on average, IC scores decline over time, although there is great heterogeneity between individuals [60, 61]. Different types of trajectories of IC have been identified in a couple of studies which fall into three main groups: those whose IC declines rapidly, those who have medium IC that declines slightly, and those who have IC with little decline over time [67, 68].

Measurement invariance is important to test when using a scale at different time points or across different groups. The presence of measurement invariance in a scale for a particular construct means that the scale measures the construct of interest differently across different time points or groups of individuals. IRT provides a useful approach to measurement invariance [319], which is tested through differential item functioning (DIF). If DIF is present in an IRT model, it means the items included in the scale measure the latent trait differently across members of separate groups [320]. In terms of longitudinal analysis, DIF indicates if the scale items are assessing equivalent levels of the latent trait across different time points.

5.1.1 Chapter objectives

This chapter explores the longitudinal element of **Objective 1**: To operationalise IC as a measure of healthy ageing (across multiple time points) in an observational study of ageing and test the score's measurement invariance over time.

The specific aim of this chapter is to generate IC in waves 2, 4, and 6 of ELSA and test the measurement invariance using IRT methodology.

5.2 Methods

Three waves of ELSA spaced 4 years apart were used in this analysis – wave 2 (2004-05), wave 4 (2008-09) and wave 6 (2012-13) – resulting in a total period of 8 years.

5.2.1 Intrinsic capacity

The IRT model used to generate an IC score in the baseline wave (wave 2) outlined in the previous chapter was applied to wave 4 and wave 6 in R using the *mirt* function.

This model included the 14 indicators covering 5 domains of IC used in **Chapter 4**, with performance on each categorised into "No difficulty" and "Difficulty" (**Table 4.1**). The indicators were: word recall and orientation in time (cognition); balance test, chair rise test, walking speed, lower mobility, and upper mobility (locomotion); self-rated eyesight and hearing (sensory); grip strength, BMI, and waist circumference (vitality); CES-D scale and Satisfaction With Life Scale (psychological).

5.2.2 Covariates

Socioeconomic and health-related covariates were included in the descriptive analysis. These were baseline age, sex, marital status, highest educational qualification, total net wealth, employment status, alcohol consumption (days per week), current smoking status, physical activity, number of chronic health conditions, and self-rated health. The measurement of these variables is described in the previous chapter.

All variables apart from baseline age, sex, and educational attainment were time-varying over the 3 waves. Educational attainment was time invariant and was collected at either wave 2 or wave 4.

5.2.3 Sample

The sample was restricted to those who had joined ELSA at or prior to wave 2. An IC score was generated in all cohort members aged ≥60 years who consented to a nurse visit at that wave, resulting in IC scores for 7,690 individuals with 14,823 observations over 3 waves.

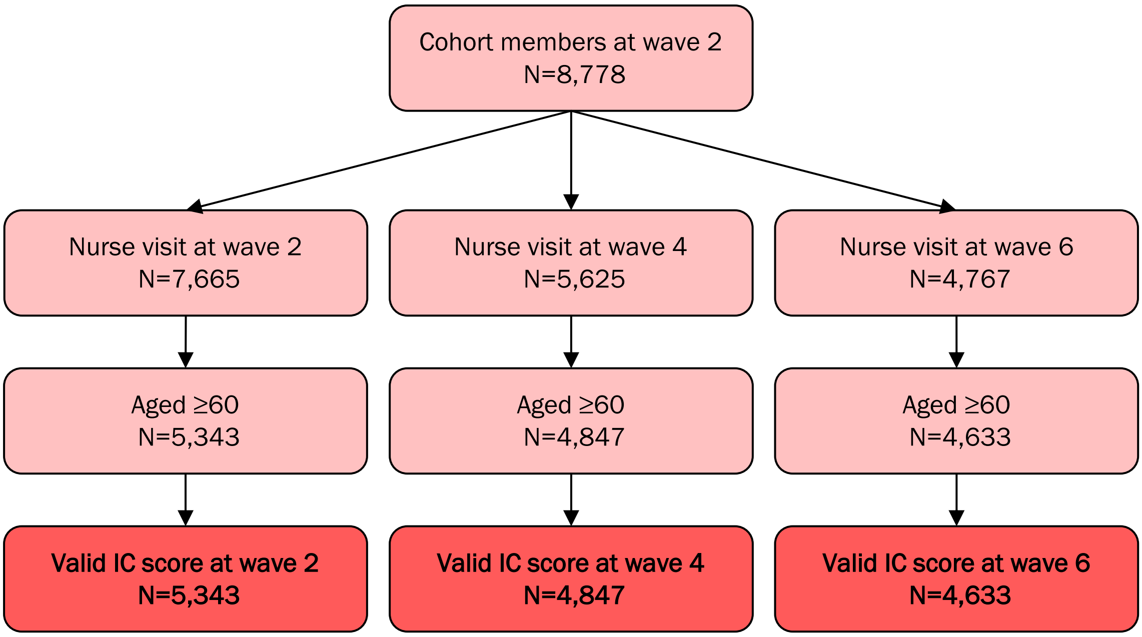


Figure 5.1 Flowchart of the sample selection process for the generation of an intrinsic capacity score in waves 2, 4, and 6 of ELSA.

5.3 Statistical analysis

5.3.1 Measurement invariance

Differential Item Functioning (DIF) was detected using logistic ordinal regression differential item functioning (LORDIF) using a graded response model. Although a 2-parameter logistic model was used for the IC generation, the specific type of model specified for LORDIF is not that important as the objective is to obtain trait estimates to serve as the matching criterion for DIF and that trait estimates for the same data based on different IRT models are virtually interchangeable [320].

Testing of DIF was completed in R using the *lordif* package [320]. This implements OLR with IRT-based trait scores that have been estimated from DIF-free “anchor” items as the conditioning variable. First, a model where all parameters are constrained to be equal across time points was tested against a model with one parameter free to be calculated per time point. Once anchor items have been identified, three nested OLR models were estimated for each item and compared to identify DIF. Model 1 included the intercept and an estimate of the trait; Model 2 added a group variable, in this case, the time point; Model 3 then added an interaction of the trait and group variable. The detection criterion for DIF was set as a 10% difference between the beta coefficients of the nested models [320, 321]. For each item, the function returned whether DIF was present or not. Detailed information about the *lordif* package algorithm is outlined in Choi, Gibbons and Crane (2011, p7-8) [320].

5.4 Results

5.4.1 Sample description

Of the 7,690 individuals in the sample, 2,962 (38.52%) had 1 measurement of IC, 2,323 (30.21%) had 2 measurements, and 2,405 (31.27%) had 3 measurements.

The mean and standard deviation of the standardised IC score remained 50 and 10, respectively and were negatively skewed (**Figure 5.2**).

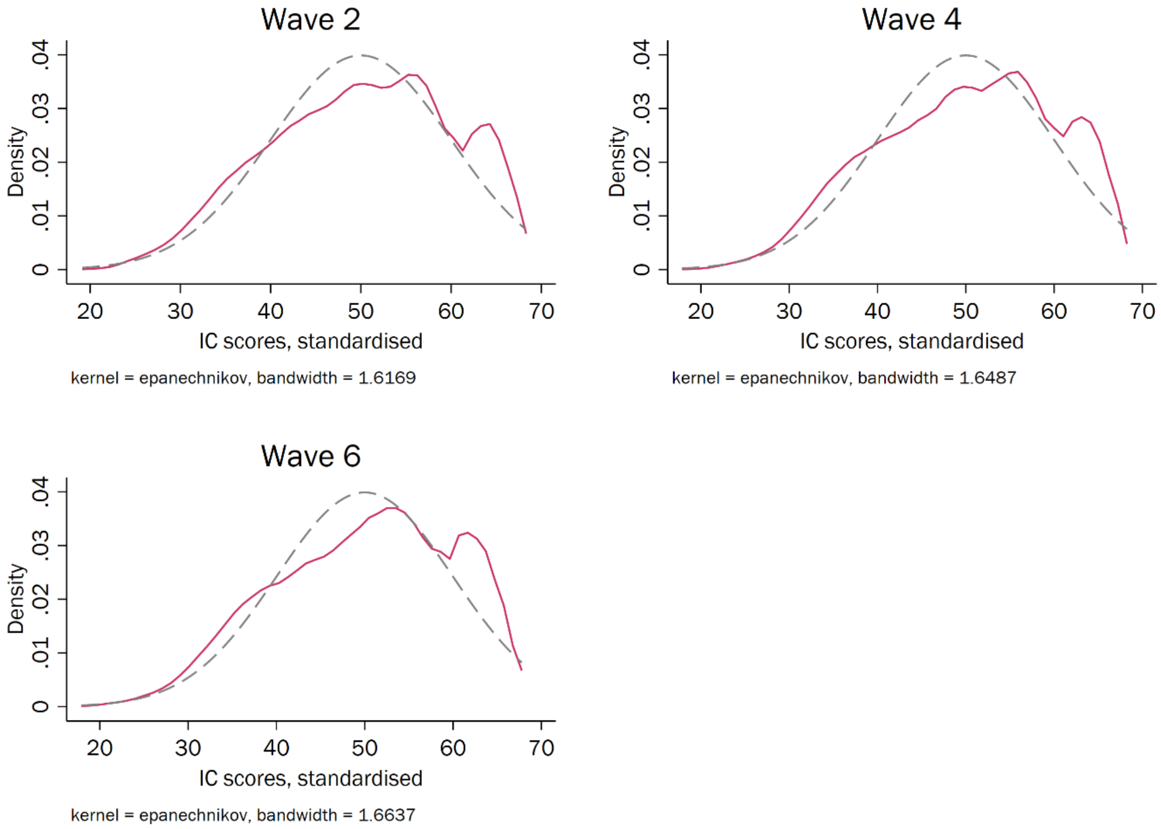


Figure 5.2 Distribution of the IC score in each wave plotted against a normal curve

Table 5.1 Mean and standard deviation of intrinsic capacity scores in wave 2, 4 and 6

Wave	N	Mean	SD
2	5,343	50.00	10
4	4,847	50.00	10
6	4,633	50.00	10

Table 5.2 Description of the IC score sample in waves 2, 4, and 6, and the mean IC score for covariate categories.

	Proportions (%) in each category / Mean [SD]			Mean IC score [SD]		
	Wave 2 N=5,343	Wave 4 N=4,847	Wave 6 N=4,633	Wave 2 N=5,343	Wave 4 N=4,847	Wave 6 N=4,633
Age (Mean [SD])	71.26 [8.20]	71.19 [8.59]	71.28 [7.48]			
60	47.93	47.82	47.66	53.55 [9.06]	53.72 [8.76]	53.39 [8.87]
70	34.98	34.89	35.61	49.18 [9.30]	49.14 [9.47]	49.18 [9.49]
80	15.59	15.45	16.73	42.16 [8.57]	42.01 [8.49]	42.09 [9.24]
90+	1.5	1.84	0	37.13 [6.57]	36.68 [6.89]	n/a
Sex						
Male	44.69	44.13	44.42	52.11 [9.39]	52.15 [9.35]	51.85 [9.66]
Female	55.31	55.87	55.58	48.30 [10.15]	48.30 [10.17]	48.52 [10.02]
Marital status						
Never married	4.57	4.48	4.58	48.86 [9.68]	48.13 [10.20]	49.09 [10.06]
Married	62.64	62.64	64.26	51.95 [9.39]	52.21 [9.25]	51.78 [9.38]
Separated/Divorced	8.31	9.92	11.31	49.61 [10.10]	49.44 [9.94]	49.11 [9.94]
Widowed	24.46	22.96	19.81	45.36 [9.98]	44.57 [9.77]	44.94 [10.18]
Missing	*0.02*	*0*	*0.04*	49.09 [0.00]	n/a	57.95 [7.77]
Highest educational level*						
Degree	10.05	14.09	15.45	55.26 [8.53]	55.21 [8.43]	54.34 [8.52]
A-Level	16.26	19.64	20.57	53.16 [9.41]	52.60 [9.30]	51.87 [9.40]
O-Level or other	29.78	30.66	29.59	51.07 [9.44]	50.64 [9.43]	49.69 [9.61]
None	43.91	35.61	28.10	46.90 [9.88]	45.95 [9.86]	45.40 [9.79]
Missing	*0*	*0*	*6.28*	n/a	n/a	55.23 [8.99]
Wealth quintiles						
Poorest	18.04	17.10	15.11	43.98 [9.33]	43.96 [9.25]	43.69 [9.40]
2	19.75	18.75	18.02	47.26 [9.82]	47.32 [9.80]	47.00 [9.95]
3	20.16	20.28	21.71	50.50 [9.39]	50.27 [9.55]	49.76 [9.64]
4	20.29	20.80	21.99	51.97 [9.41]	52.05 [9.17]	51.92 [9.03]
Richest	20.76	20.90	21.71	55.23 [8.31]	54.87 [8.62]	54.98 [8.46]

	Proportions (%) in each category / Mean [SD]			Mean IC score [SD]		
	Wave 2 N=5,343	Wave 4 N=4,847	Wave 6 N=4,633	Wave 2 N=5,343	Wave 4 N=4,847	Wave 6 N=4,633
Missing	*1.01*	*2.17*	*1.45*	53.81 [7.22]	51.65 [10.73]	52.88 [9.29]
Employment status						
Retired/Semi-retired	73.85	74.93	78.85	49.34 [9.87]	49.04 [9.95]	49.16 [9.94]
Employed	12.11	15.76	14.40	57.36 [6.60]	56.76 [6.66]	56.57 [6.83]
Permanently unable to work	3.22	3.03	2.09	38.97 [7.62]	39.22 [8.03]	36.90 [6.96]
Looking after home/family or unemployed	10.61	6.25	4.55	49.43 [9.69]	49.73 [9.35]	49.70 [9.30]
Missing	*0.21*	*0.02*	*0.11*	54.79 [9.28]	51.45 [0.00]	53.35 [13.12]
Smoking						
Never smoked	36.03	37.40	35.44	50.96 [10.09]	50.85 [10.07]	51.07 [9.73]
Ex-smoker	51.60	50.96	55.04	49.68 [9.88]	49.88 [9.91]	49.57 [9.99]
Current smoker	12.30	10.77	9.52	48.49 [9.98]	48.03 [9.78]	48.53 [10.70]
Missing	*0.07*	*0.87*	*0*	53.87 [7.19]	44.66 [9.66]	n/a
Alcohol						
5+ days a week	20.79	21.15	19.45	53.15 [9.29]	53.47 [8.80]	53.15 [9.15]
<5 days a week	67.55	67.15	71.55	49.98 [9.80]	49.86 [9.84]	49.83 [9.83]
Missing	*11.66*	*11.70*	*9.00*	44.48 [9.98]	44.51 [10.33]	44.55 [10.51]
Physical activity						
Sedentary	7.34	8.15	6.13	37.71 [7.94]	38.91 [8.92]	37.44 [9.12]
Low	27.23	25.93	26.74	45.07 [9.09]	44.29 [8.77]	44.09 [9.01]
Moderate	49.58	48.22	48.72	52.40 [8.51]	52.39 [8.52]	52.34 [8.32]
High	15.80	17.68	18.39	56.67 [7.71]	56.96 [7.07]	56.58 [7.32]
Missing	*0.06*	*0.02*	*0.02*	50.57 [3.33]	51.45 [0.00]	45.91 [0.00]
Health conditions† (Mean [SD])	1.17 [1.24]	0.83 [0.85]	0.74 [0.79]			
0	36.80	40.68	43.04	52.81 [9.51]	52.82 [9.48]	52.82 [9.35]
1	31.22	40.87	42.97	50.15 [9.73]	48.86 [9.89]	48.63 [9.94]
2	18.08	14.42	11.33	48.53 [9.84]	47.01 [9.56]	45.77 [9.59]
3	8.40	3.36	2.14	45.40 [9.40]	44.14 [9.59]	44.95 [9.92]
4	3.74	0.58	0.47	42.62 [8.51]	42.16 [9.69]	42.26 [8.28]
5	1.07	0.08	0.02	41.27 [7.97]	41.30 [9.45]	52.63 [0.00]

	Proportions (%) in each category / Mean [SD]			Mean IC score [SD]		
	Wave 2 N=5,343	Wave 4 N=4,847	Wave 6 N=4,633	Wave 2 N=5,343	Wave 4 N=4,847	Wave 6 N=4,633
6	0.62	0	0	40.96 [8.25]	n/a	n/a
7	0.06	0	0.02	49.22 [12.42]	n/a	35.55 [0.00]
8	0.02	0	0	40.82 [0.00]	n/a	n/a
SRH						
Excellent	11.06	9.72	9.24	58.27 [6.81]	58.01 [6.79]	58.60 [6.47]
Very good	26.15	27.96	28.51	54.80 [8.16]	55.14 [7.86]	55.09 [7.68]
Good	33.09	33.65	33.11	50.23 [8.65]	50.45 [8.67]	50.41 [8.50]
Fair	22.03	21.48	21.52	43.83 [8.51]	43.31 [8.07]	43.63 [8.18]
Poor	7.58	7.18	7.58	38.36 [7.68]	37.07 [7.15]	36.69 [7.75]
Missing	*0.09*	*0.02*	*0.04*	44.27 [7.17]	47.24 [0.00]	40.28 [4.89]

*Education in wave 6 is derived from the maximum value per participant from waves 1-5.

† Count of diagnosed conditions: Alzheimer’s disease, angina, arrhythmia, arthritis, asthma, cancer, chronic lung disease, coronary heart failure, dementia, diabetes, heart murmur, high blood pressure, high cholesterol, myocardial infarction, osteoporosis, Parkinson’s disease, psychiatric problems, stroke.

The mean age of the sample remained 71 years in wave 2, wave 4, and wave 6 (**Table 5.2**). The proportions in each category of the descriptive variables remained relatively similar over each wave. There was a relatively even split between men and women, with 44-45% women at each wave. Approximately 63-64% of the sample were married, 10-15% were educated to a degree level, and the majority (74-79%) were retired. There was an uneven split across wealth quintiles, with 15-18% in the lowest quintile and 21-22% in the highest. About half of the sample were ex-smokers (51-55%), with only 10-12% current smokers and the majority of the sample consumed alcohol less than 5 days per week (67-72%). Most people took part in moderate physical activity (~50%), while only ~6-8% were sedentary. The mean number of health conditions remained around 1 condition, and the majority (~71%) rated their health as "good" or better.

The mean IC score in each category of the descriptive variables also remained similar over each wave (**Table 5.2**). Mean IC score tended to be lower in older individuals, women, those with lower education, and those who were unmarried, in the lower wealth quintiles, not currently employed, current smokers, consuming alcohol less frequently, sedentary, and diagnosed with a greater number of chronic health conditions, as well as those who rated their health as poor.

5.4.2 Measurement invariance

Testing for DIF using the LORDIF approach identified no items with differential functioning across the three waves. The proportionate change in the beta coefficients of the nested models was below the critical value of 0.1 for all indicators (**Table 5.3**).

Table 5.3 Proportional change in the beta coefficients of the nested models used to identify Differential Item Functioning using the LORDIF approach

Indicators	Proportional change in the beta coefficient		
	Wave 2*	Wave 4**	Wave 6***
Word recall	0.0062	0.0002	0.0035
Orientation	0.0062	0.0007	0.0041
Chair rise	0.0013	0.0003	0.0004
Balance	0.0008	0.0001	0.0007
Walking speed	0.0000	0.0003	0.0001
Lower mobility	0.0002	0.0006	0.0004
Upper mobility	0.0019	0.0003	0.0012
Self-rated vision	0.0006	0.0001	0.0008
Self-rated hearing	0.0010	0.0004	0.0009

Grip strength	0.0025	0.0000	0.0027
BMI	0.0082	0.0001	0.0093
Waist circumference	0.0130	0.0003	0.0007
CES-D	0.0015	0.0001	0.0007
Life satisfaction	0.0090	0.0000	0.0116

*wave 2 vs. wave 4 & wave 6; ** wave 4 vs. wave 2 & wave 6; *** wave 6 vs. wave 2 & wave 4

5.5 Discussion

This chapter expanded the investigation of the IC model over two more waves of ELSA, covering a total of 8 years follow-up period. IRT methodology was used to generate the score in the additional waves in the same way as in the baseline wave, and tests found no differential item functioning in the scale across the different time points. This indicates that the model is measuring the trait of IC in the same way at each time point, therefore displaying measurement invariance.

None of the 10 studies identified in the literature review as modelling IC longitudinally (**Section 1.2.2**) described the testing of measurement invariance for their IC scale over time. More detailed research into how IC scales behave over time would be useful; however, with almost every study having a unique measurement of IC, this statistical exploration is difficult. A couple of previous studies that defined a healthy ageing scale, including measurements of IC did explore measurement invariance of scales across different groups but not over time.

Sanchez-Niubo et al. (2020) used the same LORDIF process as this study to detect DIF across different studies [73]. They used IRT to generate their healthy ageing scale from 41 items incorporating intrinsic capacity and functional ability (model 12 in **Appendix 1.2**) in 16 studies and tested DIF to establish the homogeneity of the scale across the studies. Of the 16 studies, 13 had at least 1 item displaying DIF, with the Australian Longitudinal Study of Ageing, and the Study on Global Ageing and Adult Health having the most items with DIF at 8 each. Nevertheless, there was a lot of variation in the items displaying DIF across the studies; most individual items that displayed DIF did so in a maximum of 3 studies, apart from one item on “energy” that presented DIF in 6 studies. The results from the DIF testing were used to inform an equating procedure for studies that exhibited DIF, which introduced cohort-specific parameters that rescaled scores to the main scale.

As this previous study found quite a few instances of DIF among the items, it may be surprising that no DIF was found in the current results. However, this previous study measured a different range of items, some reflecting IC but others reflecting functional ability, as well as testing DIF across countries instead of over time. Nevertheless, it does suggest that there are more differences in the functioning of IC/healthy ageing scales across different populations than over time. This makes sense as there are many reasons for a single scale to be used across groups of people from different cultures and backgrounds to be measuring a latent trait in a different way; for example, language, interpretation or understanding of the item, and cultural norms. Thus, it would be expected to see more DIF across different countries than you would expect to see when using the same scale on the same people across time.

Measurement invariance was also explicitly tested by Daskalopoulou et al. (2019) for their healthy ageing index generated using the 10/66 Dementia Research Group survey [58], which collects data from 6 countries/territories in Latin America (Cuba, Dominican Republic, Peru, Venezuela, Mexico, and Puerto Rico). Confirmatory factor analysis (CFA) was carried out on 26 indicators of functional ability and intrinsic capacity (model 8 in **Appendix 1.2**), and measurement invariance across the 6 countries and between men and women were tested with multi-group CFA using nested models with increasing parameter constraints. In this method, different parameters were set to be equal or not across the groups (country or sex), and the statistical fit of the models was examined. Configural invariance – whether the pattern of factor loadings is the same across groups [322] – was tested by allowing all the factor loadings and thresholds to be estimated freely across the groups. Scalar invariance – whether the item intercepts or thresholds are equivalent across groups [322] – was tested by constraining all the factor loadings and thresholds to be equal across groups. The change in comparative fit index (CFI) and the root mean square error of approximation (RMSEA) was examined, with a change in values of ≤0.010 for CFI and ≤0.015 for RMSEA, indicating measurement invariance. The testing revealed the same pattern of factor loadings and equal item thresholds across countries and sex, therefore, the index demonstrated both configural and scalar invariance. It was noted that metric invariance – the equivalence of factor loadings across groups [322] – could not be assessed as loadings and thresholds cannot be tested separately for ordinal items [323].

Both of these studies found measurement invariance of a healthy ageing score using different methods, suggesting that these combinations of IC and functional ability indicators are measuring healthy ageing in the same way across different countries and between men and women. However, although both include indicators of IC, neither is a model of purely IC, so there is no prior evidence of measurement invariance across groups of IC specifically. Also, neither study explored longitudinal invariance, where the invariance was tested across different time points. Of the other 8 models of IC that were explored longitudinally, none tested the measurement invariance of IC over time. Most of these models generated an overall IC score using methods that are less conducive to measurement invariance testing, such as average z-scores and sum scores, so this could not be interrogated; but some using more advanced techniques such as CFA or IRT also did not explore invariance over time. The finding from the current study that IC showed measurement invariance over time is, therefore, novel and the first step in examining the methodological properties of IC over time.

Strengths of this chapter include the use of IRT methodology, which has been identified as a good method for testing longitudinal measurement invariance [319]. Limitations of this chapter include the restriction of measurement invariance testing to only across time. Further testing of measurement invariance of the IC model across different groups, such as sex or age groups, was beyond the scope of this project but would have interrogated the measurement properties of the IC model more thoroughly. Also, the use of IRT methodology doesn’t allow for the same exploration of the different levels of invariance as with factor analysis, for example, configural, metric and scalar invariance. Further research could expand on the current work by testing for measurement invariance of the IC model across men and women and also across age groups, for example, in pre-retirement populations aged 40-59 years, older adults aged 60-79 years, and the oldest old aged ≥80 years.

5.6 Conclusion

Testing for measurement invariance is fundamental to establish whether the scale items are assessing equivalent levels of the latent trait across different time points. IRT methodology was a valuable tool for generating the IC score in all waves, consistent with the baseline wave. Testing of measurement invariance showed no differential item functioning in the IC scale across the different time points. Therefore, the same latent trait of interest was identified longitudinally.

Chapter 6: Social isolation and intrinsic capacity

6.1 Introduction

In the previous chapter, a novel model of intrinsic capacity (IC) was created using item response theory (IRT) and extended to multiple waves of the ELSA dataset. In this chapter, this model will be used to test if social isolation predicts intrinsic capacity.

Social isolation is a measure of the absence of social relationships. As seen in the literature review, social isolation is associated with a greater risk of all-cause mortality [152], hospital admission [324] and adverse physical and mental health in older age [121, 144, 325].

Only two studies were identified in the literature review that explored the relationship between social relationships and IC. Huang et al. (2021) [63] (**Appendix 1.2**, model 19) tested whether social frailty was associated with trajectories of IC, with social frailty determined by requiring financial support, living alone, not participating in social activities, and having irregular contact with others. This measure of social frailty was derived from the definition outlined by Bunt et al. (2017), which characterised social frailty as a lack of general resources (including financial situation, employment, housing and neighbourhood factors, and childhood circumstances), reduced social behaviour and activities (e.g., reduced social participation and not maintaining close relationships), and insufficient social resources (lack of close contacts, e.g., family and friends, and small social network), which result in a compromised fulfilment of social needs (e.g., social cohesion, sense of belonging, social and emotional support) [165]. The concept of social frailty arose from the biopsychosocial perspective of frailty, which posits that frailty increases with the accumulation of physical, psychological, and social deficits. Huang et al. measured social frailty in 663 respondents of the Nagoya Longitudinal Study for Healthy Elderly with 4 indicators; each scored 1 point – whether the respondent had a need for financial support, if they lived alone, if they did not participate in social activities, and if they did not have regular contact with others. The amount of participation or frequency of contact that was counted as participation or regular contact was not specified. The resulting scores (0-4) were categorised into social robustness (0 points), social prefrailty (1 point), and social frailty (2-4 points). Results found that the IC scores of those in the social prefrailty and social frailty groups declined more over time than the socially robust group, especially in the cognition, psychological, and vitality domains; socially prefrail/frail men also showed a greater reduction in the psychological and cognition domains than women. Although social frailty is a different concept from social isolation, it focuses on structural elements (participation, frequency of contact) of social relationships in a similar way to social isolation and not functional aspects like feelings about relationships captured by social support and loneliness.

The other study to explore social relationships and IC focused on social engagement and loneliness in a cross-sectional analysis. Leung et al. (2022) [50] recruited a sample of 304 community-dwelling adults aged ≥60 years living in Hong Kong and generated an IC score by summing domain scores (**Appendix 1.2**, model 45). Loneliness was assessed with one question asking if the respondents felt lonely, with the responses "not lonely", "a bit lonely", and "very lonely". Social engagement was assessed with one item, which asked the respondents about the extent of their engagement with leisure activities, hobbies, work, volunteering, supporting family, education, or spiritual activities. A 3-point Likert scale was used to determine the level of engagement, with the categories "inactive", "less active", and "active". For the analysis, a structural equation model (SEM) was used to test the associations between IC and the other study variables – self-care capacity, social engagement, loneliness, marital status, and hypertension – with the covariates age, sex, and education. Descriptive analyses found that those who needed some support with self-care, felt a bit or very lonely, or were less socially engaged had significantly lower IC scores than those who required no care, were not lonely or were socially engaged. The SEM found that younger respondents with higher education and no hypertension were more likely to have better IC, and those who had better IC were more likely to not require self-care assistance and be more socially engaged – the relationship with loneliness does not seem to have been tested here or was not found to be significant and therefore not included. A mediating role of IC between age and social engagement and education and self-care were also identified. This indicated that the association between age and education with self-care capacity and social engagement somewhat depends on an individual's IC. Focusing on social engagement, it is feasible that an individual's capacity across the IC domains would influence their ability to be engaged with different social activities, as impairments in IC domains would make it more difficult to access or enjoy social activities. However, being a cross-sectional study, it is difficult to make conclusions about the direction of any associations, and it is unclear whether associations in the opposite direction were assessed in this study. It may be the case that the association between IC and social engagement is predominantly in the other direction or potentially bidirectional, with each affecting the other.

At the time of writing, only two papers have explored the relationships between structural elements of social relationships and IC, with the findings suggesting that less engagement in activities and contact with others is potentially a predictor and outcome of worse IC. Nevertheless, this evidence was found in relatively small samples with unclear or unspecific measurements of social relationships. Further evidence on the link between structural elements of social relationships, e.g., social isolation and IC, is required, including clear measurements of social factors and robust methods. Longitudinal evidence will be particularly helpful in helping to understand the directionality of the associations.

6.1.1 Chapter objectives

This chapter explores **Objective 2**, which is to examine the association between social isolation and IC and whether social isolation predicts IC over time.

This chapter will generate a social isolation index and use cross-sectional and longitudinal analysis to test whether social isolation is associated with IC score and whether social isolation predicts the baseline level and change of IC over time.

Hypotheses

1) High social isolation is associated with a lower (worse) IC score, cross-sectionally and over time.
2) Those with low social isolation will experience less decline in IC scores over time than those with high isolation.

6.2 Methods

6.2.1 Measuring social isolation

Isolation is often examined in the context of wider social relationships and connectedness alongside other concepts such as social networks, social support, and social engagement. When deciding how to measure isolation, the first consideration is the definition of isolation and the key dimensions to capture before then identifying items that can measure these dimensions.

In 1998, House, Umberson and Landis [326] defined social integration/isolation as "the existence or quantity of social ties or relationships, which may, in turn, be distinguished as to type (e.g. marital, kin/non-kin) and frequency of contact" (p.302). Through this definition, an individual's level of isolation is only determined by the number of relationships they have or the frequency of interaction and specifically does not involve the structure of those relationships or their functional content. Isolation was defined similarly by De Jong Gierveld and Havens simply as an objective measure of the absence of relationships with other people and shortcomings in the size of social networks [131]. However, more complex definitions outline multiple dimensions. They include feelings toward the absence of contacts, such as Nicholson's [327] definition of isolation as "a state in which the individual lacks a sense of belonging socially, lacks engagement with others, has a minimal number of social contacts, and they are deficient in fulfilling and quality relationships" (p.1346).

The varied definitions of isolation are reflected when looking at measures of isolation across research and the dimensions they capture. Wang et al. [328] reviewed measurement tools for social relationships from a mental health perspective and found that models of isolation include both objective measures of social network quantity and structure and subjective measures of the perceived quality of relationships, which would reflect functional content. In a different review of social relationship measures used in epidemiological studies, Valtorta, Kanaan, Gilbody and Hanratty [122] outlined two sets of dimensions that captured: structure vs function and objective vs subjective. Measures of structure capture the number and type of people interacted with, frequency of contact, and diversity, density, and reciprocity of a person's social network, while functional measures focus on the qualitative and behavioural characteristics of interactions and the purpose or nature of relationships. Structural and functional measures also sit on a scale of subjectivity. Some capture more subjective aspects of relationships, such as perceived availability and feelings about relationships, and others measure objective features by quantifying the number of relationships and frequency of interactions. In line with this dimensional framework, Zavaleta, Samuel and Mills [329] distinguished between external and internal social isolation when outlining potential indicators of isolation. External social isolation measures include frequency of social contact, social network support, the presence of a discussion partner and reciprocity and volunteering, reflecting a more objective approach to mainly structural elements of relationships. Internal social isolation measures focus on feelings of satisfaction with relationships, the need for relatedness, feelings of belonging, loneliness, and trust, clearly reflecting the subjective, functional aspects of relationships. According to this specification, the definition of social isolation by House, Umberson and Landis only refers to external isolation.

In summary, original specifications of social isolation focused on objective elements of relationships like the presence and/or quantity of relationships and frequency of contact but have since expanded to also include subjective aspects like the perceived quality of relationships and feelings about relationships. However, feelings around the quality of and satisfaction with relationships would be more relevant for measures of loneliness, which are defined to represent the subjective negative feelings about missing relationships [131]. As such, in this thesis, the simple definitions outlined by House et al. and De Jong Gierveld and Havens will be used to direct the measurement of social isolation in order to not conflate structural and functional aspects of social relationship deficit. The index will focus on external isolation, measuring objective quantities or frequencies, and thus capture information on the structure of relationships rather than the function.

After outlining the two dimensions that social isolation measures captured, Valtorta et al. ranked existing measures/scales on these dimensions [122]. The most objective measures that focused on structural elements of relationships were the Wenger Support Network Typology [330], the Litwin Support Network Type [331] and the Berkman-Syme Social Network Index (SNI) [332]. The first two identify different social network profiles or types based on the accessibility of family members, the frequency of face-to-face contact with family, friends and neighbours, and involvement in community and religious groups. They do not identify social isolation or isolated individuals, but there are profiles that have minimal contact with others and the community who would fall under the definition of being socially isolated. The Berkman-Syme SNI aims to categorise individuals into four levels of social connection, from socially integrated to socially isolated. This index uses items on marital status, the number and frequency of contact with children, family and friends, participation in community organisations, and also questions on perceived closeness in order to capture not only the number of social ties but also their relative importance [332]. All three of these measures capture interaction with close social networks and participation in community groups, but none capture interactions through employment which could make up a large portion of an individual's contact with other people. Additionally, the Berkman-Syme SNI does not solely focus on the structural elements of relationships. The perceived closeness elements of the index include questions about the availability of a person who can give advice, love and affection, or be confided in, which capture elements of social support e.g., informational, emotional, and appraisal support (see Section 1.3.1), and therefore functional aspects of relationships.

Another standard measure of isolation is Cohen's Social Network Index [333], which collects information about 12 types of social relationships or social participation. It asks about relationships with a spouse, parents, parents-in-law, children, other family members, neighbours, friends, colleagues, and school friends and also asks about volunteering, non-religious group membership, and religious group membership. For each type of relationship, a reported interaction (in person or by phone) with someone at least once every two weeks is scored one point. Respondents can then be categorised as having low (1-3 points), moderate (4-5 points) or high (≥6 points) social network diversity, which could also feasibly be interpreted as high, moderate, and low social isolation. This index provides a comprehensive assessment of contact with others and participation in social groups, incorporating close contacts as well as the wider social network, including colleagues, to capture social contact through employment.

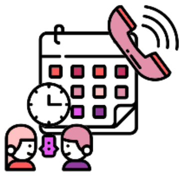
It is clear from these indexes that the common structural elements captured in these measures of (external) social isolation are frequency of contact with friends and relatives and participation in community groups. Nevertheless, some do include functional measures alongside structural which would make it more difficult to determine social isolation status without conflating with feelings of loneliness. Each of the indexes uses multiple indicators of social isolation as opposed to one indicator, such as living alone, which is important as it's been shown that complex measures of social integration show the strongest association between social relationships and mortality [153]. Although the aim of this study and others may not be to predict mortality, this finding indicates that it is the combination of social elements that impacts health outcomes the most, so capturing only one element is not that useful if exploring social relationships in a health context.

Social isolation measurement in ELSA

Focusing on previous measures of social isolation using ELSA, Shankar, McMunn, Banks and Steptoe [194] generated a social isolation index where respondents were given one point for each of five items: not married or cohabiting with a partner, less than monthly contact (in-person, telephone, written or email) with children, family and friends (each scored one) and not participating in any organisations, religious groups or committees. Bu, Zaninotto and Fancourt (2022) [334] adapted Shankar and colleagues' method for another study using ELSA data, considering only in-person meetings and telephone calls, finding that writing and emailing had low factor loadings when tested with factor analysis. They also included employment and volunteering to capture social interactions with colleagues, meaning the score ranged from 0 to 7.

