The role of education in sex differences in cognitive and functional ageing: a multi-cohort approach

Thesis presented for the degree of Doctor of Philosophy

Field of study: Epidemiology

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Declaration of authorship

I, Mikaela Bloomberg, confirm that the work presented in this thesis is a result of my own work. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Background

Sex inequalities in education may contribute to sex differences in cognitive and functional status in old age. This thesis examines the role of education in sex differences in cognitive and functional ageing across birth cohorts and in high- and middle-income countries.

Methods

The thesis includes three investigations, with analyses for each undertaken before and after adjustment for education and then stratified by education level. The thesis uses: 1) mixed effects linear models to examine sex differences in cognitive ageing in three birth cohorts (birth years 1930-1955; N = 15,924 UK-based participants); 2) weighted linear models to compare sex differences in cognitive function between the US and four middle-income countries (N = 70,846); and 3) mixed effects ordinal logistic models to examine sex differences in functional limitations in four birth cohorts (birth years 1895-1960; N = 62,375 participants from 11 countries).

Results

Before adjustment for education, women outperformed men in memory and orientation in high- but not middle-income countries. Men generally outperformed women in attention and fluency. Sex differences in cognitive function were less favourable to women in middle- compared to high- income countries and in earlier-born birth cohorts. Women were more likely to have functional limitations than men. Adjustment for education attenuated or eliminated male advantages for both cognitive and functional outcomes, increased female advantages, and reduced differences in sex inequalities across birth cohorts. For cognitive function, adjustment for education attenuated differences in sex inequalities between middle- and high-income countries. Stratification by education revealed male advantages in cognitive function were present in less educated persons only.

Conclusion

Sex inequalities in education contribute to sex inequalities in cognitive function and to a lesser extent functional limitations in old age. Gender equity in access to education is an important target to reduce sex disparities in cognitive and functional ageing.

Impact statement

This thesis presents three key findings on cognitive ageing. First, sex inequalities in education contributed to sex inequalities in cognitive function during ageing, with lower education levels among women accounting for lower cognitive performance among women compared to men. Second, reductions in sex inequalities in education contributed to better cognitive function for women born later compared to those born earlier. Third, larger sex inequalities in education level contributed to larger sex inequalities in cognitive function in older adults in middle- compared to high-income countries. In middle-income countries women performed worse compared to men even for cognitive tasks where women outperformed men in high-income countries. However, these differences in sex inequalities between countries were not observed among those individuals who were highly educated relative to the rest of the population. By contrast, the higher prevalence of functional limitations observed among women was only slightly explained by sex inequalities in education.

This thesis has several implications for cognitive health in old age. The first is that with increasing equity of access to education and higher levels of education among women in many middle- and high-income countries, there may be fewer sex disparities in cognitive health in old age. This includes better cognitive function for older women, potentially leading to better quality of life, more autonomy, and more ability to engage in valued activities. However, the findings of this thesis also potentially have implications for sex inequalities in neurocognitive disease. Currently, the evidence indicates that women have as much as a 50% increased risk of Alzheimer's disease compared to men. Having a higher education level has the potential to delay cognitive impairment in the presence of Alzheimer's disease neuropathology by contributing to better midlife cognitive function. Thus, if women have more educational opportunities, they may be afforded more of a buffer against cognitive decline caused by neuropathology. It is possible that if current trends in gender equity in education continue, there could be a reduction in the sex disparity in Alzheimer's disease incidence.

This thesis also finds that among those who were highly educated relative to the rest of the population of the country, there were negligible differences in sex inequalities in cognitive

function between high-income and middle-income countries. This finding suggests that improvements in education level for women may also reduce the larger sex disparities in cognitive function seen in middle-income compared to high-income countries.

Despite the increasing evidence that education contributes to cognitive health in old age, and to sex inequalities in cognitive health, WHO guidelines on cognitive health and dementia do not include access to education as a potential point of intervention. This thesis provides evidence that education, with an emphasis on gender equity, should be included in international guidelines to promote cognitive health.

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1 Introduction and thesis aims

1.1 Population ageing

Much of the world is in the midst of a demographic transition (Figure 1.1.1). During the 20th century, the chances of surviving past age 65 have risen from less than 50% to greater than 90% in many middle- and high-income countries [1]. The life expectancy in some of these settings has increased by 30 years or more [2]. Until the 1920s, this increase was driven primarily by decreased infant and childhood mortality resulting from efforts to combat infectious disease [2]. However, from the 1920s onward, increases in life expectancy were predominantly driven by unprecedented reductions in old age mortality [2]. The United Nations now project that by 2050, 1 in 6 persons globally will be over the age of 65, compared to 1 in 11 in 2019 [1]. Individuals in many middle and high income countries now spend a quarter or more of their adult life beyond age 65, up from less than one fifth in the 1960s [1].

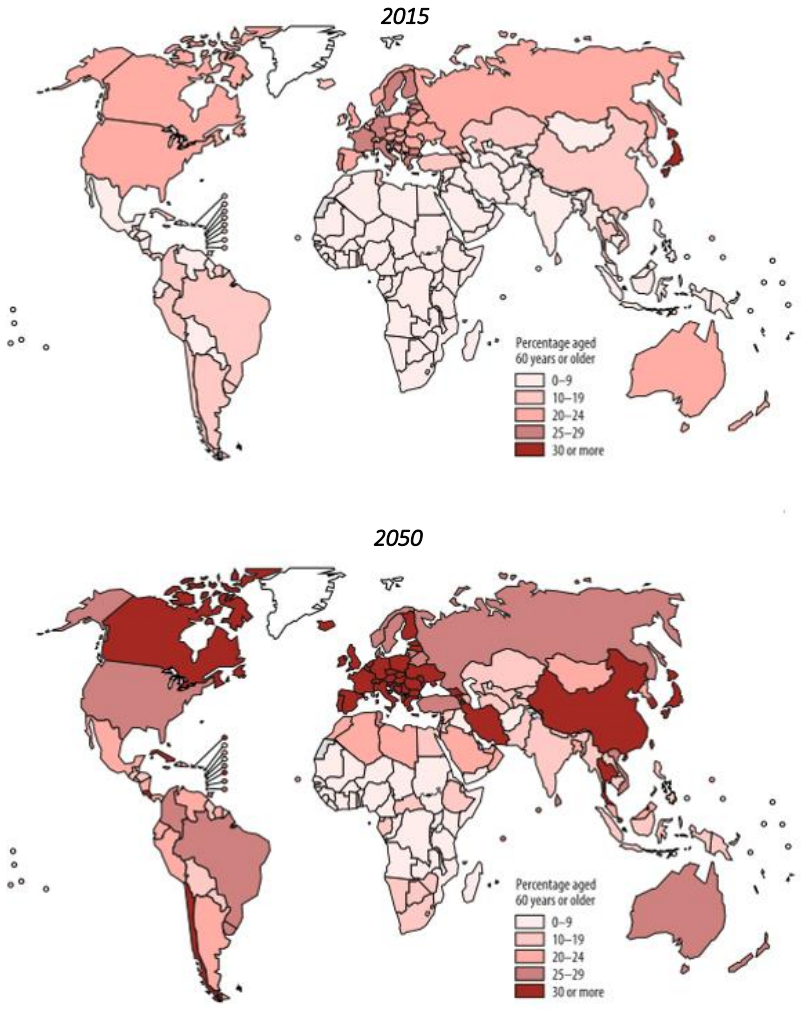


Figure 1.1.1. Proportion of population aged 60 years or older, by country in 2015 (top) and projected in 2050 (bottom) reproduced from WHO World report on ageing and health (2015).

The ageing of populations worldwide presents several challenges. Ageing is associated with increased risk of disease and functional loss. As such, ageing populations give rise to a higher prevalence of chronic diseases such as heart disease, arthritis, and diabetes [2]. Chronic disease and other age-related

cognitive and physiological dysfunction can lead to disability and loss of autonomy and independence, negatively affecting quality of life and engagement in social roles for older adults.

1.2 Healthy ageing

Traditionally, the life course is framed into early childhood, student, working, and retirement years [3]. Longevity has previously been framed as an extension of retirement, characterised by increasingly poor health and quality of life in some people, and leading to the stereotypical conception of older adults as frail, burdensome, and dependent [3, 4]. However, recent increases in life expectancy present an opportunity to change the way ageing is viewed, in line with changing attitudes of older adults who expect to work longer, and maintain active lifestyles well into retirement [3, 4]. If increased longevity occurs alongside good health, the timeline of the traditional life course can be shifted so that increased longevity is not just an extension of the retirement phase, but instead, an opportunity to prolong each stage of the life course, in order to balance life experiences like advanced education, careers, and child-rearing [3]. Furthermore, the retirement phase of the life course may not necessarily involve prolonged frailty or dependence. Increased longevity in good health may allow older adults to engage in fulfilling social activities and lead active lives for longer [3]. In light of this goal of healthy longevity, the concept of 'healthy ageing' and the factors that contribute to healthy ageing have become the subject of considerable research. Healthy ageing is "more than just the absence of disease; [healthy ageing is] the process of developing and maintaining the functional ability that enables [wellbeing] in old age." [3]

1.2.1 Sex inequalities in healthy ageing

There are many factors that influence whether individuals experience healthy ageing. Differences in health and wellbeing between older adults are the result of cumulative exposure to risk and protective factors over the life course [3]. Along with genetic factors, social, political, and environmental determinants of health and their intersection with individual sociodemographic characteristics like sex and gender can explain wide variations in health and wellbeing in old age [5]. Among these factors are social and economic

indicators such as education, occupation, and income. Less education, lower occupational class, and lower income are generally associated with negative health outcomes in old age [6]. These factors drive sociodemographic disparities in health and wellbeing in older adults when particular demographics are confined to lower social and economic positions in society due to systemic restrictions.

One of the most extensively researched examples of this intersection between demographic characteristics and socioeconomic disadvantage is the disparity in healthy ageing between men and women. Women live longer than men, but tend to be report higher levels of disability, with more co-morbidities, and poorer general health [7, 8]. This phenomenon is so consistently observed that it is named: the male-female health-survival paradox [8-10]. There is evidence that social disparities between men and women play a role in producing disparities in health in old age [11], as women historically were limited in access to education and the labour force.

However, social and economic disparities between men and women are changing. Gender disparities in education continue to decrease such that the gender gap in higher education has been eliminated or even reversed in many middle- and high-income countries [12], and women are consequently more likely to enter the paid labour force in skilled positions [13]. These changes have the potential to reduce sex disparities in healthy ageing, however their effect has not been systematically examined. Furthermore, as social disparities between men and women vary importantly between countries, particularly countries at different levels of economic development, further research is needed to examine how differences in gender disparities in social and economic factors between countries influence differences in sex inequalities in healthy ageing between countries.

1.2.2 Research on healthy ageing

Investigating sex inequalities in healthy ageing and their determinants requires precise definition of what constitutes healthy ageing. The operationalisation of the concept of healthy ageing has given rise to much debate. In a landmark 1987 review, American gerontologists John Rowe and Robert Kahn identified three major dimensions of healthy ageing: absence of disease, engagement in life, and maintenance of cognitive and physical

functioning [14, 15]. The Rowe and Kahn framework has since been criticised for its biomedical focus and emphasis on complete absence of disease [6], which may be impractical for older adults, and also does not necessarily correlate with wellbeing [16, 17]. Indeed, self-reported measures of wellbeing tend to increase from middle to oldest ages, despite concurrent increases in disease and disability [16, 17]. Further evidence suggests that maintaining the ability to participate in valued activities is most important to older adults [5]. This does not require the complete absence of disease; instead, it requires a system that is designed to address the health and accessibility needs that arise for older persons.