This study followed the method used by Bu, Zaninotto and Fancourt [334], generating an index of social isolation using seven indicators, each worth 1 point:

Living alone (1)



Less than monthly (in-person or telephone) contact with children (1), family (1), or friends (1)

Not being a member of any organisations (1)

Not working (1)

Not volunteering (1)

The scores range from 0-7 with higher scores on the index indicate more social isolation. Those who specified that they did not have children, family, or friends were classed as having less than monthly contact. Only contact through in-person meetings and telephone calls was considered; respondents needed less than monthly contact with both types to be classed as having less than monthly contact overall. The organisations included in the question on group membership were: political parties, trade unions or environmental groups; tenants or residents' groups or neighbourhood watch; church or other religious groups; charitable associations; education, arts or music groups or evening classes; social clubs; sports clubs, gym, or exercise class; and other. Not working included those who responded that they were not employed, self-employed or semi-retired, and those classed as not volunteering were those who responded with "never" when asked how often they did any voluntary work.

Marital status was not included in the index as living alone was used to capture the daily living arrangement of the respondent and the associated social interactions. Living alone was found to be significantly associated with marital status in each wave, with those not married about 6 times more likely to be living alone, so the measures are closely related. Living alone may also capture more information about daily social interaction than marital status alone, as some people who are married do not live together, plus some who are not married do not live alone. Interactions with a spouse that are not captured in the living alone indicator would also hopefully be picked up by the contact with family and friends' indicator.

In a simple manner, this index captures the objective quantity of relationships and also the frequency of contact with close friends and family. It does not attain information on the quality of the relationships or feelings about the relationships, which are the subjective, functional aspects of social isolation. Social isolation score was generated using this index in three waves of ELSA (waves 2, 4, and 6).

6.2.2 Intrinsic capacity

As outlined in the previous section, an IC score was generated using an item response theory model in three waves of ELSA (waves 2, 4 and 6), which covered a total of 8-years follow-up. This score showed measurement invariance over time, as discussed in the previous chapter (Section 5.4.2).

The model included 14 indicators covering 5 domains of IC, with performance on each categorised into "No difficulty" and "Difficulty" (Table 4.1). The indicators were: word recall and orientation in time (cognition); balance test, chair rise test, walking speed, lower mobility, and upper mobility (locomotion); self-rated eyesight and hearing (sensory); grip strength, BMI, and waist circumference (vitality); CES-D scale and Satisfaction with Life Scale (psychological).

6.2.3 Covariates

Socioeconomic and health-related covariates were included in the analysis to account for potential confounding factors and provide a more comprehensive understanding of the relationship between social isolation and IC. The included covariates were baseline age, sex, highest educational qualification, wealth quintile, alcohol consumption per week, current smoking status, physical activity, number of chronic health conditions, and self-rated health. Baseline age, sex, and highest educational qualification were time-invariant; all the other included covariates were time-varying.

Age was included to account for potential age-related differences in the relationship between isolation and IC. Baseline age was generated from each participant's baseline wave and centred around the mean. Sex was similarly included to control for sex-differences in the relationship, as sex is known to influence social interactions and health. Highest educational attainment and wealth quintile were included to account for socioeconomic position, which influences the health and social resources and experiences of older people. Highest educational attainment was not measured in wave 6, so the highest educational attainment from wave 2 or 4 was applied to wave 6. The number of chronic health conditions and self-rated health were included as they reflect the overall health status of the individuals in an objective and subjective manner, respectively, but capture elements of health not really assessed in IC. There were included as covariates to see whether isolation was associated with IC only due to these other health measurements or if there was a specific association with IC.

Employment status was not included in the analysis as the social isolation index included whether the respondent was working or not. As discussed in **Section 6.2.1**, marital status is significantly associated with living alone, thus, marital status was not included as a covariate in these analyses as living alone was also a part of the social isolation index.

6.2.4 Sample

The follow-up period ranged from the beginning of wave 2 interviews in June 2004 until the end of wave 6 interviews in May 2013. The analytical sample included only those participants who had joined ELSA at wave 2 or earlier and had a valid IC score. Of the 10,341 eligible participants, 2,534 who did not have an IC score at all or some of the waves were removed, leaving a sample of 7,690. In the sample, 2,405 (31.27%) individuals had three waves of measurement, 2,323

(30.21%) had two and 2,962 (38.52%) had one. The total number of observations across all waves was 14,823. The sample selection process can be seen in **Figure 6.1**.

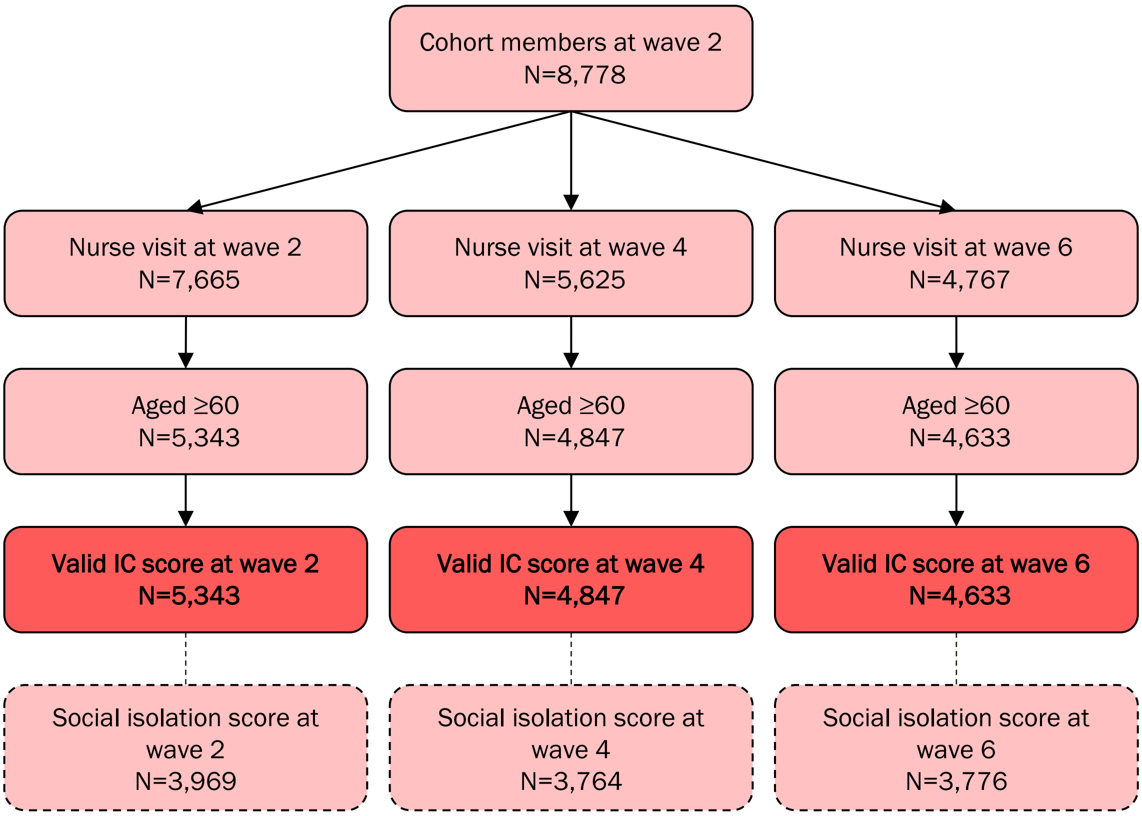


Figure 6.1 Flowchart of the sample selection process, including the number of participants with intrinsic capacity and social isolation scores at waves 2, 4, and 6 of ELSA.

The sample size was restricted to those with intrinsic capacity scores, not the social isolation scores (in dashed boxes).

The first wave of data for each participant was treated as their baseline and used for the descriptive statistics (**Table 6.1**). A social isolation score was generated in at least one wave for 5,821 individuals (76% of the sample) using the index of 7 indicators, with a higher score indicating more isolation. The social isolation indicators regarding contact with family and friends and being a member of organisations or clubs all had 13-16% missing. This was most likely due to these measures being collected in a self-completion questionnaire that was sent to the respondents and had to be posted back to the study, which was affected by a higher non-response rate. The sample was 55% female, with an average age of 69.03 years (SD 8.27). Over one third of the sample had no formal qualifications, while 12.5% had a degree. Almost 18% were in the lowest wealth quintile, while 22% were in the highest. The majority were not current smokers (87%) and consumed alcohol <5 days per week (68%). Half (50%) of the sample partook in moderate physical activity, while 25% reported low physical activity and 18% high; only 7% reported being sedentary. The number of health conditions reported ranged from 0-7, with a mean of 1.03 (SD 1.15); 73% reported zero or one condition, with very few reporting more than 4. The most common self-rating of health was "good" (33%), while 12% rated their health as "excellent" and 7% as "poor".

Table 6.1 Sample description at each participant's baseline wave, including IC score, social isolation score, social isolation indicators, and covariates (N=7,690).

Variable/Covariate		N	Mean (SD) / %	*Missing (N & %)*	
IC score		7,690	50.94 (9.90)	*0*	*0%*
Social isolation score		5,821	2.54 (1.27)	*1,869*	*24.3%*
Social isolation score indicators					
Living alone	Living alone	2,173	28.3%	*0*	*0%*
	Not living alone	5,517	71.7%		
Contact with children	Less than monthly	984	12.8%	*1,084*	*14.1%*
	More than monthly	5,622	73.1%		
Contact with family	Less than monthly	1,821	23.7%	*1,053*	*13.7%*
	More than monthly	4,816	62.6%		
Contact with friends	Less than monthly	908	11.8%	*992*	*12.9%*
	More than monthly	5,790	75.3%		
Organisations & clubs	Not a member	1,690	22.0%	*1,207*	*15.7%*
	A member	4,793	62.3%		
Working	Not working	6,094	79.3%	*11*	*0.1%*
	Working	1,585	20.6%		
Volunteering	Not volunteering	5,529	71.9%	*4*	*0.1%*
	Volunteering	2,157	28.1%		
Covariates					
Sex	Male	3,458	45.0%	*0*	*0%*
	Female	4,232	55.0%		
Age		7,690	69.03 years (8.27)	*0*	*0%*
Education	Degree	960	12.5%	*291*	*3.8%*

Variable/Covariate		N	Mean (SD) / %	*Missing (N & %)*	
	A-Level	1,378	17.9%		
	O-Level or other	2,193	28.5%		
	None	2,868	37.3%		
Wealth quintile	1 - Lowest	1,344	17.5%	*124*	*1.6%*
	2	1,478	19.2%		
	3	1,507	19.6%		
	4	1,579	20.5%		
	5 - Highest	1,658	21.6%		
Current smoker	Never smoked	2,774	36.1%	*8*	*0.1%*
	Ex-smoker	3,911	50.9%		
	Current smoker	997	13.0%		
Alcohol consumption	5+ days a week	1,599	20.8%	*889*	*11.6%*
	<5 days a week	5,202	67.7%		
Physical activity	Sedentary	498	6.5%	*3*	*0%*
	Low	1,950	25.4%		
	Moderate	3,844	50.0%		
	High	1,395	18.1%		
Health conditions †	Mean (SD)	7,690	1.03 (1.15)	*0*	*0%*
	0	3,100	40.3%		
	1	2,540	33.0%		
	2	1,223	15.9%		
	3	515	6.7%		
	4	216	2.8%		
	5	59	0.8%		
	6	33	0.4%		
	7	3	0.0%		
	8	1	0.0%		
Self-rated health	Excellent	892	11.6%	*6*	*0.1%*
	Very good	2,102	27.3%		
	Good	2,528	32.9%		
	Fair	1,614	21.0%		
	Poor	548	7.1%		

† Count of diagnosed conditions: Alzheimer's disease, angina, arrhythmia, arthritis, asthma, cancer, chronic lung disease, coronary heart failure, dementia, diabetes, heart murmur, high blood pressure, high cholesterol, myocardial infarction, osteoporosis, Parkinson's disease, psychiatric problems, stroke.

6.3 Statistical Analysis

Cross-sectional associations between social isolation score and IC score were tested with linear regression, with IC score as the dependent variable and isolation as the predictor. No missing data techniques were used, so the sample was a complete case based on the main variables and covariates in that wave, resulting in a different sample size per wave. Sequential linear regression models were run with covariates in blocks. The base model (1) included social isolation score, baseline age, and sex. The socioeconomic model (2) added the highest educational qualification and wealth quintile to the base model. The health behaviours model (3) added smoking status, alcohol consumption and physical activity to the base model. For these analyses, the non-smoker and ex-smoker categories were combined in order to make a dichotomous smoking variable, as convergence was not achieved with the three categories. The health model (4) added the number of health conditions and self-rated health to the base model. The fully-adjusted model (5) included the base model and all other covariates.

A latent growth curve model (LGCM) using a structural equation model (SEM) framework was used to model the trajectory of IC score over the 3 waves and test whether social isolation significantly predicted the baseline level (intercept) and rate of change (slope) of IC score. Latent factors representing the intercept and the slope were extracted from the three observations of IC score (at wave 2, wave 4, and wave 6). Factor loadings of the latent intercept component to all three observations were fixed to 1, and the linear slope component was defined by fixing the parameters to 0 (wave 2, baseline), 4 (wave 4), and 8 (wave 6), corresponding to the number of years from baseline. Under the SEM framework, to fix the parameters for the linear slope as equal to the observation time, the timing of each measurement or the space between measurements is required to be the same for each individual [335]. Although the data collection within one wave of ELSA spans multiple months, this requirement was assumed to be met as the measurements took place within the same data collection period and the space between each measurement was roughly 4 years for each individual. By fixing the slope parameters in this way, this model also assumes a linear growth pattern or trajectory of IC over time.

The LGCM with social isolation and covariates can be expressed as:

$$y_{jt} = a_{Ij} + a_{Sj}t_{jt} + \delta_t z_{jt} + \sum_{k=1}^{3} \beta_{jk}x_{jk} + \sum_{g=1}^{6} \gamma_{tg}x_{jtg} + \varepsilon_{jt} \qquad (1)$$

where y_{jt} represents the IC score for individual j at time t; a_{Ij} represents the intercept for individual j; a_{Sj} are individual slopes, t_{jt} represents the time score for individual j at time t. z_{jt} represents the social isolation score for individual j at time t (time-variant), x_{jk} are time-invariant covariates (age at baseline, sex, highest educational qualification), β_{jk} represents the coefficient for individual j and covariate k; x_{jtg} are time-varying covariates (wealth quintile, smoking status, alcohol consumption, physical activity, number of health conditions, self-rated health) and γ_{tg} represents the coefficient for covariate g at time t. ε_{jt} represents the time- and individual-specific residual. The intercept and slopes are functions of individual random deviations u_{Ij} and u_{Sj}. For ease of interpretation, age at baseline was centred to the mean value of 69.03.

Latent growth curve models estimate between-person differences (inter-individual variability) in within-person change (intra-individual variability) [336]. In the model outlined above, the within-person change is the change in IC over time for one individual; the between-individual change is the difference or variability in the intercepts and slopes of IC between different individuals. To capture these levels of change, latent growth curve models include both fixed and random effects. In the current model, the fixed effects are estimates of the mean intercept and mean slope that define the underlying IC trajectory of the whole sample. Random effects are estimates of the variance of individual trajectories around the group means, so, in this model, are estimates of the variability in the intercepts and slopes of IC between different individuals. Smaller random effects mean that the intercepts and slopes of the IC trajectories between different people are similar, so the group mean intercept and slope parameters model the trajectories from different individuals relatively well. Larger random effects imply that the trajectory parameters (intercept and slope) are very different between different people, so some individuals report very high or low intercepts, or very shallow or steep slopes, compared to other individuals. In the latent growth curve model specified in equation (1), the random intercepts and slopes are represented by a_{Ij} and a_{Sj} respectively.

The time-invariant predictors (age at baseline, sex, highest educational qualification) directly predict the latent growth factors, and thus the model tests whether these covariates are predictive of higher or lower intercepts and steeper or shallower rates of change [336]. These time-invariant predictors capture differences between people (inter-individual variability) [337] and cannot capture within-person differences as they do not change over time for an individual.

The time-varying predictors (social isolation, wealth quintile, smoking status, alcohol consumption, physical activity, number of health conditions, self-rated health) predict the repeated measures of IC while controlling for the influence of the growth factors (intercept and slope). This means that, in this model, IC at one time point is jointly determined by the underlying growth factors and the impact of the time-varying predictor at that time point [336]. Time-varying predictors may explain within-person change (intra-individual variability) whilst also explaining between-person differences [337]; they are included in the model to control for possible sources of variance at the individual level. In this model, the slope represents changes in IC after adjusting for the effects of social isolation and covariates at each time point.

Including this comprehensive suite of covariates covering socioeconomic, lifestyle, and health factors allows the LGCM to provide a more accurate estimation of the relationship between social isolation and IC, independent of these other factors.

Sequentially adjusted LGCMs were run to test the association when controlled for the covariates in blocks identical to those described above for the cross-sectional analyses. Full information maximum likelihood (FIML) estimation was utilised to compute parameter estimates using all available data for each individual, even if they had missing data on social isolation and/or covariates.

Cross-sectional analyses were carried out in Stata v.17, while the LGCM analysis was carried out using Mplus v.8.

6.4 Results

The IC score ranged from 19.2 to 66.5, with a mean of 50, and showed a negative skew at every wave (as seen in **Figure 5.2**). The mean social isolation score remained around 2.6 (**Table 6.2**) and had a slight positive skew (**Figure 6.2**). **Table 6.3** shows the proportion fulfilling the criteria for each of the social isolation indicators over each wave. Not working and not volunteering were the most common, with over 80% and over 65% of the sample, respectively. Less than monthly contact with children and friends was the least common, with only 12-15% of the sample reporting this. Proportions for each indicator remained similar over the three waves.

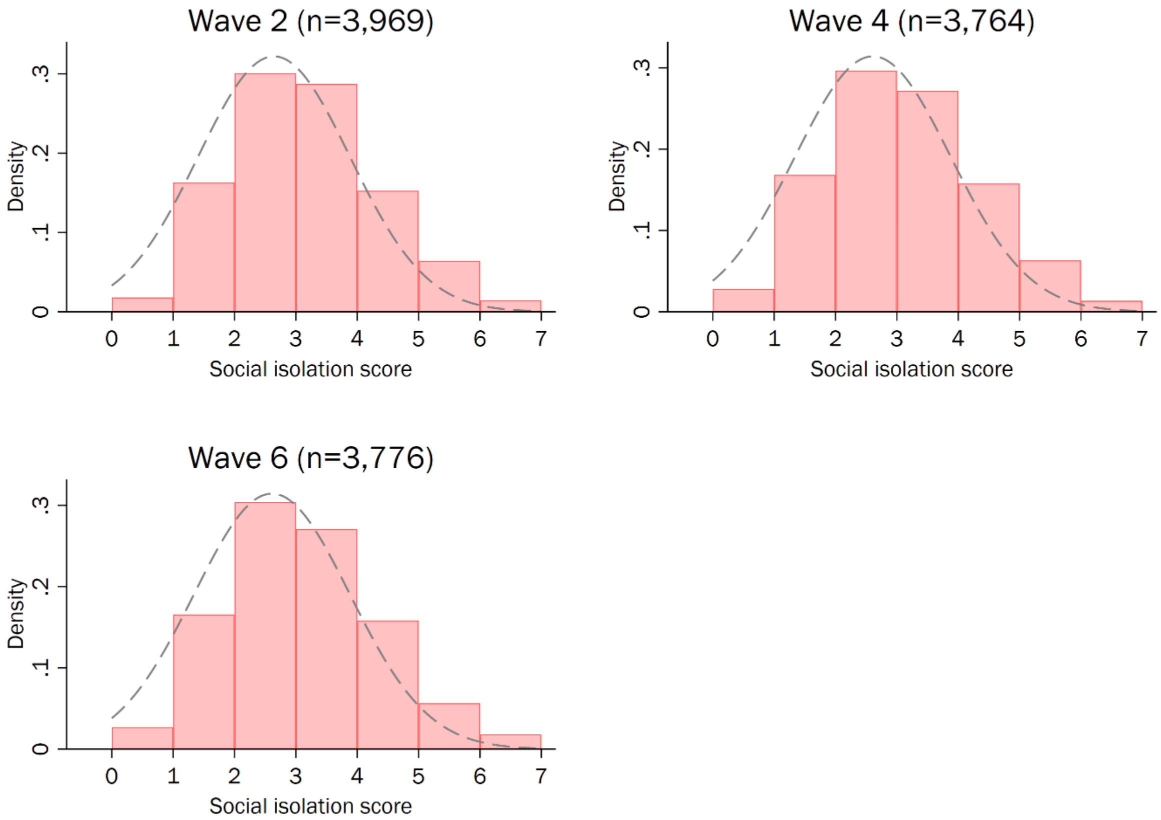
Table 6.2 Means and standard deviations of the IC score and social isolation score at waves 2, 4 and 6.

	Intrinsic capacity score			Social isolation score		
Wave	N	Mean	SD	N	Mean	SD
2	5,343	50.00	10	3,969	2.64	1.24
4	4,847	50.00	10	3,764	2.61	1.27
6	4,633	50.00	10	3,776	2.61	1.27

Table 6.3 The proportion scoring a point on each social isolation indicator at waves 2, 4, and 6.

Indicator	Wave 2 N=3,969		Wave 4 N=3,764		Wave 6 N=3,776	
	N	%	N	%	N	%
Living alone	1,178	29.7%	1,095	29.1%	1,035	27.4%
Less than monthly contact with ...children	557	14.5%	558	14.8%	580	15.4%
...family	1,121	28.2%	1,060	28.2%	1,061	28.1%
...friends	504	12.7%	446	11.9%	545	14.4%
Not a member of organisations	952	24.0%	990	26.3%	965	25.6%
Not working	3,416	86.1%	3,127	83.1%	3,201	84.8%
Not volunteering	2,745	69.2%	2,541	67.5%	2,468	65.4%

Figure 6.2 Histograms of social isolation score at waves 2, 4 and 6, with a normal distribution line overlayed.



6.4.2 Cross-sectional associations

Linear regressions in each wave revealed a significant negative association between social isolation score and IC score (**Table 6.4**), with those with higher isolation scores more likely to have poorer IC. This association was significant in all models of covariate blocks and remained in the fully-adjusted model with all covariates, although reduced in magnitude. Full results are presented in **Appendix 6.1**.

Table 6.4 Results from the cross-sectional linear regressions between social isolation score and IC score at wave 2, 4, and 6.

Social isolation score – Coefficient [95% CIs]

	N	(1) Age & Sex	(2) Model 1 + Socioeconomic	(3) Model 1 + H. behaviours	(4) Model 1 + Health	(5) All
Wave 2	3,864	-1.66** [-1.88, -1.44]	-1.06** [-1.28, -0.83]	-1.05** [-1.26, -0.84]	-0.86** [-1.05, -0.67]	-0.45** [-0.63, -0.26]
Wave 4	3,585	-1.81** [-2.03, -1.58]	-1.18** [-1.40, -0.96]	-1.15** [-1.35, -0.94]	-0.93** [-1.12, -0.75]	-0.49** [-0.68, -0.31]
Wave 6	3,433	-1.67** [-1.90, -1.44]	-1.02** [-1.25, -0.79]	-1.05** [-1.27, -0.84]	-0.83** [-1.03, -0.64]	-0.43** [-0.62, -0.24]

* p<0.05 ** p<0.001

H. behaviours = health behaviours. Covariates included in the models: (1) age, sex; (2) age, sex, highest educational qualification, wealth; (3) age, sex, smoking status, alcohol consumption, physical activity; (4) age, sex, number of health conditions, self-rated health; (5) all covariates.

6.4.3 Longitudinal associations

The main results from the LGCMs are presented in **Table 6.5**. The model fit indices suggested that models (1) and (2) fit the data the best. The models with covariates on health and health behaviours had the worst fit, but the fully adjusted model had a reasonable fit.

The intercept value of 62.30 (SE 0.41) for the fully-adjusted model (5) in **Table 6.5** refers to the mean IC score for a man aged 69.03 years at baseline (wave 2) with a social isolation score of 0 who was in the reference category for each covariate and had no health conditions. When fully-adjusted, IC score decreased at an average rate of 0.34 (SE 0.07) points every 4 years (the time between each nurse wave of the study), so 0.085 points per year. The estimated variance of the intercept growth factor was 21.81 (SE 1.36), and the slope growth factor was 0.19 (SE 0.05), which indicated that there was heterogeneity for individuals around the overall group mean for baseline IC score and the rate of change in IC score over time. The variance of the intercept and slope were the lowest in the fully-adjusted model, compared to the least-adjusted model indicating that the socioeconomic and health-related factors explained more of the variability in baseline levels of IC score and change over time. Full results of the models, including the covariates, can be found in **Appendix 6.2**.

Social isolation was found the be significantly negatively associated with the intercept of IC score in all models at all waves and was also positively associated with the rate of change (slope), demonstrating how social isolation played a role in explaining both between- and within-person variation in IC. Individuals with higher social isolation scores had lower IC scores at baseline, representing the between-person effect, but had a shallower rate of change over time in their IC compared to those with lower social isolation, representing the within-person effect. The decline in IC was more pronounced (steeper slope) over time in those with lower social isolation.

Most of the covariates did not significantly influence the rate of change in IC, with the exception of age, but most were associated with the intercept (level) of IC. Baseline age was negatively associated with the level of IC and rate of change, with older adults experiencing a lower level of IC and a steeper decline. Sex was significantly associated with the level of IC, with women experiencing lower IC scores. Having no educational qualifications or O-Level or other were significantly associated with a lower level of IC, while having A-level qualifications showed no difference in IC score intercept compared to those with a degree; no categories of education showed a significant association with the slope of IC. Significant associations with time-varying covariates indicated that the covariate was influencing the value of IC at that specific time point beyond the changes explained by the growth modelling. Wealth quintile, physical activity, number of health conditions, and self-rated health all showed significant associations with IC within every wave, with those in lower wealth quintiles, doing less physical activity, with more health conditions and poorer self-rated health having a lower IC score in that wave than that predicted by the growth modelling (the intercept and slope in the null model). Consuming alcohol more than 5 times per week was associated with a lower IC score in all waves, while being a current smoker was significantly associated with a lower IC score in waves 2 and 4, but not in wave 6.

Table 6.5 Main results from sequential growth curve models of the association between social isolation score and IC score.

Estimates with associated standard errors and p-values are presented. N=7,690. Full results including covariates can be found in Appendix 6.1.

	(1) Age & Sex		(2) Model 1 + Socioeconomic		(3) Model 1 + Health behaviours		(4) Model 1 + Health		(5) Fully-adjusted	
	Est (SE)	p-value	Est (SE)	p-value	Est (SE)	p-value	Est (SE)	p-value	Est (SE)	p-value
Growth parameters										
Intercept	58.32 (0.31)	<0.001	6.21 (0.39)	<0.001	59.37 (0.33)	<0.001	61.57 (0.33)	<0.001	62.30 (0.41)	<0.001
Intercept variance	50.06 (1.78)		43.36 (1.65)		37.43 (1.65)		27.18 (1.47)		21.81 (1.36)	
Slope	-0.54 (0.05)	<0.001	-0.47 (0.06)	<0.001	-0.50 (0.05)	<0.001	-0.35 (0.06)	<0.001	-0.34 (0.07)	<0.001
Slope variance	0.25 (0.05)		0.24 (0.05)		0.22 (0.05)		0.22 (0.05)		0.19 (0.05)	
Intercept										
Social isolation	-1.92 (0.10)	<0.001	-1.27 (0.10)	<0.001	-1.51 (0.10)	<0.001	-1.18 (0.09)	<0.001	-0.65 (0.09)	<0.001
Slope										
Social isolation	0.10 (0.02)	<0.001	0.09 (0.02)	<0.001	0.08 (0.02)	<0.001	0.06 (0.02)	0.001	0.05 (0.02)	0.008
Model fit										
Chi-square	99.21		184.40		1265.78		1263.21		1274.52	
CFI	0.99		0.99		0.90		0.91		0.92	
TLI	0.98		0.97		0.83		0.86		0.88	
RMSEA	0.04		0.02		0.07		0.07		0.04	
SRMR	0.02		0.01		0.04		0.04		0.02	

Est = estimate; SE = standard error; CFI = comparative fit index; TLI = Tucker-Lewis index; RMSEA = root mean square error of approximation; SRMR = standardised root mean square residual

6.5 Discussion

Results of cross-sectional and longitudinal analyses showed that social isolation was significantly negatively associated with baseline levels of IC score in a representative sample of adults aged ≥60 in England and was positively associated with the rate of change over time. Those experiencing less isolation tended to experience a higher (better) level of intrinsic capacity but saw a steeper decline in IC over 8 years than those experiencing more social isolation. This association remained when adjusted for demographic, socioeconomic, and health-related factors, although it did reduce in magnitude. This supports this chapter's first hypothesis that high social isolation will be associated with a worse IC score but does not support the second hypothesis that those with less social isolation will experience less decline in IC scores over time.

The significant association between isolation at baseline and IC score is in line with previous research that finds a negative association between isolation and health outcomes for older people. Previous research specifically looking at IC has not focused on isolation but has used other structural components of social relationships and found that less contact with others and less participation in social activities is associated with worse IC [50, 63]. Only one previous study tested the association between social relationships and longitudinal IC and found that those with social frailty at baseline had steeper declines in IC over 3 years [63]. This finding contrasts with the current study, which found the opposite association between social isolation on the slope or rate of change in IC over 8 years. This difference in results could be down to the samples used, as the previous study was based on a Japanese sample of adults from the specific city of Nagoya, while the current study used data from ELSA, which is representative of the English population. There may be a differential effect of social connectedness and isolation in these two countries and cultures, which would require specific cross-country comparisons to identify. The differences could also be methodological as the social frailty measure included different measures, especially the indicator of financial support, to the social isolation index used in this study; it was also unclear in the Nagoya study what was counted as low or infrequent contact and participation. IC was also measured differently in each study, with the Nagoya study using cognitive tests, walking speed, self-reported vision and hearing, the Mini Nutritional Assessment, grip strength and the Geriatric Depression Scale as indicators for the domains of IC, each transformed into a z-score. These z-scores were averaged over the indicators for each domain and then averaged over the domains to create a total IC score. This could also be a reason for different results if the IC scores are measuring different things, although similar patterns of results are often found across models of IC that use different methods, so it may be unlikely that IC methods are the driving force of these differences.

The other previous study focusing on social relationships and IC found that worse IC was associated with less social engagement [50], proposing a different direction of association than what was found in this study. Nevertheless, the previous study was cross-sectional, so it could not fully explore the direction of the association, as the finding that IC was predictive of social engagement in the cross-sectional data can only highlight an association between the two but not a direction of causation. Using longitudinal data, as in this study, can help give an idea of temporal ordering, i.e., that one event happens prior to another, but observational data can also not demonstrate causality. Both social isolation and IC were measured over time in this analysis, but because each was measured at the same time point, it is possible that the association seen between the two in the results goes in a different direction than proposed. Different statistical methods can be used to explore the direction of associations and any bidirectional associations using observational data, one of which will be adopted and discussed in the next chapter.

Interestingly, in this study, those with higher social isolation scores were found to have more shallow declines in IC over time than those who were less isolated, which is an opposite result to the one hypothesised and seen in previous research. One previous study by Huang et al. (2021) [63] explored the association between structural elements of social relationships and the rate of change in IC, finding that Japanese older adults who were socially prefrail or frail saw greater declines in IC over time than those who were socially robust. The difference in results between the current study and this previous study could be due to various reasons. Although focusing on structural elements of social relationships, such as participation and frequency of contact, Huang et al. also included a measure of needing financial support in their social frailty index, which was not included in the social isolation index in this study and is strictly not a social relationship measure. The model of IC was also different, with Huang et al. generating a total IC score by taking the average of domain-specific z-scores from the five IC domains (Appendix 1.2, model 19). These methodological differences could have given rise to different results. Additionally, Huang et al. used data from a sample of 663 older adults aged 60-89 years from Nagoya, a city in central Japan, who were recruited from a community centre to take part in a longitudinal study of diet, nutrition, and oral function. This sample is quite different to ELSA, which is a nationally representative survey of older adults across all regions of England who were recruited using probability sampling. The effect of a lack of social connection could be different between these two samples due to differences between English and Japanese older adults or potentially due to specific circumstances for older adults in Nagoya, which aren't reflective of the wider population.

Although it may seem surprising that, in this study, those who were more isolated showed a shallower decline in IC over time, as higher isolation is associated with a lower level of IC at baseline, the shallow slopes may be because isolated individuals started with a lower level of IC at baseline. It is unlikely that being less isolated is likely to *cause* a steeper decline in IC but that the change over time is more a reflection of the IC state of those with different levels of isolation. Isolated individuals may have "less to lose" and stay at a consistently lower level of IC than non-isolated individuals who start with a higher level of IC and show a steeper decline over time.

There are other possible explanations for this association being in the opposite direction than expected. The measure of social isolation generated in the current study only captured the frequency of interactions with different groups of people but did not give any information about the type or quality of those relationships. Negative interactions with others have been found to be more detrimental to health than positive interactions are beneficial to health [338] and relationship stress is thought to undermine health throughout the life course [339]. Relationship strain with a spouse is particularly detrimental to health and this becomes greater as individuals get older [340]. Those scoring lower scores on the social isolation index could be experiencing a greater number of, or more intense, negative interactions with others which means they are unable to maintain their IC over time.

As well as negative quality relationships, having and maintaining larger social networks may also require effort and result in stress. Activities involving social interactions, such as working (potentially past retirement age), participating in community activities, and caregiving, could become overwhelming physically and mentally for certain individuals. Caregiving in particular is found to involve costs to personal health [339] and be associated with psychological distress for women [341]. Caring for a spouse is also associated with negative health outcomes, including increased physical and mental illness, weakened immune response, and unhealthy behaviours [342]. To achieve the lowest score on the social isolation measure in this study, an individual would need to be living with others, interacting with children, family, and friends at least once a month each, be a member of at least one organisation, be working, and be volunteering. While this results in more social interactions, this amount of activity could also be overwhelming or stressful to maintain and ultimately have negative effects on health that outweigh the benefits of the social interactions. In modelling the linear relationship between social isolation and IC, the current analysis cannot identify any potential non-linear associations, for example, a U-shaped relationship where extremes of social isolation scores are associated with decreasing IC and the middle scores are associated with the maintenance of IC.

Those who are least isolated will also be spending more time in the company of other people meaning they potentially have increased exposure to contagious illnesses, such as flu, colds, and pneumonia. This mechanism has been identified as a possible pathway through which social relationships influence health [343] and it is clear that being exposed to and suffering from illness would take a toll on the immune system and negatively impact health.

Strengths of the analysis in this chapter include the strong methodology and longitudinal nature of the investigation as well as the use of a nationally representative sample of the older English population. Another strength was the inclusion of rich covariates on sociodemographic and health-related factors. The association between social isolation and IC remained even with the inclusion of these covariates, demonstrating an association between isolation and IC beyond that explained by health conditions, health behaviours, and socioeconomic factors. The previous study by Huang et al. [63] also found the association between social frailty and IC also remained after adjustment for age, sex, education, BMI, multimorbidity, and physical activity. These results from the previous and current work give support to the idea that being socially connected or isolated has an association with healthy ageing that is equivalent to or stronger than socioeconomic factors, health behaviours, health conditions, and other well-established risk factors [153].

The main strengths of this analysis are the longitudinal nature of the data, meaning the association can be explored over more than one time point. The richness of the ELSA data also allowed for a range of important covariates to be included. However, there are limitations to the study. As ELSA is an observational study, a causal relationship between isolation and intrinsic capacity cannot be claimed; however, the temporality of social isolation in relation to the change in IC over time ensures a stronger longitudinal design for this association. ELSA also only represents community-dwelling older adults in England and cannot represent older adults outside these parameters. There is also a limitation with the way the time-varying covariates, including social isolation, were included in the model. The variables are composed of between- and within-person change and this should ideally be separated to avoid biases in the time-specific effects of the variable on the outcome, otherwise the estimates are a compound of both the within- and between-person effects [337].

The finding that social isolation was associated with an individual's level of IC when controlling for other socioeconomic and health-related factors has implications for healthy ageing policy strategies. In order to maintain healthy ageing in a population, these results suggest policy should consider promoting social connectedness and reducing social isolation, alongside the focus on socioeconomic circumstances and healthy behaviours, in order to increase the level of IC. Nevertheless, being less isolated doesn't seem to reduce the decline in IC over time, with non-isolated individuals at baseline starting with a higher IC score but then declining over the 8-year follow-up to an IC level closer to those who were very isolated at baseline. Although not able to halt the decline in capacity, non-isolated individuals would still enjoy more years of life with higher capacity than those who were isolated. Therefore, interventions that aim to improve IC could focus on promoting social connectedness to improve an individual's "starting point" level of IC so they can maintain a higher level of IC over time, even with inevitable declines.

Future research should focus on understanding the direction of the associations between social isolation and IC, as the current evidence cannot give clear indications of this. There is also no evidence on the association between changing levels of social connectedness or social isolation and IC and whether worsening isolation over time or isolation at different points in the life course has different impacts on IC. This analysis did include longitudinal measures of social isolation, which were taken at the same time as the IC, so any changes in social isolation were controlled for in this analysis but not explored explicitly. Future analyses could also explore potential gender differences in the association between social isolation and IC, which was beyond the scope of this thesis. Previous research has indicated that men tend to be more isolated over the life course than women [215] and may experience the effects of isolation differently from women [219, 220]. A clear gap in the literature also relates to the processes that link social isolation to health outcomes and what social-biological processes are occurring to embed the effect of social isolation into the body. Identifying plausible mechanisms for this relationship will also help support the case for a causal path from isolation to IC.