A 2015 WHO report extended the Rowe and Kahn model to define healthy ageing as the maintenance of functional capacity in order to facilitate wellbeing, not necessarily requiring the complete absence of disease [3]. The choice of measures of healthy ageing in this thesis is driven by this idea that it is not necessary for older adults to be disease-free to 'age successfully'; rather the emphasis is on maintaining cognitive and basic physical abilities so that function in everyday life and active engagement in valued activities does not severely decline with age. For this reason, the investigations undertaken as part of this thesis will concern cognitive function and functional limitations, or limitations in those activities that are necessary for daily living.

There are well-documented sex disparities in both cognitive function and functional limitations in old age, where women are more likely to be functionally limited, perform worse than men across a number of cognitive tasks, and sex differences in cognitive function have been observed to differ between countries at different levels of economic development. Describing and understanding the reasons for these sex disparities—particularly, the influence of inequalities in education between men and women—and examining variation across national contexts are the driving questions underlying this thesis.

1.3 Thesis aims and objectives

The overarching aim of this thesis is to examine the role of education in sex differences in cognitive function and functional limitations in older adults in middle- and high-income countries. The research objectives are as follows:

Objective 1: Cognitive function

a. Examine the role of education in sex differences in cognitive ageing with attention to decreases in sex inequalities in education over time.
b. Examine and compare the role of education in sex differences in cognitive function in older adults in middle- and high-income countries.

Objective 2: Functional limitations

Examine the role of education in sex differences in functional limitations in older adults with attention to decreases in sex inequalities in education over time and severity of limitations.

To this end, the thesis is organised into three investigations, which will be referred to hereafter as papers 1, 2, and 3, each addressing objectives 1a, 1b, and 2 respectively.

1.4 Thesis outputs

Publications

1. **Bloomberg M**, Dugravot A, Landré B, Britton A, Steptoe A, Singh-Manoux A, Sabia S. Sex differences in functional limitations and the role of socioeconomic factors: a multi-cohort analysis. *The Lancet Healthy Longevity* 2021. doi: 10.1016/S2666-7568(21)00249-X
2. **Bloomberg M**, Dugravot A, Dumurgier J, Kivimäki M, Fayosse A, Steptoe A, Britton A, Singh-Manoux A, Sabia S. Sex differences and the role of education in cognitive ageing: analysis of two UK-based prospective cohort studies. *The Lancet Public Health* 2021. doi: 10.1016/S2468-2667(20)30258-9.

Submitted for publication

1. **Bloomberg M,** Dugravot A, Sommerlad A, Kivimäki M, Fayosse A, Singh-Manoux A, Sabia S. Comparison of sex differences in cognitive function between high- and middle-income countries and the role of education: a population-based multicohort study. Currently under review with *Age and ageing.*

Conference presentations

1. **Bloomberg M**, Dugravot A, Landré B, et al. Sex differences in functional limitation level and the role of socioeconomic factors. *European Journal of Public Health 2021*; 31(Supplement_3). European Public Health Conference, 11 November 2021.
2. **Bloomberg M**, Dugravot A, Landré B, et al. Sex differences in functional limitations and the effect of socioeconomic factors: a retrospective multi-cohort study. *The Lancet* 2021; 398: S25. UK Public Health Science Conference, 26 November 2021.

1.5 Overview of data sources

This thesis uses data from the Whitehall II Study and the Health and Retirement Study family of cohort studies. The Whitehall II study is a longitudinal study of British civil servants who worked in the Whitehall neighbourhood of London. In addition to the Whitehall II study, this thesis uses a family of large cohort studies of health in ageing designed to be comparable to the US-based Health and Retirement Study (HRS). HRS was conceived as a means to study population ageing at a large scale in order to inform research and policy development in the United States [18]. Since its inception in 1992, at least 45 other countries have undertaken similar efforts to produce 18 large-scale longitudinal studies in total. In 11 of the 18 HRS-family studies harmonised datasets are available. These datasets are harmonised according to standard protocol in order to facilitate cross-national comparisons between studies. The HRS-family of studies provides an invaluable resource for studying ageing among older populations across many geographical contexts. The size and depth of these studies as well as their comparability made them ideally suited to address the study aims of this thesis.

1.6 Organisation of thesis

After this introduction, the second chapter of the thesis first overviews healthy ageing, and cognitive function and functional limitations, the domains of healthy ageing that will be examined in this thesis. I then proceed into a review of the literature concerning sex inequalities in cognitive function and functional limitations. Chapter 3 summarises the literature and presents the knowledge gaps and rationale for the thesis investigations. Chapter 4 provides a broad overview of the methods. Chapter 5 goes into detail in each of the three papers, with methods, results, and discussion for each. Chapter 6 is the concluding

chapter of the thesis, first summarising the findings of the thesis, then presenting several key takeaways, strengths and limitations, novelty of the findings, and implications for future research and policy. Chapters 7 and 8 are references and appendices respectively.

2 Background and literature review

In Chapter 2, I will first overview biological ageing, healthy ageing, and cognitive function and functional limitations, the domains of healthy ageing of focus in this thesis. I then present the evidence for sex differences in cognitive function and functional limitations. Chapter 2 then proceeds into an overview of the mechanisms thought to underlie sex differences in cognitive function and functional limitations, including biological and social factors, with an emphasis on social factors as these factors are the focus of the thesis.

2.1 Overview of ageing processes and health during ageing

There is no universally accepted definition of ageing. Suggested definitions include ageing as "the result of progressive accumulation of changes in the body which occur with the passing of time and which cause the increase in probability of disease and death of the individual" or "the wearing of structures and functions that reach a peak or plateau during development and maturations of the individuals of a given species." [20] According to the American gerontologist Bernard Strehler, ageing is universal, intrinsic, progressive, and deleterious [20].

Biological ageing is characterised by progressive loss of efficiency in physiological functions and reduced ability to maintain homeostasis in the face of external stress [20]. This manifests in reduced ability to endure extreme temperatures, infections, or other physiological stressors among older adults [20]. Ageing results in reduced skeletal muscular system integrity and losses in vision, hearing, memory, and other neurological abilities [20]. During ageing, the majority of organs and intercellular materials are subject to degeneration or atrophy [20].

The cellular processes that underlie age-related physiological changes are still not fully understood. There are at least 300 theories of ageing, with various attempts made to unite them. What ultimately emerged in the field of biogerontology were nine "hallmarks of aging", described by López-Otín and colleagues in a landmark 2013 paper [21]. The authors define these hallmarks of ageing as genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction,

cellular senescence, stem cell exhaustion, and altered intercellular communication [21]. The hallmarks of ageing are defined in brief in Table 2.1.1, though in-depth discussion of the cellular basis of ageing is beyond the scope of this thesis. These nine hallmarks have provided a uniting framework to describe the cellular effects of ageing but do not necessarily provide comprehensive insight into the mechanistic causes of ageing [22].

Table 2.1.1. Overview of the hallmarks of ageing adapted from López-Otín et al. 2013 [21].

Hallmark of ageing	Description
Genomic instability	Accumulation of genetic damage with ageing
Telomere attrition	Progressive degradation of telomere protective sequences as the end of chromosomes
Epigenetic alterations	Environmental influences that affect gene expression
Loss of proteostasis	The loss of the ability to stabilise correctly folded proteins and degrade misfolded proteins
Mitochondrial dysfunction	The reduction in ability of mitochondria to generate power for cellular processes
Cellular senescence	An arrest to the cell cycle resulting in phenotypic changes in aged tissues
Stem cell exhaustion	A decline in the regenerative potential of tissues
Altered intercellular communication	Changes at the level of intercellular communication in the endocrine and nervous systems

Age is among the strongest risk factors for physiological and cognitive dysfunction and a range of chronic conditions. Immune function decreases with age, giving rise to auto-immune disorders and other chronic diseases, and increasing susceptibility to infection [20]. By age 60, age-related losses in hearing, vision, and physical function, and conditions including heart disease, stroke, respiratory disorders, cancer, and dementia are the leading causes of disability and death [3]. Ageing is also associated with greater risk of multimorbidity, and impacts functional capacity, healthcare utilisation, and cost of care [3, 23]. Though the overall trajectory of ageing may be toward physiological and cognitive decline and increased risk of disease and disability, there is wide variability in experiences of health in ageing [3, 24], giving rise to the study of healthy ageing.

2.2 Healthy ageing

Some individuals have relatively good health and quality of life well into old age. These individuals are said to have experienced 'healthy ageing.' Healthy ageing is a concept that

sums up the importance of longevity, functional capacity, autonomy, and wellbeing for older adults. Rowe and Kahn's idea of healthy ageing as comprising lack of disease, engagement in life, and maintenance of cognitive and physical functioning [15] is further expanded in the WHO definition: healthy ageing is "the process of developing and maintaining functional ability that enables [wellbeing] in older age." [3] According to the WHO definition, functional ability is dependent on "intrinsic capacity" and "environmental characteristics and their interactions", where intrinsic capacity is the "composite of all the physical and mental capacities of an individual", and environments "comprise all the factors in the extrinsic world that form the context of an individual's life" [3].

Building intrinsic capacity starts well before birth, with genetic inheritance and epigenetic influences in the womb and during early development [3]. Throughout the life course, fixed and dynamic characteristics impact lifestyle, experiences, and the environments and social norms to which individuals are subject, further shaping intrinsic capacity [3]. Fixed characteristics include factors like biological sex and ethnicity, while dynamic characteristics include geographical location, education, occupation, and other social and economic markers [3]. Those who start out with high intrinsic capacity due to early life genetic or environmental advantages may experience a lifelong advantage against declines in intrinsic capacity with age.

Cognitive and physical impairments and other physiological dysfunctions reflect reduced intrinsic capacity. Some reductions in intrinsic capacity have a greater impact on quality of life for older adults, while others may have little impact if they are effectively managed. For example, chronic disease reflects reduced intrinsic capacity, but many conditions may nonetheless result in little interruption to daily life if they are well-managed [3, 25]. Indeed, self-reported wellbeing increases from middle to old age [3, 26], despite concurrent increases in incidence of disease [16, 17]. Older age is associated with shifting priorities, with many older adults compensating for disease-related and other functional losses by selecting fewer but more meaningful activities [27], and by focussing on transcendent rather than material goals [3, 28, 29]. These findings suggest that there are dimensions of intrinsic capacity beyond absence of disease that are important to older adults in order to maintain a fulfilling lifestyle.

It is therefore important that research aiming to reduce disparities in healthy ageing does not just focus on presence or absence of disease, but also includes examination of other outcomes that affect quality of life and wellbeing. Older adults identify maintaining a sense of identity, relationships, enjoyment, autonomy, security, and opportunities for personal growth as the factors that are most important for maintaining quality of life [3, 30-33]. With this in mind, the focus of this thesis is on sex differences in cognitive function and functional limitations in activities of daily living and basic mobility activities. Cognitive function is strongly associated with autonomy [14] and is necessary for maintenance of relationships, personal growth, and maintaining sense of self. The maintenance of basic physical capacity and the ability to take care of everyday needs plays a fundamental role in independence, security, and enjoyment. Disparities in cognitive function and functional limitations therefore have the potential to drive considerable disparities in wellbeing. The decision to focus on sex inequalities in these aspects of healthy ageing is thus driven by the importance of cognitive function and lack of functional limitations to those factors that older adults identify as valuable for quality of life. These two domains of healthy ageing are described in detail in the following sections.