6.6 Conclusion

In conclusion, the work in this chapter focused on the computation of an index of social isolation using 7 indicators of structural relationships. The social isolation index was negatively associated with the baseline level of IC and positively associated with the rate of change over time. This association remained when adjusted for socioeconomic variables, health behaviours, and other measures of health, suggesting that isolation is as important a factor for healthy ageing as other key risk factors.

Chapter 7: Inflammation as a mediator

7.1 Introduction

The previous chapter found that social isolation significantly predicted baseline IC scores, with higher levels of isolation predicting lower IC scores, but did not predict the rate of change in IC over time. This chapter expands on this relationship to explore the mediatory role of inflammation between social isolation and IC.

7.1.1 Inflammation, social isolation, and intrinsic capacity

As outlined in the introduction and literature review, inflammation has been identified as a potential mechanism for social factors influencing health. Evidence has found links between poor social relationships and raised inflammation [186-188], as well as between raised inflammation and IC [49, 62, 203, 204]. There has been some evidence of inflammation as a mediator between social relationships and healthy ageing outcomes [210, 211], although this hasn't yet been explored in the context of IC. There is also a lack of evidence using longitudinal data to test the mediating effect of inflammation.

The evidence linking inflammation to IC is mixed (**Section 1.4.2**), with different biomarkers of inflammation implicated in different studies. Giudici et al. (2019) found a greater decline in IC in those with raised inflammation, measured with CRP and homocysteine, but this association was rendered non-significant when adjusted for age, sex, education, BMI, intervention group, and time interaction [62]. This indicates that these other factors may be more important for IC than inflammation. However, this study was carried out using a sample of older adults taking part in a cognitive decline intervention study who reported memory complaints, had limitations with ≥1 ADLs or had slow walking speed, therefore may not be generalisable to the general population or other samples of older adults.

In other studies, the inflammatory biomarkers C-reactive protein (CRP), tumour necrosis factor receptor 1 (TNF-R1), interleukin-6 (IL-6), E-selectin, serum albumin, and folate were found to be associated with IC [49, 203, 204]. However, the same studies found no association with IC for the inflammatory biomarkers white blood cells, CRP, fibrinogen, IL-6, insulin-like growth factor-1 (IGF-1), and vaspin. Even across these three studies, results for CRP and IL-6 were mixed, demonstrating how inconclusive the current evidence is for these markers. However, these previous studies have some methodological limitations, including small and specialist (non-representative) samples, so further testing is required in larger population-representative samples.

The mediating role of inflammation between social relationships and health outcomes has been tested in a couple of studies but not yet in relation to IC specifically. Boen et al. [210] found that higher levels of satisfaction with social support were associated with lower levels of the inflammatory markers CRP, IL-6 and TNF-alpha in a sample of cancer patients and that these inflammatory markers were positively associated with mortality risk. Formal tests of mediation revealed that CRP and IL-6 accounted for much of the association between social support and mortality risk, but these tests were limited by low power. Another study found that inflammation mediated the relationship between social isolation and all-cause and disease-specific mortality, accounting for 12-24% of the associations [211]. This indicated that with all other factors remaining equal, inflammation in individuals with social isolation greatly increases the likelihood of mortality. As a mediating role of inflammation has been found in the relationship between social relationships and mortality, it is possible that a similar mediating effect of inflammation would be found between social relationships and IC. Mortality is the final outcome of declines in IC, so finding a mediating role for mortality may mean there is a mediating role of inflammation earlier on for outcomes that occur ahead of mortality, such as changes in IC.

7.1.2 Mediation models

Mediation models identify and test a process or mechanism underlying an observed relationship between two variables. At the most basic level, mediation requires three variables, an independent variable (X), a dependent variable (Y), and an intermediary variable, the mediator (M), which is proposed to convey some or all of the causal effect of X to Y [344]. In their seminal

1986 paper describing mediation, Baron and Kenny specified three relationships between X, M, and Y that are a requirement of mediation: (1) X must be a significant predictor of Y, (2) X must be a significant predictor of M, (3) M must be a significant predictor of Y and the strength of the association between X and Y must approach zero with the inclusion of M [209].

The effects in a simple mediation model are split into direct and indirect. The direct effect is the association between the independent variable X and dependent variable Y (path c in **Figure 7.1**), while the indirect impact is the product of the path coefficients between the predictor X and mediator M, and mediator M and outcome Y (paths a & b in **Figure 7.1**). When full mediation takes place, the relationship between the predictor and outcome (path c) reduces to zero; with partial mediation, the relationship is reduced, but some direct relationship remains.

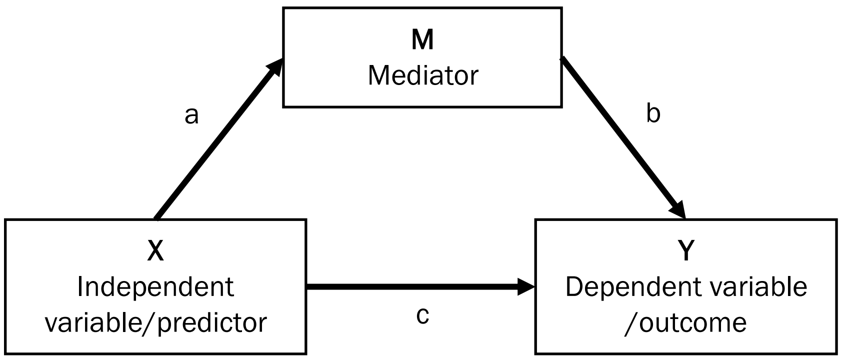


Figure 7.1 Diagram of a simple mediation model

Mediation can be tested in cross-sectional data; however, it is difficult to identify the direction of association when all the elements have been measured at the same time point. Using longitudinal data is beneficial because it allows for the fundamental requirement of understanding the direction of association – a cause must precede an outcome in time [345].

Structural equation modelling (SEM) approaches can test mediation in longitudinal data by examining the structural relationships between repeatedly measured variables [346]. One such model is termed a cross-lagged panel model (CLPM), sometimes also referred to as a linear panel model, and autoregressive cross-lagged model [346] – an example is shown in **Figure 7.3**. A CLPM can be used with different numbers of repeated measurements, but at least three measurements are required for a full mediation model, and it can be used with observed variables or latent constructs [347]. A CLPM is composed of two parts: autoregressive and cross-lagged. In the autoregressive part, the repeatedly measured predictor, mediator, and outcome at a certain time point are regressed on their previous time point (all d, e, and f paths in **Figure 7.3**). The ability to test for mediation comes from the cross-lagged part, where dependent variables are regressed on predictors from the previous time points. In a CLPM with 3 time points, for example, the indirect effect is the product of the path coefficient between the predictor at time t and mediator at time t+1 (path a in **Figure 7.3**) and the path coefficient between the mediator at time t+1 and outcome at time t+2 (path b in **Figure 7.3**). A direct effect from the predictor at time t and the outcome at time t+2 can also be specified (path c in **Figure 7.3**).

CLPMs are a popular model for mediation analysis with longitudinal panel data [348] and have several advantages over mediation models using cross-sectional data, such as the traditional three-variable mediation model in **Figure 7.1**. The first advantage is that they allow for the exposure to precede the mediator in time, which is rarely possible in cross-sectional mediation models. Second, they reduce the bias in estimation parameters because they include repeated measures of the exposure and outcome [349]. Third, CLPMs allow for the estimation and testing of overall indirect effects (i.e., via the mediator) while also testing for paths in the reverse direction, thus supporting stronger inference about the direction of the associations [347].

Latent growth curve models (LGCM) are another SEM model that can test mediation in longitudinal data. They model longitudinal data by representing intercepts and slopes as latent variables that are allowed to vary across individuals [347]. Proponents of LGCMs argue that they are better suited to test longitudinal mediation as they specify how individuals are expected to change and identify correlates of intraindividual change [347, 350], which are not captured by CLPMs, which focus on interindividual differences over time. Others argue that LGCMs are models of mean structure change and are not sensitive to covariation patterns across time between the variables and argue that CLPMs are well suited for research questions focusing on the pattern of influence, as opposed to the direction of change [346].

7.1.3 Chapter objectives

This chapter explores **Objective 3**: To test the direct and indirect associations between social isolation and IC through inflammation.

The specific aim is to test whether social isolation predicts inflammation and whether inflammation predicts IC score before testing whether inflammation is a mediator of the relationship between social isolation and IC. This will be carried out using longitudinal data with an SEM approach.

Hypotheses

1) Inflammation predicts IC, with those with raised inflammation experiencing lower IC scores at baseline and larger declines in IC scores over time.
2) Social isolation is associated with inflammation, with those with high social isolation more likely to experience raised inflammation.
3) The association between social isolation and IC will be partially mediated by inflammation.

7.2 Methods

7.2.1 Sample

Three waves of ELSA spaced 4 years apart were used in this analysis – wave 2 (baseline, 2004-5), wave 4 (2008-9) and wave 6 (2012-13) – with a maximum follow-up time of 9 years.

The sample for cross-sectional analyses was restricted to participants aged ≥60 years who joined the study at or prior to wave 2, with no missing data on main variables (social isolation score, CRP measurement, and IC score) and covariates within that wave. This resulted in a sample of 2,728 for wave 2, 2,489 for wave 4, and 1,310 for wave 6.

The analytical sample for the mediation analysis was restricted to participants aged ≥60 years who joined the study at or prior to wave 2 and had a valid IC score at any wave. Full information maximum likelihood was implemented to use all available information from the participants. This resulted in a full sample of 7,690 individuals.

Sensitivity analyses carried out the same analysis on a sample excluding those who died during the follow-up period, defined as the period from the first interview of wave 2 (June 2004) to the final interview of wave 6 (May 2013).

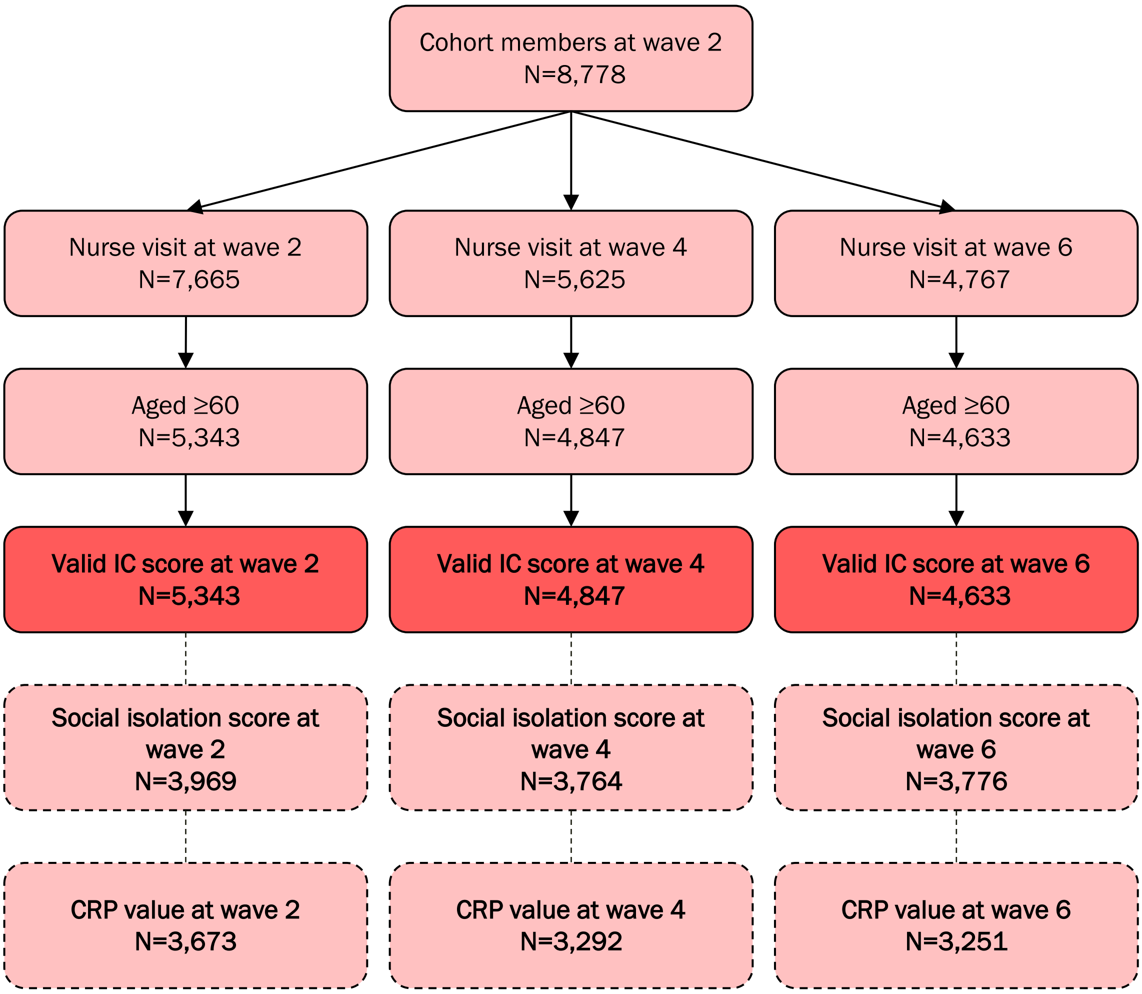


Figure 7.2 Flowchart of the sample selection process, including the number of respondents with intrinsic capacity scores, social isolation scores, and a CRP concentration at wave 2, 4, and 6 of ELSA.

The sample was restricted to those with intrinsic capacity scores, not the social isolation scores or CRP concentrations (in dashed boxes).

7.2.2 Measures

The measures of IC, social isolation, and inflammation were each measured at all three waves (wave 2, 4, and 6).

The IC score was generated with a 2-parameter logistic item response theory (IRT) model using 14 indicators of capacity (**Table 7.1**), as described in **Chapter 4**. An individual's performance on each indicator was categorised into "difficulty" or "no difficulty" based on previously defined cut-offs, where available. The IRT model generated a total IC score per person at each time point, which was standardised to a mean of 50 and a standard deviation of 10.

The social isolation score was constructed as the sum of seven indicators as described in **Chapter 6**, each worth one point: living alone, less than monthly in-person or telephone contact with children, family, or friends, not being a member of any organisations, not working, and not volunteering.

Systemic inflammation was measured using high-sensitivity C-reactive protein (CRP; mg/L). This was measured from a blood sample drawn during the nurse visit; those with clotting or bleeding disorders did not give a blood sample. CRP was measured using the N Latex CRP mono immunoassay on the Behring Nephelometer II analyser at the Royal Victoria Infirmary laboratory in Newcastle upon Tyne, UK. CRP values above 10mg/L were excluded from the analysis as they may indicate the presence of a current infection. CRP was chosen as the inflammatory biomarker of interest as it has been shown to be a more stable marker of inflammation than fibrinogen [351] – another inflammatory biomarker measured from blood in ELSA. Fibrinogen shows a greater dependence on an individual's cardiovascular risk profile [352], and it is suggested that it represents a different aspect of inflammation to CRP [353]. Another biomarker of inflammation, white blood cell count, was only measured at nurse waves from wave 4, so it was not included in this study.

Table 7.1 The indicators used to generate the intrinsic capacity score and their cut-off values.

Domain	Indicator	"No difficulty"	"Difficulty"
Cognitive	Word recall	Score in top two tertiles	Score in lowest tertile
	Orientation in time	All questions correct	≥1 question incorrect
Locomotion	Balance test	Successful completion of three stances	≥1 stance failed
	Chair rise test	Five rises in ≤16.7 seconds	Five or fewer rises in ≥16.7 seconds
	Walking speed	≥0.8 m/s	<0.8 m/s
	Lower mobility (5 items)	No problems reported	≥1 problem reported
	Upper mobility (4 items)	No problems reported	≥1 problem reported
Sensory	Self-rated eyesight	Rated good, very good, or excellent	Rated fair or poor
	Self-rated hearing	Rated good, very good, or excellent	Rated fair or poor
Vitality	Grip strength	≥30kg (men) or ≥20kg (women)	<30kg (men) or <20kg (women)
	Body mass index (BMI)	≥18.5kg/m^2 and <30kg/m^2	<18.5kg/m^2 or ≥30kg/m^2
	Waist circumference	<94cm (men) or <80cm (women)	≥94cm (men) or ≥80cm (women)
Psychological	Center for Epidemiological Studies Depression scale (CES-D)	Score <4	Score ≥4
	Satisfaction With Life Scale	Score ≥20	Score <20

7.2.3 Covariates

A selection of covariates was included to account for potential confounding factors that might influence the relationship between social isolation and IC and the mediating role of inflammation.

These included age, sex, highest educational attainment, wealth quintiles, smoking status, alcohol consumption, physical activity, number of health conditions, and self-rated health. Age and sex were included to account for age- and sex-related confounding of the relationships between isolation, inflammation, and IC, as both these characteristics are known to be associated with the key variables of interest. Highest educational attainment and wealth quintile were included to account for the socioeconomic position of individuals, as there are known socioeconomic gradients in the key variables which could introduce confounding. Alcohol consumption, smoking, and physical activity are all health behaviours that have all been found to be associated with inflammation and health, with mixed associations with social isolation (see **Section 3.3**). Including these as covariates helps to control for their potential confounding effects on the mediation pathway and allows for a more accurate assessment of the specific role of inflammation as a mediator. Similarly, number of health conditions and self-rated health were included as covariates to isolate the analysis to specific relationships between social isolation, inflammation, and IC, and see whether these relationships remained when other measures of health were controlled for.

Employment status and marital status were not included in the cross-sectional or longitudinal analyses, as they were captured in the social isolation score.

All the specified covariates were available in waves 2, 4 and 6; however, different waves were used across the analyses in this chapter. The specific waves from which the covariates were used will be outlined in the following section for each analysis.

7.3 Statistical analysis

7.3.1 Cross-sectional analysis

First, the cross-sectional associations between social isolation, CRP, and IC were tested separately at waves 2, 4 and 6 using linear regression, with (1) CRP as the dependent variable and isolation as the predictor and (2) IC as the dependent variable and CRP as the predictor. This was adjusted for age and sex, and then a fully-adjusted model included the covariates: age, sex, highest educational qualification, wealth quintile, current smoking, alcohol consumption, physical activity, number of health conditions, and self-rated health. Each analysis was carried out only using variables within that wave, including the covariates.

7.3.2 Mediation analysis

As this analysis was focused on the pattern of influence, as opposed to the direction of change, a CLPM was used to examine the direct effects of social isolation (Iso), indirect effects mediated by inflammation (CRP), and total effects on intrinsic capacity (IC) (**Figure 7.3**). Paths are plotted in the hypothesised “causal” direction, in this case, from social isolation to intrinsic capacity, via inflammation.

In this analysis, the direct effect is the association between social isolation at wave 2 and IC at wave 6 (path c). The indirect impact is the product (path a * path b) of the coefficient of social isolation at wave 2 on the mediator CRP at wave 4 (path a) and the coefficient of the mediator CRP at wave 4 on IC at wave 6 (path b). The total effect is the sum of the direct effects and the indirect effects. Paths in the reverse direction were also added to test reverse associations between the variables (all g and h paths). The remaining paths (d, e, and f) all represent the autoregressive paths where the variable is regressed on its previous time point.

CLPMs make several assumptions about the data and relationships being modelled [354]. Synchronicity assumes that all the measurements at each time point happened at the exact same time. This is important as variables that are measured closer together in time tend to be correlated more highly than those measured further apart in time, so different amounts of lag between the predictor, mediator, and outcome in the CLPM could bias the associations [355]. All three main variables (isolation, CRP, and IC) were measured in the same wave at each time point; however, practicalities of data collection means that they were not measured at exactly the same time across cohort members as data collection for each wave was spread out over a year (the maximum was 14 months at wave 4). There was also a time difference in the indicators being measured for each individual. The social isolation variables and some of the IC indicators were measured in the main interview and self-completion questionnaire and then blood was drawn (CRP) and the other IC indicators were measured in the following nurse visit – the majority of nurse visits in waves 2, 4, and 6 were carried out within 2 months of the main interview but the maximum amount of time between the main interview and nurse visit for an individual was 14 months (1.2 years, in wave 4). The minimum time difference for an individual’s measurements between subsequent waves was 33 months (2.75 years, between wave 4 and wave 6) and the mean time difference ranged between 45 to 48 months (3.75 to 4 years). Therefore, the time difference between measurements within the same wave was not equal or greater than the difference between measurements from subsequent waves so the within-wave measurements should still be more correlated with each other than those across-wave, meaning the results shouldn't be biased by this difference.

Another key assumption is that of stationarity, or that the primary causal structure remains the same over time. This was tested using a model adjusted for baseline age and sex by fixing equivalent paths (e.g., a and a') to be equal in sequential models and using a χ^2 difference test and the change in the model fit statistics to examine if the model fit was negatively impacted. Equivalent paths are displayed using the same letter and colour in **Figure 7.3**.

CLPMs also assume that the included variables have no measurement error, which can lead to misleading results, particularly in models with only two time points, as the changes due to error in the measurement can be mistakenly identified as real change in the variables [354]. The variables in the current analysis most likely contain measurement error, but this was not explicitly tested. Another assumption of CLPMs is that model effects are fixed across individuals [356] so an individual's values fluctuate around a group mean of each of the involved variables over time, so the model does not capture between-person differences in these variables [357]. CLPMs also don't consider that the average level of a variable across time is higher than for some individuals that others. This means that if between-person differences are present, they are included in the autoregressive and cross-lagged paths, which again can lead to misleading results.

The current analysis tested the assumption of stationarity but the other assumptions of synchronicity, measurement error, and fixed effects were not empirically tested in the model – the implications of this on the results will be discussed in **Section 7.5**.

Model fit was evaluated using the comparative fit index (CFI), Tucker-Lewis index (TLI), root mean square error of approximation (RMSEA) and standardised root mean squared residual (SRMR). Criteria of CFI >0.9, TLI>0.9, RMSEA<0.08 and SRMR<0.8 were used to indicate adequate model fit [358-360].

For the model estimation, a maximum likelihood (ML) estimator was used. This obtains parameter estimates by maximising the likelihood function derived from the multivariate normal distribution and calculates standard errors based on the covariance matrix obtained by inverting the information matrix [361]. Full information maximum likelihood (FIML) was implemented to use all available data for each participant. Bootstrapped confidence intervals were calculated using 1,000 iterations.

The least-adjusted model included age and sex at baseline as covariates. Adjustment for covariates was carried out in blocks, adding covariates onto the base model with age and sex. The time-invariant covariates were fixed at their baseline value, while the time-varying covariates were allowed to vary across the three time-points. The socioeconomic model added the highest educational qualification (time-invariant) and wealth quintile (time-varying). The health behaviour model added current smoking status, alcohol consumption, and physical activity (all time-varying). As in the previous chapter, the non-smoker and ex-smoker categories were combined for these analyses in order to make a dichotomous smoking variable, as convergence was not achieved with the three categories. The health model added the number of health conditions and self-rated health (both time-varying). The fully-adjusted model included all the covariates. All model variables and covariates at wave 2 (baseline) were allowed to covary with each other.

Data preparation and cross-sectional analyses were carried out in Stata v16, while the CLPM was carried out in Mplus v8.4.

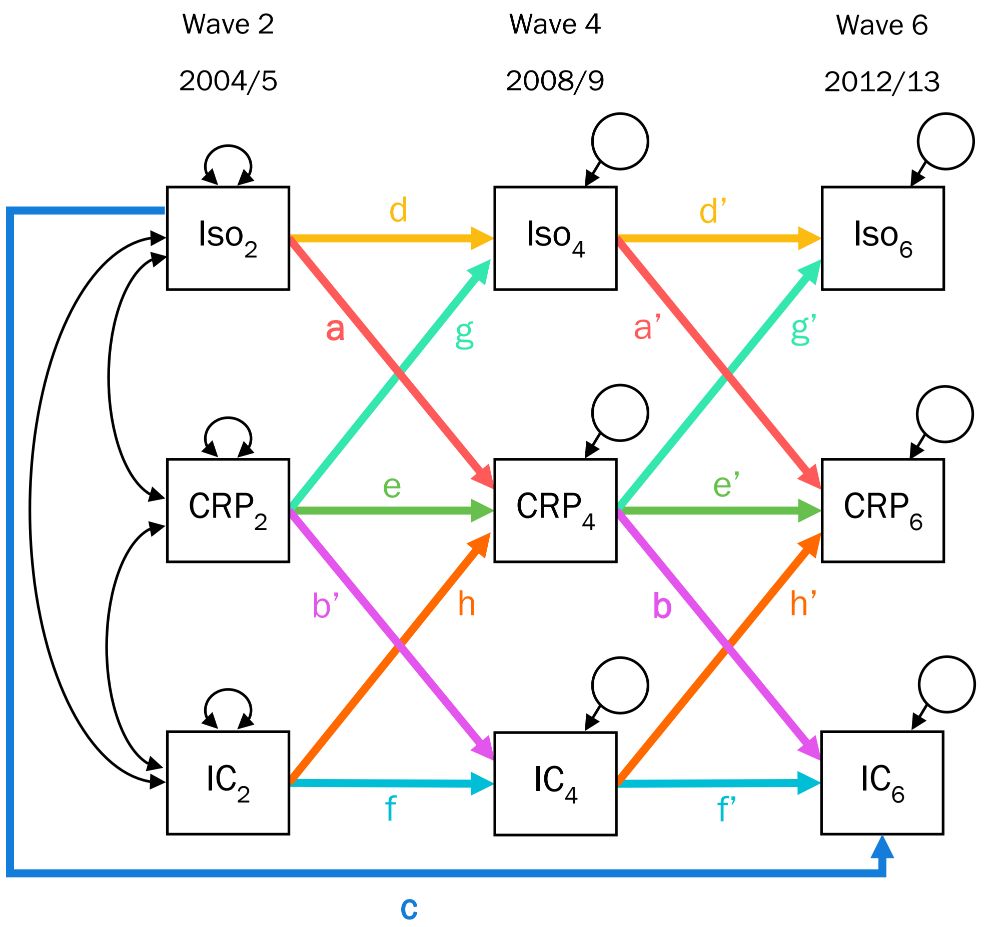


Figure 7.3 The specification of the cross-lagged panel model of the relationship between social isolation (Iso), C-reactive protein (CRP) and intrinsic capacity (IC) using SEM notation. Equivalent paths labelled with the same letter and displayed in the same colour are all fixed to be equal. Wave 2 variables have covariances displayed by the curved arrows. Paths of residual covariances are omitted from the figure. Paths: a & a’ (red) = isolation association with subsequent CRP; b & b’ (pink) = CRP association with subsequent IC; c (dark blue) = direct path from isolation to IC; d & d’ (yellow), e & e’ (green), f & f’ (light blue) = autocorrelation paths between isolation, CRP, and IC, respectively; g & g’ (turquoise)= CRP association with subsequent isolation (reverse path); h & h’ (orange) = IC association with subsequent CRP (reverse path).

7.4 Results

7.4.1 Data description

The mean social isolation score remained around 2.5 across each wave (**Table 7.2**). The mean CRP level reduced from 2.61 in wave 2 to 2.18 in wave 6, while the IC score reduced from 50.0 to 49.62. CRP was positively skewed (**Figure 7.4**), while IC scores were negatively skewed. The sample was the same as used in **Chapter 6**, so the description at baseline was the same as reported in **Table 6.1.** The mean baseline age of the full sample (N=7,690) was 69.03 years (SD=8.27), and 55.03% of the sample was female.

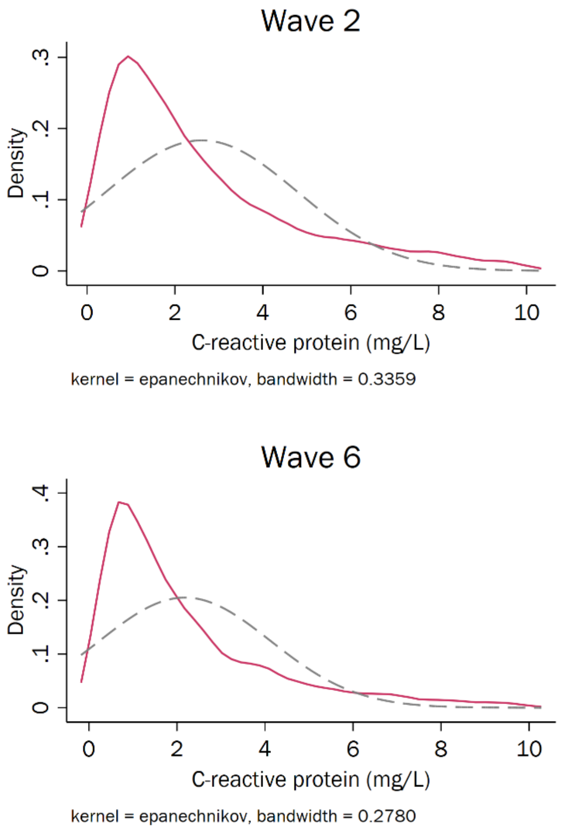


Figure 7.4 Distribution of C-reactive protein concentrations in each wave plotted against a normal curve.

Table 7.2 Means and standard deviations (SD) of social isolation score, C-reactive protein (CRP) level and intrinsic capacity (IC) score across the 3 waves.

	Social isolation score		CRP (mg/L)		IC score	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Wave 2	3,969	2.64 (1.24)	3,673	2.61 (2.18)	5,343	50.00 (10)
Wave 4	3,764	2.61 (1.27)	3,292	2.51 (2.15)	4,847	50.00 (10)
Wave 6	3,776	2.61 (1.27)	3,251	2.18 (1.94)	4,633	50.00 (10)

7.4.2 Cross-sectional associations

The results of the linear regressions between (1) social isolation and CRP and (2) CRP and IC score within each wave are presented in **Table 7.3.** Social isolation was a significant predictor of CRP in waves 2 and 6 when only adjusted for age and sex, but this effect was attenuated in the fully-adjusted model, apart from at wave 6. The isolation score was not found to be a predictor of CRP at wave 4. CRP was found to be a significant predictor of IC score at every wave in the least- and full-adjusted models. Full results for the cross-sectional analyses are shown in **Appendix 7.1.**

Table 7.3 The cross-sectional associations between (1) isolation score and CRP, and (2) CRP and intrinsic capacity score at waves 2, 4, and 6 in models adjusted for age, sex, and all covariates.

Wave	N	Age & Sex adjusted model				Fully-adjusted* model			
		b	95% CIs		p-value	b	95% CIs		p-value
(1) Isolation score predicting CRP									
Wave 2	2,733	**0.17**	**0.10**	**0.24**	**<0.001**	0.05	-0.02	0.12	0.148
Wave 4	2,494	0.07	-0.00	0.13	0.063	-0.04	-0.11	0.03	0.275
Wave 6	2,461	**0.12**	**0.06**	**0.19**	**<0.001**	0.04	-0.02	0.10	0.222
(2) CRP predicting IC score									
Wave 2	2,733	**-0.70**	**-0.84**	**-0.56**	**<0.001**	**-0.26**	**-0.38**	**-0.14**	**<0.001**
Wave 4	2,494	**-0.78**	**-0.93**	**-0.64**	**<0.001**	**-0.37**	**-0.48**	**-0.25**	**<0.001**
Wave 6	2,461	**-0.97**	**-1.14**	**-0.80**	**<0.001**	**-0.44**	**-0.58**	**-0.30**	**<0.001**

*Included covariates: age; sex; highest educational qualification; wealth quintile; current smoking; alcohol consumption; physical activity; number of health conditions; self-rated health.

b = unstandardised coefficient; CIs = confidence intervals; IC = intrinsic capacity

7.4.3 Mediation analysis

Fixing equivalent paths (denoted by the same letter and colour in **Figure 7.3**) to be equal in sequential models was found to not significantly negatively affect model fit; thus, the assumption of stationarity was observed (**Table 7.4**). Fixing the autoregressive paths for the mediator CRP (paths e and e') and outcome IC (paths f and f') each showed a significant change in the chi-squared statistic, but the other model fit indicators remained the same, so the model was accepted.

The main results of the mediation analysis for each CLPM model (adjusted for different blocks of covariates) are presented in **Table 7.5.** Estimation results for the paths in each CLPM are presented in **Appendix 7.2**, while full results for the covariates in each model are presented in **Appendix 7.3.**

Table 7.4 Model fit results from sequential models with fixed paths.

Model	χ^2 (df)	χ^2 (df) change	p-value	CFI	TLI	RMSEA	SRMR
All paths free	1075.46 (18)	-	-	0.932	0.797	0.087	0.082
Fixed autoregressive paths d & d' (Iso)	1075.50 (19)	0.04 (1)	0.843	0.932	0.808	0.085	0.082
+ Fixed autoregressive paths e and e' (CRP)	1082.62 (20)	7.12 (1)	0.008	0.932	0.816	0.083	0.082
+ Fixed autoregressive paths f and f' (IC)	1090.43 (21)	7.81 (1)	0.005	0.932	0.824	0.081	0.083
+ Fixed paths a & a' (Iso -> CRP)	1093.44 (22)	3.02 (1)	0.082	0.931	0.832	0.080	0.083
+ Fixed paths g & g' (CRP -> Iso)	1095.80 (23)	2.36 (1)	0.124	0.931	0.839	0.078	0.083
+ Fixed paths b & b' (CRP -> IC)	1095.95 (24)	0.15 (1)	0.698	0.931	0.846	0.076	0.083
+ Fixed paths h & h' (IC -> CRP)	1097.75 (25)	1.80 (1)	0.180	0.931	0.852	0.075	0.083

The path labels and colours correspond to the paths in **Figure 7.3**. The "χ^2 (df) change" refers to the difference in the chi2 statistic in the current model from the previous model (in the row above). The p-value is the probability associated with the test statistic "χ^2 (df) change".

χ^2 = chi squared statistic; df = degrees of freedom; CFI = comparative fit index; RMSEA = root mean squared error of approximation; SRMR = standardised root mean squared residual

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Least-adjusted model

For the least-adjusted model that was only adjusted for age and sex, model fit indices showed adequate fit to the data (CFI=0.93; TLI=0.85; RMSEA=0.08; SRMR=0.08). Direct effects showed social isolation score at wave 2 was significantly associated with the intrinsic capacity score at wave 6 (b=-0.436, 95% CIs= -0.647, -0.233). There was no evidence of an indirect effect on intrinsic capacity mediated by CRP at wave 4 (b=-0.005, 95% CIs= -0.020, 0.008).

Estimated path coefficients in the least-adjusted CLPM are shown in Table 7.6. Figure 7.5 shows the CLPM with only significant path coefficients plotted, along with residual variances. Results showed significant associations for all the autoregressive paths – the direct effect of each variable on itself over time. CRP and IC were found to predict each other over time; higher CRP predicted later lower IC, and higher IC predicted later lower CRP, although the association from CRP to subsequent IC was larger in magnitude than the opposite direction. Social isolation did not significantly predict later CRP, but CRP was significantly positively associated with later social isolation, with higher CRP values predicting higher social isolation scores.

The associations between the model variables and the covariates (baseline age and sex) are displayed in Appendix 7.3.

Table 7.5 Estimation results of the total, direct and indirect effects of social isolation in Wave 2 (2004/5) on intrinsic capacity in Wave 6 (2012/13) in each model. Model fit statistics are also reported.

Model		β	b	SE	Lower 95% CI	Upper 95% CI	*p*-value	χ^2 (df)	CFI	TLI	RMSEA	SRMR
(1) Age & sex	Total	**-0.049**	**-0.436**	**0.106**	**-0.647**	**-0.233**	**0.000**	1097.75 (25)	0.931	0.852	0.075	0.083
	Direct	**-0.049**	**-0.431**	**0.106**	**-0.639**	**-0.224**	**0.000**					
	Indirect	-0.001	-0.005	0.007	-0.020	0.008	0.482					
(2) Socio-economic	Total	**-0.027**	**-0.237**	**0.112**	**-0.460**	**-0.028**	**0.034**	807.18 (97)	0.959	0.920	0.031	0.024
	Direct	**-0.027**	**-0.236**	**0.111**	**-0.460**	**-0.033**	**0.034**					
	Indirect	0.000	-0.001	0.006	-0.013	0.010	0.892					
(3) Health behaviours	Total	**-0.035**	**-0.304**	**0.104**	**-0.058**	**-0.011**	**0.004**	1467.60 (115)	0.928	0.882	0.039	0.034
	Direct	**-0.035**	**-0.302**	**0.104**	**-0.058**	**-0.011**	**0.004**					
	Indirect	0.000	-0.002	0.005	-0.001	0.001	0.758					
(4) Health	Total	**-0.027**	**-0.234**	**0.093**	**-0.422**	**-0.052**	**0.012**	1120.84 (115)	0.951	0.920	0.034	0.029
	Direct	**-0.027**	**-0.232**	**0.093**	**-0.420**	**-0.050**	**0.012**					
	Indirect	0.000	-0.002	0.005	-0.013	0.006	0.656					
(5) Fully-adjusted	Total	-0.011	-0.098	0.098	-0.288	0.097	0.317	1135.65 (277)	0.962	0.937	0.020	0.012
	Direct	-0.011	-0.098	0.098	-0.287	0.098	0.315					
	Indirect	0.000	0.000	0.004	-0.007	0.007	0.976					

Bold text indicates statistically significant results ($p<0.05$). Covariates included in each model: (1) age, sex; (2) highest educational, wealth quintile; (3) physical activity, smoking status, alcohol consumption; (4) number of health conditions, self-rated health; (5) all covariates.

β = standardised regression coefficient; b = regression coefficient; SE = standard error; CI = confidence interval.

Table 7.6 Estimation results for the least-adjusted cross-lagged panel model (adjusted for baseline age and sex) (n=7,690).

	Path	β	b	SE	Lower 95% CI	Upper 95% CI	*p*-value
d	Iso2 -> Iso4	**0.702**	**0.727**	**0.009**	**0.709**	**0.746**	**0.000**
d’	Iso4 -> Iso6	**0.721**	**0.727**	**0.009**	**0.709**	**0.746**	**0.000**
e	CRP2 -> CRP4	**0.527**	**0.520**	**0.016**	**0.490**	**0.552**	**0.000**
e’	CRP4 -> CRP6	**0.566**	**0.520**	**0.016**	**0.490**	**0.552**	**0.000**
f	IC2 -> IC4	**0.668**	**0.707**	**0.009**	**0.688**	**0.723**	**0.000**
f’	IC4 -> IC6	**0.667**	**0.707**	**0.009**	**0.688**	**0.723**	**0.000**
a	Iso2 -> CRP4	0.008	0.014	0.019	-0.021	0.055	0.478
a’	Iso4 -> CRP6	0.009	0.014	0.019	-0.021	0.055	0.478
g	CRP2 -> Iso4	**0.037**	**0.022**	**0.006**	**0.009**	**0.034**	**0.000**
g’	CRP4 -> Iso6	**0.036**	**0.022**	**0.006**	**0.009**	**0.034**	**0.000**
b’	CRP2 -> IC4	**-0.075**	**-0.365**	**0.038**	**-0.444**	**-0.295**	**0.000**
b	CRP4 -> IC6	**-0.070**	**-0.365**	**0.038**	**-0.444**	**-0.295**	**0.000**
h	IC2 - > CRP4	**-0.099**	**-0.021**	**0.003**	**-0.027**	**-0.016**	**0.000**
h’	IC4 -> CRP6	**-0.114**	**-0.021**	**0.003**	**-0.027**	**-0.016**	**0.000**
c	Iso2 -> IC6	**-0.049**	**-0.431**	**0.106**	**-0.704**	**-0.224**	**0.000**

Path letters and colours correspond to the paths in **Figure 7.3**. Bold text indicates statistically significant results ($p<0.05$).

β = standardised regression coefficient; b = regression coefficient; SE = standard error; CI = confidence interval.

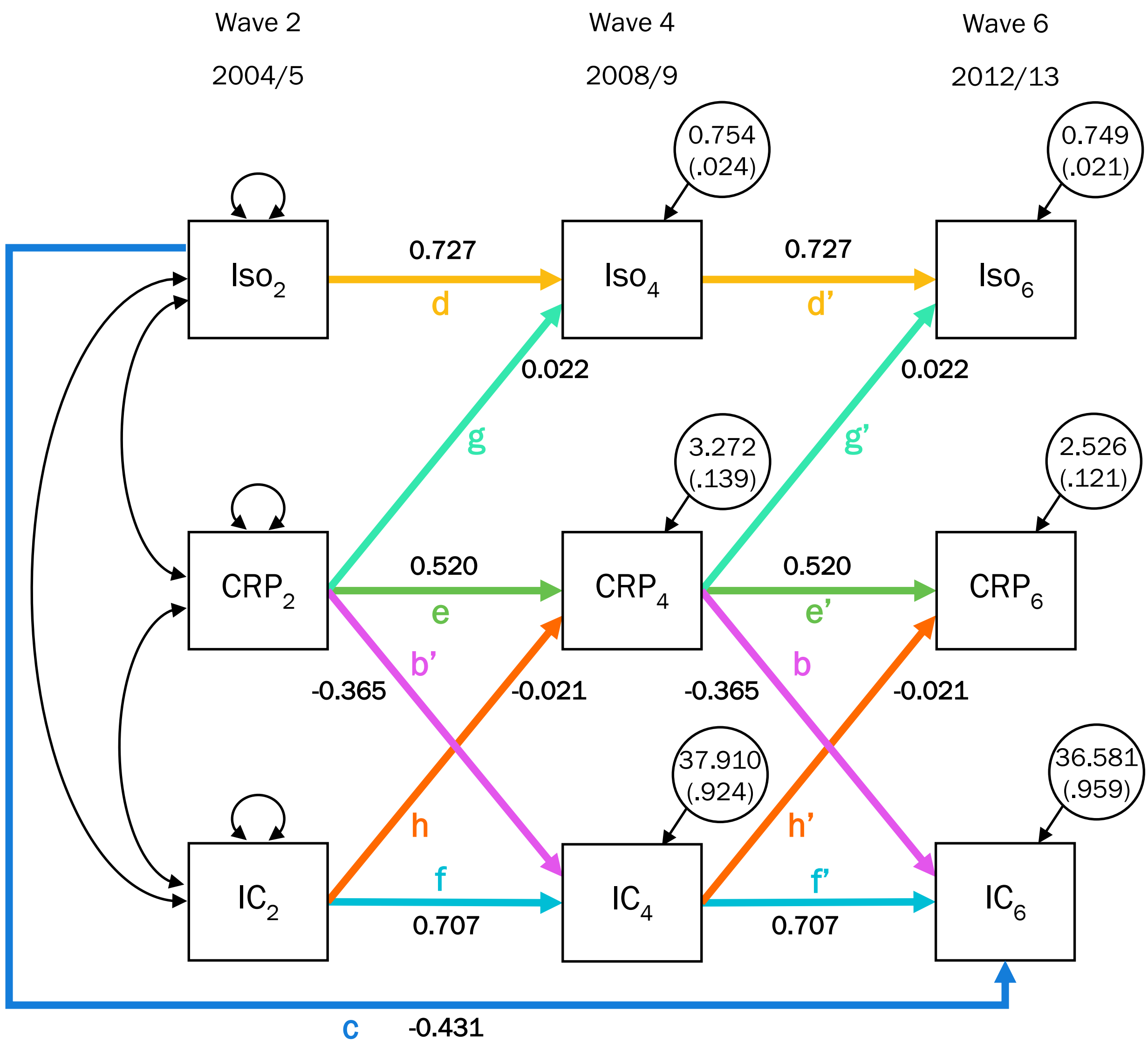

Figure 7.5 The least-adjusted cross-lagged panel model (adjusted for age and sex) with only unstandardised significant ($p<0.05$) path coefficients shown.

The baseline covariates age and sex have been omitted from the figure. Residual variances are displayed in the balloons with their standard error in brackets. Paths are labelled as in Figure 7.3: b & b' = CRP association with subsequent IC; c = direct path from isolation to IC; d & d', e & e', f & f' = autocorrelation paths between isolation, CRP, and IC, respectively; g & g' = CRP association with subsequent isolation (reverse path); h & h' = IC association with subsequent CRP (reverse path).

Partially adjusted models

The model fit statistics remained adequate or improved in models with socioeconomic, health behaviour, and health covariates (Table 7.5).

No indirect effects between social isolation and IC were significant in the model adjusted for the socioeconomic covariates (education and wealth). Significant total and direct effects between social isolation and IC were found in the models adjusted for health behaviours (smoking, alcohol consumption, physical activity) and health (health conditions and self-rated health), but the indirect effect of social isolation on IC via inflammation was not significant.

Full estimation results for the adjusted models, including path coefficients and associations with covariates, can be found in Appendix 7.2 and Appendix 7.3. Autocorrelation paths for all main variables remained significant in all adjusted models. The bidirectional paths between social isolation and CRP (paths a and g in Figure 7.3) were non-significant in all three partially-adjusted models. The bidirectional paths between CRP and IC (paths b and h in Figure 7.3) remained significant in all the partially-adjusted models.

Fully-adjusted model

The main results of the fully adjusted model are presented in Table 7.5. Model fit indices showed adequate fit to the data (CFI=0.96; TLI=0.94; RMSEA=0.02; SRMR=0.01). When fully adjusted, there was no evidence of a direct effect of social isolation at wave 2 on intrinsic capacity at wave 6 (b=-0.098, 95% CIs= -0.288, 0.098) or an indirect effect on intrinsic capacity mediated by CRP at wave 4 (b=0.000, 95% CIs=-0.007, 0.007).

Estimates of the path coefficients were similar to those in the base model (Table 7.7). All autocorrelation paths remained significant, with isolation, CRP, and IC significantly positively predicting themselves at the next wave, i.e., higher isolation at wave 2 predicted higher isolation at wave 4, and so on. However, in the fully adjusted model, social isolation and CRP were not found to be significantly associated with each other in either direction (Figure 7.6). Social isolation did not significantly predict CRP, and vice versa. However, the significant bidirectional relationship between CRP and IC remained, with CRP and IC found to predict each other over time; higher CRP predicted later lower IC, and higher IC predicted later lower CRP, but the latter association was smaller in magnitude.

The associations between the model variables and the covariates are displayed in **Appendix 7.3.**

Table 7.7 Estimation results for the fully adjusted cross-lagged panel model (n=7,690).

	Path	β	b	SE	Lower 95% CI	Upper 95% CI	*p*-value
d	Iso2 -> Iso4	**0.654**	**0.682**	**0.010**	**0.662**	**0.702**	**0.000**
d’	Iso4 -> Iso6	**0.678**	**0.682**	**0.010**	**0.662**	**0.702**	**0.000**
e	CRP2 -> CRP4	**0.517**	**0.512**	**0.016**	**0.481**	**0.543**	**0.000**
e’	CRP4 -> CRP6	**0.562**	**0.512**	**0.016**	**0.481**	**0.543**	**0.000**
f	IC2 -> IC4	**0.471**	**0.490**	**0.010**	**0.469**	**0.509**	**0.000**
f’	IC4 -> IC6	**0.460**	**0.490**	**0.010**	**0.469**	**0.509**	**0.000**
a	Iso2 -> CRP4	0.000	-0.001	0.020	-0.038	0.040	0.975
a’	Iso4 -> CRP6	0.000	-0.001	0.020	-0.038	0.040	0.975
g	CRP2 -> Iso4	-0.006	-0.003	0.006	-0.016	0.008	0.568
g’	CRP4 -> Iso6	-0.006	-0.003	0.006	-0.016	0.008	0.568
b’	CRP2 -> IC4	**-0.037**	**-0.179**	**0.034**	**-0.251**	**-0.118**	**0.000**
b	CRP4 -> IC6	**-0.035**	**-0.179**	**0.034**	**-0.251**	**-0.118**	**0.000**
h	IC2 - > CRP4	**-0.044**	**-0.010**	**0.003**	**-0.016**	**-0.004**	**0.005**
h’	IC4 -> CRP6	**-0.051**	**-0.010**	**0.003**	**-0.016**	**-0.004**	**0.005**
c	Iso2 -> IC6	-0.011	-0.098	0.098	-0.287	0.098	0.315

Path letters and colours correspond to the paths in **Figure 7.3**. Bold text indicates statistically significant results ($p<0.05$). The fully adjusted model is adjusted for age, sex, highest educational qualification, wealth quintile, physical activity, smoking status, alcohol consumption, number of health conditions, and self-rated health.

β = standardised regression coefficient; b = regression coefficient; SE = standard error; CI = confidence interval.

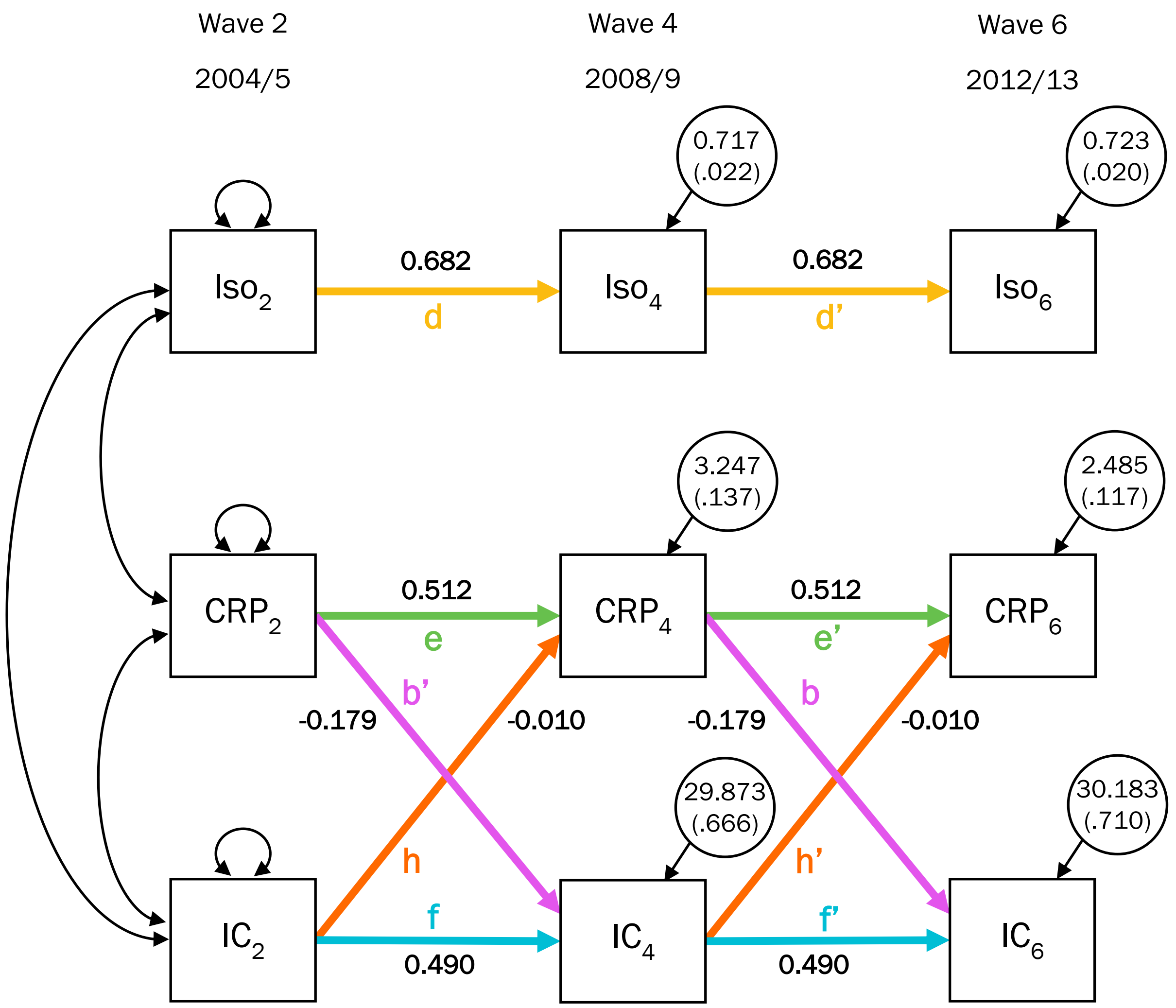

Figure 7.6 The fully-adjusted cross-lagged panel model with only unstandardised significant ($p<0.05$) path coefficients shown.

The baseline covariates have been omitted from the figure. Residual variances are displayed in the balloons with their standard error in brackets. Paths are labelled as in Figure 7.3: b & b' = CRP association with subsequent IC; d & d', e & e', f & f' = autocorrelation paths between isolation, CRP, and IC, respectively; h & h' = IC association with subsequent CRP (reverse path).

Sensitivity analyses

Sensitivity analyses excluding those who died during the follow-up period (N=1,282) showed the same pattern of results. There with minor changes to the coefficient values but no change to the significance of the associations. Results are displayed in **Appendix 7.4**.

7.5 Discussion

In this chapter, the mediating role of inflammation in the relationship between social isolation and IC score was explored using CLPMs. In the model adjusted for age and sex, and in the fully-adjusted model, there was no evidence of a direct or indirect effect for the association between social isolation score and IC score 8 years later. In both models, social isolation score was not found to significantly predict CRP level 4 years later; however, CRP level was significantly negatively associated with IC score 4 years later, with those with higher levels of inflammation more likely to have lower IC scores. The results were replicated in a sample excluding those who died during the follow-up period, so they were not driven by individuals in particularly poor health or at risk of death.

The descriptive statistics showed that the mean social isolation score remained similar across all the waves, while the mean IC score decreased slightly, which is as expected with a measure of healthy ageing over time. However, the mean concentration of CRP decreased over the 8-year follow-up, which is slightly unexpected as inflammation generally increases with age. Nevertheless, the slight increases witnessed in these results could be due to unmeasured factors, such as greater awareness of raised inflammation and the use of anti-inflammatory treatments to keep inflammatory markers at a more acceptable level. It could also be due to a healthy survivor effect, with those who had lower CRP more likely to stay healthy and remain in the study and give a blood sample. Although FIML was used to account for missing data, there are some respondents who were included in the earlier waves which were not included in the later waves as they were no longer taking part in the study or were not eligible for/did not consent to a nurse visit. Those remaining in the study and achieving valid IC scores are those who did not die or leave the study or become too unwell for a nurse visit and, thus, are more likely to be healthier and have lower inflammation.

The cross-sectional analyses did not show strong support for the association between social isolation and CRP levels, with no significant associations when fully adjusted. This lack of adjusted association is in line with a previous systematic review that found a significant association between social isolation and CRP in least-adjusted (maximum of two confounders) models but found that adjusting for important covariates rendered the association non-significant [190]. Interestingly, the association with fibrinogen, another biomarker of inflammation, remained significant even in most-adjusted analyses. Nevertheless, the authors found that many of the differences in findings between studies included in the review were down to methodological differences, with the associations between social isolation and inflammation mostly found in studies that were methodologically less rigorous and didn't control for important confounders, including sociodemographics, chronic conditions, cardiometabolic abnormalities, and lifestyle. This indicates that the link between social isolation and inflammation may be explained by these other factors and is not a straightforward relationship.

There were also differences in the CLPM between the least- and fully-adjusted models. In the model adjusted for only age and sex, paths of reverse association between CRP and isolation were found, but these were attenuated in the partially and fully adjusted models. With explorations into the potential relationship between social isolation and inflammation, the direction of causality is often discussed. The Berkman et al. framework [118], discussed in **Section 1.4**, specifies immune system function as one potential physiologic pathway for social relationships to influence health, with poor social relationships eliciting a stress response and raising inflammatory markers, which over time, results in poorer health. However, it is possible that this relationship moves in the opposite direction for some individuals. Those who have poor health and raised inflammatory markers due to illness may become more socially isolated as they are not able or don't feel well enough to meet friends or participate in social occasions. A path in this direction was captured by the least adjusted CLPM, with higher CRP levels associated with higher levels of social isolation 4 years later, while a path in the opposite direction was not significant. However, as this path from CRP to isolation was not found in all the models adjusted for covariates and the fully-adjusted model, the relationship between social isolation and CRP, in both directions, is likely to be accounted for by important confounders, with all socioeconomic, health behaviour, and health-related covariates attenuating this association.

Similarly, a reverse path was found in the basic, partially, and fully-adjusted models between CRP and IC score, with higher IC associated with lower CRP 4 years later. It is possible that as well as contributing to poor health, raised inflammation may be a result of poor physical or mental health itself or the stress associated with poor health or low capacity. The result that raised levels of inflammation were associated with lower IC scores supports previous studies that find associations between inflammatory biomarkers and IC scores [49, 62, 203, 204]. These previous studies tended to have small samples that were not necessarily representative of the wider population of older adults, so the result from this study provides evidence of the association between inflammation and IC in a representative sample of older adults, as well as evidence that this relationship may also go in the opposite direction which was not discussed in the previous studies.

The direct effect of social isolation at baseline on IC score 8 years later was found to be significant in all models except the fully adjusted, with higher social isolation predicting lower IC scores. This supports the findings of the previous chapter, where baseline social isolation was associated with a lower level of IC and showed how this association could last for many years. Nevertheless, once all the socioeconomic and health covariates were mutually adjusted, this direct effect became non-significant, indicating that these covariates were important confounders of the association between social isolation and IC score after 8 years. It is important to note that, although this result is different from that of the previous chapter, where the association between isolation and IC was significant even when adjusting for these covariates, the methodological approaches used differed as they aimed to answer different questions. The analysis of this chapter utilises IC after 8 years, whereas the analysis in the previous chapter focused on time-varying IC. It is likely that baseline isolation doesn't have a significant effect on the one value of IC after 8 years but does impact the baseline level and change of IC over time.

The current study found no evidence for a mediating role of inflammation in the relationship between social isolation and IC. This conflicts with previous studies that found that CRP and IL-6 accounted for a large amount of the association between social support and mortality risk [210] and that CRP, fibrinogen and serum albumin accounted for 12-24% of associations between social isolation and mortality [211]. However, these were both cross-sectional studies, so they cannot indicate the direction of causality. It is possible that the mediating effect of inflammation occurs only in the short term but is not acting in the same manner over a number of years, where the impact of other socioeconomic and health factors is much more critical.

Strengths of this chapter include the use of a CLPM with a total length of time of 8 years, allowing for the exploration of all patterns of association between the exposure, mediator, and outcome variables, including paths of reverse association. This is particularly important as these had not been explored in previous research and are crucial to understanding the potential mechanisms of action. Furthermore, the CLPM also means the values of the exposure, mediators and outcomes at previous waves were also accounted for. The rich ELSA data also allows for important sociodemographic and health-related confounders to be adjusted for, which is important particularly as previous evidence for the links between social isolation and inflammatory markers has not always included these [190].

Limitations of this chapter include the use of only one biomarker of inflammation. Future research could incorporate other biomarkers, such as fibrinogen and white blood cell count, as these may show a different association with social isolation and IC. The sample of individuals with a CRP value is also smaller than the main sample based on IC (Table 7.2) because it is extracted from a blood sample that fewer respondents consented to or were able to give. Although FIML was implemented to use all available data for each participant, this meant that there was more missing information for CRP in the result estimation.

Another limitation of the analysis was the probable violation of some of the assumptions of CLPMs. The nature of the ELSA data collection for the variables of interest meant that they were not measured at exactly the same time point between or within individuals, therefore violating the assumption of synchronicity. Nevertheless, the time difference between measurements at one time point (e.g., within wave 4) were not equal or greater than the difference between measurements at subsequent time points (e.g., wave 4 to wave 6). Therefore, the cross-lagged effects in the model are most likely not capturing a greater correlation between variables at different time points because they just happen to be closer in time than the other variables within the same time point. The CLPM used in this analysis also assumes that there is no measurement error in the variables, which is unlikely in the current analysis due to the nature of measurement in a survey setting as there is the possibility of different interpretations of the questions and responses, differences in measurement between interviewers or nurses, and other variations. This means that the parameter estimates may be biased by this unmeasured error and the results less reliable; however, they are less affected by measurement error in a model with three time points than one with only two [354].

The current analysis also used a classic CLPM which has fixed effects across individuals and does not really consider between-person effects. There are some more contemporary methods that try to overcome this limitation [357]. Random-intercept cross-lagged panel models build upon the classic CLPMs but allow for estimation of the pure within-person autoregressive and cross-lagged effects as individuals are allowed to fluctuate around their own mean over time, instead of a group mean. Autoregressive latent trajectory models with structured residuals contain a latent growth curve and cross-lagged panel part, which also allows this method to model between- and within-person effects, as well as include non-linear trends over time. Another alternative model proposed is the Dual Change Score Model, which is part of the latent difference/change score model family. This method also combines features of growth models and CLPMs and capture the overall rate of change across all time points, between-person differences in this change, and how change in a variable between measurement occasions depends on the variable's level at the previous time point. As the relationships between social isolation, inflammation, and IC have not yet been explored in depth, future research should consider these novel methods to model the relationships which should reveal if results from a particular method are artefacts of the model used.

7.6 Conclusion

This study found no evidence of a mediating effect of inflammation on the relationship between social isolation and IC score. Furthermore, the association between social isolation and CRP was attenuated by socioeconomic and health-related covariates. Pathways in both directions were found between CRP and IC, with CRP negatively associated with subsequent IC and IC negatively associated with subsequent CRP. These remained significant even when models were fully adjusted for selected relevant covariates indicating that inflammation is more related and important to IC than social isolation. Nevertheless, this evidence does not provide support for the role of inflammation as being part of the mechanistic pathway for social isolation to influence healthy ageing and highlights the complexity of this relationship.

Chapter 8: Discussion

8.1 Summary of objectives and hypotheses

This thesis aimed to investigate the association between social isolation and intrinsic capacity (IC) in older adults in England and assess whether inflammation is a mediator of this relationship. This section will recap the three main objectives and associated hypotheses and whether these were validated.

The first objective was to operationalise IC as a measure of healthy ageing (across multiple time points) in an observational study of ageing. The first hypothesis was that the IC score would be negatively associated with adverse health and functional outcomes such as functional impairment, hospital admissions, and mortality. This hypothesis was supported, with a higher IC score at baseline, and thus more healthy ageing found to be associated with a reduced risk of ADL and IADL disability over 4 and 8 years and a reduced risk of hospital admissions and mortality over 14 years. The second hypothesis for this objective was that the IC score would be associated with key sociodemographic factors, such as age, sex, and socioeconomic position, and health-related factors, such as subjective health ratings. Additionally, the hypothesis that higher IC scores will be associated with younger, more socioeconomically advantaged, and “healthier” individuals was also supported. Lower (worse) IC scores were found to be associated with older age, women, those in lower wealth quintiles, not in employment, with lower physical activity levels, more chronic health conditions and lower self-ratings of health.

The second objective of this thesis was to examine the association between social isolation and IC and whether social isolation predicts IC over time. The first hypothesis was that high social isolation would be associated with a lower (worse) IC score, cross-sectionally and over time. This hypothesis was supported by cross-sectional and longitudinal analyses. Cross-sectionally, a negative association was found between social isolation and IC score, with those with higher isolation scores more likely to have poorer IC, which remained when adjusted for socioeconomic and health-related covariates. Longitudinal analyses revealed a significant negative association between social isolation and the intercept, or level, of IC, with those with higher social isolation having lower IC scores. The second hypothesis for this objective was that those with low social isolation would experience less decline in IC scores over time than those with high isolation. This hypothesis was not supported in longitudinal analyses. Social isolation was found to be positively associated with the slope, or rate of change, of IC, with those who were less socially isolated showing a steeper decline in IC over time than those who were more socially isolated.

The third and final objective of this thesis was to test the direct and indirect associations between social isolation and IC through inflammation. The first hypothesis for this objective was that inflammation would predict IC, with those with raised inflammation experiencing lower IC scores at baseline and larger declines in IC scores over time. This hypothesis was supported as C-reactive protein (CRP) was shown to be significantly associated with IC in cross-sectional and longitudinal analyses. The longitudinal analysis revealed a bidirectional relationship between CRP and IC, with each significantly negatively predicting the other over 4-year intervals. The second hypothesis was that social isolation would be associated with inflammation, with those with high social isolation more likely to experience raised inflammation. This hypothesis was not supported in cross-sectional or longitudinal analyses. Cross-sectionally, the social isolation score was not shown to be associated with CRP when fully adjusted for socioeconomic and health-related factors. In the longitudinal analysis, social isolation was not found to be associated with subsequent CRP in any models. The final hypothesis was that the association between social isolation and IC would be partially mediated by inflammation. This hypothesis was also not supported. The mediation model found no direct or indirect effect of the association between social isolation at baseline and IC score 8 years later.

8.2 Intrinsic capacity as a model of healthy ageing

The novel measure of IC generated in this study supported the theoretical model of IC outlined by the WHO [30]. It measured IC in the five domains of capacity [32], captured at least one of the measurable components identified for each domain [35], and was shown to measure IC in the same way over time. The IRT method meant that an IC score was produced for each individual that was weighted based on the indicators' contribution to the underlying latent IC factor, which allowed for a more nuanced score than a simple sum of the indicators. The longitudinal analysis found that the IC score decreased with increasing age and over time, which is a key characteristic of measures of healthy ageing.

Previous models of IC have used many different indicators to measure capacity in the domains and different methods to generate a total IC score. Multiple studies have shown that IC scores generated with diverse methods are predictive of health outcomes for older people, particularly functional ability, and mortality, demonstrating that the IC concept captures relevant and useful information about the health state of an older individual even when measured in different ways.

The current study generated an IC score using IRT methodology, thus the resulting score was a factor score and a composite of all the included items. This means that it summarises capacity across the indicators and domains of IC but cannot give detailed information about these underlying elements – even if domain-specific scores were generated, these would be a summary of the domain items and not give item-level information. Therefore, a composite score of this type is more useful for monitoring and describing healthy ageing at a population level but is less useful on an individual level or for exploring the specific aetiology of healthy ageing. To fully understand the aetiological pathways, it would be more informative to breakdown healthy ageing into individual components and explore the causes of each of these and how they interact to produce overall health in older age. This highlights the difficulty in finding the balance between modelling IC and healthy ageing as multidimensional complex concepts and being able to pick apart the causal pathways affecting each dimension, which could be quite domain- or indicator-specific.

A non-composite/summary score would also be more useful for identifying IC in individuals, demonstrated by the ICOPE screening tool that is being applied to clinical settings [41, 51, 53]. This focuses on domain-specific capacity with simple tests and then refers individuals with poor capacity to in-depth assessment of the specific domain, so the area of decline can be identified and hopefully ameliorated. For example, if an individual struggles with the chair rise test (locomotion domain), their mobility is further assessed using the SPPB or other physical performance test. If they score poorly on these tests, the individual is assessed for associated conditions, such as bone or joint conditions, frailty or sarcopenia, or pain, and their social and physical environments are checked with the aim of managing and improving mobility [41]. In this personalised care scenario, breaking down IC into its constituent components is crucial to identify declines and direct intervention.

There is also an argument that complex composite scores are not required at all, and healthy ageing or IC could be better assessed with one simple indicator, for example, self-rated health. Using one indicator to represent healthy ageing would be simple and easy to use and understand and would forgo many of the issue with creating composite scores. The chosen indicator would need to be shown to be a reliable indicator of health in older age by, for example, predicting adverse health outcomes. Self-rated health (SRH) is a candidate for a single indicator of healthy ageing, and has been shown to predict subsequent mortality across multiple studies and populations [362] and to almost the same degree as objective health measures in the short-term (<10 years) [363]. However, using multiple indicators and/or a composite score results in a holistic and comprehensive assessment of IC (or healthy ageing) which fits with the theory and empirical evidence that the concept is multidimensional. In addition, particularly when compared to SRH, IC is a more objective measure of capacity that is less reliant on individual biases, perceptions, and interpretations of health that SRH [364]. IC may also capture changes in capacity that are smaller than those captured in SRH – one unit change in SRH from “excellent” to “good” may be bigger, or certainly more up to interpretation, than a unit decrease in IC score; therefore, IC could potentially model changes in health before subjective or one-dimensional indicators.

As composite scores allow for easier analysis and interpretation of a multidimensional concept, they are useful to model such concepts at a population level, where the more granular information may not be needed. For the current research aim, which was to investigate the association between social isolation and IC and assess whether inflammation is a mediator of this relationship, the domain- or indicator-level information was not needed and the composite score that summarised IC was more appropriate. Future research may use more complex modelling techniques, such as structural equation modelling, to model IC as a whole but also identify key domain-specific pathways and associations; however, more investigation of the ontology of IC and effects of different types of modelling, e.g., IRT versus factor analysis versus other methods, would be useful beforehand.

As well as thinking about the utility of composite scores versus single indicators, it is also important to think about the method used to generate composite scores. This study used IRT to generate a complex summary score but simple techniques, such as summing domain-specific scores, are alternative methods that have been applied to IC. A simple score of IC made by summing indicator or domain "pass/fails" would give an easily understandable scale where a one unit increase or decrease directly translates to one "pass/fail" on an indicator or domain. There are strengths and limitations to using a sum score, as opposed to an empirically driven approach such as factor analysis [365]. Advocates of sum scores highlight their simplicity in calculation and interpretation, especially across disciplines and non-academic audiences. Sum scores can also make it easier to compare across different populations as they are not dependent on data-driven methods but are instead dependent on theoretical justifications for the inclusion/exclusion of certain indicators that are thought to be related to the trait in question [366]. They also recognise that the occurrence of multiple indicators may be determinative of health and that better performance across multiple indicators is associated with better outcomes. Nevertheless, sum scores also receive some criticism. Without weighting, they assume that each indicator is equally important to total IC, which may not model the relationship between the indicators and IC in the most appropriate way. Although often posited as opposite to factor scores, which weight each indicator in the calculation of the summary score, others see sum scores as a type of very restricted factor score which gives equal weighting to each variable [367] and therefore are subject to the same, if not more, criticisms as factor scores. In practice, the utility of a sum score versus a complex score depends on the situation. In a clinical setting, a sum score probably gives a good enough estimate of the severity of a condition, but when trying to understand the nature of a condition, a complex score can give more precision, while sum scores are too imprecise for research applications [367].

The current study used IRT to generate a complex score representing IC, which has been recommended instead of sum scores when carrying out longitudinal data analysis [368]. In a simulation study, sum scores were found to lead to systematic bias in variance estimates in longitudinal analysis by underestimating the between-person variance and over-estimating the within-person variance. IRT was found to be better at estimating the variance in all conditions, but particularly when there was a smaller number of items, smaller sample size, and non-normally distributed data [368]. As the IC score was used for longitudinal analyses in the current study, IRT was an appropriate method and potentially resulted in more precise results than a sum score. The use of IRT in this study allows for some understanding about the items that would not be possible with a sum score. The item difficulty and discrimination parameters identify the items that best discriminate between those with similar levels of IC and those that are the "easiest" or most "difficult" with which to achieve good capacity. With a sum score, there is none of this information, unless compared with a large population where you could potentially infer the item difficulty from the proportion of people doing well or having difficulty with the item. In future research, it would be interesting to see a more in-depth exploration of the effect of modelling IC in different ways with different methods and in-depth assessment of the psychometric properties of IC. This would give some justification to the methods used in the field, which is currently diverging into two camps: sum scores used for clinical practice versus more detailed factor scores used in research.

The IC score in this study was found to be lower, on average, in women and those who were older, in lower wealth quintiles and not in employment, with lower physical activity levels, more health conditions, and lower self-ratings of health. The findings that less advantaged individuals with poorer wealth and lower education had lower IC scores reflect health inequalities between most and least advantaged groups that are seen across all ages in England [369] and support the idea from the WHO framework that environmental and societal factors in an individual's life can affect their IC and functional ability [30]. It seems obvious that those with a higher number of chronic health conditions and who rate themselves as having poorer health also have lower IC scores, but it is important to show that IC tracks these other measures of health. Additionally, the fact that IC was shown to predict functional ability, hospital admissions, and mortality even when these other health measures had been accounted for suggests that IC can provide the information above that is garnered by simple counts of diagnoses and subjective opinions on health. This bolsters the WHO strategy's focus on measuring health without using a deficit model and focusing on disease. In fact, looking at the descriptives of the sample used to create the IC score, a majority of 63% had at least one chronic condition diagnosis, and 32% had two or more (**Table 4.3**). In comparison, for 11 of the 14 indicators of IC, over 63% of the sample had "no difficulty" with the task or criteria and over half of the indicators had over 70% of the sample achieving performance on the indicator above cut-offs indicating risk of adverse outcomes (**Table 4.1**). One criticism of original models of successful ageing was that a majority of older people were not passing the "successful" criteria [2], which doesn't seem to be the case with this IC measure.

There were only two indicators of IC in which a majority of the sample performed under the cut-offs – waist circumference and lower mobility, with 21% and 39% experiencing, respectively, "no difficulty". Waist circumferences in England have been found to be increasing over time in older adults [370], and approximately 75% of adults in England aged ≥55 years are overweight or obese in 2022 [371], so it is perhaps not surprising that the majority of the sample had a waist circumference bigger than the recommended length. This is also interesting as the indicator of BMI showed a higher proportion (67%) of the sample achieving BMI values within the "no difficulty" range. This is most likely due to the fact that BMI values indicating overweight were included in this range because research has shown that being overweight (but not obese) as an older adult does not necessarily increase the risk of mortality and morbidity [299]. This demonstrates the utility of combining BMI and waist circumference as measures of body composition as, although over two thirds of the sample had BMI values that did not reflect an increased risk of adverse outcomes, three quarters of the sample showed abdominal adiposity that did increase their risk.