2.2.1 Cognitive function

Cognitive function refers to the range of abilities used to process data in the real world. This term encompasses abilities such as learning and memory, but also management of day-to-day activities, information processing, and reaction to stimuli [14]. Healthy ageing necessitates some degree of autonomy and independence, of which cognitive function is an important predictor [14]. Poor cognitive function is associated with institutionalisation [34], limitations in ability to perform daily activities [35-37], and reduced life expectancy [14, 38, 39]. Even so-called 'normal' cognitive ageing can result in declines in complex functional abilities, such as the ability to drive [40, 41] which can have wide-ranging impacts on day-to-day life. Mild cognitive impairment in older adults has also been found to be associated with reduced autonomy, social participation, and intimacy [42]. As such, maintenance of cognitive function is an important component of healthy ageing.

Cognitive function is organised into cognitive domains [43]. These domains are categorised based on the involved processes (e.g. memory, language, executive functioning), by region

of the brain (e.g. deriving from the frontal, temporal, or parietal lobes), or hierarchically based on the complexity of their operations (e.g. basic sensory operations as the least complex and reasoning and problem solving as the most) [43]. This thesis uses categorisation of domains based on involved processes, as the cognitive tasks used to measure cognitive function in this thesis use this categorisation.

There are a range of neuropsychological tests designed to assess each cognitive domain, though most neuropsychological tests require at least some degree of coordination of multiple domains. There are also neuropsychological tests that aim to examine global cognitive scores. One such test that is commonly administered is the Mini Mental State Exam (MMSE) [44], which has been found to be valid for identification of severe cognitive impairment, but is not as sensitive to mild cognitive impairment [45, 46]. Other common global cognitive assessments include the Montreal Cognitive Assessment Scale, the Addenbrooke's Cognitive Examination Revised, the Abbreviated Mental Test, the General Practitioner Assessment of Cognition, and the Mini-Cog [47]. In this thesis, I use neuropsychological testing by domain rather than using one of these tests of global cognitive function or constructing global cognitive score from component tests due to availability of cognitive tests in the HRS-family of studies and the evidence of differences in sex inequalities between cognitive domains. This approach also reduces ceiling effects and biases.

2.2.1.1 Domains of cognitive function

Sensation and perception refers to the domain broadly encompassing basic sensory abilities. Sensation refers to the ability to detect a stimulus using the five senses [43]. Tests of sensation include visual and auditory acuity [43]. Perception refers to the processing and integration of sensory information and can be tested using the ability to recognise objects or sounds [43].

Another domain of cognitive function is *motor skills and construction*. Motor skills include manual dexterity, motor speed, reaction time, and balance [43]. Tasks of motor skills include finger tapping (tapping the tip of index finger against the thumb), and the pegboard task

(placing a peg into a small hole) [43]. Construction refers to the ability to copy or produce drawings of common objects [43].

The domain of *attention and concentration* refers to abilities pertaining to attending information [43]. Selective attention is the process of attending relevant and ignoring irrelevant information [43]. Selective attention tasks require individuals to specifically attend relevant information while presented with distracting information [43]. Sustained attention refers to the ability to maintain attention over time [43]. Tests of sustained attention may require detection of a stimulus presented infrequently in the midst of other stimuli [43]. Serial 7s is another task of sustained attention, in which participants are asked to count backwards from 100 by seven [48]. Divided attention is the ability to focus on multiple simultaneous tasks [41]. Attention is required for activities such as engaging in conversation in a noisy environment, driving a car, or multitasking [41].

Memory is among the broadest and most complex domains. There are two broad categorisations of memory: declarative and non-declarative memory [41]. Declarative or explicit memory includes conscious recollections of events and facts, including semantic and episodic memory [41]. Semantic memory refers to long-term storage of verbal information, while episodic memory is the process of encoding, maintaining, and retrieving information for longer-term recall [43], including recollection of events in time [41]. A commonly administered test of episodic memory is word recall, where participants are read a list of words and asked to recall it out loud or write it down immediately and then after some time. Other processes of declarative memory include prospective memory, or remembering to perform tasks in the future [43]. Non-declarative or implicit memory is memory outside of a person's awareness, for example, ability to recall a familiar song [41]. Non-declarative memory subdomains also include procedural memory, or memory for motor skills or actions [43]. Other memory subdomains include working memory, or the ability to hold information in the consciousness, including verbal and nonverbal information [43]. Working memory tasks include the digit task, where a participant is asked to recall information (for example a sequence of letters and numbers) in reverse order [43].

Executive function is another broad domain that includes all processes involving reasoning and problem solving [43]. Executive function requires the coordination of many less

complex cognitive domains and processes, and there is considerable overlap between executive function and certain subdomains of memory, particularly prospective memory [43]. Tests of executive function include the Trail Making Test, where individuals are asked to draw lines between consecutive numbers spaced out on a piece of paper [49]. Other tests that are intended to examine other domains of cognitive function may require elements of executive functioning such as the Stroop test—requiring correctly naming coloured words—and verbal fluency tests [49].

Processing speed refers to the ability to perform tasks that require rapid performance, often scored using time elapsed or number of correct responses in a given period of time [43]. The domain of *language* refers to the ability to understand and produce language, use semantic memory, identify objects, and respond to behavioural instructions [43]. Assessments of language skills include tasks of verbal fluency, such as phonemic and semantic recall tasks, in which participants name words starting with a given letter or in a given category respectively [43]. Other tests of language skills include object naming and following instructions [43].

Visuospatial skills refer to the ability to understand 2D and 3D space, requiring the coordination of multiple cognitive domains [41]. Some construction tasks can also require visuospatial ability, such as building models, making a bed, or assembling furniture [50]. Other visuospatial abilities include object perception, spatial perception, and understanding of physical position of objects alone or with respect to other objects [41]. Mental rotation is one common task used to assess visuospatial abilities, where an individual must identify what a 3-D object or letter would look like if rotated [51].

2.2.1.2 Brain ageing

Cognitive function reflects brain function, with differences in brain structure and function giving rise to differences in cognitive function. Cognitive function changes with age, with many cognitive domains showing decline from middle to old age. Brain ageing refers to the age-related anatomical changes in the brain which give rise to age-related declines in cognitive function. Brain ageing is characterised by grey matter volume decline beginning in early adulthood [52], particularly in the prefrontal cortex, which is implicated in planning

complex cognitive behaviour [41]. Grey matter loss is thought to be attributable to a combination of neuron death, changes in neuron size and number of connections [52, 53], and accumulation of beta-amyloid peptides in the brain [41].

Beta-amyloid peptides are protein fragments that aggregate in the brain and block the transport and metabolism of nutrients, resulting in neuronal death and degradation of brain structures [54]. Though beta-amyloid accumulation is generally associated with Alzheimer's disease, cognitively healthy older adults may also be affected. Some studies indicate 20% to 30% of cognitively healthy adults also show beta-amyloid deposits in PET scans [41, 55, 56]. It is possible that some degree of beta-amyloid deposition can be present in normal cognitive ageing, or that those cognitively 'normal' adults who showed beta-amyloid deposits would have eventually gone on to develop cognitive impairment or Alzheimer's disease [41, 57].

Other age-related changes in the brain include reductions in synaptic density due to changes in the morphology of the synapses [58], and reductions in white matter volume, which may be implicated in age-associated memory decline [41, 59]. There are also moderate changes in the temporal lobe, including reductions in hippocampal volume [41, 60]. These changes in brain structure give rise to many of the observed reductions in cognitive function with age. Nonetheless, some degeneration of brain structures occurs concurrently with increased efficiency of existing neural networks, such that age-related or even pathological neurodegeneration does not necessarily manifest in reductions in cognitive ability.

2.2.1.3 Cognitive ageing

Cognitive ageing describes the manifestation of age-related changes in brain function in changes to cognitive abilities. Cognitive ageing can be visualised by plotting cognitive trajectories, where each trajectory is made up of an individual's scores on neuropsychological tests over time. These trajectories give insight into the way cognitive abilities change with age and can be averaged to examine differences in cognitive ageing between groups.

There is an important distinction between normal age-related cognitive decline, cognitive impairment, and neurocognitive disease. Most cognitive domains show some degree of age-

related decline. When an individual declines more than expected—based on standard deviations from the mean in age-matched and sometimes education-matched peers—but impairment does not yet interfere with daily activities, they are said to have mild cognitive impairment [61]. When cognitive impairment begins to interfere with daily activities, it may necessitate evaluation for dementia or other neurological disorders [62]. However, even cognitive decline that is within the scope of what might be expected with ageing can involve some decline in wellbeing and quality of life without reaching the threshold for impairment.

Cognitive ageing trajectories generally peak during early midlife and decrease thereafter, with an increase in cognitive decline occurring in old age [63]. As such, where individuals 'start out'—i.e. their peak cognitive performance, usually occurring during early adulthood—influences whether they reach the threshold for cognitive impairment. To illustrate this point, Figure 2.2.1 shows two cognitive trajectories. Person A starts out with high midlife cognitive performance and shows moderate decline that does not meet the threshold for cognitive impairment. Person B shows more modest midlife cognitive performance with the same rate of decline as person A and reaches the threshold of cognitive impairment. Though the rate of decline is the same, the higher initial performance of person A means that they are able to retain better cognitive function to an older age than person B. Thus, factors that affect cognitive performance in early adulthood can influence late life cognitive outcomes. This underscores the necessity of considering determinants of cognitive function from a life course perspective.

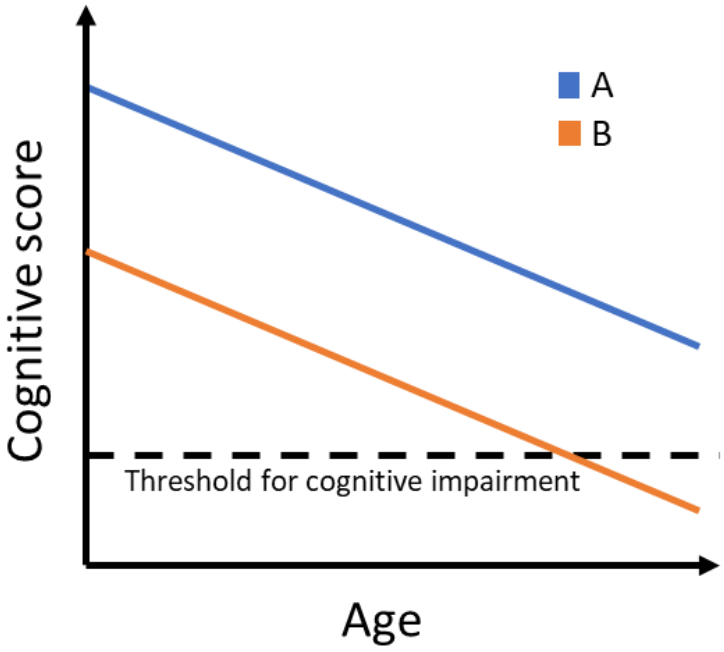


Figure 2.2.1. Example cognitive trajectories.

Even among cognitively healthy adults, cognitive trajectories vary considerably by domain. Some cognitive abilities like vocabulary [41] are resilient to age-related decline. Other abilities like reasoning, processing speed, and memory [43] tend to decline with time [41]. Broadly, those domains which comprise crystallised intelligence—skills, ability, or knowledge that is well-practised and familiar [64] such as vocabulary or general knowledge—tend to remain stable or improve [41]. By contrast, fluid intelligence—referring to problem-solving, reasoning, and the innate ability to attend and manipulate the environment and process and learn new information [65]—tends to decline with age [41]. Crystallised intelligence accumulates with age and as such, older adults tend to perform better than younger adults [41]. By contrast, domains of fluid intelligence including executive function, processing speed, and psychomotor ability peak for most individuals in their 30s and then decline thereafter [41, 66].

One cognitive domain that shows age-related decline is memory. Older adults perform worse than younger adults across a range of memory tasks, with some exceptions by memory subdomain [41]. Age-related memory changes likely occur due to a combination of reduced processing speed [67], reductions in selective attention [68], and having fewer strategies to improve learning and memory [41, 69-71]. Declines in semantic memory occur late in life, while episodic memory shows lifelong deterioration [41, 72]. Other memory subdomains that show decline include memory retrieval, or the ability to access newly learnt information [41, 73-75], and memory acquisition, or the ability to encode new information into memory [71, 74]. In general, declarative memory seems to decline with age, while nondeclarative memory is maintained across the lifespan [41, 64]. Rate of

memory acquisition declines, but information that is successfully learnt is preserved [41, 76]. A summary of age-related changes in memory is reproduced from Harada et al. (2013) in Table 2.2.1.

Table 2.2.1. Age-related changes in memory reproduced from Harada et al. (2013) [41].

Declines with age	**Remains stable with age**
Delayed free recall: spontaneous retrieval of information from memory without a cue [73, 77] Example: Recalling a list of items to purchase at the grocery store without a cue	Recognitive function memory: ability to retrieve information when given a cue Example: Correctly giving the details of a story when given yes/no questions
Source memory: knowing the source of the learned information Example: Remembering if you learned a fact because you saw it on television, read it in the newspaper, or heard it from a friend	Temporal order memory: memory for the correct time or sequence of past events Example: Remembering that last Saturday you went to the grocery store after you ate lunch with your friends
Prospective memory: remembering to perform intended actions in the future [78] Example: Remembering to take medicine before going to bed	Procedural memory: memory of how to do things Example: Remembering how to ride a bike

Processes of executive function including formation, abstraction, and mental flexibility show age-related declines, particularly from age 70 [41, 64]. Older adults tend to think more concretely [79-82], and are inhibited in their ability to produce novel responses [41, 83]. There is also evidence of a decline in verbal and mathematic inductive reasoning from age 45 [80]. Other executive functioning abilities remain stable throughout life, including the ability to appreciate similarities, explain proverbs, and reason through familiar material [41].

Processing speed falls under the domain of fluid intelligence. Adults tend to show declines in processing speed from their 30s onward [41, 79, 84, 85]. Declines in processing speed also impact many other cognitive abilities, which require processing speed to perform efficiently. As such, declines in processing speed can result in a progressive decrease in scores on a range of neuropsychological tests, including verbal fluency [41].

Language skills comprise both fluid and crystallised cognitive abilities. Generally, language remains intact with ageing. Vocabulary is one cognitive ability that shows stability or even increases with time [41, 80, 86-88]. There are, however, some language skills that decline in normal cognitive ageing. The ability to see a common object and name it declines after age

70 [41, 89]. Verbal fluency also shows age-related declines [19, 41, 79, 80] in part due to declines in processing speed [41].

Cognitive trajectories may differ between individuals. Some variability in cognitive ageing trajectories is attributable to heritable differences in ability; indeed, it is estimated that 60% of general cognitive ability is due to genetic predisposition [41, 90]. However, there remains a large portion of individual cognitive performance and decline that is susceptible to a vast array of social, behavioural, and environmental influences during the life course. These factors can shape cognitive health at old age either by influencing peak cognitive performance during early adulthood, by mitigating the rate of cognitive decline during ageing, or both. There is some evidence that maintaining an active and intellectually stimulating lifestyle reduces age-related cognitive declines [41, 91-93]. Activities associated with better cognitive performance for older adults include playing intellectually stimulating games (e.g. puzzles, bridge, or board games) [92, 94-96], being in complex occupations [97-99], high education level [100, 101], and exercise [41, 102, 103].

Though these studies suggest a link between lifestyle and cognitive function it is unclear whether these associations are causal. Examining cognitive ageing necessitates high quality longitudinal studies over long periods of time. Cross-sectional studies are subject to confounding due to cohort differences in cognitive function, as different birth cohorts are exposed to different culture, lifestyle, and educational factors that make cognitive abilities differ systematically between them [41]. There is evidence that cross-sectional studies particularly overestimate age-related cognitive decline in women due to cohort differences in education [80]. There is also the potential for reverse causation, where it is unclear whether these activities precipitate better cognitive function, or whether better cognitive function leads individuals to engage in these activities. Lastly, due to the long preclinical period associated with dementia, it is possible that study participants who were considered cognitively normal were actually in early stages of disease onset [41]. As such, research into the effect of intellectual lifestyle factors on cognitive ageing is still ongoing. Even so, there is some evidence that education has a causal link with dementia [104-106], likely through its protective effect against cognitive decline.

2.2.2 Functional limitations

The second component of healthy ageing examined in the thesis is functional limitations. Functional limitations are often used as a proxy for disability. Their study is complicated by overlapping or at times conflicting usage throughout the literature. The terms 'disability', 'functional ability', 'functional limitation', and 'functional impairment' are often used apparently interchangeably. Nonetheless, disability is distinct from functional limitation and impairment. WHO use the term disability to include impairment ("loss of body structure or function"), activity limitation ("difficulty with the execution of a task or action by an individual"), and participation restriction (restrictions from "involvement in a life situation" or engagement in life roles such as employment, education, or relationships) [107]. The WHO definition overlaps with another popular disability model developed by Nagi et al. (1991) [108] and refined by Verbugge et al. (1994) [109]. This model proposes a hierarchical "disablement process" whereby impairment ("anatomical, physiological, mental, or emotional abnormalities or loss") precedes functional limitation ("limitation in performance at the level of the whole organism or person") which results in disability ("limitation in performance of socially defined roles and tasks within a sociocultural and physical environment") [109].

Nagi, Verbugge, and colleagues use disability to refer to end-stage participation restriction, while WHO use disability as an umbrella term that includes the same elements of impairment, activity limitation, and participation restriction. Despite these differences, the different frameworks agree that disability includes restriction in the social roles an individual is able to play in a society. Functional limitations are a component of disability, but do not inevitably result in disability if an individual has access to means to compensate for limitations. As such, because the thesis does not explicitly examine meaningful engagement in social roles, throughout I will refer to functional limitations and not disability.

Limitations in activities of daily living (ADL), instrumental activities of daily living, and mobility activities are commonly used to examine functional limitations and were used in this thesis. ADL refer to those most basic activities that are necessary to perform for daily life. ADL include activities such as dressing, getting in and out of bed, or eating. IADL are

more complex activities of daily living, and may be necessary for engagement in social roles. IADL include using the telephone, taking medications, or preparing meals. Many studies examining limitations in ADL and IADL also include several simple mobility activities, such as the ability to stand up from a chair, walk 100 meters, or climb a flight of stairs. Together, ADL, IADL, and mobility activities paint a picture of an individuals' functional capacity, or their ability to perform those activities that are generally necessary to engage in life.

“Functional limitations” in this thesis refers to being limited in these activities. In order to assess functional limitations, individuals are usually asked whether they have "some difficulty" with a given activity, and they are considered to be limited in that activity if they answer yes. Other objective measures of physical functioning are sometimes included in assessments of physical limitations in addition to self-report of limitations in ADL, IADL, and mobility activities. These include grip strength, walking speed, balance tests, and chair-rise tests. An advantage of these tests is that they provide objective measures of physical functioning rather than relying on self-report, however these tests may not reflect functional capacity. Using these measures in the HRS-family studies can also pose a challenge, as they are available in few studies and only in selected waves when provided. For these reasons, ADL, IADL, and simple mobility activities are used in this thesis.

Though functional limitations are not synonymous with disability, functional limitations nonetheless have the potential to dramatically reduce quality of life and independence for older adults, as well as increasing the likelihood of institutionalisation [110-112]. Limitations in ADL are also predictive of use of paid home care and hospitalisation [113-117]. Functional limitations are used in a clinical setting to determine the need for rehabilitation or home assistance or whether reference to a nursing home or care facility is required [117]. Limitations in simple mobility activities can also be indicative of increased fall risk, where falls are associated with poor prognosis and increased mortality, particularly after age 65 years [117]. As such, maintaining functional capacity and reducing functional limitations is an important dimension of healthy ageing.

Functional limitations occur progressively, with some estimates showing 10% of adults over 70 without limitations developing limitations in ADL and IADL with each additional year of ageing [112, 118]. Even more older adults experience mobility limitations, which occur at

younger ages and with greater prevalence than IADL and ADL limitations [112, 118, 119]. There is evidence that functional limitations occur hierarchically, with mobility limitations increasing from middle age, followed by IADL limitations, and finally ADL limitations at the oldest ages [120], reflecting the decreasing physical and cognitive demands of mobility activities, IADL, and ADL respectively.

Functional limitations at old age occur due to normal age-related decline in physical function or due to musculoskeletal, circulatory, sensory, or neurological conditions such as Alzheimer's disease or other cognitive dysfunction [36, 117, 121]. Other factors influencing the ability to perform ADL include medication effects, social isolation, or home environment [117]. Functional limitations may also occur following hospitalisation or acute illness [117].

Factors associated with limitations in activities of daily living include depression, multimorbidity, BMI below or above the healthy range, lack of physical activity, alcohol abstinence compared to moderate use, poor self-perception of health, and smoking [122]. Social and economic factors that have been associated with functional limitations include low education [123-125], manual occupations [123, 126], lower income [127], fewer household assets [124] as well as poor early life socioeconomic conditions as measured by parental occupational position, number of books at home, household overcrowding, and housing quality [128]. There is evidence that the association between childhood socioeconomic position and limitations in ADL and IADL is partially mediated by education level and occupation [128].

Functional limitations are categorised in various ways for analysis. The number of limited activities in each functional outcome can be summed to yield a score for each functional outcome, or an overall score that might combine multiple functional outcomes (for example, limitations in ADL and IADL are commonly summed and combined). However, functional limitations are most commonly examined using a dichotomous indicator, where for each functional outcome, if an individual reports limitation in a single activity, they are considered to be limited in that outcome. Determining categorisation of functional limitations for research can therefore be challenging. The interpretation of a one unit increase in a continuous scale that combines multiple functional outcomes may not be intuitive or clinically meaningful. A dichotomous indicator also includes those individuals

with one limited activity in the same category as those with multiple limited activities, when the experiences of individuals with multiple limited activities are likely to differ from those with a single limited activity. Ideal categorisation of functional limitations might group individuals into severity categories representing no limitations, mild, moderate, and/or severe limitations for each functional outcome. Taking these considerations into account, in this thesis, I chose to model functional limitations in severity categories using numbers of limitations.