The majority of the sample also had difficulty with the lower mobility indicator. This indicator included six actions involving lower mobility with which respondents were asked if they had difficulties – walking 100 yards, sitting for 2 hours, getting up from a chair after a long period of sitting, climbing several flights of stairs without resting, climbing one flight of stairs without resting, and stooping, kneeling, or crouching. Respondents reporting difficulties with one or more of the tasks meant that they were categorised into the "difficulty" category, which was 62.1% of the sample eligible for IC in wave 2 (Table 4.1). This high proportion seems to be driven by two actions which both had over 40% of the sample reporting difficulties (Appendix 4.1) – climbing several flights of stairs without resting and stooping, kneeling, or crouching. These actions have been previously identified as the tasks that many older people report difficulty with, particularly those with frailty [372]. The high proportion reporting a lower mobility difficulty is also not surprising, considering that mobility limitations are common among older adults, with estimates that they affect ~35% of 70-year-olds and the majority of people aged ≥80 years in the United States [284, 373]. However, in ELSA, the difficulties with these actions are self-reported and not assessed objectively by an interviewer or nurse evaluating performance on the task. Thus, it is not known for certain whether those reporting difficulties actually do experience difficulties to the degree that a clinician or objective assessment would categorise as difficulty. This self-judgement would also be influenced by the respondent's interpretation of the task and their beliefs about what a "difficulty" with the task would look like for them. Studies comparing self-reported difficulties with performance-based assessment find that self-reported difficulties do tend to correlate with and predict limitations seen in objective tests [374, 375]. On the other hand, in a sample of older adults visiting the emergency department, Roedersheimer et al. found moderate rates of overestimation of their ability to perform tasks, which was higher among those reporting some need for assistance on a task [376]. This highlights how there may be some inaccuracy in self-reported mobility, although it is not certain if this has resulted in over- or underestimation of the prevalence of mobility limitations. Nevertheless, the high proportion reporting mobility difficulties in this study is worrying as it is estimated that the mobility of older adults has been reduced significantly by the Covid-19 pandemic and associated lockdowns [377] with older adults not able to keep fit and mobile. It may be the case that future assessments show even greater proportions of older adults reporting mobility limitations.

The IC was shown to predict subjective and objective health outcomes 8-14 years post-measurement, even when adjusted for socioeconomic and health-related covariates. This supported previous research that found other models of IC predictive of mortality, functional ability, nursing home admission and hospital admissions [47, 61, 64] and showed that the IC score was capturing the risk profile of individuals for adverse health outcomes and, therefore, a useful measurement of health in older age.

Although shown to predict adverse health outcomes, there is still a question as to the difference between IC and other measures such as frailty and disability which also predict further adverse health outcomes. Measures of IC often include similar indicators to frailty indexes, such as tests of physical functioning, grip strength, and even cognition and mental health measures in more comprehensive frailty indexes. Although IC and frailty have been posited as "two sides of the same coin" [21] with one representing reserves of capacity and one representing deficits, the frequent overlap in indicators does bring into question the utility and distinctiveness of IC from established measures of frailty, as well as measures of disability such as ADLs and IADLs. A study investigating trajectories of IC impairment and frailty in Chinese older adults found that these states overlap and co-exist in older adults [378], but that the prevalence of IC impairment was more common. They discovered that IC impairment, particularly new impairment in the locomotion and vitality domains, was associated with transitions from non-frail to frail states, giving support to the idea that IC impairment is a precursor to frailty. Other studies in Chinese older adults have similar findings, with declines in IC found to be present prior to the clinical manifestation of frailty [379] and transitions of IC, but not physical frailty, associated with a higher risk of incident disability (needing assistance with any ADLs or IADLs) [380].

These results start to demonstrate the difference between IC and frailty or disability, but the evidence base explicitly exploring this is currently small. Nevertheless, findings so far give credence to IC being an indicator of states of capacity prior to the manifestation of frailty and frailty being the outcome of significant losses in IC. One study mentioned previously found a progressive decrease in composite IC score across those judged robust, pre-frail, and frail by the Fried phenotypic criteria and found decline in all 5 domains of IC more likely in pre-frail and frail individuals [379]. This indicates that IC decline can give information about capacity prior to being judged frail; however, it is less clear what the utility of IC is beyond the categorisation of pre-frail. Both declines in IC and being deemed pre-frail precede frailty so more information about how IC could indicate capacity even prior to pre-frailty would be beneficial. Proponents of IC as a preceding indicator of frailty stipulate that because frailty is a state of reduced resilience to stressful events and deficits across physiological and/or psychosocial domains means, it is a less reversible state and has a point of no-return where it turns into a pre-death phase; thus, IC is a monitoring tool of the state prior to frailty where intervention and reversibility may be possible [378].

In practice, the difference between IC and frailty is all dependent on the operationalised definition of each and the language used within each framework. Since the introduction of frailty index by Rockwood and colleagues developed in the 1990s [16], frailty indexes have become more comprehensive measures than historical definitions like the Fried phenotype [15] which focused on deficits in physical functioning, and as such have much more overlap with the multidimensional concept of healthy ageing and IC. If IC is to be a useful measure in the period preceding frailty, the operationalised definitions of each measure need to reflect this, with any cut-offs or indicators used in IC set to capture a level of capacity that reflects a higher level of functioning so it can distinguish between excellent, good, fair performance, for example. Indicators and cut-offs for frailty would then be set to capture deficits and distinguish between levels of capacity at the other end of the capacity-deficit spectrum. This means IC will be able to pick up more subtle changes in capacity before obvious deficit occurs and implement intervention at a stage where reversal may be possible, and frailty can identify and distinguish the most vulnerable who need more intense monitoring and support. Additionally, the healthy ageing framework and IC were, in part, developed in an effort to move away from the stigmatising language around and focus on deficits in the study of health in older age which is present in frailty frameworks. It may be that future research begins to combine IC and frailty so they are not distinct frameworks being compared and pitted against each other, but useful tools along the same continuum, providing information about health and functioning that can be used to prevent and manage declines in health while avoiding stigmatising language and stereotypes that act as a barrier to some people engaging with the concepts.

8.2.1 Strengths and limitations

The main strengths of the IC model generation were the use of a nationally representative sample with links to objective health outcomes over an extended follow-up. The ELSA data allowed for the inclusion of rich information on covariates as well as the longitudinal modelling of IC with identical indicators over time. The IRT methodology and implementation of FIML meant a complex IC score was generated for all those who were eligible.

Handling missing data in the generation of IC score was important as missing data can lead to bias in parameter estimates of a model, reduce the precision and power of a model, as well as reduce the representation of the sample and thus the generalisability of the findings. With higher proportions of missing data (≥50%), the estimation of item- and person-parameters in IRT models is severely affected [381]. To mitigate the impact of missing data on the model estimation, a FIML approach was used which included all the available data in the estimation of the parameters. An assumption of FIML is that data are missing at random (MAR) [382], which means that the pattern of missing on a variable is dependent on other observed variables and so there is no remaining relationship between the missing and non-missing data after controlling for these observed variables. The MAR assumption is less restrictive than the missing completely at random (MCAR) assumption, where the pattern of missing data is not dependent on any observed or unobserved values, but is more restrictive than the missing not at random (MNAR) assumption, where the probability of missingness depends on the missing values [383]. There is no way to properly distinguish between MAR and MNAR as we do not have the missing values to determine whether the missingness depends on them, so we must make assumptions about the data available. Looking at the distribution of missing data amongst the IC indicator variables in **Table 4.1**, there is generally a small amount of missing data for most items (0 – 10%), with the highest amount of missing data for the chair rise test (20%). It is possible that the missing data on this variable is dependent on the value of the chair rise test, as some people did not have a nurse visit, and therefore were not asked to do the chair rise test, potentially because they were not well enough to complete the nurse visit and would not have passed the chair rise test. This could also apply to the other indicators that were assessed in the nurse visit at wave 2 – the balance tests and grip strength. It is not possible to say for certain whether the data were MNAR or MAR in this case, but it is possible that the MAR assumption was violated, making the estimates from the FIML estimation open to bias. Other methods for handling missing data, such as multiple imputation, use auxiliary variables in the imputation process to help reinforce the MAR assumption. Auxiliary variables are not of substantive interest to the main analysis but are associated with the values of missing data in an incomplete variable [383] and so help reduce bias in the estimation of the missing values; however, FIML does not allow for the inclusion of these variables [384].

There are also other methods of handling missing data that could have been applied in this case. Listwise and pairwise deletion are traditional methods of handling missing data where an individual’s data is discarded if they have missing values (also known as complete-case and available-case analysis) but both require data to be MCAR [383] which unlikely with surveys such as ELSA, and as such are not recommended. Listwise and pairwise deletion were used in the descriptive and predictive validity analysis of IC where individuals with missing data on sociodemographic and health-related covariates and each health outcome (ADLs/IADLs, hospital admission, and mortality) were excluded from the analyses (see **Figure 4.1**). This means that the parameter estimates from these analyses may have been distorted as the data was most likely not MCAR – a limitation of these analyses.

Some other limitations of the IC model and analyses in this chapter were that the IC score was generated based on cut-offs for each indicator which are sensitive to the values chosen; some were also based on the data and not defined in previous research so they are sensitive to the population used when measuring the indicator. The ELSA sample is representative of the general English population over 50 years but is based only on community-dwelling older adults, so results are not as relevant or generalisable to clinical settings or institutionalised samples, where IC measurement may be particularly important. The IRT model also does not allow for the exploration of the specific domains of IC and which are the most important to the latent factor of IC. Nevertheless, this may not be so important when measuring IC in observational studies at the population level compared to measuring IC in individuals to identify those at most risk of declines and inform personal care and intervention plans. IC measurement in these settings will potentially be carried out by healthcare professionals with limited time and budget, so identifying key domains of IC to focus on may save time and money when assessing many individuals. However, the goal of IC should always be a multi-domain assessment as every domain of IC is important to the functional ability and ultimate wellbeing of older adults [32].

The IC model also technically includes indicators that could be deemed functional ability, as opposed to IC. The walking speed test allows the use of walking aids, such as sticks or frames, which is an element of the environment that works in combination with the individual's intrinsic capacity to enable them to complete the task. Both self-rated vision and hearing include the use of aids like glasses, contact lenses, and hearing aids if these are usually worn by the respondent, which is also an environmental adjustment to an individual's IC. This demonstrates the difficulty with measuring IC in secondary-data observational studies, which collect a lot of information for general research needs, as well as the difficulty in extracting IC from the environment in which an individual lives. Although challenging, future studies may expand upon IC to create measures of healthy ageing that include intrinsic capacity and functional ability, such as the model created by the ATHLOS consortium [67, 73, 385, 386] (model 12 in **Appendix 1.2**).

In relation to IC and the wider WHO healthy ageing model, to date, no studies have specifically included environmental factors from the micro- to macro-level, such as the built environment, relationships with other people, health and social policies, and attitudes and values, the extrinsic factors identified in the WHO framework that interact with IC to produce functional ability [30]. A body of research is emerging exploring the impact of environmental factors on healthy ageing (albeit not IC or the WHO healthy ageing model), for example, how the built environment can form barriers or opportunities to health for older people. Access to local recreational facilities and parks, reduced vehicular traffic, accessible pavements, street lighting, and walkable neighbourhoods are all shown to promote walking and physical activity among older adults [387]. Particular elements of the built environment are especially important for the mobility of those with decreased functional ability, such as barrier-free level surfaces, benches, and accessible toilets. As well as physical activity and mobility, environments can be beneficial to cognitive health, with more community and recreational resources, closer proximity to public transport, and public spaces being in good condition, all associated with better cognitive function [388, 389]. The impact of attitudes and values towards ageing has also been researched. A longitudinal study of American older adults found that those who held negative stereotypes about ageing made a poorer recovery from disability [390] and lived 7.5 years less than those with positive attitudes [391]. This is concerning given the high prevalence of ageist attitudes around the world - in a survey of over 80,000 individuals from 57 countries, 60% of countries were classified as having moderately or highly ageist attitudes [392]. It is clear that environmental factors influence healthy ageing, but more research is needed to explore how environmental factors can be measured and integrated into a model of healthy ageing alongside IC and functional ability as posited by the WHO framework.

The IC model also does not address the issue of age-specificity and that some indicators will be more sensitive for particular age ranges and not that useful for others. For example, the high proportion of the sample having “no difficulty” with the orientation indicator is probably due to this measure’s lack of sensitivity for younger individuals or those with normal cognitive functioning. Therefore, the measure is better suited to identifying those with cognitive impairment [393] or at risk of dementia [394]. In some ways, this is not a problem, as a measure being particularly sensitive at one end of the range means that changes in that indicator are a clear indication of a health change. On the other hand, such an indicator may not pick up on potential subtle changes in health that precede a significant health decline or morbidity. There is currently no strategy in the WHO framework for how to address age-specificity in IC. It could be that the assessments and/or the cut-offs for IC indicators change according to the age of the respondent, but there is not yet research on how this could be applied to research or clinical applications of IC and how longitudinal monitoring of IC could take age-related sensitivity into account.

Another important reflection on the IC model is that, although the overall predictive validity was assessed, the validity of the indicators and associated cut-offs is not confirmed. Although the cut-offs chosen for each indicator were based on previous research that indicated an increased risk of negative health outcomes, it is not known whether being classified as experiencing “difficulty” with the indicator reflects morbidity or a meaningful change in capacity for the individual. Without having a healthcare professional confirm the presence of conditions such as cognitive impairment, depression, or physical disability, some may question the validity and meaning of the IC measure. It is controversial whether a diagnosis or indication of morbidity can be decided based on measures like orientation in time or the CES-D. For example, the Mini-Mental State Exam (MMSE), which includes an assessment of memory (word recall) and orientation among other cognitive functions, has limited diagnostic accuracy for mild cognitive impairment (MCI) and dementia or Alzheimer’s disease [395] and particularly for distinguishing between these states [396, 397]. As such, it is not recommended that a diagnosis of MCI or dementia be confirmed based on the MMSE alone [398], and there are other non-neurological reasons for a low score, such as low education, language difficulties, or other health conditions resulting in similar symptoms, that need to be accounted for. Similarly, the CES-D scale is not recommended for the diagnosis of depression but is more suited for the screening of depressive symptoms in a population [351]. Nevertheless, IC is not aiming to identify morbidity and instead focuses on measuring overall capacity in older populations or application in clinical settings as a primary screening tool ahead of further investigations. Therefore, it may not need to include indicators that are valid for confirming morbidity but those that give an indication of the individual's risk profile.

8.3 Social isolation and intrinsic capacity

The index of social isolation used in this study follows the definition of social isolation as an absence of relationships related to small network size, little diversity and low frequency of contact, representing the structural aspect of missing relationships [128]. It makes use of seven indicators that capture the objective quantity of relationships and frequency of contact with others and does not measure the quality of our feelings about relationships which would constitute the functional elements of social relationships and be more appropriate for a measure of loneliness. Although the index tried to capture a comprehensive picture of the social interactions that an individual may experience, covering the interactions with members of the household, family, friends, colleagues, and other volunteers or members of organisations or clubs, there may be some relationships that the index misses. It does not capture interactions with carers or other professionals that may interact with the respondent, perhaps in some cases regularly, or neighbours and other people in the respondent's community who they may not classify as friends but interact with regularly. Nevertheless, the index captures the majority of relationships and activities that the sample would likely be involved in and improves on some previous scales with the inclusion of interactions through employment and volunteering.

In longitudinal analyses, the social isolation scores were found to be negatively associated with the level of IC at baseline and positively associated with the rate of change over time. This supports and contrasts with previous studies, which found that less social connectedness was associated with lower levels of IC [50] and a steeper decline in IC over time [63]. Differences in the results of the current study to previous findings could be due to differences in the samples and cultures between the studies, as well as methodological differences in the measurement of social relationships and/or IC. However, there are other possible explanations for this result. The finding that isolation had a significant positive association with the rate of change in IC suggests that older adults in England who are not isolated start with a higher baseline level of IC but then have “more to lose” over time and see a greater decline in IC than individuals who are very isolated. Older adults who are very isolated start with a lower level of IC and seem to maintain this over time, seeing a less dramatic decline. This is somewhat positive, showing that people who are isolated and have lower IC are not experiencing a compounding effect of isolation on how rapidly their IC declines, but also that not being isolated and having frequent interactions with others is not protective against declines in IC over time. Nevertheless, the result could demonstrate a negative effect of a larger amount or higher frequency of social interactions of different types on the maintenance of IC. As the measure of social isolation generated in this study did not capture information about the quality of the social interactions, it could be that those with low social isolation scores were experiencing more negative interactions, which have been shown to be more detrimental to health than positive interactions are helpful [338]. The social isolation score also didn’t capture information about the effort required to maintain larger social networks or a more diverse range of social activities. Those with the lowest social isolation score in this study would need to be living with others, interacting with children, family, and friends at least once a month each, be a member of at least one organisation, be working, and be volunteering. This amount of activity may be overwhelming and stressful to maintain, especially if some of these activities involve negative interactions or more effortful activities, such as caregiving, and could result in negative impacts that hider the maintenance of health over time.

There is still the possibility of the reverse association between IC and social isolation. Although a significant association was found between isolation and the rate of change in IC, it is possible that the direction of influence also works in the opposite direction. The mean social isolation score did not change much over time (Table 6.2), but this could be masking different trajectories of social isolation. Looking at the relationship between IC and social isolation may reveal that a certain level of IC influences the likelihood of experiencing certain trajectories of social isolation. For example, most people may experience a stable level of social isolation over time, but there may be particular groups of people for which a poor IC score results in an increase in social isolation over time as their capacity reduces their ability or desire for social interaction. This would be supported by previous research that finds bidirectional relationships between IC and social engagement [50], as well as physical functioning and social isolation [399].

This result has implications for our understanding of the relationship between social isolation and health in older age. The evidence in this and previous studies clearly indicates that the two are linked in a negative fashion, where more isolation is associated with poorer health, and (from previous research) in the opposite direction, where better health is associated with less isolation. However, the impact of social isolation on change in IC is unclear. If reducing the amount of isolation experienced by older adults does not improve their IC and health and slows the rate of decline over time, social policies and interventions with this strategy would not be the most effective way of improving health for older adults. However, reducing social isolation could give older adults a higher "starting point" of IC and allow more years with a higher capacity even if there are inevitable declines. It may also be the case that reducing social isolation is more effective for certain domains of capacity, e.g., psychological wellbeing, than others, as IC is an overall measure of health and is not broken down into domains in this research. A battery of interventions focusing on different domains could be most effective instead of "reducing social isolation" being the panacea against general ill health in older age.

8.3.1 Strengths and limitations

The main strengths of the analysis were the multiple measurements of social isolation and IC with identical indicators than enabled direct comparison and longitudinal modelling. The ELSA data also allowed for the inclusion of rich time-invariant and time-varying covariates, which allowed the analysis to show that social isolation was associated with IC even when socioeconomic and health-related factors were considered. In the fully-adjusted model, most of the socioeconomic and health-related factors showed an association with IC, even when mutually adjusted for each other and social isolation. As seen in the IC analysis in the previous chapter, poorer wealth, less physical activity, more health conditions, and lower self-rated health were associated with worse IC scores, while smoking and alcohol consumption showed slightly more complex patterns of association. Having longitudinal measurements of these covariates allowed the analysis to show that these socioeconomic and health factors had an association with IC score for individuals beyond that which was predicted by simple modelling of the IC intercept and slope, which has not yet been explored in previous studies of IC.

One of the main limitations of the social isolation analysis was that no causal relationship can be ascertained between social isolation and IC using observational data. Although longitudinal data can allow for the temporal ordering of predictors and outcomes to be seen, this analysis measured social isolation and IC within the same wave and modelled associations between the two over time, not whether one occurred prior to the other or if one caused the other. Therefore, it is not possible to say that social isolation is a cause of IC. Future analyses could explore the longitudinal relationships in more detail and maybe use lagged effects to see the association of social isolation measured at a prior time point with IC. The analysis also only included social isolation as a time-varying predictor and did not assume that social isolation also goes through growth processes (i.e., it did not model an intercept and slope for isolation); future analysis could use multivariate growth modelling to model social isolation as well as IC to explore the growth processes of both variables and how they affect each other.

With the introduction of longitudinal analysis and multiple waves of data, the problem of attrition, or people dropping out of the study, becomes more apparent. Non-random attrition of the sample can reduce the representativeness of a study. As the initial sample is often chosen carefully to reflect the characteristics of the population (e.g., older adults in England), losing respondents can impact this careful selection and mean that some groups become over- or under-represented. In longitudinal studies, responding groups tend to be those in more advantaged socioeconomic circumstances and better health compared to non-respondents [400, 401], so attrition often results in the study sample reflecting a more advantaged and healthy population than it is supposed to. Missing data in this analysis was managed using full-information maximum likelihood (FIML) in the estimation of the latent growth curve models. This method does not fill in missing values with an imputed value but generates estimates for model parameters and standard errors using all the available information. Another missing data method, multiple imputation, is considered more efficient (more powerful, thus obtaining smaller standard errors for parameter estimates) than FIML, but the two have been found comparable in terms of recovering correct parameter values [402], and both perform similarly with a continuous outcome [384] and in structural equation models [403]. Nevertheless, FIML does work under the assumption that the data are missing at random (MAR) and, as discussed in **Section 8.2.1**, it is possible that the data do not meet this assumption and may be missing not at random (MNAR). The proportion of missing data on the social isolation score was ~24% (**Table 6.1**) with the individual social isolation indicators proportion of missing ranging from 0 to 16% and most on the items measured using a self-completion questionnaire. It is possible that having missing data on these self-completion (and other) items is associated with other observed variables in the dataset; however, FIML does not allow the inclusion of auxiliary variables to aid in the estimation [384] so these other observed variables would not have been considered in the model estimation. This means that the parameter estimates generated using FIML may be biased by the data being MNAR. As mentioned above, multiple imputation does produce comparable parameter values to FIML, but does allow for the inclusion of auxiliary variables which could help reinforce the MAR assumption and reduce the bias in the estimates, although is more computationally intensive, complex, and time-consuming than FIML. Other approaches such as listwise and pairwise deletion are often used but would not be preferable to FIML or multiple imputation as produce distorted results when the data is not missing completely at random, which is most likely is not in the current data.

Another limitation of this analysis, which was also discussed in the previous section, is that ELSA is only representative of community-dwelling adults in England, meaning results from these analyses may not be generalisable to other populations, for example, institutionalised older adults. This is important as these populations may be more vulnerable to being socially isolated and the impacts of social isolation on health, as well as experiencing lower IC, and therefore these groups may benefit most from interventions. Future research could explore the relationships between social isolation and IC in these groups and whether it differs from community-dwelling populations.

8.4 The mediating role of inflammation

Results from this study did not find evidence of a mediating role of inflammation in the association between social isolation and IC. Cross-sectional analyses did not find a significant association between isolation and CRP, a biomarker of inflammation, when the analysis was adjusted for socioeconomic and health factors and the mediation model also found no significant association between social isolation and CRP over 4-year intervals. A previous meta-analysis of associations between social isolation and CRP found that the association was significant in least-adjusted analyses but rendered non-significant when most-adjusted [190]. The meta-analysis did identify significant associations between social isolation and fibrinogen and loneliness and IL-6, which both remained in most-adjusted analyses. The mixed evidence for an association between social isolation and markers of inflammation may be down to methodological differences between studies, but it also could be due to the complex relationship between social stressors, like social isolation, and the immune response. It is hypothesised that social isolation activates a stress response in humans that is taxing on physiological systems [171]. Inflammation is a result of the immune system's reaction to infection and trauma, and potentially stress, with the latter hypothesised to cause long-term raised systemic inflammation, which is harmful to the body. Studies have identified associations between social stressors and raised inflammation, but the whole process, from the initial immune or stress response to activation of the inflammation system to the release of inflammatory biomarkers, which are then measured for the research study has not been measured. It is possible that even if social stressors are eliciting a physiological response that is deleterious to health that inflammation is not the main marker of this effect.

In a different result to that found in the previous chapter using latent growth curve modelling, the cross-lagged panel model found no direct or indirect effect for the association between social isolation and IC over the 8-year follow-up. As no association was found between social isolation and CRP in this model, it is not surprising that inflammation was not found to be a mediator and on the causal path between social isolation and IC. However, the lack of a direct effect is opposite to the result of the previous analysis, where social isolation was found to be significantly negatively associated with the level of IC. Nevertheless, the direct effect on the CLPM was testing the association between social isolation at wave 2 on IC on wave 6, which is an interval of 8 years. It may be that the effect of social isolation on IC does not extend for that amount of time, with other factors being much more important for IC over that time period than social isolation. Furthermore, the methodology used was different as the aim was to answer a different question: the LGCM in the previous analysis looked at the association between social isolation and IC at each time point and not the lagged effect. Future analyses could find a middle ground between the LGCM and CLPM and explore the association of social isolation on IC with a shorter time lag.

The CLPM did reveal a significant bidirectional between CRP and IC, with each predicting the other over 4-year intervals. This bidirectional relationship supported the theory of Borras et al. [202], who posited that those with higher IC might be able to overcome chronic, low-grade inflammation ("inflammageing") and suggested that this could be an explanation for why centenarians often avoid or postpone the onset of age-related diseases or declines. This relationship is not surprising, seeing as one of the known risk factors for and potential causes of chronic inflammation is central obesity [179, 404] and that greater mobility may allow for more physical activity, which could have anti-inflammatory properties (although the evidence is mixed) [405]. Both central obesity and mobility are captured in the IC score, so IC predicting inflammation may reflect the influences of these elements of IC on inflammatory processes. This highlights the difficulty of untangling the biomarkers of ageing from the potential causes of biological ageing, as they are often inextricably linked. The finding that CRP predicted IC levels 4-years later is novel as no study has explicitly tested the lagged association of CRP on IC. Previous studies have found associations between inflammation and IC in cross-sectional analyses [49, 203, 204] and that chronic inflammation (2 consecutively high readings) was associated with a decline in IC over 5 years [62], but none have explored the temporal lag of inflammation on IC. The lasting association between inflammation and IC could be due to the deleterious effects of inflammation at a certain time point having a long tail of impact on capacity. It could also be due to levels of inflammation at one time point indicating something about the inflammatory and immune processes (or another unmeasured confounder) occurring during the 4-year interval that are not measured in the model but are reflected in changes in IC. Further research could focus on the temporal parameters of the association between CRP and IC to understand how long this association lasts, whether it is chronically raised inflammation that is driving the association with health, and how long inflammation needs to be raised to result in a change in IC.

8.4.1 Strengths and limitations

The main strengths of this analysis were the use of three measurements of the predictor, mediator, and outcome and the use of a CLPM which can account for temporality. Although more time points would have strengthened the analysis, three time points enabled the creation of a full longitudinal mediation model. Only two time points would have required a half longitudinal mediation analysis where the predictor, mediator, and outcome are measured at the first time point, and the mediator and outcome are measured at the second time point [406] and all paths of reverse association are not captured. The use of a CLPM also allowed for the accounting of temporality in the analysis, which is one of the criteria for causal inference. However, causation is still not possible to determine with observational data as there is always the possibility of spurious associations that are affected by unmeasured external variables, which only be fully avoided through the use of randomisation of people to groups, such as in a randomised control trial [407]. As a traditional randomised control trial for the mediation effect of inflammation on the association between social isolation and IC is not feasible, it may not be possible to ever ascertain causation fully for this association, but certain statistical methods like CLPMs can give indications.

Another strength of the analysis is the use of FIML to estimate model parameters with all the available information, which allows the model to include those who had missing data on some variables. The implications of not handling the missing data include the model not accounting for the unbalanced panel, where different individuals have different numbers of observations over the three time points, which can reduce the power and introduce bias into the parameter estimation [408]. However, as discussed previously, a cornerstone assumption of FIML is that the data is at least MAR. It is not possible to truly determine whether the data is MAR or MNAR but it is possible that the missingness depends on the value of the missing data and is not explained fully by observed variables. There was some missing data in the CRP measurement, with not everyone eligible for or taking part in the nurse visit obtained a valid CRP result from their blood test and whether or not this is missing could be dependent on the CRP value itself, for example, those with chronic low-level inflammation could be unwell and not able to take part in the blood draw. It is possible that missing data for this reason would be captured in other observed variables measuring health but, as discussed previously, FIML does not allow for the inclusion of auxiliary variables to aid the model estimation in the presence of missing data. Multiple imputation is a method for handling missing data that can incorporate auxiliary variables to reinforce the MAR assumption, although there are few examples of multiple imputation being used for a CLPM in Mplus. Other missing data handling options such as listwise and pairwise deletion have more limitations than FIML in terms of biasing the estimations so were not considered.

It is also important to highlight the biomarker of inflammation used in this study, serum CRP. CRP in the blood (serum) is a sensitive and stable marker of inflammation [409]; concentrations of CRP >10 mg/L are judged clinically significant and indicate high inflammation and the potential presence of a current infection [410]. CRP does not generally rise above 3mg/L in most people, and historically, concentrations 3-10 mg/L were not thought to be clinically significant [409]. However, subsequent research found an association between slightly elevated CRP (3-10mg/L) and the risk of developing cardiovascular disease [409, 411]. CRP concentrations below 10mg/L are termed low-grade inflammation and have been used in epidemiological studies to indicate systemic chronically raised inflammation without active infection. This is the level of inflammation implicated in the theories linking social stressors to health, with stress responses evoking chronically raised inflammation which is harmful to the body in the long term. In this study, those with CRP concentrations >10mg/L were excluded from the analyses as these values were indicative of a current infection, which was not the type of inflammation of interest. CRP was chosen as the biomarker in this study as it is a well-evidenced inflammatory biomarker that has been explored in previous studies of social connectedness and IC, and it was available in all the nurse visit waves of ELSA so it could be measured longitudinally. Future studies could also focus on other biomarkers, such as fibrinogen and IL-6, as these were shown in previous research to have potentially different relationships with social isolation and IC than CRP.

Another limitation of this analysis is that the results can only be interpreted as association and establishing causality in these relationships is not possible. This is a common problem in observational studies, even when confounders are controlled for, as it is virtually impossible to account for every aspect of an individual's life. As many exposures, mediators, and other variables of interest in observational studies are not truly randomised in a population, there may always be confounding factors that are not captured in the model. The current analysis accounted for known confounders in an effort to identify the associations between social isolation, inflammation, and IC while holding these other factors steady; however, there is still the high likelihood of unmeasured confounding, as well as particular types of confounding not controlled for using the CLPM analysis that violates assumptions of causal mediation analysis.

Causal mediation analysis is a method to estimate causal effects and is based on the counterfactual framework [412]. This type of analysis estimates causal effects by taking the difference between two counterfactual outcomes, which are outcomes for an individual that would be observed when the exposure and/or mediator is at a certain value. For example, it could compare the outcome IC in scenarios where everyone in the population is not socially isolated (low exposure) or everyone is very isolated (high exposure) while holding the mediator inflammation constant. In comparing these scenarios, it is possible to estimate the direct effect of isolation on the outcome IC. Then, by comparing scenarios of the mediator, (e.g., everyone has high inflammation versus everyone has low inflammation) while holding the exposure social isolation constant, it is possible to estimate the indirect effect of isolation on the outcome IC through the mediator inflammation [412].

There are four main assumptions required for the direct and indirect effects in mediation analysis to be interpreted causally, including when using a counterfactual approach [413]: (1) control for exposure-outcome confounding, (2) control for mediator-outcome confounding, (3) control for exposure-mediator confounding, and (4) that there is no mediator-outcome confounder that is itself affected by the exposure. The first three assumptions mean that all the included covariates in a model control for confounding on all three main pathways in the mediation model, which is quite a strong assumption. The second assumption is unique to the mediation context and is needed for the analysis of direct and indirect effects, even if the exposure has been randomised. The fourth assumption means that a confounder of the mediator and outcome relationship cannot be affected by the exposure. This is because such a confounder variable then itself becomes a mediator of the effect of the exposure on the outcome which is problematic for the estimation of direct and indirect effects. This assumption is a particularly hard to meet when there is a large gap in time between the exposure and mediator, as it requires that there is nothing on the pathway from the exposure to the mediator that itself also independently affects the outcome, which is more likely to occur if more time has elapsed. Violations of these assumptions can lead to misleading results, for example, violations of the second assumption regarding control of mediator-outcome confounding can result in results where the effects are in the complete opposite direction to those seen when the confounding is controlled [413].

The current analysis did not use a counterfactual framework to help identify causal effects, but the assumptions of causal interpretation can be applied. In order to meet these assumptions in the current mediation analysis and results, the covariates (sex, age, education, wealth, smoking, alcohol, physical activity, health conditions, and self-rated health) would need to control for confounding on all three paths identified in assumptions 1 to 3, while also not be themselves affected by the exposure social isolation to meet assumption 4. It could be argued that they are confounders of the mediator-outcome (CRP-IC) relationship as they are related to the level of inflammation someone experiences as well as their level of IC; however, some could also be affected by social isolation, for example, isolated individuals could not be working therefore have lower wealth and be carrying out fewer healthy behaviours. So, the inclusion of these confounders in a blanket manner would likely violate the assumptions for causal mediation. Further analysis could use DAGs to help visualise and understand potential confounding and other causal pathways in order to create a mediation model that capture the nuances in the confounding and ensure the model meets the assumptions of causal mediation analysis.

8.5 Implications for research and policy

The results from this thesis have implications for future academic research as well as policy.

With population ageing an increasing phenomenon of global significance, it is more important than ever to have tools to measure healthy ageing. The novel model of IC generated in this study demonstrated the utility of IRT for generating factor scores to summarise multiple indicators of health. The indicators of capacity utilised in this model are or are similar to, those commonly measured in observational studies of ageing, which makes this model accessible for use across different studies. The IRT method also provides a good framework to assess measurement invariance across different groups, which will be important for future cross-study research and application. IC forms a central part of the WHO healthy ageing framework [30], which will be a key framework throughout the 2020-2030 United Nations Decade of Healthy Ageing [31], so the model and methods in this thesis can inform the strategy for the measurement of IC over this important decade. As well as the worldwide perspective of the WHO, IC measurement and monitoring is also important in the national context. Health surveillance produces important information about the state of health across the UK and how it varies over geographies, time and different groups of people – data and evidence which is then used to inform policy actions [414]. This surveillance is particularly important with the changing societal and health contexts brought about by the Covid-19 pandemic and the ageing population. In 2023, the UK Office for Health Improvement and Disparities, alongside a range of charity, public health, academic and health organisations shared their commitments to healthy ageing in a shared consensus statement. One of the five principles outlined in the policy paper is to put prevention first through individual-level interventions and population-level policies [415]. This principle on prevention matches the

WHO's healthy ageing framework and is where routine measurement of IC prior to declines in function and health could aid surveillance and effectiveness of population-level interventions.

The model of IC also demonstrates that a meaningful measure of health that is shown to predict health and functional outcomes does not have to include diagnoses of health conditions or label individuals as unsuccessful. Results from this work showed that IC could provide information about subsequent functional ability, hospital admissions, and mortality beyond that from the number of health conditions with which a person has been diagnosed. This is a simple but important distinction, as it is crucial that older adults are engaged with the research and the potential policies or interventions that may arise from the WHO healthy ageing framework, such as IC monitoring. Since ageism is still a widespread problem, it is key that the research community does not perpetuate notions of failure and success and promote negative stereotypes, inadvertently or otherwise, as it is only damaging to the population that the research is supposed to be benefitting. This more positive framing of ageing also matches with the rhetoric and attitudes of the consensus statement on healthy ageing, described above, which included a principle to challenge "ageist and negative language, culture and practices wherever they occur, in both policy and practice" [415]. This principle aims to shift attitudes and conversation to those which celebrate the successes and benefits of ageing and an ageing population. Although IC still has to identify between "good" and "bad" performance to be able to capture capacity, the overall focus and framing of the concept around capacity instead of deficit means IC doesn't provoke the same negative connotations about ageing as other measures such as frailty or "unsuccessful" ageing.

The IC score's association with key socioeconomic and health-related factors provides more evidence towards the well-documented inequalities in health for older people in England. In a recent bulletin, the Office for National Statistics revealed that, compared to the least deprived areas, the reduction in healthy life expectancy for those in the most deprived areas of England is now 19.3 years for women and 18.6 years for men [416]. This means that those born between 2018-2020 in the most deprived areas of England could expect to have almost 20 fewer years in good health than those born in the most affluent areas, and this is expected to worsen due to the effects of the Covid-19 pandemic [417]. Overall life expectancy improvements have also stalled in the UK, and have potentially reversed for older ages [418]. Closer monitoring of health in the older population may help to target strategies to improve or promote healthy ageing to ensure that life and healthy life expectancy do not continue to stall or even decline. IC is a useful tool for monitoring the overall health across multiple domains in the older population and so would be useful in this national context.