2.3 Sex inequalities in cognitive function and functional limitations

Cognitive function and functional limitations comprise two important dimensions of healthy ageing, however cognitive and functional ageing trajectories differ considerably between individuals. Sex and gender are two factors that contribute to heterogeneity among older adults in cognitive function and functional limitations.

Sex refers to genetic, gonadal, and hormonal variations arising from XY (male) and XX (female) chromosomal patterns [129]. It is nonetheless important to note that there are some hormonal and chromosomal variations such that sex chromosomes do not necessarily dictate typically male or female hormonal profiles [130]. The balance of sex hormones produced also varies widely within each sex [131].

By contrast, gender comprises the socially constructed roles assigned to men and women and refers to experiences that arise as a result of how society and institutions react to individual presentation of masculinity and femininity [129]. Many sex disparities in old age health arise due to gender roles in addition to biological sex. Gender is not binary, nor necessarily aligned with sex assigned-at-birth. However, as the available evidence does not tend to distinguish between sex and gender, this thesis will refer to sex as a binary variable without distinguishing it from gender, with the understanding that this is an oversimplification and an area for future research.

Women live longer than men, but generally report worse health during ageing [11]. The longevity advantage among women is likely to be attributable to a combination of female advantages in biological ageing [132, 133], differences in risk-taking behaviour between men and women where men are more likely to engage in risky behaviours like substance

use [134], and differences in chronic disease where women may be more likely to experience disabling though non-fatal chronic diseases, while men may be more likely to experience fatal diseases [109]. By contrast, women may be more socioeconomically disadvantaged than men, leading to more exposure to health risk factors and worse health outcomes. These and other factors interact to produce the male-female health-survival paradox.

Cognitive function and functional limitations both show sex differences consistent with this paradox. Older women perform worse than men across a range of cognitive tests, and may be more likely to develop neurocognitive diseases such as Alzheimer's disease [135]. Older women are also more likely to report functional limitations in basic and instrumental activities of daily living and mobility activities than men. Evidence for sex differences in cognitive function and functional limitations during ageing are detailed in the following sections.

2.3.1 Sex differences in cognitive function during ageing

2.3.1.1 Cognitive function

There are a range of observed sex differences in cognitive function, where men outperform women on tests of some cognitive domains, while tests of other cognitive domains show no sex differences or female advantages in performance. In general, men outperform women on tasks of visuospatial ability while women outperform men in verbal abilities [51, 136].

The male advantage in visuospatial abilities is seen in the mental rotation task [137], and this advantage increased when the task was time limited [51, 136]. There are also consistent male advantages found for multiple tasks of visuospatial working memory [51, 138]. In addition to visuospatial abilities, men tend to show better speed and accuracy in tasks of sustained attention than women [139-141], with mixed results for sex differences in tasks of selective attention [51]. For tests that require coordination of multiple cognitive domains, sex differences in cognitive performance frequently differ depending on which component cognitive processes are engaged. For example, the Stroop task—a test of selective attention in which participants look at a list of colours written in ink that does not correspond to the colour written and name the colour of the ink and not the colour that the word says—

requires drawing on verbal abilities. Consequently, the Stroop task shows a female advantage, while men perform better on other tasks of selective attention [51].

Other domains and processes of cognitive function that have been evaluated for evidence of sex differences include memory, language skills, and orientation in time. Women have been found to consistently perform better on tests of episodic memory than men [142-144]. By contrast, sex differences in language skills are mixed. Language skills are commonly assessed using verbal fluency, usually by listing words starting with the same letter (phonemic recall) or in the same category (semantic recall). Results for sex differences in both phonemic and semantic recall generally point to no sex difference after education is taken into account [145-147], though some earlier studies show a female advantage in phonemic recall [51, 148-150]. Orientation in time is a component of the Mini-Mental State Exam, which is commonly administered in longitudinal studies and clinically to assess overall cognitive ability [44]. There is mixed evidence for sex differences in orientation in time [151].

Taken together, the evidence indicates that sex differences in cognitive performance vary both by cognitive domain and within domains by task. These findings point to the importance of considering cognitive tests individually for characterising sex differences in cognitive function, rather than focussing on global cognitive scores.

2.3.1.2 Sex differences in cognitive ageing

The evidence for sex differences in the rate of cognitive decline with age is mixed. In studies of adults older than age 60 with follow up periods of 10 years or less, no sex difference in cognitive decline was found for tests of vocabulary [152, 153], reasoning [154, 155], fluency [153], memory [153-158], and on measures of global cognitive function [155, 159-161]. Another study of over 3000 participants followed up over up to 9 years indicated steeper rates of decline for males in mental status, motor speed, and visuospatial ability [162]. A study of 2225 adults aged 31-99 and followed up over 27 years also found steeper rates of global cognitive decline in men [163]. Another study with a follow up period of 13 years showed evidence that sex differences in cognitive decline emerged after age 80, with women showing steeper rates of global cognitive decline than men [161, 164]. All of these studies included up to 6000 people, with the exception of one study with just over 9000

participants over up to 10 years of follow up in which cognitive decline did not vary by sex after adjustment for age, education, and baseline cognitive status [155, 161].

Two considerations for studies of cognitive ageing are practice and attrition effects. Practice effect refers to the tendency of individuals to perform better on cognitive tests after the first time it is administered, due to familiarity with the test instruments and protocol [165]. Attrition affects findings for sex differences in cognitive function if men are more likely to drop out of longitudinal studies than women or vice versa. The effect of attrition on sex differences in cognitive trajectories is exacerbated as the most severely cognitively impaired are also more likely to drop out [165]. In one 17-year longitudinal study that explicitly took into account practice effects and differential attrition, the authors observed no sex differences in decline on the Cumulative Verbal Learning Test, intelligence tests, Mill Hill "A" and "B" vocabulary tests, and verbal free recall tasks [161, 166]. A study of over 5000 English adults found that results were substantively similar for sex differences in memory performance and decline when comparing linear mixed models and joint models where differential attrition was taken into account [165]. Another study examining memory and fluency in 8 studies of ageing from the US, Canada, France, and England found that while accounting for attrition influenced the shape of the cognitive trajectory, sex differences were also largely similar between joint models and linear mixed models [167].

Taken together, the evidence points to a lack of sex differences in cognitive decline, however this varies by task, and may not hold for the oldest old. The findings may be influenced by the duration of the period of follow-up as the follow-up period must be sufficiently long to observe meaningful cognitive decline. The literature also suggests that accounting for attrition is potentially of less importance when sex differences rather than overall cognitive trajectories are of primary interest.

2.3.2 Sex differences in functional limitation during ageing

There is a general consensus in the literature that the prevalence of functional limitations is higher among older women than men [168-174], however whether this is attributable to increased incidence of functional limitations among women or simply the fact that women live longer is still unclear [175]. Though the majority of evidence of sex differences in

functional limitations concerns adults aged 65 years and older—likely because functional limitations, particularly in ADL and IADL are less prevalent in middle age—one study of 76,465 participants aged 55 to 65 from 23 countries suggested that there were few sex differences in functional limitations in ADL and IADL prevalence in this age range [176].

There have been many studies using large multi-national study populations to examine sex differences in prevalence of functional limitations in older adults. This is due to the wide availability of these data in the HRS family of ageing studies. Evidence from these large-scale multi-cohort studies showed that the higher prevalence of limitations among women compared to men seemed to be remarkably consistent across settings, with some regional variations in the magnitude of the sex difference [170, 173, 177]. For example, one multi-cohort study of 83,167 participants from Western, Northern, and Southern European countries and the United States found a higher prevalence of ADL limitations in women that reached significance in 8 of 13 countries after adjusting for age, while in France, men reported more ADL limitations [170]. IADL and mobility limitations were more prevalent for women in all countries [170]. When functional limitations were assessed by summing up the number of limited activities into a score, there was evidence that women accumulated functional limitations more quickly than men [178-181].

Whether sex differences in functional limitations are attributable to longer life expectancy among women or if women are actually at higher risk of functional limitations is unclear. There is some evidence that women have a higher incidence of functional limitations than men for ADL [169], IADL [182], and mobility limitations [169]. A study using survival methods found that sex was associated with incident moderate (1-2 limited activities) and severe (≥3 limited activities) ADL limitation [183]. These findings suggest that higher life expectancy among women is not the sole reason for sex differences in functional limitations.

Taken together, the evidence indicates functional limitations in ADL, IADL, and mobility activities are consistently more prevalent among women than among men in many countries. There is also some evidence that incidence of functional limitations is also higher for women, and that women are more likely to have more limitations than men.

2.4 Factors contributing to sex inequalities in cognitive function and functional limitations and their mechanisms

Some of the variability in health during ageing is attributable to the randomness of age-related processes in the body. In large part, however, heterogeneity in ageing is due to a combination of differences in biological and social factors between individuals. Sex differences in cognitive function and functional limitations in old age arise through biological differences between sexes, disparities in social and economic determinants of health, and other factors that are both biological and social. The pathways through which sex differences in cognitive function and functional limitations are proposed to arise are shown in Figure 2.4.1.

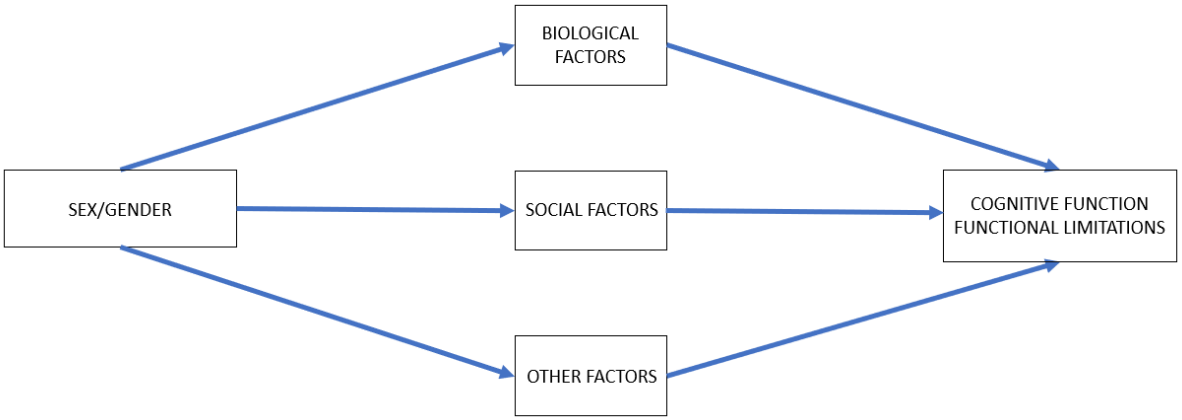


Figure 2.4.1. Pathways through which sex and gender contribute to cognitive function and functional limitations.

Biological factors include sex differences in longevity, endocrine function, and chronic disease development. Social factors comprise the social and economic disparities between men and women, which influence the risk factors men and women are exposed to during the life course, and therefore affect cognitive and functional health in old age. There are also other factors that contribute to sex differences in cognitive function and functional limitations, which have both biological and social elements. These include differences in health-seeking behaviour and treatment outcomes. The focus of this thesis is on social determinants of sex differences in cognitive function and functional limitations, however I also include an overview of the other factors that are thought to contribute these sex differences.

2.4.1 Biological factors

2.4.1.1 Biological determinants of sex differences in cognitive function during ageing

Biological sex differences in cognitive function are rooted in the impact of gonadal steroid hormones on the maintenance and organisation of brain structures. These hormones—namely testosterone and the primary oestrogen, oestradiol—are implicated in neurological development and maintenance throughout the life span [184]. The way in which gonadal hormones affect sex differences in cognitive function can be broadly categorised into: 1) fluctuations in hormones impacting development of brain structures during prenatal development, adolescence, and early midlife; and 2) sex differences in the rate at which gonadal hormones decrease in late middle age, influencing risk factors for neurocognitive disease.

Sex differences in brain structure

Sex hormones play an important role in developing brains. Exposure to oestradiol and testosterone during prenatal development is critical to the organisation of sex-specific neuroanatomical characteristics, with greater exposure to testosterone increasing masculinisation of brain structures [184]. Though the organisational effects of gonadal hormones are thought to have the greatest impact prenatally and during puberty, the sex differences in brain structure organised at birth modify how individual brains react to adverse exposures at all stages of life by contributing to the resiliency of the brain against neurodegeneration induced by ageing or pathology [184]. As such, sex differences in brain structure influenced by the presence and balance of steroidal sex hormones can impact cognitive function in old age.

There is a large body of evidence documenting neuroanatomical sexual dimorphism, though the precise mechanisms through which gonadal hormones affect brain structures are not well understood [129]. Men have on average 10% larger head size and cerebral brain volume compared to women and a higher concentration of white matter, while women typically have a higher concentration of grey matter [129]. There is evidence that women show increased volume and density in areas of the brain involved with language [185]. Even within brain systems such as the limbic system, some structures have larger average

volumes in males, while other structures show larger average volumes in females [185]. As such, disentangling which anatomical differences correspond to differences in behaviour and cognitive function is not straightforward.

Despite the challenges of associating sexual dimorphism in brain structure with cognitive function, there is nonetheless some evidence of correlation between sex differences in brain structure and sex differences in performance on cognitive tests. One study found that the larger grey matter volume in the occipital lobe among males corresponded to better visual function, possibly contributing to better performance on visuospatial tests, while a larger hippocampal gyrus contributed to better memory performance in females [186]. A review of sex differences in neuroanatomy and neuropsychological testing suggested that differences in cognitive function between men and women arise from greater interhemispheric communication in females, while male brains are optimised for within-hemisphere signalling [187]. Thus sex differences in brain structure may give rise to sex differences in aptitude for certain cognitive tasks.

Sex differences in neurocognitive disease

Sex hormones are also thought to influence the pace of brain ageing and cognitive decline through their influence on development of neurodegenerative conditions. In particular, there is evidence of higher rates of Alzheimer's disease in women compared to men [188]. While women do not necessarily experience more rapid decline in cognitive function with normal cognitive ageing than men, sex differences in hormonal fluctuations in late middle age may lead women to be more susceptible to conditions that cause faster than usual cognitive decline such as Alzheimer's disease [188]. This is thought to occur because gonadal hormones have a strong protective effect against neurodegeneration [184, 189-191].

The rapid decline of oestradiol in women following menopause versus the gradual age-related decline of testosterone in men is likely to be a contributor to sex disparities in Alzheimer's disease risk [189]. Endogenous brain oestradiol is implicated in many cellular processes that reduce the impact of neurodegenerative conditions, particularly in the hippocampus [190, 191], the region of the brain involved in memory [191]. Oestradiol is both implicated directly in mitigating neurodegenerative processes [190] and also

moderates neuronal processes associated with the development of neuropathology—for example, stress in the hippocampus leads to atrophy and cognitive decline and oestradiol has been found to blunt the stress response, thus improving memory [190]. Higher oestradiol concentration also reduces the vulnerability of neural cells to apoptosis in the presence of beta-amyloid pathology, particularly in the hippocampus [191, 192].

Despite the observed protective effects of oestrogens, trials of hormone-replacement therapy (HRT) in postmenopausal women to reduce deleterious cognitive effects of falling oestrogen concentration are inconsistent. Explanations for inconclusive results for trials of HRT include the Window of Opportunity Hypothesis which suggests there is a window during which oestrogen therapy is helpful and after this point it is ineffective, and the Healthy Cell Bias of Oestrogen Benefit Hypothesis which posits oestrogen yields neuroprotective benefits only on healthy neurons, and neurons that have already been damaged due to ageing or pathology do not experience a neuroprotective effect [129].

There are also sex differences in genetic susceptibility to Alzheimer's disease. Apolipoprotein E genotype has long been identified as associated with risk of late onset Alzheimer's disease, where the $\mathcal{E}3$ (ApoE3) allele is most prevalent, the $\mathcal{E}4$ (ApoE4) allele increases risk, and the $\mathcal{E}2$ (ApoE2) allele decreases risk [54, 193-195]. ApoE is a protein produced in the central nervous system that binds to the beta-amyloid peptide [196]. The ApoE protein facilitates the degradation of beta-amyloid peptides and ApoE4 appears to increase plaque-formation compared to other variants [195]. The ApoE4 allele is found in 50% of Alzheimer's disease patients compared to 15% of healthy controls [194].

Several studies suggest the effect of the ApoE4 allele is stronger in women than in men [194]. In one case control study undertaken in a large pooled dataset, women heterozygous for the ApoE4 allele were found to have a four-fold increase in risk of Alzheimer's disease compared with ApoE3 homozygous women [197]. ApoE4 heterozygous men experienced little or no increase in risk compared to ApoE3 homozygous men [197]. One study undertaken using data from the Alzheimer's Disease Neuroimaging Initiative found significant differences between men and women in the effect of ApoE genotype for mild cognitive impairment to Alzheimer's disease conversion with an 81% increased risk of conversion among ApoE4-carrying women compared to a 27% risk among ApoE4 men [194].

Among patients with mild cognitive impairment, female ApoE4 carriers were also more likely to have more severe markers of pathology compared to male ApoE4 carriers [194].

ApoE4 also appears to be implicated in sex differences in brain structure that contribute to susceptibility to neurodegenerative conditions. Sex differences in hippocampal volume have been found to be more pronounced among ApoE4 carriers [191]. There is evidence of a greater negative impact of ApoE4 on cortical thickness and memory performance in women compared to men at a similar stage of Alzheimer's disease [129].

Lastly, sex differences in cardiovascular disease and metabolic conditions can give rise to sex differences in risk of Alzheimer's disease, possibly leading to sex differences in the rate of cognitive decline with age. Chronic conditions such as obesity, diabetes, heart failure, high blood pressure, atrial fibrillation, and atherosclerosis are thought to be risk factors for dementia for both sexes [198, 199]. Nonetheless, there is evidence that the impact of cardiovascular disease on dementia risk may differ by sex, with women experiencing a greater increase in risk than men despite having lower prevalence of cardiovascular disease [184, 198]. For example, though both sexes experience an increased risk of myocardial infarction and coronary heart disease with diabetes, the increase in risk of these complications compared to nondiabetics is higher in women than in men [200]. Given that myocardial infarction and coronary heart disease are associated with dementia risk, women may therefore experience a disproportionate increase in risk of dementia with respect to these diabetic complications [198].

2.4.1.2 Biological determinants of sex differences in functional limitations during ageing

Biological drivers of sex differences in functional limitations act primarily through impacting life expectancy, where life expectancy for women is longer in the vast majority of countries [11]. Because age is the major risk factor for many diseases and other declines in health, women living longer than men means women have a greater lifetime risk of developing age-related chronic diseases and physiological and cognitive dysfunction, and are thus more likely to report functional limitations. As such, the biological factors that contribute to a longevity advantage in women also contribute to sex inequalities in functional limitations. These include: 1) the factors that influence sex differences in the biological ageing process

including genetics, anatomy and endocrine function; and 2) sex differences in type, severity, and prognosis of chronic conditions that influence both how long individuals survive with chronic conditions and how likely chronic conditions are to result in functional limitations.

It should be noted that sex differences in longevity and chronic diseases between men and women are also likely to influence sex differences in cognitive function, in addition to functional limitations. Nonetheless, sex differences in longevity and chronic disease are included in this section due to their contribution to physical and mental impairments that may lead to functional limitations.

Biological sex differences in longevity

There is evidence of sex differences in the cellular processes that characterise senescence, with age-related cellular degeneration occurring faster in males in part due to protective effects of female hormones [132, 133]. Females may have more responsive immune function, and a better ability to maintain homeostasis and reduce oxidative stress [11, 201-206]. There is evidence from rodent studies that females may exhibit increased wound healing ability [207-209] and liver regeneration [210, 211]. Females may also be more susceptible to lifespan-increasing drug therapies [211].

There are also genetic advantages for longevity in females. Mitochondrial metabolism has been implicated in cell senescence. As mitochondria are inherited matrilineally, there is no selective pressure against deleterious mutations for males [212], leading to strong disadvantages for males in ageing and survival [11]. Furthermore, the fact that females have two X chromosomes whereas males have one may also be advantageous for survival in females as the redundant X chromosome can compensate for mutations that may be otherwise debilitating and/or lethal for males [11].

In addition to genetic and cellular advantages for females, there are sex differences in brain structure that may lead to sex-specific behaviours influencing longevity. Many structures of the brain exhibit sexual dimorphism. The limbic system, which is implicated in emotion and memory, shows marked differences between males and females, potentially contributing to sex differences in behaviours that may impact longevity, for example impulsivity, sex drive,

and aggression [132, 213]. All of these factors may lead to a longevity advantage for females.

Sex differences in type and severity of chronic disease

In general, men have earlier and higher incidence of cardiovascular disease, whereas women are more likely to report pain, musculoskeletal, and autoimmune diseases [9, 214, 215]. Age-associated neurocognitive diseases such as Alzheimer's disease are more common in women [216], while related dementias such as vascular dementia may be more common in men, likely in part due to higher prevalence of cardiovascular disease in men [217]. Women have worse self-rated health than men, more hospitalisation episodes [218], and also have worse scores on indices of frailty, where frailty is measured using scales of mental and physical functioning and health assessments [7]. All of these factors likely contribute to women reporting worse mental health and wellbeing than men [219], and more functional limitations than men.

Sex differences in the presentation and severity of chronic disease as well as susceptibility to different kinds of disease partly arise due to the influence of sex hormones. One example is obesity, where overall, prevalence of obesity among older adults has gradually increased [211, 220]. Changing activity levels after retirement combined with shifts in sex hormones can lead to accumulation of fat tissue [221], and fat redistribution from subcutaneous areas to abdominal areas [211, 222]. However, due to sex-specific hormone profiles, while women tend to have more body fat than men and are generally more likely to be obese, women are more likely to store adipose tissue in the hips and thighs, which may be protective against cardiovascular and metabolic diseases such as atherosclerosis and type 2 diabetes [211, 223].

Many cardiovascular diseases are both more common and more severe in men than in women. For example, men present with coronary artery disease earlier and with more severe atherosclerosis than women [211]. Men are also more likely to have occlusive coronary artery disease, while women are more likely to have less severe non-obstructive coronary artery disease [224]. Accordingly, men experience myocardial infarction on average 10 years earlier than women [225]. Other cardiovascular diseases such as heart

failure may be more common in women than in men [226], but women are still more likely to survive than men and are also older at disease onset [211, 225]. There is evidence that these differences are in part due to oestrogen signalling [211].