This current study found positive effects of not smoking and taking part in physical activity on IC. These are health behaviours and changeable risk factors; however, this simplistic view ignores the fact that these behavioural risk factors are themselves driven by social inequalities [419]. We know that the prevalence of health behaviours is socioeconomically patterned in England, with the least socioeconomically advantaged groups showing the highest prevalence of smoking, lowest of daily consumption of fruit and vegetables, and low prevalence of physical activity [420]. The shared drivers of social and behavioural causes of health inequalities include the unequal distribution of power, income, employment, education, and services, as well as the levels of poverty. All these factors have consequences for the attentional, emotional, and material resources of an individual [419], which enable or disable them from carrying out certain lifestyle behaviours. With this in mind, in the context of IC and healthy ageing, any intervention aiming to improve IC needs to consider more than a behaviourist approach that assumes all behaviours of an individual represent a conscious choice and not one of circumstance, necessity, or a non-conscious process. Health inequality literature suggests that the most effective interventions to improve health need to focus on tackling behaviours and social determinants in parallel [419].

The finding that social isolation negatively impacts an individual's level of IC but results in a shallower rate of change over time has implications for the understanding of how social connectedness interacts with health. One main goal of policies relating to population ageing is to prolong good health for older people for as long as possible so they can remain active and well for their own wellbeing but also to reduce the resources that are required from health and social care services. The results from the current research would suggest that focusing this sort of policy on interventions against social isolation would not slow the rate of decline in capacity over time but could promote a higher starting point and, thus, potentially more years with a higher capacity even with inevitable declines. A social isolation intervention may not be an effective way to prevent declines in IC in a population, but it could promote a higher capacity overall. As discussed in **Section 8.3**, there is still the possibility of a reverse pathway between IC and social isolation, where an individual's capacity influences their ability or desire for social interaction, but this was not able to be tested in the current analysis.

It will also be important to explore the association between social isolation and healthy ageing in the years including and following 2020. The COVID-19 pandemic meant that people, and particularly older adults, experienced long periods of social isolation due to the lockdown measures and guidance for those more vulnerable to the negative effects of the virus. The significant short-term negative effects of lockdown and isolation on mental health is known, but the longer term is yet to be revealed [414]. The framework by which social relationships could influence health described in **Section 1.4** suggests a cascading model from societal to psycho-biological processes over a long period of time [118] so the health effects of social isolation may not manifest until sometime later. The current work describes the associations between social isolation and IC in ELSA covering the period 2004 to 2012 but future analyses should be expanded to beyond the 2020 pandemic. This information about how pandemic-induced isolation may have affected health will be important for the lessons learnt from the Covid-19 pandemic and aid the UK's preparedness for any similar future events.

The main result of the final analysis showed no mediating role of inflammation in the relationship between social isolation and IC, which does not support the notion that inflammation is the key mechanism by which social stressors get "under the skin" and influence health. Additionally, the bidirectional relationship between inflammation and IC indicates that a more compelling element to focus on with interventions to improve IC would be inflammation – either directly or through driving factors other than social isolation. Promoting anti-inflammatory behaviours (e.g., healthy diet, weight loss, not smoking) might be a way to increase or maintain IC in older people, while promoting multidimensional capacity in older people may help to reduce systemic inflammation and the risks associated with it. Much of the research directly testing the effect of inflammation interventions has focused on longevity and relies on research in animal models [421, 422], as the ethics of giving long-term medications to healthy adults for the prevention of subsequent age-related disease or health problems is doubtful. Nevertheless, some observational and pharmaceutical studies have explored the possible protective effects of anti-inflammatory drugs, specifically non-steroidal anti-inflammatory drugs (NSAIDs), on the risk for some age-related diseases. The evidence remains mixed, with some finding protective effects against Alzheimer's disease [423], but others finding no effect for dementia or cognitive decline [424] or that the anti-inflammatory role of the NSAIDs was not likely involved in any observed effect [425]. Another approach to promote anti-inflammatory processes focuses on nutrition and the gut microbiota [422]. A healthy diet will have other beneficial effects on healthy ageing than just reducing inflammation, so it is potentially an effective intervention to focus on. However, as discussed above, diet, like other health behaviours, is driven by many more factors than purely health-oriented conscious choice so intervention here is complex and requires a multi-angle approach. This result and the indication it gives about the links between inflammation and healthy ageing are relevant to public health policy. One of the principles of the UK Government and other organisations in their shared commitments to healthy ageing is the prevention of ill health in older ages through individual level interventions (such as exercise classes and smoking cessation support) and also population-level policies (such as food marketing) [415]. This result suggests that some of these interventions and policies should involve anti-inflammatory measures as well as strategies to avoid social isolation in order to try and prevent ill health for older people.

In summary, I believe these results suggest that strategies to help people maintain good levels of intrinsic capacity as they age should involve creating opportunities for older people to maintain social connections and avoid social isolation. Continuing to promote anti-inflammatory lifestyles and behaviours as well as supporting society to be able to make these lifestyle changes would be beneficial to intrinsic capacity.

8.6 Future research

In order to further understand IC, I have identified areas of future research interest that were beyond the scope of this thesis project. One area to explore in more detail would be sex differences in the relationship between social isolation and IC. Research finds that men and women tend to experience different levels and effects of social isolation [215, 219, 220], but this hasn't yet been explored in the context of IC. A very recent study found a significant mediating role of inflammation between social isolation and cognitive function for men only [426], which was attributed partly to a greater inflammatory response in men, and it would be interesting to expand on this for other outcomes like IC.

An additional important area for research is the pathway between social isolation and IC through health behaviours. Although only included in the current study as covariates, health behaviours could also be mediators between social isolation and IC. Previous research finds that social relationships are related to health-compromising and promoting behaviours [229], and it is likely that these behaviours then influence an individual's IC. For example, an isolated individual may not partake in physical activity because they have no family or friends to encourage them to be active, or they might drink excessive amounts of alcohol as a coping mechanism for being alone. These behaviours could then impact IC by resulting in increased body mass and fat deposits (decreasing vitality), decreased muscle mass and function (decreasing locomotion and vitality), and increasing risk of cognitive decline [427], among other effects.

Another element of the conceptual framework (**Section 2.1**) that deserves further research is the interaction of IC with environmental factors. The WHO healthy ageing framework describes these as all environmental factors from the micro- to macro-level (e.g., from home accessibility to national social care policy) and posits that they interact with IC to produce an individual's functional ability. Unsurprisingly given the wide definition and range of these factors, no studies have yet explicitly included these sorts of factors in models of functional ability or started to explore the interaction between them and IC. Future research into how the environment interacts with IC in different ways and from different levels would build a fuller picture of how an individual can build and maintain the functional ability which enables them to live the life they wish into older age, giving the opportunity for IC and functional ability models to have increased policy relevance and impact.

An additional element of the conceptual framework that was not investigated in this project is genetic predisposition. Genetics is identified in the WHO healthy ageing framework as a determinant of IC (**Figure 1.1**) but has not yet been explored in this context. An individual's genotype would predispose them to have a certain capacity in each domain of IC, and this genotype could interact with the environment in a different way than another genotype – a gene-environment interaction. Exploring genetics and interactions in the context of IC may help identify certain risk factors that particular genotypes are more susceptible to, which would be relevant for the genetic epidemiology of healthy ageing.

8.7 Concluding remarks

In conclusion, IC is a recent measure of healthy ageing that has been shown to be a valid measurement of health in older age that can portray risk for future adverse health outcomes. Social isolation was found to be associated with the level of IC in longitudinal analyses, with higher isolation associated with poorer IC and associated with the decline of IC over time, with higher isolation associated with less decline in IC over time. A full longitudinal mediation model revealed bidirectional associations between low-grade inflammation and IC over 4-year intervals but no association between social isolation and IC directly or via inflammation when adjusted for socioeconomic and health-related factors.

These results have implications for the measurement of IC in future studies, as well as the mechanistic role of inflammation between social stressors and health. They highlight how a capacity-focused approach, instead of one deficit and disease-based, can measure healthy ageing in a comprehensive manner without perpetuating negative language and stereotypes about older adults. Healthy ageing in England is deeply entangled within health inequalities, and any health-improving interventions need to take into account both the individual- and systemic-level driving factors of lifestyle and behaviour. The results suggest that focusing a healthy ageing policy on the reduction of social isolation would not halt declines in health but could promote higher health “starting points” for older people. Strategies focusing on anti-inflammatory processes and behaviours may be more effective in improving the IC of a population, although these come with mixed evidence on efficacy and would require a multi-disciplinary and multi-faceted approach.

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Appendices

Appendix to Chapter 1: Background

Appendix 1.1 Literature review search terms

1.1.1 Intrinsic capacity

The literature review of previous models of intrinsic capacity was carried out through publication alerts, keyword search and manual search.

Keywords for the PubMed database search:

("intrinsic capacity") AND ("healthy ageing" OR "healthy aging" OR "successful ageing" OR "successful aging" OR "ageing phenotype" OR "aging phenotype" OR "longevity phenotype" OR "ageing index" OR "aging index")

Keywords for Google Scholar alerts:

“intrinsic capacity” “ageing” – new results

"Evidence for the domains supporting the construct of intrinsic capacity" - new citations

"The structure and predictive value of intrinsic capacity in a longitudinal study of ageing" - new citations

1.1.2 Social relationships and multi-dimensional measures of healthy ageing

Keywords for the PubMed database search:

("healthy ageing" OR "healthy aging" OR "successful ageing" OR "successful aging")

AND (("multidimensional" OR "multi-dimensional" OR "multi dimensional" OR "multidimensionality" OR "multi-dimensionality")

OR ("ageing phenotype" OR "aging phenotype" OR "longevity phenotype") OR ("ageing index" OR "aging index"))

AND ("social relationships" OR "social network*" OR "social support" OR "social isolation" OR "loneliness" OR "social activit*" OR "social participation" OR "social engagement")

Keywords for Google Scholar alerts:

"social relationships" "healthy ageing" – new results

"social relationships" "intrinsic capacity" - new results

Appendix 1.2 Indicators used to assess each domain of intrinsic capacity in papers identified through the literature search.

Table columns are based on the five domains of IC defined in the WHO's development work. All articles are presented in chronological order of publication. Multiple papers using the same model of IC have been included in the same row.

No.	Authors	Data; Place	Cognition	Locomotion	Sensory	Vitality	Psychological	Other	Total IC score
1	Chan, Yau, Yu & Woo (2019) [428]	Mr Os & Ms Os; Hong Kong	-	VO_2 peak	-	VO_2 peak	-	-	-
2	Ramírez-Velez et al. (2019) [79]	SABE; Colombia	Modified MMSE	Presence of sarcopenia; the prevalence of falls; functional impairments (ADLs); difficulty walking 400m; SPPB (standing balance, walking speed, chair rises)	Self-reported vision & hearing	Loss of appetite; weight loss	GDS; the prevalence of mental health problems	-	Pooled odds ratio across all domains
3	Ho, Chen & Merchant (2019) [429]	HOPE; Singapore	-	ADL & IADL impairment; Timed Up-and-Go test	-	Grip strength	Perceived health-related quality of life: EuroQoL-Visual Analogue Scale in EuroQoL-5D-5L	-	-
4	WHO (2019) [41] Guyonnet et al. (2020) [51]	n/a INSPIRE-T cohort; France	Delayed recall; orientation (time & space)	Chair rise test	Self-reported visual impairment; hearing loss (whisper test or audiometry or app-based digits-in-noise test)	Malnutrition (weight loss & appetite loss)	Depressive symptoms (feeling down, depressed, or hopeless; little interest or pleasure in doing things)	-	-
5	Giudici et al. (2019) [62] Giudici et al. (2020) [430]	MAPT; France and Monaco	Free & total recall; Orientation; Digit symbol substitution test; Category naming test	SPPB (standing balance, walking speed, chair rise test)	-	Grip strength	GDS	-	Average of domain z-scores
6	Gutiérrez-Robledo, García-Chanes & Pérez-Zepeda (2019) [78]	CRELES; Costa Rica	Modified MMSE	Chair rise test; Walking speed; Pick-pencil	Self-reported vision & hearing	Peak flow test; Grip strength; BMI	GDS; life satisfaction; locus of control; social participation	-	Sum of each domain score (range 0-10)

No.	Authors	Data; Place	Cognition	Locomotion	Sensory	Vitality	Psychological	Other	Total IC score
7	Beard, Jotheeswaran, Cesari & Araujo de Carvalho (2019) [56]	ELSA; England	Delayed recall; animal naming; letter cancellation	Standing balance; walking speed; chair rise test	Self-reported vision & hearing	Grip strength; DHEAS, IGF-1; Haemoglobin; FEV	CES-D; Sleep	-	Summary score of IC factor from CFA
8	Daskalopoulou et al. (2019) [58] Daskalopoulou et al. (2019) [59]	10/66 Dementia Research Group; Latin America*	Instant recall; delayed recall; long term memory; immediate recall; verbal fluency; time orientation; praxis; story recall; difficulty in finding right word (i); forgets where he/she is (i)	Time (s) taken to walk 10m; difficulty with walking a km	Hearing problems (p&i); eye problems (p&i)	Gets worn out or exhausted during daytime or evening	Sleep trouble or recent change in pattern; feeling of not coping with everyday routine	Change in daily activities (i); difficulties with household responsibilities, washing whole body, getting dressed, carrying out work & everyday activities, making decisions (i), using the toilet (i), handling money (i), completing chores (i)	Summary score of healthy ageing general factor from E/CFA (bifactor model)
9	Charles et al. (2020) [76]	SENIOR cohort; Belgium	MMSE (orientation in time and memory)	SPPB (standing balance, walking speed, chair rise test)	Strawbridge questionnaire items on self-reported vision & hearing	Abdominal circumference; BMI; MNA; Grip strength	EuroQol-5D (anxiety/depression item), CES-D (two fatigue items)	-	-
10	Masciocchi et al. (2020) [89]	INCUR; France	-	-	-	3 items from GDS (mental vitality); Grip strength (physical vitality); & combined vitality	-	-	-
11	Stephens et al. (2020) [55]	Health, Work and Retirement longitudinal surveys; New Zealand	-	-	-	-	-	No. of chronic conditions	-
12	Moreno-Agostino et al. (2020) [67] Critselis et al. (2020) [385] Nguyen et al. (2020) [386] Sanchez-Niubo et al. (2020) [73]	ATHLOS project; 26 †-38 †† countries & ELSA; England	Memory; immediate recall; delayed recall; verbal fluency; orientation in time; processing speed; numeracy	Stooping; kneeling or crouching; lifting or carrying weights; climbing stairs; getting up from sitting down; walking alone without any equipment; pulling or pushing large objects; sitting for long periods; reaching or extending arms; walking speed; dizziness when walking on a level surface;	Near vision; far vision; eyesight (incl. corrections); hearing in general; hearing in conversation	Experiencing some degree of pain; having high level of energy; urine incontinence	Sleep	ADLs; IADLs	Score generated from two-parameter logistic item response theory model

No.	Authors	Data; Place	Cognition	Locomotion	Sensory	Vitality	Psychological	Other	Total IC score
				picking up things with fingers					
13	Huang et al. (2020) [65]	Toyota Prevention Intervention for Cognitive decline & Sarcopenia; Japan	Delayed and immediate recall from Wechsler Memory Scale-Revised; MMSE tests (category & letter fluency, pentagon copying); Digit symbol test from Wechsler Adult Intelligence Scale-III; Trail making test part A & B	One leg stand test; Walking speed (5m); Five Times Sit to Stand Test	-	Grip strength	GDS-15; Generalized Anxiety Disorder-7 Scale	-	Average of domain z-scores
14	González-Bautista et al (2020) [431]	MAPT; France and Monaco	MMSE	SPPB	Monoyer vision chart; Hearing Handicap Inventory for the Elderly Screening	MNA	GDS-15	-	-
15	Ma et al. (2020) [203]	Paper-specific recruited sample; China	Delayed recall; orientation (time & space)	Chair rise test	Self-report visual impairment; hearing loss (whisper test or audiometry or app-based digits-in-noise test)	Malnutrition (weight loss & appetite loss)	Depressive symptoms (feeling down, depressed, or hopeless; little interest or pleasure in doing things)	-	Sum of domain scores (0-6)
16	Ma et al. (2020) [204]	Cardiovascular Health, Cognition and Aging Study; China	MMSE	SPPB	Self-reported vision & hearing impairments	Weight loss & BMI	GDS	-	Sum of each item score (0/1)
17	Gutierrez-Robledo, Gárcia-Chanes, González-Bautista & Rosas-Carrasco (2020) [432]	Frailty Dynapenia & Sarcopenia in Mexican Adults Study; Mexico	MMSE	Walking speed & Chair rise test; or SPPB	Snellen test of visual acuity; Self-reported hearing	Phase angle; Grip strength; MNA	CES-D7; Goldberg Anxiety Scale	-	General & domain specific IC scores estimated with PCA

No.	Authors	Data; Place	Cognition	Locomotion	Sensory	Vitality	Psychological	Other	Total IC score
18	de Breij et al. (2021) [433]	Longitudinal Aging Study Amsterdam; Netherlands	-	-	-	Frailty index score <=0.15 (sum of health deficits divided by number measured, max 32)	-	-	
19	Huang et al. (2021) [434] Huang et al. (2021) [63]	Nagoya Longitudinal Study for Healthy Elderly; Japan	Five cognitive tests: attention, memory, visuospatial, language, reasoning	Walking speed	Self-reported vision & hearing	MNA; Grip strength	GDS-15	-	Average of domain z-scores
20	Yu et al. (2021) [71] Yu et al. (2022) [72] Yeung et al. (2022) [435]	Mr Os & Ms Os; Hong Kong	MMSE	Walking speed; Chair rise test; Dynamic balance	Snellen "Tumbling E" chart; Frisby Stereotest	Grip strength; Adiposity to muscle ratio	GDS-15	-	Summary scores for IC and domains generated from CFA (items standardised)
21	Zeng et al. (2021) [74]	Paper-specific recruited sample of inpatients; China	MMSE	Tinetti Performance-Orientated Mobility Assessment; Walking speed	Self-reported vision & hearing	Grip strength; MNA-SF	GDS-15	-	Total sum of domain impairments (0-5)
22	Sanchez-Rodriguez et al. (2021) [52]	n/a	App: yes/no Monitor: Delayed recall; Orientation (time & space)	App: yes/no Monitor: Chair rise test	App: yes/no Monitor: Self-reported vision impairment; hearing loss (whisper test or audiometry or app-based digits-in-noise test)	App: yes/no Monitor: Malnutrition (weight loss & appetite loss)	App: yes/no Monitor: Depressive symptoms (feeling down, depressed, or hopeless; little interest or pleasure in doing things)	-	App: Sum of yes/no
23	Angioni et al. (2021) [53]	n/a	Delirium & short cognitive assessment	Physical therapist assessment & exercise program	Recommended to nurses that patients wear hearing aids & glasses where needed	Assessment by dietician (malnutrition)	Psychological support & video calls with relatives	-	-
24	González-Bautista et al. (2021) [44]	MAPT; France and Monaco	Orientation (time and space); Word recall	Chair rise test	Self-reported vision & hearing	Self-reported weight loss or appetite loss	Answering yes to GDS-15 item 2 and item 7 (dropped activities/interests & feeling happy)	-	Total sum of IC impairments

No.	Authors	Data; Place	Cognition	Locomotion	Sensory	Vitality	Psychological	Other	Total IC score
25	Lu et al. (2021) [60]	Paper-specific recruited sample; Hong Kong	Cantonese Chinese Montreal Cognitive Assessment (attention, memory, orientation, abstraction & language)	Grip strength (dynamometer) and self-reported steadiness when walking & turning	Self-reported vision & hearing	FRAIL Scale (fatigue, resistance, ambulation, illness, weight loss, 0-5)	Chinese version of 1-item GDS	-	CFA to generate composite IC score for each time point
26	Cheng et al. (2021) [45]	Paper-specific recruited sample; Taiwan	Orientation (time and space); Word recall	Chair rise test	Self-reported vision problems, diseases, or medical treatments; Whisper test	Self-reported weight loss (>3kg over 3 months) or appetite loss	Feeling down, depressed, or hopeless, or having little pleasure in doing things over the last 2 weeks	-	Total sum of IC impairments
27	Beard et al. (2021) [70]	CHARLS; China	Delayed word recall; TICS serial 7 test, orientation in time and reproducing a drawing	Walking speed; Chair stand test; Balance	Self-reported vision & hearing	Grip strength; FEV; Haemoglobin	CES-D; Sleep quantity & quality	-	Summary score of IC factor from CFA
28	Gómez, Oscorio-Garciá, Panesso & Curcio (2021) [54]	SABE; Colombia	-	-	-	-	-	Self-rated health; Physiobiological markers (BMI & grip strength); Medical conditions; Physical activity; Childhood adversity (economic & physical violence); Social capital (participation & networks)	-
29	Guitierrez-Robledo, Gárcia-Chanes & Pérez-Zepeda (2021) [46]	Mexican Health and Aging Study; Mexico	Delayed recall (3 words)	Self-reported difficulty walking and climbing stairs	Self-reported vision & hearing	Weight loss (≥5kg in 2 years); Reduction in food consumption (appetite loss, digestive problems, chewing or swallowing problems)	Feeling depressed; Feeling everything is an effort	-	Sum of domain scores (0-6)
30	Prince et al. (2021) [77]	10/66 Dementia Research Group; Latin America*	Community Screening Instrument for Dementia	Walking speed	Self-reported vision & hearing impairments	Weight loss in last 3 months; Mid-upper arm circumference	EURO-D depression scale	Continence via informant	-
31	Strand et al. (2021) [436]	NORSE; Norway	Montreal Cognitive Assessment; 10 word immediate & delayed recall; Cognitive Function	SPPB (standing balance, walking speed, chair rise test); one-leg standing balance	-	Grip strength	-	-	-

No.	Authors	Data; Place	Cognition	Locomotion	Sensory	Vitality	Psychological	Other	Total IC score
			Screening Instrument						
32	Sánchez-Sánchez, Rolland, Cesari & De Souto Barreto (2021) [437]	INCUR; France	Abbreviated Mental Test (spatial and time orientation, memory, executive function)	SPPB	Self-reported vision & hearing impairments	MNA-SF	GDS-10	-	Average of domain z-scores
33	Stolz et al. (2021) [61]	Yale Precipitating Events Project Study; USA	MMSE	Walking speed; Chair rise test; Balance test	Near vision acuity with Jaeger chart; Hearing impairment with audiometer	Grip strength; Peak expiratory flow value	CES-D	-	Mean score over domains
34	Zhao et al. (2021) [69]	Beijing Longitudinal Study of Aging II; China	MMSE	Tinetti test	Self-reported vision & hearing impairments	MNA	GDS-15	-	-
35	Arokiasamy, Selvamani, Jotheeswaran & Sadana (2021) [438]	SAGE; China, Ghana, India, Mexico, Russia, South Africa	Index score on three domains (verbal fluency; verbal recall; digit span forwards & backwards)	Walking speed	Visual acuity with “Tumbling E" logMAR chart	FVC	Composite International Diagnostic Interview (depression); Perceived stress control & coping	-	-
36	Rivadeneira et al. (2021) [439]	SABE; Ecuador	Assessment of dementia & cognitive impairment	ADLs; Self-reported mobility	-	-	Absence of physical, sexual, and psychological abuse; Absence of depression	Physiological and metabolic health (chronic conditions); Geriatric syndromes (incontinence); Risk factors (cardiovascular risk, alcohol & tobacco use, physical activity)	-
37	Yu et al. (2021) [47]	Paper-specific recruited sample; China	Short Portable Mental Status Questionnaire (10 items)	Chair rise test	Self-reported vision & hearing	Weight loss; Appetite loss	Feeling down; Feeling like can't get going	-	-
38	Locquet et al. (2022) [64]	SarcoPhAge study; Belgium	MMSE	SPPB	-	MNA	GDS-15	-	Average of domain z-scores

No.	Authors	Data; Place	Cognition	Locomotion	Sensory	Vitality	Psychological	Other	Total IC score
39	Pagès et al (2022) [48]	MAPT; France and Monaco	Delayed recall (3 words); orientation (time & space)	Chair rise test	Self-reported vision & hearing	Malnutrition (weight loss & appetite loss)	2 items from GDS-15 (feeling happy; dropping activities or interests)	-	-
40	Jiang et al. (2022) [440]	China Aging Longitudinal Study (CALS); China	Montreal Cognitive Assessment 5-min	Grip strength; Walking speed; Chair rise test	-	-	-	-	-
41	Salinas-Rodríguez, González-Bautista, Rivera-Almaraz & Manrique-Espinoza (2022) [68]	SAGE; Mexico	Composite z-score (immediate & delayed recall, forward & backward digit span, animal naming)	Walking speed	Self-reported vision & hearing	BMI; Grip strength	18 questions from Composite Diagnostic Interview (presence of 10 depression symptoms within 12 months)	-	Item-response theory graded response model
42	Cheong et al. (2022) [57]	SLAS; Singapore	MMSE	Timed Up-&-Go test; Walking speed; Knee extension strength	LogMar in best eye; whisper test	FEV1; Elderly Nutritional Indicators for Geriatric Malnutrition Assessment; Nutritional Screening Initiative; Energy questions from SF-12 Quality of Life scale	GDS-15	-	Sum of domain scores; factor score extracted using PCA
43	Meng et al. (2022) [49]	SEBAS, subsample of TLSA; Taiwan	Short Portable Mental Status Questionnaire; MMSE language and 3-item recall	Walking speed; Chair rise test	Self-reported vision & hearing impairments; Snellen chart	BMI; Grip strength	CES-D-10; Perceived Stress Scale-10	-	Weighted sum of items
44	Chen, Liu & Chang (2022) [75]	National long-term care dataset; Taiwan	Short Portable Mental Status Questionnaire	Physical assistive device use	Vision and hearing status	BMI	CES-D	-	Sum of domain scores (0-6)
45	Leung et al. (2022) [50]	Paper-specific recruited sample; Hong Kong	Montreal Cognitive Assessment	SPPB; MobilePAL; Grip strength	Whisper test; Weber and Rinne test; WHO simple eye chart	MNA	Patient Health Questionnaire-9	-	Sum of domain scores (0-6)
46	López-Ortiz et al. (2022) [441]	n/a	MMSE	SPPB	Self-reported vision & hearing impairments	MNA	Cornell scale of depression in dementia	-	Score 0-10 from domain scores (each 0-2)

No.	Authors	Data; Place	Cognition	Locomotion	Sensory	Vitality	Psychological	Other	Total IC score
47	Lim et al. (2022) [66]	New Strategies for Developing Healthy Aging and Happy Diet; Taiwan	MMSE (Taiwan version)	Back scratch test; Chair-sit-and-reach test; Chair rise test; One-foot-standing test; Timed Up-and-Go test		MNA; Grip strength; Two-minute step-in-place test	GDS-15	-	-

Items answered by an informant are indicated with (i) or both participant and informant with (p&i). When papers did not specify a domain for each indicator, the indicators were manually categorised into the domains and thus may not reflect the indicator clustering that was reported in the study. CFA = confirmatory factor analysis; EFA = exploratory factor analysis; PCA = principal components analysis.

Study acronyms: ATHLOS – Ageing Trajectories of Health: Longitudinal Opportunities and Synergies; CHARLS – China Health and Retirement Longitudinal Study; CRELES – Costa Rican Longevity and Healthy Ageing Study; ELSA – English Longitudinal Study of Ageing; HOPE – Healthy Older People Everyday; INCUR – Incidence of pneumonia and related consequences in nursing home Residents; MAPT – Multidomain Alzheimer Preventive Trial; NORSE – Norwegian Survey of Health and Ageing; SABE – Salud, Bienestar & Envejecimiento (Survey on Health, Well-Being, and Aging in Latin America and the Caribbean); SEBAS – Social Environment and Biomarkers of Aging Study; SENIOR cohort – Sample of Elderly Nursing home Individuals: an Observational Research cohort; TLSA – Taiwan Longitudinal Study of Aging.

Indicator acronyms: ADLs – Activities of Daily Living; IADLs – Instrumental Activities of Daily Living; CES-D – Center for Epidemiologic Studies Depression Scale; DHEAS – Dehydroepiandrosterone Sulphate; FEV(1) – Forced Expiratory Volume (1 second); FVC – Forced Vital Capacity; GDS – Geriatric Depression Scale; IGF-1 – Insulin-like growth factor 1; MMSE – Mini Mental State Exam; MNA(-SF) – Mini Nutritional Assessment (- Short Form); SPPB – Short Physical Performance Battery; SF-12 – 12-item Short Form survey.

*Latin American countries included: Cuba, Dominican Republic, Peru, Venezuela, Mexico, and Puerto Rico.

† Studies (and countries) from the ATHLOS project included in Moreno-Agostino et al. (2020): Australian Longitudinal Study of Ageing (Australia), English Longitudinal Study of Ageing (England), Study on Nutrition and Cardiovascular Risk in Spain (Spain), Health and Retirement Study (USA), Japanese Study of Ageing and Retirement (Japan), Korean Longitudinal Study of Ageing (South Korea), Mexican Health and Aging Study (Mexico), Survey of Health Ageing and Retirement in Europe (Austria, Belgium, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Luxembourg, Netherlands, Poland, Portugal, Slovenia, Sweden, Switzerland).

†† Further studies (and countries) from the ATHLOS project included in Critselis et al. (2020) & Sanchez-Niubo et al. (2020): The 10/66 Dementia Research Group Population-Based Cohort Study (Cuba, Dominican Republic, Venezuela, Mexico, Peru, China, India), The China Health and Retirement Longitudinal Study (China), Collaborative Research on Ageing in Europe (Finland, Poland, Spain), The Health, Alcohol and Psychosocial factors In Eastern Europe study (Russia, Poland, Lithuania, Czech Republic), The Health 2000/2011 study (Finland), The Longitudinal Aging Study in India (India), The Study on Global Ageing and Adult Health (China, Ghana, India, Mexico, Russia, South Africa), The Irish Longitudinal study on Ageing (Ireland)

Appendix to Chapter 4: Operationalising intrinsic capacity

Appendix 4.1 Intrinsic capacity indicators, cut-offs and proportions in each category or missing at baseline (wave 2) in the IC eligible sample (N=5,343) – including underlying variables for composite indicators

Variable	"No difficulty"		"Difficulty"		Missing
Word recall (20 words, immediate & delayed recall)	Top 2 tertiles	3,275 61.3%	Bottom tertile	2,051 38.4%	17 0.3%
Orientation (day of the week, day, month, year)	All questions correct	4,104 76.8%	≥1 incorrect answer	1,227 23.0%	12 0.2%
Day of the week		*5,197* *97.3%*		*134* *2.5%*	*12* *0.2%*
Day of the month	*Correct*	*4,242* *79.4%*	*Incorrect*	*1,089* *20.4%*	*12* *0.2%*
Month		*5,172* *96.8%*		*159* *3.0%*	*12* *0.2%*
Year		*5,191* *97.2%*		*140* *2.6%*	*12* *0.2%*
Balance (side-by-side, semi-tandem and full tandem tests)	Score of 4	3,614 67.6%	Score > 4	1,681 31.5%	48 0.9%
Side-by-side	*1 point*	*5,033* *94.2%*		*262* *4.9%*	*48* *0.9%*
Semi-tandem	*1 point*	*4,720* *88.3%*	*0 points*	*309* *5.8%*	*314* *5.9%*
Full tandem	*1 point*	*968* *18.1%*		*131* *2.5%*	*630* *11.8%*
	2 points	*3,614* *67.6%*			
Chair rise test	5 rises within 16.7s	3,708 69.4%	5 rises in >16.7s	568 10.6%	1,067 20.0%
Walking speed	≥0.8 m/s	2,870 53.7%	<0.8 m/s	2,015 37.7%	458 8.6%
Upper mobility: self-reported difficulties with 4 actions	No difficulties	3,368 63.0%	≥1 difficulties	1,974 37.0%	1 0.0%

Variable	“No difficulty”		“Difficulty”		Missing
Reaching or extending arms above shoulder level		*4,689 87.8%*		*653 12.2%*	*1 0.0%*
Pulling or pushing large objects		*4,216 78.9%*		*1,126 21.1%*	*1 0.0%*
Lifting or carrying weights over 10 pounds (~4.5kg)		*3,792 71.0%*		*1,550 29.0%*	*1 0.0%*
Picking up a 5p coin from a table		*5,002 93.6%*		*340 6.4%*	*1 0.0%*
Lower mobility: self-reported difficulties with 6 actions	No difficulties	2,025 37.9%	≥1 difficulties	3,317 62.1%	1 0.0%
Walking 100 yards		*4,596 86.0%*		*746 14.0%*	*1 0.0%*
Sitting for 2 hours		*4,556 85.3%*		*786 14.7%*	*1 0.0%*
Getting up from chair after sitting for long periods		*3,757 70.3%*		*1,585 29.7%*	*1 0.0%*
Climbing several flights of stairs without resting		*2,997 56.1%*		*2,345 43.9%*	*1 0.0%*
Climbing one flight of stairs without resting		*4,392 82.2%*		*950 17.8%*	*1 0.0%*
Stooping, kneeling, or crouching		*3,039 56.9%*		*2,303 43.1%*	*1 0.0%*
Self-reported eyesight	Rated good-excellent	4,519 84.6%	Rated fair-poor	824 15.4%	0 0%
Self-reported hearing	Rated good-excellent	4,015 75.2%	Rated fair-poor	1,328 24.9%	0 0%
Grip strength	≥30kg (men) or ≥20kg (women)	4,003 74.9%	<30kg (men) or <20kg (women)	1,247 23.3%	93 1.7%
Body Mass Index	≥18.5 and <30	3,536 66.2%	<18.5 or ≥30	1,447 27.1%	360 6.7%
Waist circumference	<94cm (men) or <80cm (women)	1,083 20.3%	≥94cm (men) or ≥80cm (women)	4,053 75.9%	207 3.9%
Center for Epidemiology Studies – Depression scale *Much of the time over the past week,*	Score < 4	4,476 83.8%	Score ≥ 4	802 15.0%	65 1.2%
...have you felt depressed?	*No*	*4,454 83.4%*	*Yes*	*864 16.2%*	*25 0.5%*
...have you felt that everything you did was an effort?	*No*	*4,105 76.8%*	*Yes*	*1,212 22.7%*	*26 0.5%*
...has your sleep been restless?	*No*	*3,108 58.2%*	*Yes*	*2,205 41.3%*	*30 0.6%*
...have you felt happy?	*Yes*	*4,816 90.1%*	*No*	*485 9.1%*	*42 0.8%*
...have you felt lonely?	*No*	*4,511 84.4%*	*Yes*	*804 15.1%*	*28 0.5%*
...have you enjoyed life?	*Yes*	*4,837 90.5%*	*No*	*473 8.9%*	*33 0.6%*

Variable	"No difficulty"		"Difficulty"		Missing
...have you felt sad?	*No*	*4,202* *78.6%*	*Yes*	*1,111* *20.8%*	*30* *0.6%*
...could you not get going?	*No*	*4,168* *78.0%*	*Yes*	*1,141* *21.4%*	*34* *0.6%*
Satisfaction With Life Scale	Score ≥ 20	4,109 76.9%	Score < 20	705 13.2%	529 9.9%

Appendix 4.2 Linear regression between intrinsic capacity scores and sociodemographic and health-related covariates at baseline.

Regression coefficients (not standardised) are presented with 95% confidence intervals.

(N=4,662)

Predictors		Individual predictors Coefficients [95% CI]	Mutually-adjusted Coefficients [95% CI]
Age (years)		-0.51** [-0.55, -0.48]	-0.32** [-0.35, -0.29]
Sex Ref = Male	Female	-3.71** [-4.27, -3.16]	-2.89** [-3.28, -2.43]
Marital status Ref = Married	Never married	-2.98** [-4.31, -1.66]	-0.84 [-1.78, 0.09]
	Separated/divorced	-2.02** [-3.05, -0.99]	-0.46 [-1.20, 0.28]
	Widowed	-6.25** [-6.91, -5.59]	-0.88* [-1.41, -0.36]
Education Ref = Degree	A-Level	-1.81* [-2.87, -0.76]	0.09 [-0.67, 0.84]
	O-Level/Other	-4.09** [-5.05, -3.13]	-0.33 [-1.04, 0.38]
	None	-7.86** [-8.79, -6.93]	-1.04* [-1.77, -0.32]
Wealth quintile Ref = Highest	1 (Lowest)	-10.88** [-11.73, -10.03]	-3.13** [-3.85, -2.42]
	2	-7.62** [-8.43, -6.80]	-2.25** [-2.90, -1.60]
	3	-4.56** [-5.36, -3.77]	-1.29** [-1.91, -0.68]
	4	-3.29** [-4.08, -2.50]	-0.88* [-1.47, -0.29]
Occupation Ref = Employed	Retired/Semi-retired	-7.44** [-8.26, -6.63]	-0.87* [-1.49, -0.25]
	Permanently unable to work	-17.78** [-19.50, -16.05]	-5.65** [-6.94, -4.35]
	Looking after home/family or unemployed	-7.54** [-8.65, -6.43]	-1.01* [-1.85, -0.17]
Smoking status Ref = Never smoked	Ex-smoker	-1.34** [-1.94, -0.73]	-0.82** [-1.24, -0.40]
	Current smoker	-2.57** [-3.51, -1.63]	-0.48 [-1.13, 0.18]
Alcohol consumption Ref = <5 days a week	≥5 days week	3.24** [2.58, 3.89]	0.65* [0.18, 1.12]
Physical activity Ref = Moderate	Sedentary	-14.35** [-15.38, -13.31]	-5.19** [-6.08, -4.29]
	Low	-7.22** [-7.80, -6.64]	-2.75** [-3.23, -2.27]
	High	4.06** [3.38, 4.74]	1.43** [0.89, 1.97]
No. of health conditions		-2.32** [-2.54, -2.10]	-0.37** [-0.54, -0.21]
Self-rated health Ref = Excellent	Very good	-3.39** [-4.20, -2.58]	-1.67** [-2.33, -1.00]
	Good	-7.88** [-8.67, -7.09]	-5.07** [-5.74, -4.41]
	Fair	-14.17** [-15.02, -13.33]	-9.41** [-10.16, -8.66]
	Poor	-19.79** [-20.89, -18.70]	-12.45** [-13.47, -11.44]

*p<0.05 **p<0.001

Appendix 4.3 Association between intrinsic capacity scores at baseline and subsequent difficulties with ≥1 ADLs and IADLs after 4 years (N=3,055) and 8 years (N=2,348).