Other disabling though non-lethal disorders are more common in women. Eye conditions leading to difficulty seeing or blindness such as glaucoma and macular degeneration are more common in women than in men, likely in part due to hormonal influences [211]. Females may be more immunoreactive than males, leading to increased resistance to infections, but also increased susceptibility to autoimmune and other inflammatory conditions [227]. All of these factors contribute to a higher prevalence of functional limitations in women than in men, as women may be more likely to have chronic conditions that are less likely to be fatal. As a result, women live longer, albeit with functional limitations. There is evidence from a decomposition analysis of Indian data that sex differences in ADL limitations are 14% attributable to sex differences in health status and chronic morbidity prevalence, while 6% of sex differences in IADL limitations are attributable to sex differences in health status and chronic morbidity prevalence [228].

2.4.2 Social factors

While biological factors refer to differences in physiology, function, and behaviour arising from genetic and neuroendocrine differences between sexes, social factors, also referred to as social determinants of health, comprise the non-biological factors affecting health outcomes; they are the conditions under which individuals live and the structural influences that shape those conditions [229]. Among these social determinants are social class (based on the relationship to means of production and explicitly non-hierarchical) and social status (based on perception of prestige and fundamentally including a hierarchy) [230]. Despite this difference in technical definitions, social class and social status are still used interchangeably in some of the literature, and many indicators that are referred to as markers of class nonetheless have ingrained hierarchy. Two terms, social position and socioeconomic position, are commonly used to refer to social class and social and/or economic status. Indicators of social position include education and occupation. Indicators of socioeconomic position usually combine markers of social position and a marker of economic status such as income or wealth.

2.4.2.1 Social determinants of health

Social determinants of health became a subject of major interest with the publication of a landmark 1978 paper by Michael Marmot and colleagues linking occupational grade and mortality from cardiovascular disease in a cohort of British civil servants [231]. The paper established that there was an inverse relationship between occupational grade and coronary heart disease mortality [231]. One of the most striking findings of the Marmot paper was the existence of the gradient itself: the ill-effects of low occupational grade were not confined to those with the lowest grade; instead each occupational grade lower down the hierarchy was associated with a commensurate increase in mortality [229, 231]. This occurred despite universal availability of healthcare through the National Health Service (NHS).

Following the Marmot paper, the Black Report [232] was published by the UK Department of Health and Social Security in 1980 and was the first attempt to broadly summarise the observed social inequalities in mortality with the aim of informing policy to reduce these inequalities [233]. The Black Report showed that mortality between the 1950s and 1970s in England and Wales was strongly related to "general standing in the community based on occupational skill," where less-skilled and manual occupations were associated with higher mortality [233]. The results of the Black Report were subsequently reproduced in other European countries and even in countries such as the US, Canada, and Australia that do not have such traditionally defined class structure as the UK [233]. Since the publication of the Black Report, numerous adverse health outcomes have been shown to be correlated with low socioeconomic position including other cardiovascular diseases, neurological diseases, hypertension, arthritis, diabetes, and cancer [234, 235].

Social determinants of health can be viewed as "[causes] of causes" [236]; social determinants of health act distally to influence the distribution of disease risk factors in the population [229]. When they are amenable to intervention, addressing these factors can therefore produce population-wide shifts in the distribution of health outcomes. Where traditionally efforts to reduce social inequalities in health have focussed on behavioural interventions, these efforts may not be particularly successful as they do not address underlying drivers of behaviours, which may be guided by social position [233]. Even

interventions like the formation of the NHS did not have the expected impact of reducing social inequalities in health, because disease is the culmination of a lifetime worth of exposures [233]. Increasing access to healthcare at this last stage where disease is clinically diagnosable does little to address the driving forces that produce inequalities in disease incidence [233].

Instead, it is important to design interventions to address social determinants of health early on in the life course, as the effects of these determinants on health are cumulative. Socioeconomic disadvantage at one stage of the life course commonly sets up individuals for further disadvantages [229]. While there is not a particular major factor that predisposes socioeconomically disadvantaged individuals to adverse health outcomes, there are numerous factors that accumulate to impact late-life health [229]. By contrast, previous socioeconomic advantages can minimise the impact of subsequent socioeconomic disadvantage or other hardships on health [229]. Thus, there is a snowball effect of early socioeconomic disadvantage that plays out during the life course. Socioeconomic advantages and disadvantages accumulate during the life course to influence health and functional status in old age.

Mechanisms of social determinants of health

There are three broad mechanisms thought to underlie the relationship between social and economic factors and health. These include behavioural/cultural, psychosocial, and materialist pathways (Figure 2.4.2).

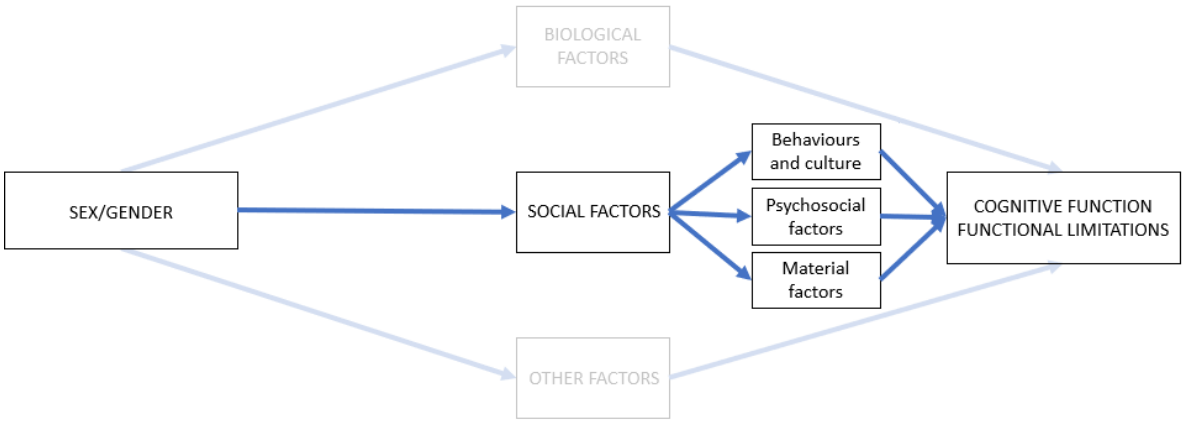


Figure 2.4.2. Mechanisms of social determinants of health.

Behaviours and culture

The behavioural model of culture suggests that culture is composed of learnt behaviours shaped by exposure to a particular social environment [233]. Choices as diverse as leisure pursuits and diet are used to claim membership to a given cultural group, as well as establish distance from other groups [233]. Behaviours like smoking or going to the gym may be perceived as status symbols. The difference in behaviours between social strata is to do with what is viewed as 'appropriate behaviour' within a given stratum, not necessarily solely due to lack of education around the dangers or benefits of health-related behaviours [233]. This concept of the effect of culture on behaviour is supported by studies that find no evidence of difference in understanding of health risks and benefits for healthy eating [237] and smoking [237, 238] between social strata despite the fact that these behaviours are associated with 'higher' and 'lower' social strata respectively [233].

Psychosocial factors

Psychosocial factors include "social support, control and autonomy at work, the balance between home and work, and the balance between efforts and rewards" [233, 239]. The psychosocial model emphasises the way social inequity makes individuals feel and how this manifests physiologically and results in adverse health outcomes.

The psychosocial determinants of health are thought to act through their activation of the fight-or-flight response, which refers to the physiological changes that occur in response to a perceived threat [240]. The neuroendocrine systems implicated in the fight-or-flight

response are the sympathetic adrenomedullary and the hypothalamic-pituitary-adrenocortical (HPA) pathways [241]. The sympathetic adrenomedullary pathway coordinates the rapid release of adrenaline, leading to raised blood pressure, cognitive arousal, bronchodilation, sensory vigilance, haemoconcentration, and energy mobilisation, with the ultimate function of preparing the body for physical exertion [241]. The magnitude of the stress response varies substantially between individuals, dependent on factors including previous experiences with a given stressor [242] and psychological coping resources [241, 243].

The HPA pathway regulates production of cortisol. In the short term, glucocorticoids such as cortisol promote vigilance [241, 243]. However, cortisol also profoundly suppresses the immune system and prolonged exposure is associated with numerous adverse health outcomes such as depression, paranoia, and Cushing's syndrome [241]. Furthermore, the HPA response has the effect of mobilising sugars and fats for rapid energy. However, modern psychosocial stressors frequently do not require physical activity in response, resulting in the deposition of atheroma in blood vessels, which increases the risk of clotting [233]. Health-promoting behaviours and positive states that are largely associated with higher socioeconomic strata including exercise and psychological wellbeing may blunt the response of the HPA pathway and thus reduce chronic exposure to cortisol in the face of stressors [241]. By contrast, stressful life events may be more common in lower social strata and exposure to chronic stress can make individuals more susceptible to an array of adverse health outcomes [233].

Material factors

The Black Report ultimately came to the conclusion that "diffuse consequences of the class structure: poverty, work conditions […] and deprivation in its various forms in the home and immediate environment at work, in education and the upbringing of children and more generally in family and social life" [232] were primarily responsible for the observed social gradient in health. This is the materialist view of health, where poor health results primarily from material deprivation. Much of the evidence for this theory is based on the income gradient in health and life expectancy, with worse health and lower life expectancy among individuals with lower incomes [233, 244]. Though income itself may not affect health,

income is an indicator of exposure to physical hazards that occurs due to material deprivation, and it is this exposure to physical hazards that contributes to poor health [233].

2.4.2.2 Social determinants of sex differences in cognitive function and functional limitations during ageing

Social determinants of health interact with gendered social norms throughout the life course to produce sex differences in cognitive function and functional limitations in old age. Physiological differences between sexes are compounded by the roles men and women are expected to play in society. Using the framework of cultural-behavioural, psychosocial, and materialist pathways, women are subject to cultural and behavioural norms that traditionally discourage education, joining the paid labour force, and involvement in intellectually demanding occupations, psychosocial stressors from low-paid or domestic work and other gendered expectations of behaviour, and the resultant material deprivation may lead to lack of healthcare access and increased exposure to health risk factors. This combination of factors is likely to contribute to sex differences in cognitive function and functional limitations in older adults.

Social determinants of sex differences in cognitive function during ageing

Social factors are thought to effect sex differences in cognitive function in old age through their influence on cognitive reserve. Ageing involves changes in brain structure which usually manifest in cognitive changes. However, age-related or pathological neurodegeneration in the brain does not necessarily result in a commensurate degree of cognitive decline. Beta-amyloid accumulation, pathology that is generally associated with Alzheimer's disease and its characteristic severe cognitive decline, is observed in 20 to 30% of cognitively normal adults [41, 55, 56]. Even among patients with Alzheimer's disease, severity of pathology does not necessarily correlate with severity of clinical disease [189]. There is a clear disconnect between neuroanatomical changes in the brain and cognitive function.

The concept of reserve is used to explain the inconsistency between structural markers of brain ageing or neurodegeneration and performance on cognitive tests. Reserve comprises characteristics of the person or anatomical features of the brain that allow resilience to

neuropathological or age-related decline in brain structures such that these declines do not result in decreased performance on neuropsychological tests [100]. Research over the past 20 years has identified two conceptualisations of reserve: the active and passive models [245].