Fully adjusted models are presented.

Predictors		ADLs (4 years) OR [95% CI]	ADLs (8 years) OR [95% CI]	IADLs (4 years) OR [95% CI]	1 IADLs (8 years) OR [95% CI]
Intrinsic Capacity score		0.93** [0.91, 0.94]	0.93** [0.91, 0.95]	0.90** [0.89, 0.92]	0.92** [0.91, 0.94]
Age (years)		1.04** [1.02, 1.06]	1.04** [1.02, 1.07]	1.05** [1.03, 1.07]	1.06** [1.04, 1.08]
Sex Ref = Male	Female	0.82 [0.64, 1.04]	0.94 [0.72, 1.22]	1.53** [1.21, 1.94]	1.13 [0.87, 1.46]
Baseline (I)ADLs difficulties Ref = None	Difficulties with ≥1	4.40** [3.46, 5.58]	3.61** [2.75, 4.75]	1.83** [1.43, 2.33]	1.94** [1.47, 2.56]
Marital status	Never married	1.82* [1.13, 2.94]	1.24 [0.71, 2.16]	0.96 [0.59, 1.59]	0.79 [0.44, 1.43]
Ref = Married	Separated/divorced	1.26 [0.86, 1.84]	1.33 [0.89, 1.99]	0.73 [0.49, 1.09]	1.12 [0.75, 1.66]
	Widowed	0.90 [0.68, 1.20]	1.04 [0.76, 1.44]	1.12 [0.86, 1.45]	1.16 [0.85, 1.57]
Education	A-Level	1.10 [0.73, 1.67]	1.11 [0.71, 1.74]	1.03 [0.68, 1.56]	1.22 [0.79, 1.90]
Ref = Degree	O-Level/Other	0.93 [0.62, 1.37]	1.06 [0.69, 1.62]	0.80 [0.54, 1.18]	0.84 [0.55, 1.29]
	None	1.03 [0.70, 1.53]	1.25 [0.81, 1.93]	0.90 [0.61, 1.33]	1.09 [0.71, 1.67]
Wealth quintile	1 (Lowest)	1.01 [0.69, 1.49]	0.79 [0.51, 1.23]	0.87 [0.59, 1.29]	1.06 [0.69, 1.63]
Ref = Highest	2	0.88 [0.62, 1.25]	0.99 [0.67, 1.46]	1.03 [0.73, 1.46]	1.49* [1.02, 2.18]
	3	0.83 [0.59, 1.17]	0.89 [0.62, 1.29]	1.24 [0.89, 1.73]	1.18 [0.82, 1.71]
	4	0.86 [0.62, 1.20]	1.01 [0.71, 1.44]	1.20 [0.87, 1.65]	1.30 [0.92, 1.84]
Occupation	Retired/Semi-retired	0.70 [0.48, 1.01]	0.91 [0.62, 1.35]	0.95 [0.64, 1.40]	0.81 [0.56, 1.19]
Ref = Employed	Permanently unable to work	1.01 [0.52, 1.96]	1.07 [0.51, 2.22]	1.18 [0.61, 2.26]	1.30 [0.63, 2.70]
	Looking after home/family or unemployed	0.78 [0.48, 1.26]	0.74 [0.44, 1.24]	0.79 [0.49, 1.29]	0.89 [0.54, 1.46]
Smoking status	Ex-smoker	1.02 [0.81, 1.28]	1.08 [0.84, 1.39]	0.89 [0.71, 1.11]	0.92 [0.72, 1.17]
Ref = Never smoked	Current smoker	1.11 [0.78, 1.58]	1.04 [0.70, 1.57]	1.32 [0.94, 1.86]	1.21 [0.82, 1.77]
Alcohol consumption Ref = <5 days a week	≥5 days week	0.91 [0.70, 1.19]	1.30 [0.97, 1.74]	1.11 [0.86, 1.43]	1.22 [0.91, 1.62]
Physical activity	Sedentary	1.91* [1.11, 3.28]	2.09* [1.02, 4.25]	1.00 [0.59, 1.69]	1.54 [0.77, 3.11]
Ref = Moderate	Low	1.03 [0.80, 1.32]	1.11 [0.84, 1.46]	0.95 [0.75, 1.20]	1.09 [0.83, 1.41]
	High	0.95 [0.69, 1.32]	1.01 [0.73, 1.41]	0.96 [0.70, 1.33]	0.76 [0.55, 1.06]

Predictors		ADLs (4 years) OR [95% CI]	ADLs (8 years) OR [95% CI]	IADLs (4 years) OR [95% CI]	1 IADLs (8 years) OR [95% CI]
No. of health conditions		1.06 [0.97, 1.16]	1.00 [0.90, 1.10]	1.06 [0.97, 1.15]	1.11* [1.01, 1.22]
Self-rated health	Very good	1.56 [0.95, 2.54]	2.15* [1.25, 3.70]	1.04 [0.66, 1.63]	1.55 [0.96, 2.52]
Ref = Excellent	Good	1.97* [1.22, 3.18]	2.88** [1.69, 4.90]	1.63* [1.05, 2.52]	1.86* [1.16, 2.98]
	Fair	2.75** [1.65, 4.60]	3.40** [1.91, 6.05]	2.47** [1.54, 3.96]	2.70** [1.62, 4.52]
	Poor	3.73** [1.96, 7.09]	4.06** [1.96, 8.43]	4.19** [2.28, 7.69]	3.75** [1.89, 7.44]

*p<0.05 **p<0.001

ADLs = Activities of Daily Living; IADLs = Instrumental Activities of Daily Living; OR = Odds Ratio; 95% CI = 95% Confidence interval

Appendix 4.4 Association between intrinsic capacity scores at baseline (as continuous scores and quartiles) and subsequent hospital admission (N=4,489) and mortality (N=4,545) during the 14-year follow-up.

Fully-adjusted models are presented.

Predictors		Hospital admission SHR [95% CI]	Mortality HR [95% CI]
Intrinsic capacity score (continuous)		**0.99** [0.98, 0.99]**	**0.98** [0.98, 0.99]**
Intrinsic capacity score (quartiles) Ref = Highest	1 (Lowest)	**1.33** [1.16, 1.51]**	**1.43** [1.18, 1.74]**
	2	**1.29** [1.16, 1.43]**	**1.30* [1.09, 1.54]**
	3	1.09 [0.99, 1.19]	1.12 [0.95, 1.32]
Age (years)		**1.02** [1.01, 1.02]**	**1.10** [1.09, 1.11]**
Sex Ref = Male	Female	0.93 [0.86, 1.00]	**0.56** [0.50, 0.62]**
Marital status Ref = Married	Never married	0.98 [0.83, 1.15]	1.25 [1.01, 1.56]
	Separated/divorced	1.08 [0.95, 1.22]	1.08 [0.89, 1.32]
	Widowed	0.92 [0.84, 1.01]	**1.17* [1.04, 1.31]**
Education Ref = Degree	A-Level	1.09 [0.95, 1.24]	1.00 [0.81, 1.23]
	O-Level/Other	0.99 [0.87, 1.12]	1.00 [0.83, 1.22]
	None	0.98 [0.86, 1.12]	1.03 [0.85, 1.26]
Wealth quintile Ref = Highest	1 (Lowest)	1.14 [1.00, 1.29]	1.05 [0.88, 1.26]
	2	**1.21* [1.08, 1.35]**	0.99 [0.83, 1.17]
	3	1.04 [0.93, 1.15]	1.08 [0.91, 1.27]
	4	1.08 [0.98, 1.19]	1.07 [0.91, 1.25]
Occupation Ref = Employed	Retired/Semi-retired	1.04 [0.94, 1.16]	1.23 [0.98, 1.55]
	Permanently unable to work	1.08 [0.83, 1.40]	**1.45* [1.04, 2.00]**
	Looking after home/family or unemployed	0.99 [0.86, 1.15]	1.09 [0.82, 1.43]
Smoking status Ref = Never smoked	Ex-smoker	1.01 [0.93, 1.08]	**1.17* [1.05, 1.30]**
	Current smoker	1.02 [0.92, 1.14]	**1.93** [1.66, 2.26]**
Alcohol consumption Ref = <5 days a week	≥5 days week	1.05 [0.97, 1.14]	0.96 [0.86, 1.09]
Physical activity Ref = Moderate	Sedentary	1.00 [0.84, 1.19]	**1.42** [1.19, 1.68]**
	Low	1.04 [0.96, 1.13]	**1.14* [1.02, 1.28]**
	High	0.99 [0.90, 1.08]	0.91 [0.78, 1.07]
No. of health conditions		**1.09** [1.06, 1.13]**	**1.06* [1.02, 1.10]**
Self-rated health Ref = Excellent	Very good	**1.17* [1.05, 1.31]**	**1.28* [1.03, 1.59]**
	Good	**1.22* [1.09, 1.37]**	**1.49** [1.20, 1.84]**
	Fair	**1.43** [1.25, 1.65]**	**1.81** [1.44, 2.28]**
	Poor	**1.36* [1.09, 1.68]**	**2.38** [1.82, 3.11]**

*p<0.05 **p<0.001

SHR = Subdistribution Hazard Ratio; HR = Hazard Ratio; 95% CI = 95% Confidence interval

Appendix 4.5 Association between intrinsic capacity and subsequent hospital admission using the Cox proportional hazards model (N=4,489).

Fully-adjusted results are presented.

Predictors		**Hospital admission HR [95% CI]**
Intrinsic capacity score		**0.99** [0.98, 0.99]**
Age (years)		**1.02** [1.01, 1.02]**
Sex Ref = Male	Female	**0.93* [0.86, 1.00]**
Marital status	Never married	0.98 [0.83, 1.15]
	Separated/divorced	1.07 [0.95, 1.22]
Ref = Married	Widowed	0.92 [0.84, 1.01]
Education	A-Level	1.09 [0.96, 1.24]
Ref = Degree	O-Level/Other	0.99 [0.87, 1.12]
	None	0.98 [0.87, 1.11]
Wealth quintile	1 (Lowest)	**1.14* [1.00, 1.29]**
Ref = Highest	2	**1.21* [1.08, 1.35]**
	3	1.04 [0.93, 1.15]
	4	1.08 [0.97, 1.20]
Occupation	Retired/Semi-retired	1.05 [0.94, 1.17]
Ref = Employed	Permanently unable to work	1.08 [0.87, 1.35]
	Looking after home/family or unemployed	0.99 [0.86, 1.15]
Smoking status	Ex-smoker	1.01 [0.94, 1.08]
Ref = Never smoked	Current smoker	1.02 [0.91, 1.14]
Alcohol consumption Ref = <5 days a week	≥5 days week	1.05 [0.97, 1.13]
Physical activity	Sedentary	1.00 [0.86, 1.16]
Ref = Moderate	Low	1.04 [0.96, 1.13]
	High	0.99 [0.90, 1.08]
No. of health conditions		**1.09** [1.06, 1.12]**
Self-rated health	Very good	**1.17* [1.04, 1.32]**
Ref = Excellent	Good	**1.22* [1.08, 1.38]**
	Fair	**1.43** [1.25, 1.64]**
	Poor	**1.36* [1.12, 1.63]**

*p<0.05 **p<0.001

HR = Hazard Ratio; 95% CI = 95% Confidence interval

Appendix to Chapter 6: Social isolation and intrinsic capacity

Appendix 6.1 Estimation results for the covariates in the cross-sectional linear regressions in waves 2, 4, and 6.

6.1.1 Wave 2

Wave 2	N = 3,864	Coefficient [95% CIs]				
		(1) Age & Sex	(2) Socioeconomic	(3) Health behaviours	(4) Health	(5) All
Social isolation score		-1.66 [-1.88, -1.44]	-1.06 [-1.28, -0.83]	-1.05 [-1.26, -0.84]	-0.86 [-1.05, -0.67]	-0.45 [-0.63, -0.26]
Age (years)		-0.43 [-0.47, -0.39]	-0.39 [-0.43, -0.36]	-0.33 [-0.36, -0.30]	-0.39 [-0.42, -0.36]	-0.32 [-0.35, -0.29]
Sex (Ref = Male)		-3.31 [-3.84, -2.77]	-2.82 [-3.34, -2.31]	-2.69 [-3.19, -2.19]	-3.59 [-4.03, -3.15]	-3.01 [-3.45, -2.57]
Education (Ref = Degree)	A-Level		0.27 [-0.70, 1.24]			0.17 [-0.63, 0.96]
	O-Level/Other		-0.66 [-1.57, 0.25]			-0.19 [-0.94, 0.55]
	None		-1.61 [-2.55, -0.68]			-0.71 [-1.48, 0.06]
Wealth quintile (Ref = Highest)	1 - Lowest		-6.79 [-7.71, -5.87]			-3.28 [-4.06, -2.49]
	2		-4.76 [-5.60, -3.91]			-2.13 [-2.84, -1.42]
	3		-2.68 [-3.48, -1.88]			-1.20 [-1.86, -0.53]
	4		-1.74 [-2.51, -0.97]			-0.64 [-1.27, 0.00]
Current smoking status (Ref = Never smoked)	Ex-smoker			-1.40 [-1.93, -0.87]		-0.79 [-1.25, -0.33]
	Current smoker			-2.37 [-3.20, -1.55]		-0.41 [-1.14, 0.32]
Alcohol consumption (Ref = <5 times per week)				2.15 [1.58, 2.71]		0.79 [0.28, 1.30]
Physical activity (Ref = Moderate)	Sedentary			-11.02 [-12.14, -9.89]		-6.18 [-7.21, -5.15]
	Low			-5.07 [-5.67, -4.47]		-2.78 [-3.31, -2.24]
	High			2.84 [2.17, 3.50]		1.49 [0.90, 2.07]
No. of health conditions					-0.51 [-0.70, -0.32]	-0.37 [-0.55, -0.18]
Self-rated health (Ref = Excellent)	Very good				-2.20 [-2.95, -1.45]	-1.81 [-2.53, -1.10]
	Good				-6.09 [-6.83, -5.35]	-5.10 [-5.82, -4.39]
	Fair				-11.43 [-12.27, -10.59]	-9.44 [-10.27, -8.62]

	Poor				**-16.45 [-17.59, -15.32]**	**-12.66 [-13.80, -11.53]**

Bold indicates p<0.05

6.1.2 Wave 4

Wave 4	**N = 3,585**	**Coefficient [95% CIs]**				
		(1) Age & Sex	**(2) Socioeconomic**	**(3) Health behaviours**	**(4) Health**	**(5) All**
Social isolation score		**-1.81 [-2.03, -1.58]**	**-1.18 [-1.40, -0.96]**	**-1.15 [-1.35, -0.94]**	**-0.93 [-1.12, -0.75]**	**-0.49 [-0.68, -0.31]**
Age (years)		**-0.43 [-0.46, -0.39]**	**-0.40 [-0.44, -0.37]**	**-0.33 [-0.37, -0.30]**	**-0.37 [-0.40, -0.35]**	**-0.32 [-0.35, -0.29]**
Sex (Ref = Male)		**-3.54 [-4.08, -3.00]**	**-3.08 [-3.60, -2.56]**	**-2.75 [-3.26, -2.25]**	**-3.33 [-3.77, -2.89]**	**-2.76 [-3.20, -2.32]**
Education (Ref = Degree)	A-Level		-0.54 [-1.41, 0.32]			-0.03 [-0.74, 0.67]
	O-Level/Other		-0.78 [-1.60, 0.04]			-0.13 [-0.81, 0.54]
	None		**-1.98 [-2.86, -1.10]**			-0.50 [-1.22, 0.23]
Wealth quintile (Ref = Highest)	1 - Lowest		**-6.75 [-7.67, -5.83]**			**-3.52 [-4.30, -2.75]**
	2		**-4.70 [-5.54, -3.86]**			**-2.47 [-3.17, -1.77]**
	3		**-2.60 [-3.40, -1.81]**			**-1.53 [-2.18, -0.87]**
	4		**-1.65 [-2.41, -0.89]**			**-0.92 [-1.53, -0.30]**
Current smoking status (Ref = Never smoked)	Ex-smoker			**-1.20 [-1.73, -0.67]**		**-0.46 [-0.92, 0.00]**
	Current smoker			**-2.24 [-3.12, -1.35]**		-0.24 [-1.02, 0.53]
Alcohol consumption (Ref = <5 times per week)				**1.97 [1.40, 2.55]**		**0.64 [0.13, 1.15]**
Physical activity (Ref = Moderate)	Sedentary			**-8.57 [-9.68, -7.47]**		**-4.66 [-5.64, -3.68]**
	Low			**-5.41 [-6.04, -4.79]**		**-3.18 [-3.73, -2.64]**
	High			**3.29 [2.64, 3.94]**		**1.74 [1.18, 2.31]**
No. of health conditions					**-0.65 [-0.92, -0.37]**	**-0.56 [-0.82, -0.29]**
Self-rated health (Ref = Excellent)	Very good				**-1.92 [-2.71, -1.13]**	**-1.28 [-2.04, -0.53]**
	Good				**-5.45 [-6.24, -4.66]**	**-4.23 [-4.99, -3.48]**
	Fair				**-11.74 [-12.60, -10.87]**	**-9.29 [-10.14, -8.43]**
	Poor				**-16.79 [-17.99, -15.59]**	**-13.16 [-14.35, -11.97]**

Bold indicates p<0.05

6.1.3 Wave 6

Wave 6	N = 3,433	Coefficient [95% CIs]				
		(1) Age & Sex	(2) Socioeconomic	(3) Health behaviours	(4) Health	(5) All
Social isolation score		**-1.67 [-1.90, -1.44]**	**-1.02 [-1.25, -0.79]**	**-1.05 [-1.27, -0.84]**	**-0.83 [-1.03, -0.64]**	**-0.43 [-0.62, -0.24]**
Age (years)		**-0.48 [-0.52, -0.44]**	**-0.44 [-0.48, -0.40]**	**-0.36 [-0.40, -0.32]**	**-0.40 [-0.43, -0.36]**	**-0.32 [-0.36, -0.29]**
Sex (Ref = Male)		**-3.04 [-3.62, -2.47]**	**-2.50 [-3.06, -1.94]**	**-2.24 [-2.77, -1.71]**	**-3.22 [-3.69, -2.75]**	**-2.53 [-3.00, -2.07]**
Education (Ref = Degree)	A-Level		-0.74 [-1.61, 0.12]			0.04 [-0.67, 0.74]
	O-Level/Other		-0.69 [-1.54, 0.15]			-0.19 [-0.88, 0.50]
	None		**-2.22 [-3.15, -1.29]**			**-0.87 [-1.63, -0.11]**
Wealth quintile (Ref = Highest)	1 - Lowest		**-7.45 [-8.46, -6.44]**			**-3.82 [-4.67, -2.97]**
	2		**-4.94 [-5.86, -4.02]**			**-1.97 [-2.73, -1.20]**
	3		**-2.91 [-3.74, -2.08]**			**-1.53 [-2.21, -0.85]**
	4		**-2.07 [-2.86, -1.27]**			**-1.22 [-1.87, -0.57]**
Current smoking status (Ref = Never smoked)	Ex-smoker			**-1.58 [-2.13, -1.02]**		**-0.84 [-1.32, -0.35]**
	Current smoker			-0.95 [-1.95, 0.05]		0.80 [-0.08, 1.67]
Alcohol consumption (Ref = <5 times per week)				**1.86 [1.24, 2.48]**		0.54 [-0.01, 1.09]
Physical activity (Ref = Moderate)	Sedentary			**-11.31 [-12.58, -10.03]**		**-6.20 [-7.36, -5.05]**
	Low			**-6.13 [-6.76, -5.49]**		**-3.32 [-3.90, -2.74]**
	High			**2.86 [2.18, 3.54]**		**1.64 [1.05, 2.24]**
No. of health conditions					**-0.58 [-0.90, -0.27]**	**-0.33 [-0.63, -0.03]**
Self-rated health (Ref = Excellent)	Very good				**-2.58 [-3.45, -1.70]**	**-1.99 [-2.82, -1.16]**
	Good				**-6.30 [-7.17, -5.43]**	**-5.12 [-5.96, -4.29]**
	Fair				**-12.07 [-13.02, -11.13]**	**-9.59 [-10.52, -8.66]**
	Poor				**-18.49 [-19.75, -17.23]**	**-14.37 [-15.63, -13.12]**

Bold indicates p<0.05

Appendix 6.2 Estimation results for the covariates in the stepwise latent growth-curve models.

N = 7,690	(1) Age & Sex		(2) Socioeconomic		(3) Health behaviours		(4) Health		(5) Fully-adjusted	
	Est (SE)	p-value	Est (SE)	p-value	Est (SE)	p-value	Est (SE)	p-value	Est (SE)	p-value
Time -invariant covariates										
Age (intercept)	-0.46 (0.01)	<0.001	-0.42 (0.01)	<0.001	-0.38 (0.01)	<0.001	-0.41 (0.01)	<0.001	-0.34 (0.01)	<0.001
Age (slope)	-0.03 (0.00)	<0.001	-0.03 (0.00)	<0.001	-0.03 (0.00)	<0.001	-0.02 (0.00)	<0.001	-0.02 (0.00)	<0.001
Sex (intercept)	-3.29 (0.21)	<0.001	-2.77 (0.21)	<0.001	-2.68 (0.20)	<0.001	-3.36 (0.18)	<0.001	-2.73 (0.17)	<0.001
Sex (slope)	-0.02 (0.03)	0.948	-0.01 (0.03)	0.847	0.01 (0.03)	0.696	-0.00 (0.03)	0.920	0.02 (0.03)	0.560
Education (intercept)										
A-Level			-0.51 (0.39)	0.194					-0.13 (0.33)	0.697
O-Level/Other			-1.33 (0.37)	<0.001					-0.46 (0.31)	0.142
None			-2.74 (0.37)	<0.001					-1.18 (0.32)	0.000
Education (slope)										
A-Level			-0.07 (0.05)	0.187					-0.02 (0.05)	0.757
O-Level/Other			-0.02 (0.05)	0.741					-0.02 (0.05)	0.669
None			-0.05 (0.05)	0.317					-0.03 (0.05)	0.546
Time-varying covariates										
IC at wave 2 on										
Wealth quintile (Ref = Highest)										
1 - Lowest			-5.55 (0.35)	<0.001					-3.37 (0.32)	<0.001
2			-3.82 (0.32)	<0.001					-2.38 (0.29)	<0.001
3			-1.93 (0.30)	<0.001					-1.21 (0.28)	<0.001
4			-1.05 (0.29)	<0.001					-0.80 (0.27)	0.003
Current smoking status (Ref = Non-/Ex-smoker)					-1.09 (0.30)	<0.001			0.06 (0.27)	0.835
Alcohol consumption (Ref = <5 times per week)					-1.70 (0.23)	<0.001			-0.60 (0.22)	0.006
Physical activity (Ref = Moderate)										
Sedentary					-8.36 (0.40)	<0.001			-5.44 (0.37)	<0.001
Low					-3.53 (0.22)	<0.001			-2.36 (0.21)	<0.001
High					1.81 (0.25)	<0.001			1.30 (0.24)	<0.001
No. of health conditions							-0.42 (0.07)	<0.001	-0.35 (0.07)	<0.001
Self-rated health (Ref = Excellent)										
Very good							-1.53 (0.30)	<0.001	-1.34 (0.29)	<0.001
Good							-4.61 (0.30)	<0.001	-4.10 (0.29)	<0.001

N = 7,690	(1) Age & Sex		(2) Socioeconomic		(3) Health behaviours		(4) Health		(5) Fully-adjusted	
	Est (SE)	p-value	Est (SE)	p-value	Est (SE)	p-value	Est (SE)	p-value	Est (SE)	p-value
Fair							-9.09 (0.34)	<0.001	-7.84 (0.33)	<0.001
Poor							-13.73 (0.45)	<0.001	-11.21 (0.44)	<0.001
IC at wave 4 on										
Isolation	-0.42 (0.07)	<0.001	-0.43 (0.08)	<0.001	-0.43 (0.08)	<0.001	-0.45 (0.08)	<0.001	-0.32 (0.08)	<0.001
Wealth quintile (Ref = Highest)										
1 - Lowest			-5.23 (0.33)	<0.001					-3.18 (0.31)	<0.001
2			-3.35 (0.30)	<0.001					-2.18 (0.28)	<0.001
3			-1.77 (0.27)	<0.001					-1.26 (0.27)	<0.001
4			-1.00 (0.25)	<0.001					-0.78 (0.25)	0.002
Current smoking status (Ref = Non-/Ex-smoker)					-0.95 (0.31)	0.002			0.14 (0.28)	0.615
Alcohol consumption (Ref = <5 times per week)					-1.61 (0.21)	<0.001			-0.79 (0.21)	<0.001
Physical activity (Ref = Moderate)										
Sedentary					-4.93 (0.35)	<0.001			-3.54 (0.34)	<0.001
Low					-2.94 (0.22)	<0.001			-2.25 (0.21)	<0.001
High					2.01 (0.23)	<0.001			1.35 (0.22)	<0.001
No. of health conditions							-0.48 (0.10)	<0.001	-0.44 (0.10)	<0.001
Self-rated health (Ref = Excellent)										
Very good							-1.55 (0.25)	<0.001	-1.16 (0.26)	<0.001
Good							-4.50 (0.27)	<0.001	-3.83 (0.27)	<0.001
Fair							-8.80 (0.31)	<0.001	-7.56 (0.32)	<0.001
Poor							-13.15 (0.43)	<0.001	-11.32 (0.43)	<0.001
IC at wave 6 on										
Isolation	-0.87 (0.12)	<0.001	-0.72 (0.12)	<0.001	-0.75 (0.12)	<0.001	-0.55 (0.12)	<0.001	-0.41 (0.11)	<0.001
Wealth quintile (Ref = Highest)										
1 - Lowest			-5.57 (0.38)	<0.001					-3.41 (0.35)	<0.001
2			-3.77 (0.34)	<0.001					-2.04 (0.31)	<0.001
3			-2.51 (0.31)	<0.001					-1.60 (0.29)	<0.001
4			-1.53 (0.29)	<0.001					-1.04 (0.27)	<0.001
Current smoking status (Ref = Non-/Ex-smoker)					-0.32 (0.35)	0.363			0.93 (0.32)	0.004
Alcohol consumption (Ref = <5 times per week)					-1.22 (0.25)	<0.001			-0.35 (0.23)	0.134
Physical activity (Ref = Moderate)										
Sedentary					-6.42 (0.42)	<0.001			-4.65 (0.41)	<0.001

N = 7,690	(1) Age & Sex		(2) Socioeconomic		(3) Health behaviours		(4) Health		(5) Fully-adjusted	
	Est (SE)	p-value	Est (SE)	p-value	Est (SE)	p-value	Est (SE)	p-value	Est (SE)	p-value
Low					-3.67 (0.23)	<0.001			-2.46 (0.23)	<0.001
High					2.23 (0.26)	<0.001			1.61 (0.24)	<0.001
No. of health conditions							-0.70 (0.12)	<0.001	-0.52 (0.12)	<0.001
Self-rated health (Ref = Excellent)										
Very good							-2.01 (0.33)	<0.001	-1.73 (0.32)	<0.001
Good							-5.22 (0.33)	<0.001	-4.56 (0.33)	<0.001
Fair							-9.61 (0.37)	<0.001	-8.26 (0.37)	<0.001
Poor							-14.44 (0.48)	<0.001	-12.20 (0.48)	<0.001
Model fit statistics										
Chi-square test of model fit (df)	99.21 (8), p<0.001		184.40 (35), p<0.001		1265.78 (38), p<0.001		1263.21 (38), p<0.001		1274.52 (95), p<0.001	
CFI	0.991		0.986		0.900		0.914		0.924	
TLI	0.979		0.974		0.834		0.857		0.877	
RMSEA	0.039		0.024		0.065		0.065		0.040	
SRMR	0.024		0.009		0.037		0.036		0.015	

Est = estimate; SE = standard error; (df) = degrees of freedom; CFI = comparative fit index; TLI = Tucker-Lewis index; RMSEA = root mean square error of approximation; SRMR = standardised root mean square residual

Appendix to Chapter 7: Inflammation as a mediator

Appendix 7.1 Full results for the cross-sectional associations between social isolation, inflammation, and IC

7.1.1 Wave 2

Wave 2	N = 2,733	Coefficient [95% CIs]	
		Age & Sex adjusted	Fully-adjusted
Isolation predicting CRP			
Social isolation score		**0.17 [0.10, 0.24]**	0.05 [-0.02, 0.12]
Age (years)		0.01 [0.00, 0.02]	0.00 [-0.01, 0.01]
Sex (Ref = Male)		**0.20 [0.04, 0.37]**	0.13 [-0.04, 0.29]
Education (Ref = Degree)	A-Level		0.26 [-0.03, 0.56]
	O-Level/Other		0.25 [-0.03, 0.53]
	None		**0.30 [0.01, 0.59]**
Wealth quintile (Ref = Highest)	1 - Lowest		**0.51 [0.20, 0.81]**
	2		**0.47 [0.20, 0.74]**
	3		**0.49 [0.24, 0.74]**
	4		0.22 [-0.01, 0.46]
Current smoking status (Ref = Never smoked)	Ex-smoker		0.10 [-0.07, 0.28]
	Current smoker		**0.59 [0.31, 0.88]**
Alcohol consumption (Ref = <5 times per week)			**0.12 [-0.07, 0.32]**
Physical activity (Ref = Moderate)	Sedentary		0.12 [-0.35, 0.59]
	Low		**0.45 [0.25, 0.66]**
	High		**-0.28 [-0.49, -0.07]**
No. of health conditions			0.06 [-0.01, 0.14]
Self-rated health (Ref = Excellent)	Very good		**0.27 [0.02, 0.53]**
	Good		**0.36 [0.10, 0.62]**
	Fair		**0.39 [0.08, 0.70]**
	Poor		**0.49 [0.02, 0.96]**
CRP predicting IC score			
CRP		**-0.70 [-0.84, -0.56]**	**-0.26 [-0.37, -0.14]**
Age (years)		**-0.48 [-0.52, -0.44]**	**-0.35 [-0.38, -0.31]**
Sex (Ref = Male)		**-2.88 [-3.49, -2.27]**	**-2.74 [-3.25, -2.23]**
Education (Ref = Degree)	A-Level		0.13 [-0.77, 1.03]
	O-Level/Other		-0.25 [-1.10, 0.61]
	None		**-0.93 [-1.82, -0.05]**
Wealth quintile (Ref = Highest)	1 - Lowest		**-2.92 [-3.84, -1.99]**
	2		**-2.00 [-2.82, -1.18]**
	3		**-1.21 [-1.98, -0.45]**
	4		-0.54 [-1.25, 0.17]
Current smoking status (Ref = Never smoked)	Ex-smoker		**-0.98 [-1.52, -0.45]**
	Current smoker		-0.64 [-1.52, 0.24]
Alcohol consumption (Ref = <5 times per week)			**-0.80 [-1.38, -0.21]**
Physical activity (Ref = Moderate)	Sedentary		**-6.58 [-8.00, -5.15]**
	Low		**-2.44 [-3.07, -1.80]**
	High		**1.22 [0.58, 1.87]**
No. of health conditions			**-0.26 [-0.48, -0.03]**

Self-rated health (Ref = Excellent)	Very good		**-1.51 [-2.30, -0.73]**
	Good		**-4.88 [-5.68, -4.09]**
	Fair		**-9.34 [-10.29, -8.38]**
	Poor		**-12.59 [-14.02, -11.15]**

Bold indicates p<0.05

7.1.2 Wave 4

Wave 4	N = 2,494	Coefficient [95% CIs]	
		Age & Sex adjusted	Fully-adjusted
Isolation predicting CRP			
Social isolation score		0.07 [0.00, 0.13]	-0.04 [-0.11, 0.03]
Age (years)		**0.02 [0.01, 0.03]**	0.01 [0.00, 0.02]
Sex (Ref = Male)		**0.26 [0.09, 0.43]**	**0.19 [0.02, 0.36]**
Education (Ref = Degree)	A-Level		0.17 [-0.10, 0.45]
	O-Level/Other		0.02 [-0.23, 0.28]
	None		0.11 [-0.17, 0.40]
Wealth quintile (Ref = Highest)	1 - Lowest		**0.66 [0.35, 0.96]**
	2		**0.36 [0.09, 0.63]**
	3		**0.29 [0.04, 0.55]**
	4		0.19 [-0.05, 0.43]
Current smoking status (Ref = Never smoked)	Ex-smoker		0.12 [-0.06, 0.30]
	Current smoker		**0.42 [0.11, 0.73]**
Alcohol consumption (Ref = <5 times per week)			0.20 [0.00, 0.40]
Physical activity (Ref = Moderate)	Sedentary		0.37 [-0.07, 0.81]
	Low		**0.32 [0.10, 0.54]**
	High		-0.19 [-0.40, 0.03]
No. of health conditions			0.08 [-0.03, 0.18]
Self-rated health (Ref = Excellent)	Very good		0.21 [-0.07, 0.49]
	Good		**0.45 [0.17, 0.73]**
	Fair		**0.47 [0.14, 0.80]**
	Poor		0.43 [-0.08, 0.95]
CRP predicting IC score			
CRP		**-0.78 [-0.93, -0.64]**	**-0.37 [-0.48, -0.25]**
Age (years)		**-0.47 [-0.51, -0.43]**	**-0.32 [-0.35, -0.29]**
Sex (Ref = Male)		**-3.30 [-3.92, -2.67]**	**-2.61 [-3.13, -2.09]**
Education (Ref = Degree)	A-Level		0.35 [-0.46, 1.17]
	O-Level/Other		-0.32 [-1.09, 0.45]
	None		-0.64 [-1.48, 0.20]
Wealth quintile (Ref = Highest)	1 - Lowest		**-3.13 [-4.04, -2.22]**
	2		**-2.66 [-3.48, -1.85]**
	3		**-1.51 [-2.27, -0.76]**
	4		**-1.16 [-1.87, -0.45]**
Current smoking status (Ref = Never smoked)	Ex-smoker		-0.47 [-1.00, 0.06]
	Current smoker		-0.39 [-1.32, 0.54]
Alcohol consumption (Ref = <5 times per week)			-0.58 [-1.18, 0.02]
Physical activity (Ref = Moderate)	Sedentary		**-3.50 [-4.83, -2.18]**
	Low		**-3.03 [-3.69, -2.36]**
	High		**1.49 [0.86, 2.13]**
No. of health conditions			**-0.45 [-0.77, -0.13]**
Self-rated health (Ref = Excellent)	Very good		**-0.86 [-1.69, -0.03]**
	Good		**-4.14 [-4.98, -3.29]**
	Fair		**-9.28 [-10.27, -8.30]**
	Poor		**-13.20 [-14.75, -11.65]**

Bold indicates p<0.05

7.1.3 Wave 6

Wave 6	N = 2,461	Coefficient [95% CIs]	
		Age & Sex adjusted	Fully-adjusted
Isolation predicting CRP			
Social isolation score		**0.12 [0.06, 0.19]**	0.04 [-0.02, 0.10]
Age (years)		**0.01 [0.00, 0.03]**	0.00 [-0.01, 0.01]
Sex (Ref = Male)		**0.25 [0.10, 0.40]**	**0.17 [0.02, 0.33]**
Education (Ref = Degree)	A-Level		0.16 [-0.07, 0.39]
	O-Level/Other		0.12 [-0.11, 0.34]
	None		0.20 [-0.06, 0.45]
Wealth quintile (Ref = Highest)	1 - Lowest		0.16 [-0.13, 0.45]
	2		0.13 [-0.13, 0.38]
	3		0.10 [-0.13, 0.33]
	4		0.21 [0.00, 0.43]
Current smoking status (Ref = Never smoked)	Ex-smoker		**0.16 [0.00, 0.32]**
	Current smoker		0.30 [0.00, 0.60]
Alcohol consumption (Ref = <5 times per week)			0.17 [-0.01, 0.35]
Physical activity (Ref = Moderate)	Sedentary		0.22 [-0.22, 0.66]
	Low		**0.41 [0.21, 0.61]**
	High		-0.14 [-0.33, 0.06]
No. of health conditions			**0.12 [0.02, 0.23]**
Self-rated health (Ref = Excellent)	Very good		-0.09 [-0.35, 0.17]
	Good		0.24 [-0.03, 0.50]
	Fair		**0.42 [0.12, 0.73]**
	Poor		0.34 [-0.12, 0.80]
CRP predicting IC score			
CRP		**-0.97 [-1.14, -0.80]**	**-0.44 [-0.58, -0.30]**
Age (years)		**-0.47 [-0.52, -0.43]**	**-0.31 [-0.35, -0.27]**
Sex (Ref = Male)		**-3.26 [-3.91, -2.60]**	**-2.53 [-3.07, -1.99]**
Education (Ref = Degree)	A-Level		0.29 [-0.51, 1.09]
	O-Level/Other		-0.09 [-0.88, 0.70]
	None		-0.69 [-1.57, 0.19]
Wealth quintile (Ref = Highest)	1 - Lowest		**-4.25 [-5.25, -3.25]**
	2		**-2.03 [-2.92, -1.15]**
	3		**-1.34 [-2.14, -0.55]**
	4		**-1.15 [-1.90, -0.41]**
Current smoking status (Ref = Never smoked)	Ex-smoker		**-0.71 [-1.27, -0.15]**
	Current smoker		0.34 [-0.69, 1.37]
Alcohol consumption (Ref = <5 times per week)			-0.52 [-1.16, 0.12]
Physical activity (Ref = Moderate)	Sedentary		**-5.47 [-6.99, -3.95]**
	Low		**-3.13 [-3.82, -2.44]**
	High		**1.31 [0.64, 1.97]**
No. of health conditions			-0.35 [-0.70, 0.01]
Self-rated health (Ref = Excellent)	Very good		**-2.00 [-2.90, -1.10]**
	Good		**-4.88 [-5.80, -3.95]**
	Fair		**-9.52 [-10.58, -8.47]**
	Poor		**-14.52 [-16.11, -12.93]**

Bold indicates p<0.05

Appendix 7.2 Main estimation results for the stepwise cross-lagged panel models

7.2.1 Least-adjusted model adjusted for age and sex (N=7,690).

	Path	β	b	SE	Lower 95% CI	Upper 95% CI	*p*-value
d	Iso2 -> Iso4	0.702	0.727	0.009	0.709	0.746	0.000
d’	Iso4 -> Iso6	0.721	0.727	0.009	0.709	0.746	0.000
e	CRP2 -> CRP4	0.527	0.520	0.016	0.490	0.552	0.000
e’	CRP4 -> CRP6	0.566	0.520	0.016	0.490	0.552	0.000
f	IC2 -> IC4	0.668	0.707	0.009	0.688	0.723	0.000
f’	IC4 -> IC6	0.667	0.707	0.009	0.688	0.723	0.000
a	Iso2 -> CRP4	0.008	0.014	0.019	-0.021	0.055	0.478
a’	Iso4 -> CRP6	0.009	0.014	0.019	-0.021	0.055	0.478
g	CRP2 -> Iso4	0.037	0.022	0.006	0.009	0.034	0.000
g’	CRP4 -> Iso6	0.036	0.022	0.006	0.009	0.034	0.000
b’	CRP2 -> IC4	-0.075	-0.365	0.038	-0.444	-0.295	0.000
b	CRP4 -> IC6	-0.070	-0.365	0.038	-0.444	-0.295	0.000
h	IC2 - > CRP4	-0.099	-0.021	0.003	-0.027	-0.016	0.000
h’	IC4 -> CRP6	-0.114	-0.021	0.003	-0.027	-0.016	0.000
c	Iso2 -> IC6	-0.049	-0.431	0.106	-0.704	-0.224	0.000

β = standardised regression coefficient; b = regression coefficient; SE = standard error; CI = confidence interval.

7.2.2 Socioeconomic model (adjusted for age, sex, highest educational qualification, and wealth quintile) (N=7,690).

	Path	β	b	SE	Lower 95% CI	Upper 95% CI	*p*-value
d	Iso2 -> Iso4	0.672	0.697	0.010	0.677	0.717	0.000
d’	Iso4 -> Iso6	0.693	0.697	0.010	0.677	0.717	0.000
e	CRP2 -> CRP4	0.522	0.518	0.016	0.487	0.549	0.000
e’	CRP4 -> CRP6	0.566	0.518	0.016	0.487	0.549	0.000
f	IC2 -> IC4	0.635	0.671	0.009	0.653	0.688	0.000
f’	IC4 -> IC6	0.636	0.671	0.009	0.653	0.688	0.000
a	Iso2 -> CRP4	0.002	0.003	0.020	-0.034	0.042	0.891
a’	Iso4 -> CRP6	0.002	0.003	0.020	-0.034	0.042	0.891
g	CRP2 -> Iso4	0.016	0.010	0.006	-0.003	0.022	0.116
g’	CRP4 -> Iso6	0.016	0.010	0.006	-0.003	0.022	0.116
b’	CRP2 -> IC4	-0.063	-0.305	0.037	-0.382	-0.233	0.000
b	CRP4 -> IC6	-0.059	-0.305	0.037	-0.382	-0.233	0.000
h	IC2 - > CRP4	-0.088	-0.019	0.003	-0.025	-0.013	0.000
h’	IC4 -> CRP6	-0.102	-0.019	0.003	-0.025	-0.013	0.000

c	Iso2 -> IC6	-0.027	-0.236	0.111	-0.460	-0.033	0.034

7.2.3 Health behaviour model (adjusted for age, sex, physical activity, smoking status, and alcohol consumption) (N=7,690).

Path		β	b	SE	Lower 95% CI	Upper 95% CI	*p*-value
d	Iso2 -> Iso4	0.680	0.706	0.010	0.688	0.726	0.000
d’	Iso4 -> Iso6	0.701	0.706	0.010	0.688	0.726	0.000
e	CRP2 -> CRP4	0.521	0.515	0.016	0.484	0.546	0.000
e’	CRP4 -> CRP6	0.564	0.515	0.016	0.484	0.546	0.000
f	IC2 -> IC4	0.593	0.617	0.010	0.598	0.636	0.000
f’	IC4 -> IC6	0.582	0.617	0.010	0.598	0.636	0.000
a	Iso2 -> CRP4	0.004	0.006	0.020	-0.029	0.048	0.756
a’	Iso4 -> CRP6	0.004	0.006	0.020	-0.029	0.048	0.756
g	CRP2 -> Iso4	0.013	0.008	0.006	-0.004	0.020	0.205
g’	CRP4 -> Iso6	0.013	0.008	0.006	-0.004	0.020	0.205
b’	CRP2 -> IC4	-0.057	-0.270	0.035	-0.348	-0.208	0.000
b	CRP4 -> IC6	-0.053	-0.270	0.035	-0.348	-0.208	0.000
h	IC2 - > CRP4	-0.066	-0.014	0.003	-0.020	-0.009	0.000
h’	IC4 -> CRP6	-0.075	-0.014	0.003	-0.020	-0.009	0.000
c	Iso2 -> IC6	-0.035	-0.302	0.104	-0.501	-0.093	0.004

7.2.4 Health model (adjusted for age, sex, number of health conditions, and self-rated health) (N=7,690).

Path		β	b	SE	Lower 95% CI	Upper 95% CI	*p*-value
d	Iso2 -> Iso4	0.684	0.711	0.009	0.692	0.728	0.000
d’	Iso4 -> Iso6	0.706	0.711	0.009	0.692	0.728	0.000
e	CRP2 -> CRP4	0.522	0.516	0.016	0.486	0.547	0.000
e’	CRP4 -> CRP6	0.563	0.516	0.016	0.486	0.547	0.000
f	IC2 -> IC4	0.518	0.538	0.010	0.519	0.558	0.000
f’	IC4 -> IC6	0.507	0.538	0.010	0.519	0.558	0.000
a	Iso2 -> CRP4	0.005	0.009	0.019	-0.025	0.051	0.651
a’	Iso4 -> CRP6	0.006	0.009	0.019	-0.025	0.051	0.651
g	CRP2 -> Iso4	0.013	0.008	0.006	-0.005	0.019	0.198
g’	CRP4 -> Iso6	0.013	0.008	0.006	-0.005	0.019	0.198
b’	CRP2 -> IC4	-0.052	-0.246	0.035	-0.324	-0.180	0.000
b	CRP4 -> IC6	-0.048	-0.246	0.035	-0.324	-0.180	0.000
h	IC2 - > CRP4	-0.059	-0.013	0.003	-0.019	-0.007	0.000
h’	IC4 -> CRP6	-0.067	-0.013	0.003	-0.019	-0.007	0.000
c	Iso2 -> IC6	-0.027	-0.232	0.093	-0.420	-0.050	0.012

7.2.5 Fully-adjusted model (adjusted for age, sex, highest educational qualification, wealth quintile, physical activity, smoking status, and alcohol consumption, number of health conditions, and self-rated health) (N=7,690).

Path		β	b	SE	Lower 95% CI	Upper 95% CI	*p*-value
d	Iso2 -> Iso4	0.654	0.682	0.010	0.662	0.702	0.000
d’	Iso4 -> Iso6	0.678	0.682	0.010	0.662	0.702	0.000
e	CRP2 -> CRP4	0.517	0.512	0.016	0.481	0.543	0.000
e’	CRP4 -> CRP6	0.562	0.512	0.016	0.481	0.543	0.000
f	IC2 -> IC4	0.471	0.490	0.010	0.469	0.509	0.000
f’	IC4 -> IC6	0.460	0.490	0.010	0.469	0.509	0.000
a	Iso2 -> CRP4	0.000	-0.001	0.020	-0.038	0.040	0.975
a’	Iso4 -> CRP6	0.000	-0.001	0.020	-0.038	0.040	0.975
g	CRP2 -> Iso4	-0.006	-0.003	0.006	-0.016	0.008	0.568
g’	CRP4 -> Iso6	-0.006	-0.003	0.006	-0.016	0.008	0.568
b’	CRP2 -> IC4	-0.037	-0.179	0.034	-0.251	-0.118	0.000
b	CRP4 -> IC6	-0.035	-0.179	0.034	-0.251	-0.118	0.000
h	IC2 - > CRP4	-0.044	-0.010	0.003	-0.016	-0.004	0.005
h’	IC4 -> CRP6	-0.051	-0.010	0.003	-0.016	-0.004	0.005
c	Iso2 -> IC6	-0.011	-0.098	0.098	-0.287	0.098	0.315

Appendix 7.3 Estimation results for the covariates in the stepwise cross-lagged panel models.

N = 7,690. Regression coefficients are presented with p-values indicated by asterisks. Baseline age, sex, and highest educational qualification were time-invariant. All other covariates were time varying so they were associated with the model variables within each wave, for example, wealth quintile at wave 2 on isolation score at wave 2, wealth quintile at wave 4 on isolation score at wave 4, and wealth quintile at wave 6 on isolation score at wave 6.

Covariate & model variable	Category	(1) Age & sex	(2) Socio-economic	(3) Health behaviours	(4) Health	(5) Fully-adjusted
Baseline age on:						
Iso2		0.047**	0.037**	0.042**	0.043**	0.035**
Iso4		0.019**	0.016**	0.015**	0.016**	0.013**
Iso6		0.013**	0.010*	0.011**	0.011**	0.008*
CRP2		0.015**	0.005	0.005	0.008	-0.001

Covariate & model variable	Category	(1) Age & sex	(2) Socio-economic	(3) Health behaviours	(4) Health	(5) Fully-adjusted
CRP4		0.007	0.005	0.007	0.009	0.007
CRP6		0.003	0.004	0.001	0.003	0.002
IC2		**-0.545****	**-0.456****	**-0.393****	**-0.447****	**-0.347****
IC4		**-0.293****	**-0.275****	**-0.252****	**-0.300****	**-0.263****
IC6		**-0.304****	**-0.299****	**-0.257****	**-0.321****	**-0.279****
Sex on: (Ref = Male)						
Iso2	Female	-0.008	**-0.089***	-0.050	0.004	**-0.071***
Iso4	Female	0.024	-0.011	-0.005	0.021	-0.013
Iso6	Female	-0.033	**-0.062***	-0.047	-0.025	-0.050
CRP2	Female	**0.180***	0.112	0.073	**0.183***	0.079
CRP4	Female	0.050	0.037	0.034	0.076	0.044
CRP6	Female	0.013	0.017	-0.007	0.043	0.021
IC2	Female	**-3.284****	**-2.687****	**-2.393****	**-3.485****	**-2.774****
IC4	Female	**-0.871****	**-0.775****	**-0.588***	**-1.346****	**-1.099****
IC6	Female	**-0.856****	**-0.771****	**-0.707****	**-1.473****	**1.253****
Highest educational qualification on: (Ref = Degree)						
Iso2	A-Level		**0.189***			**0.177***
	O-Level or other		**0.255****			**0.224****
	None		**0.503****			**0.440****
Iso4	A-Level		0.076			0.063
	O-Level or other		**0.136***			**0.125***
	None		**0.208****			**0.168***
Iso6	A-Level		-0.045			-0.050
	O-Level or other		0.043			0.042
	None		0.087			0.067
CRP2	A-Level		**0.294***			**0.278***
	O-Level or other		**0.255***			0.162
	None		**0.421****			**0.292***
CRP4	A-Level		0.050			0.018
	O-Level or other		0.051			0.033
	None		0.131			0.093
CRP6	A-Level		**0.194***			0.164
	O-Level or other		0.144			0.113
	None		0.088			0.057
IC2	A-Level		-0.374			-0.038
	O-Level or other		**-1.164***			-0.321
	None		**-2.710****			**-1.112***
IC4	A-Level		**-0.682***			-0.185
	O-Level or other		-0.533			-0.097
	None		**-1.201****			-0.305
IC6	A-Level		-0.522			0.038
	O-Level or other		-0.452			-0.273
	None		**-1.116***			-0.510
Wealth quintile on: (Ref = 5 – Highest)						
Iso2	1 – Lowest		**0.832****			**0.624****
	2		**0.493****			**0.363****
	3		**0.217****			**0.160***
	4		**0.138***			**0.107***
Iso4	1 – Lowest		**0.318****			**0.212****
	2		**0.219****			**0.156***
	3		**0.108***			0.088

Covariate & model variable	Category	(1) Age & sex	(2) Socio-economic	(3) Health behaviours	(4) Health	(5) Fully-adjusted
	4		**0.097***			**0.085***
Iso6	1 – Lowest		**0.330****			**0.272****
	2		**0.233****			**0.190****
	3		**0.112***			**0.099***
	4		0.066			0.061
CRP2	1 – Lowest		**0.911****			**0.560****
	2		**0.672****			**0.395****
	3		**0.653****			**0.487****
	4		**0.335****			**0.230***
CRP4	1 – Lowest		0.220			0.180
	2		0.104			0.067
	3		0.076			0.060
	4		0.132			0.121
CRP6	1 – Lowest		-0.009			-0.085
	2		0.164			0.080
	3		0.007			-0.045
	4		0.113			0.077
IC2	1 – Lowest		**-7.665****			**-3.581****
	2		**-5.690****			**-2.666****
	3		**-2.947****			**-1.413****
	4		**-1.957****			**-1.037****
IC4	1 – Lowest		**-2.667****			**-1.603****
	2		**-1.861****			**-1.125****
	3		**-1.001***			**-0.765***
	4		**-0.888***			**-0.571***
IC6	1 – Lowest		**-2.345****			**-1.505****
	2		**-1.794****			**-0.941***
	3		**-1.324****			**-0.927***
	4		**-0.872***			**-0.661***
Current smoking status on: (Ref = Non/ex-smoker)						
Iso2	Smoker			**0.576****		**0.349****
Iso4	Smoker			**0.258****		**0.191***
Iso6	Smoker			**0.136***		0.091
CRP2	Smoker			**0.640****		**0.468****
CRP4	Smoker			0.194		0.166
CRP6	Smoker			0.012		0.004
IC2	Smoker			**-2.177****		-0.090
IC4	Smoker			-0.510		0.278
IC6	Smoker			-0.601		**1.218****
Alcohol consumption on: (Ref = <5 days a week)						
Iso2	5+ days a week			**0.092***		-0.078
Iso4	5+ days a week			0.036		-0.030
Iso6	5+ days a week			-0.032		**-0.086***
CRP2	5+ days a week			**0.285***		0.104
CRP4	5+ days a week			0.124		0.088
CRP6	5+ days a week			0.086		0.068
IC2	5+ days a week			**-2.027****		**-0.444***
IC4	5+ days a week			**-1.019****		**-0.448***
IC6	5+ days a week			-0.115		0.302
Physical activity on: (Ref = Moderate)						
Iso2	Sedentary			**0.693****		**0.349****

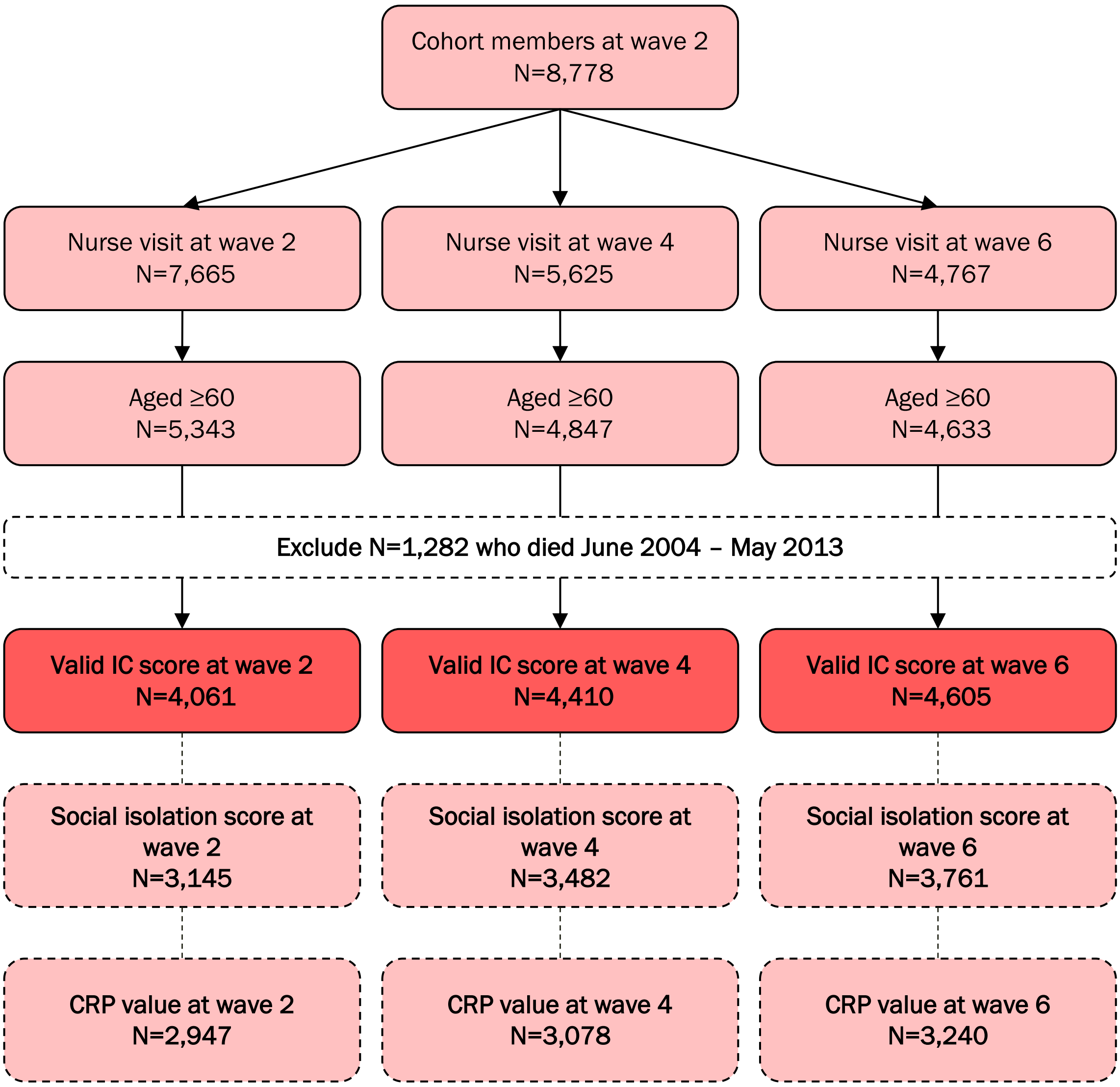
Covariate & model variable	Category	(1) Age & sex	(2) Socio-economic	(3) Health behaviours	(4) Health	(5) Fully-adjusted
	Low			**0.362****		**0.188****
	High			**-0.103***		-0.003
Iso4	Sedentary			**0.402****		**0.258****
	Low			**0.184****		**0.101***
	High			**-0.117***		-0.065
Iso6	Sedentary			**0.352****		**0.193***
	Low			**0.126***		0.044
	High			**-0.101***		-0.063
CRP2	Sedentary			**0.465***		0.152
	Low			**0.677****		**0.510****
	High			**-0.41****		**-0.293****
CRP4	Sedentary			0.147		0.107
	Low			**0.219***		**0.181***
	High			-0.045		0.002
CRP6	Sedentary			-0.006		-0.063
	Low			**0.273****		**0.219***
	High			**-0.153***		-0.124
IC2	Sedentary			**-11.677****		**-6.133****
	Low			**-5.783****		**-3.027****
	High			**3.157****		**1.564****
IC4	Sedentary			**-4.150****		**-2.457****
	Low			**-2.961****		**-1.893****
	High			**2.053****		**1.292****
IC6	Sedentary			**-5.593****		**-3.421****
	Low			**-3.187****		**-1.897****
	High			**1.536****		**1.050****
Number of health conditions on:						
Iso2					0.004	-0.005
Iso4					0.032	0.029
Iso6					**0.046***	0.038
CRP2					0.034	0.028
CRP4					0.015	0.009
CRP6					0.048	0.045
IC2					**-0.528****	**-0.412****
IC4					**-0.387***	**-0.344***
IC6					**-0.513****	**-0.394***
Self-rated health on: (Ref = Excellent)						
Iso2	Very good				**0.140***	0.092
	Good				**0.333****	**0.211****
	Fair				**0.640****	**0.339****
	Poor				**0.982****	**0.471****
Iso4	Very good				0.011	-0.022
	Good				0.101	0.027
	Fair				**0.281****	0.118
	Poor				**0.522****	**0.267***
Iso6	Very good				0.058	0.025
	Good				0.088	0.035
	Fair				**0.281****	**0.173***
	Poor				**0.316****	0.144
CRP2	Very good				**0.349****	**0.230***
	Good				**0.699****	**0.478****

Covariate & model variable	Category	(1) Age & sex	(2) Socio-economic	(3) Health behaviours	(4) Health	(5) Fully-adjusted
	Fair				**0.932****	**0.503****
	Poor				**1.369****	**0.763****
CRP4	Very good				0.189	0.164
	Good				**0.327***	**0.282***
	Fair				**0.305***	0.182
	Poor				**0.440***	0.258
CRP6	Very good				-0.036	-0.060
	Good				0.179	0.128
	Fair				**0.300***	0.216
	Poor				0.299	0.246
IC2	Very good				**-2.470****	**-1.893****
	Good				**-6.534****	**-5.266****
	Fair				**-12.255****	**-9.615****
	Poor				**-17.656****	**-13.109****
IC4	Very good				**-0.771***	-0.469
	Good				**-3.140****	**-2.581****
	Fair				**-6.494****	**-5.448****
	Poor				**-9.916****	**-8.277****
IC6	Very good				**-1.416****	**-1.257****
	Good				**-3.541****	**-3.195****
	Fair				**-7.010****	**-6.243****
	Poor				**-10.108****	**-8.768****

* p<0.05 ** p<0.001

Appendix 7.4 Results from the sensitivity analysis excluding those who had died during the follow-up period

7.4.1 Flowchart showing the sample selection process for the sensitivity analysis excluding those who died during the follow-up period



7.4.2 (In the sample excluding those who died during the follow-up period)

Means and standard deviations (SD) of social isolation score, C-reactive protein (CRP) level and intrinsic capacity (IC) score across the 3 waves.

	Social isolation score		CRP (mg/L)		IC score	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Wave 2	3,145	2.50 (1.20)	2,947	2.54 (2.12)	4,061	51.88 (9.41)
Wave 4	3,482	2.54 (1.25)	3,078	2.47 (2.12)	4,410	50.90 (9.64)
Wave 6	3,761	2.61 (1.27)	3,240	2.18 (1.94)	4,605	50.07 (9.96)

7.4.3 (In the sample excluding those who died during the follow-up period)

The cross-sectional associations between (1) isolation score and CRP, and (2) CRP and intrinsic capacity score at waves 2, 4, and 6 in models adjusted for age, sex, and all covariates.

Wave	N	Age & Sex adjusted model				Fully-adjusted* model			
		b	95% CIs		p-value	b	95% CIs		p-value
(3) Isolation score predicting CRP									
Wave 2	2,254	**0.13**	**0.06**	**0.21**	**0.001**	0.03	-0.05	0.10	0.477
Wave 4	2,364	0.06	-0.01	0.13	0.121	-0.05	-0.12	0.02	0.197
Wave 6	2,455	**0.12**	**0.05**	**0.18**	**<0.001**	0.03	-0.03	0.10	0.297
(4) CRP predicting IC score									
Wave 2	2,254	**-0.73**	**-0.89**	**-0.57**	**<0.001**	**-0.30**	**-0.43**	**-0.17**	**<0.001**
Wave 4	2,364	**-0.81**	**-0.97**	**-0.66**	**<0.001**	**-0.39**	**-0.52**	**-0.27**	**<0.001**
Wave 6	2,455	**-0.98**	**-1.15**	**-0.81**	**<0.001**	**-0.45**	**-0.59**	**-0.31**	**<0.001**

7.4.4 (In the sample excluding those who died during the follow-up period) Estimation results of the total, direct and indirect effects of social isolation in Wave 2 (2004/5) on intrinsic capacity in Wave 6 (2012/13) in each model. Model fit statistics are also reported. (N=6,408)

Model		β	b	SE	Lower 95% CI	Upper 95% CI	*p*-value	χ^2 (df)	CFI	TLI	RMSEA	SRMR
(1) Age & sex	Total	**-0.051**	**-0.430**	**0.107**	**-0.637**	**-0.222**	**0.000**	976.65 (25)	0.930	0.850	0.077	0.084
	Direct	**-0.051**	**-0.429**	**0.106**	**-0.632**	**-0.222**	**0.000**					
	Indirect	0.000	-0.001	0.007	-0.016	0.010	0.848					
(2) Socio-economic	Total	**-0.028**	**-0.234**	**0.111**	**-0.448**	**-0.020**	**0.035**	752.48 (97)	0.957	0.916	0.032	0.024
	Direct	**-0.028**	**-0.237**	**0.111**	**-0.455**	**-0.029**	**0.032**					
	Indirect	0.000	0.002	0.006	-0.010	0.016	0.722					
(3) Health behaviours	Total	**-0.036**	**-0.301**	**0.107**	**-0.513**	**-0.091**	**0.005**	1358.88 (115)	0.924	0.875	0.041	0.035
	Direct	**-0.036**	**-0.302**	**0.106**	**-0.509**	**-0.094**	**0.005**					
	Indirect	0.000	0.001	0.005	-0.010	0.011	0.917					
(4) Health	Total	**-0.028**	**-0.233**	**0.093**	**-0.435**	**-0.053**	**0.012**	1060.77 (115)	0.947	0.913	0.036	0.029
	Direct	**-0.028**	**-0.233**	**0.093**	**-0.436**	**-0.056**	**0.012**					
	Indirect	0.000	0.000	0.005	-0.010	0.011	0.974					
(5) Fully-adjusted	Total	-0.012	-0.100	0.098	-0.308	0.092	0.307	1078.11 (277)	0.959	0.932	0.021	0.012
	Direct	-0.012	-0.102	0.098	-0.309	0.091	0.297					
	Indirect	0.000	0.002	0.004	-0.005	0.010	0.653					

7.4.5 (In the sample excluding those who died during the follow-up period)

Main estimation results: Basic model adjusted for age and sex (N=7,690).

	β	b	SE	Lower 95% CI	Upper 95% CI	*p*-value
Iso2 -> Iso4	**0.700**	**0.727**	**0.010**	**0.707**	**0.743**	**0.000**
Iso4 -> Iso6	**0.717**	**0.727**	**0.010**	**0.707**	**0.743**	**0.000**
CRP2 -> CRP4	**0.533**	**0.527**	**0.016**	**0.494**	**0.556**	**0.000**
CRP4 -> CRP6	**0.566**	**0.527**	**0.016**	**0.494**	**0.556**	**0.000**
IC2 -> IC4	**0.679**	**0.710**	**0.009**	**0.691**	**0.726**	**0.000**
IC4 -> IC6	**0.670**	**0.710**	**0.009**	**0.691**	**0.726**	**0.000**
Iso2 -> CRP4	0.002	0.004	0.019	-0.035	0.043	0.847
Iso4 -> CRP6	0.002	0.004	0.019	-0.035	0.043	0.847
CRP2 -> Iso4	**0.040**	**0.024**	**0.006**	**0.012**	**0.032**	**0.000**
CRP4 -> Iso6	**0.039**	**0.024**	**0.006**	**0.012**	**0.032**	**0.000**
CRP2 -> IC4	**-0.081**	**-0.370**	**0.040**	**-0.446**	**-0.292**	**0.000**
CRP4 -> IC6	**-0.075**	**-0.370**	**0.040**	**-0.446**	**-0.292**	**0.000**
IC2 - > CRP4	**-0.095**	**-0.021**	**0.003**	**-0.027**	**-0.016**	**0.000**
IC4 -> CRP6	**-0.106**	**-0.021**	**0.003**	**-0.027**	**-0.016**	**0.000**
Iso2 -> IC6	**-0.051**	**-0.429**	**0.106**	**-0.632**	**-0.222**	**0.000**

β = standardised regression coefficient; b = regression coefficient; SE = standard error; CI = confidence interval.

7.4.6 (In the sample excluding those who died during the follow-up period)

Main estimation results: Socioeconomic model (adjusted for age, sex, highest educational qualification, and wealth quintile) (N=7,690).

	β	b	SE	Lower 95% CI	Upper 95% CI	*p*-value
Iso2 -> Iso4	**0.669**	**0.697**	**0.011**	**0.677**	**0.718**	**0.000**
Iso4 -> Iso6	**0.690**	**0.697**	**0.011**	**0.677**	**0.718**	**0.000**
CRP2 -> CRP4	**0.529**	**0.524**	**0.016**	**0.492**	**0.555**	**0.000**
CRP4 -> CRP6	**0.567**	**0.524**	**0.016**	**0.492**	**0.555**	**0.000**
IC2 -> IC4	**0.643**	**0.673**	**0.009**	**0.655**	**0.691**	**0.000**
IC4 -> IC6	**0.638**	**0.673**	**0.009**	**0.655**	**0.691**	**0.000**
Iso2 -> CRP4	-0.004	-0.007	0.020	-0.047	0.031	0.720
Iso4 -> CRP6	-0.005	-0.007	0.020	-0.047	0.031	0.720
CRP2 -> Iso4	0.018	0.011	0.006	-0.001	0.021	0.063
CRP4 -> Iso6	0.017	0.011	0.006	-0.001	0.021	0.063
CRP2 -> IC4	**-0.067**	**-0.311**	**0.039**	**-0.388**	**-0.232**	**0.000**
CRP4 -> IC6	**-0.063**	**-0.311**	**0.039**	**-0.388**	**-0.232**	**0.000**
IC2 - > CRP4	**-0.083**	**-0.019**	**0.003**	**-0.024**	**0.013**	**0.000**
IC4 -> CRP6	**-0.094**	**-0.019**	**0.003**	**-0.024**	**0.013**	**0.000**

Iso2 -> IC6	-0.028	-0.237	0.111	-0.455	-0.029	0.032

7.4.7 (In the sample excluding those who died during the follow-up period)

Main estimation results: Health behaviour model (adjusted for age, sex, physical activity, smoking status, and alcohol consumption) (N=7,690).

	β	b	SE	Lower 95% CI	Upper 95% CI	*p*-value
Iso2 -> Iso4	0.680	0.707	0.010	0.687	0.727	0.000
Iso4 -> Iso6	0.700	0.707	0.010	0.687	0.727	0.000
CRP2 -> CRP4	0.529	0.523	0.016	0.490	0.553	0.000
CRP4 -> CRP6	0.565	0.523	0.016	0.490	0.553	0.000
IC2 -> IC4	0.608	0.624	0.010	0.602	0.642	0.000
IC4 -> IC6	0.591	0.624	0.010	0.602	0.642	0.000
Iso2 -> CRP4	-0.001	-0.002	0.019	-0.042	0.036	0.916
Iso4 -> CRP6	-0.001	-0.002	0.019	-0.042	0.036	0.916
CRP2 -> Iso4	0.016	0.010	0.006	-0.002	0.020	0.099
CRP4 -> Iso6	0.016	0.010	0.006	-0.002	0.020	0.099
CRP2 -> IC4	-0.061	-0.278	0.037	-0.346	-0.209	0.000
CRP4 -> IC6	-0.057	-0.278	0.037	-0.346	-0.209	0.000
IC2 - > CRP4	-0.063	-0.014	0.003	-0.020	-0.008	0.000
IC4 -> CRP6	-0.070	-0.014	0.003	-0.020	-0.008	0.000
Iso2 -> IC6	-0.036	-0.302	0.106	-0.509	-0.094	0.005

7.4.8 (In the sample excluding those who died during the follow-up period)

Main estimation results: Health model (adjusted for age, sex, number of health conditions, and self-rated health) (N=7,690).

	β	b	SE	Lower 95% CI	Upper 95% CI	*p*-value
Iso2 -> Iso4	0.685	0.711	0.010	0.691	0.730	0.000
Iso4 -> Iso6	0.704	0.711	0.010	0.691	0.730	0.000
CRP2 -> CRP4	0.529	0.523	0.016	0.491	0.554	0.000
CRP4 -> CRP6	0.564	0.523	0.016	0.491	0.554	0.000
IC2 -> IC4	0.529	0.541	0.010	0.522	0.561	0.000
IC4 -> IC6	0.509	0.541	0.010	0.522	0.561	0.000
Iso2 -> CRP4	0.000	-0.001	0.019	-0.043	0.036	0.973
Iso4 -> CRP6	0.000	-0.001	0.019	-0.043	0.036	0.973
CRP2 -> Iso4	0.016	0.009	0.006	-0.002	0.020	0.100
CRP4 -> Iso6	0.016	0.009	0.006	-0.002	0.020	0.100
CRP2 -> IC4	-0.056	-0.255	0.036	-0.319	-0.184	0.000
CRP4 -> IC6	-0.053	-0.255	0.036	-0.319	-0.184	0.000

IC2 - > CRP4	-0.056	-0.013	0.003	-0.019	-0.006	0.000
IC4 -> CRP6	-0.062	-0.013	0.003	-0.019	-0.006	0.000
Iso2 -> IC6	-0.028	-0.233	0.093	-0.436	-0.056	0.012

7.4.9 (In the sample excluding those who died during the follow-up period)

Main estimation results: Fully-adjusted model (adjusted for age, sex, highest educational qualification, wealth quintile, physical activity, smoking status, and alcohol consumption, number of health conditions, and self-rated health) (N=7,690).

	β	b	SE	Lower 95% CI	Upper 95% CI	*p*-value
Iso2 -> Iso4	0.655	0.683	0.011	0.662	0.703	0.000
Iso4 -> Iso6	0.677	0.683	0.011	0.662	0.703	0.000
CRP2 -> CRP4	0.525	0.520	0.016	0.487	0.550	0.000
CRP4 -> CRP6	0.563	0.520	0.016	0.487	0.550	0.000
IC2 -> IC4	0.482	0.495	0.011	0.475	0.515	0.000
IC4 -> IC6	0.465	0.495	0.011	0.475	0.515	0.000
Iso2 -> CRP4	-0.005	-0.009	0.020	-0.050	0.030	0.649
Iso4 -> CRP6	-0.006	-0.009	0.020	-0.050	0.030	0.649
CRP2 -> Iso4	-0.003	-0.002	0.006	-0.014	0.009	0.757
CRP4 -> Iso6	-0.003	-0.002	0.006	-0.014	0.009	0.757
CRP2 -> IC4	-0.042	-0.189	0.035	-0.253	-0.118	0.000
CRP4 -> IC6	-0.039	-0.189	0.035	-0.253	-0.118	0.000
IC2 - > CRP4	-0.042	-0.009	0.004	-0.016	-0.002	0.008
IC4 -> CRP6	-0.047	-0.009	0.004	-0.016	-0.002	0.008
Iso2 -> IC6	-0.012	-0.102	0.098	-0.309	0.091	0.297

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