The passive model suggests that neuroanatomical features such as brain size and synapse count allow the individual to withstand more neurodegeneration such that there is little impact on cognitive function [246, 247]. The mechanism is seen to be passive as the emphasis is not on the way individuals process information or develop compensatory mechanisms [246, 247]. Nevertheless, passive reserve provides a lifelong buffer against the manifestation of neurodegeneration in decreased cognitive performance. Early life environmental exposures—such as education—are involved in the development of brain structures [248] and may be markers of passive reserve.

Active models of reserve are thought to slow cognitive ageing due to individual differences in the ability of the brain to develop compensatory mechanisms to deal with neurodegeneration [249]. Intrinsic to the theory of active reserve is the idea that brains are continuously developing mechanisms to reduce functional loss in the presence of neurodegeneration or injury [247]. Factors that influence active reserve might mitigate the rate of cognitive decline rather than affecting peak midlife performance. Contributors to passive reserve instead influence peak cognitive performance, thus providing a lifelong cognitive advantage.

It has been proposed that sex differences in reserve contribute to sex differences in cognitive function. Sex differences in reserve are thought to arise when women have less access to 'intellectually enriching' lifestyles—for example, less education and thus less participation in intellectually demanding occupations—than men and therefore fewer opportunities to build and maintain reserve. Contributors to reserve that show important differences in distribution between men and women include education, employment in intellectually demanding occupations, degree of social support, and participation in cognitively demanding leisure activities [250]. Women born during the early to mid 19th century may be less likely to be educated and more likely to be in low-paid or unskilled positions, unemployed, or homemakers than men [129]. Homemaking is also associated

with a higher likelihood of being depressed, living alone, hypertension, and obesity, all of which contribute to increased risk of cognitive decline [250]. These sex disparities are hypothesised to lead to lower reserve in women than in men, and therefore sex differences in both cognitive function and susceptibility to neurocognitive disease [250].

Of these factors, gender inequalities in education may contribute to other gender disparities in occupation and lifestyle. Education has been linked with higher midlife cognitive performance [100], and is thought to confer a cognitive benefit that persists throughout the life course [101]. Education is also distinct as multiple studies have indicated that it is the only social factor that is causally linked to dementia in studies using instrumental variable approaches to address confounding [104, 251, 252], likely through its protective effect on cognitive function. Though the precise mechanism through which education influences reserve is not well understood, education seems to facilitate efficiency of memory encoding and retrieval, better organisation of information, use of prior-knowledge to enhance processing speed, and the development of more efficient neural algorithms for problem solving [253]. As the evidence indicates that education influences midlife cognitive performance rather than mitigating the rate of decline [100, 101], education is thought to be a marker of passive rather than active reserve, and thus provides a buffer to cognitive decline with ageing or pathology.

Because of the observed effect of education on cognitive function, sex disparities in education are thought to be particularly relevant as a contributor to sex differences in reserve, leading to sex differences in cognitive outcomes [250]. Higher education level also allows access to more intellectually demanding occupations, contributing to an intellectual lifestyle that helps build and maintain reserve over the life course [198]. Complex occupations are associated with better cognitive function [97-99], and at least one study suggests the association occurs independently of education level [254]. Lifestyle factors such as exercise that have been associated with better cognitive function [41, 102, 103] are also associated with higher education level [255]. Thus with education comes a slew of other associated lifestyle factors and behaviours that may shape cognitive performance during the life course, giving rise to sex differences in cognitive function in old age when women are less likely to be educated and engage in these healthier lifestyles. Correspondingly, there is evidence that sex differences in education contribute to sex

differences in cognitive performance, with sex differences attenuated after adjustment for education [19, 151, 256-260].

Comparisons of sex differences in cognitive function across levels of economic development

There are differences between high and lower-income countries in cognitive sex disparities, where larger sex disparities in cognitive function that are less favourable to women have been found in middle- compared to high-income countries [151, 257]. In studies of Indian cohorts, a female disadvantage was found across a number of cognitive tasks, including in composite cognitive scores comprised of memory, digit span, and verbal fluency tests [260], MMSE and memory [261], and other global cognitive scores [262]. A similar female disadvantage in memory was also found in China [260]. The findings for memory are particularly notable as there is generally a consistent female advantage in memory tasks in high-income settings [143]. In a study undertaken using data from 54 countries, there was evidence that higher female-to-male ratio in education and labour force participation, higher overall levels of education and employment in the population, and GDP per capita were associated with larger female advantages in episodic memory [144]. This is consistent with studies that indicate education plays an important role in sex differences in cognitive function in middle-income countries [151, 257-260], similar to high-income countries. Despite the evidence that sex differences in cognitive function may vary between countries at different levels of economic development, there are few studies that directly compare sex differences between countries, and those that do show results for high- and middle-income countries do not use nationally representative study populations [151, 257] and as such cross-national comparison is not the primary aim of these studies.

Social determinants of sex differences in functional limitations

Social determinants of sex differences in functional limitations primarily act through impacting the kinds of environments to which individuals are exposed. This affects both risk of disease and the ability to access resources to mitigate the manifestation of disease in functional limitations. Social and economic factors such as education, occupation, and income can also influence behavioural norms that may impact disease risk and thus risk of functional limitations.

Education has been identified as playing a role in sex differences in functional limitations, in part as it is a 'gatekeeper' to other socioeconomic conditions. Education reflects elements of childhood socioeconomic position and associated environmental exposures. However, education is also to an extent prescriptive of adult socioeconomic position. Education level influences the occupations individuals are eligible to engage in, the social circles they interact with, and even choice of spouse [263]. All of these factors impact health-related behaviours like diet, exercise, smoking, and alcohol consumption. As women are likely to be less educated, and are subsequently more likely to be in unpaid or domestic labour, with lower incomes than men, women may be more likely to be exposed to conditions that increase risk of disabling chronic disease, with less access to healthcare to address these risks.

In a decomposition analysis of over 63,000 participants from 57 countries, approximately 45% of sex inequalities in prevalence of functional limitations in adults over age 50 were attributed to sex inequalities in social and economic factors including employment, education, marital status, and household economic status [124]. Of these factors, employment was the strongest contributor, as a significantly higher proportion of men than women were in paid labour; the main reason women gave for not being in paid labour was that they were homemakers or caring for the family [124]. Education was another strong contributor to sex differences in prevalence of functional limitations [124]. There is evidence that education acts to affect functional limitations through occupation and income [264]. Another decomposition analysis undertaken using an Indian cohort study also found significant sex differences in ADL and IADL limitations [228]. Sex differences in ADL limitations were attributable partly to sex differences in labour force participation (18%), formal education (15%), and marital status (13%) [228]. Sex differences in IADL limitations were also partly attributable to sex differences in formal education (28%) and marital status (10%) [228].

Comparisons of sex differences in functional limitations across levels of economic development

There is evidence that sex differences in functional limitations at older ages vary by country based on level of economic development. In one weighted analysis of data from China,

Ghana, India, Mexico, Russia, and South Africa, all of which except for Russia and South Africa are lower or upper middle-income countries, women were more disadvantaged with a higher prevalence of ADL limitations across all age groups [265]. However, the sex disparities in each age-group in India, Ghana, and Mexico were the largest [265]. One study used HRS-family data from Mexico, the US, Korea, and multiple European countries to examine how macro-level measures of gender inequality—in this case, the United Nations Gender Inequality index—affected gender inequality in incident ADL limitations, where higher gender inequality is observed in lower income countries [266]. The authors found that women in the pooled analytic sample were significantly more likely to experience ADL limitations, higher gender inequality index was associated with higher incidence of limitations for both men and women, and adjusting for gender inequality index attenuated the association between gender and incident limitations [266].

Another study of midlife disability from ages 55-65 found that of 23 countries of Europe, Asia, and the Americas, in which China and Mexico were the only included middle-income countries, only China and Mexico showed a higher prevalence of ADL limitations among women than among men [176]. Taken together, the evidence suggests that incidence and prevalence of functional limitations in women in lower income countries may be higher than in some high-income countries.

Birth cohort effects and sex differences in cognitive function and functional limitations in ageing

Overall, the evidence points to a considerable contribution of sex inequalities in social and economic factors to sex differences in cognitive function and functional limitations from midlife to old age. However, over the 20th century, social and economic conditions in middle- and high-income countries have generally improved for both men and women. Men and women tend to be more educated, more likely to work in skilled positions, and healthcare, sanitation, and disease management have substantially improved. This has led to broad trends towards decreasing mortality in successive generations [267, 268] and in much of the world, a shift from morbidity and mortality caused by infectious disease to chronic disease, as individuals live longer, employed in office-based occupations rather than in manual labour [269]. This epidemiological transition has led to large-scale differences in

health between successive generations. For some diseases, such as Alzheimer's disease and related dementias, against which higher education level and intellectually-demanding occupations are protective, these generational differences may result in reductions in incidence with increasing year of birth [270]. Cardiovascular disease incidence and mortality has also broadly decreased across birth cohorts, with some variation between countries [271].

The tendency of groups to vary from each other due to shared temporal exposures, in this case, exposures that occur due to year of birth, is referred to as the birth cohort effect [272]. Within birth cohorts, individuals have similar environmental exposures—such as educational systems, nutrition, sanitation, and healthcare—and thus birth cohorts are more internally than externally comparable. For example, cognitive function decreases with age. However, when birth cohort effects are not considered, the age effect can be overestimated, because the oldest individuals in a study population are also exposed to worse environmental conditions and therefore may have worse cognitive function than later-born birth cohorts. As such, consideration of birth cohort is important for age-related outcomes. Birth cohort effects are distinguished from period effects as a period effect refers to an exposure occurring at a specific time that applies equally to individuals of all ages and cohorts [272].

A birth cohort effect in sex inequalities in health is observed when successive generations of men and women are exposed to progressively more equal conditions during the life course. Due to changing gender norms, sex inequalities in many social determinants of health are decreasing. Women were historically restricted from access to education and participation in certain forms of labour [12]. However, in many countries, equity of educational opportunities for men and women was introduced by law during the mid to late 20th century [273]. Women in high- and middle-income countries have better access to education and are encouraged to attain higher degrees and enter the workforce. Younger generations of women may have different and largely less restrictive experiences of gender norms than older generations. These generational reductions in social and economic inequalities between men and women may lead to reductions in cognitive and functional disparities between men and women in old age, since health in old age is influenced by the cumulative impact of environmental exposures during the life course.

Differences in sex inequalities in cognitive function across birth cohorts

There is evidence of differences in cognitive outcomes by birth cohort. The phenomenon of increasing intelligence quotient in successive birth cohorts of American adults was first observed by American political scientist James Flynn in a 1984 paper and is accordingly referred to as the Flynn effect [274, 275]. Other cognitive outcomes such as language, executive function, attention/processing speed, and verbal memory show a similar effect, with successive birth cohorts having both higher cognitive performance at the same age, and also reduced rate of cognitive decline [270, 276, 277], though at least one study found better performance but steeper rates of logical reasoning and spatial ability decline in later born cohorts [278]. These effects are generally attributed to improvements in living standards, education, and increases in the intellectual demands of daily life and occupations [279]. As women are more likely to be educated to higher levels in successive birth cohorts, there is some evidence of concurrent reductions in sex differences in cognitive performance with successive birth cohorts, and that education may play a role [80, 151, 256, 278].

Differences in sex inequalities in functional limitations across birth cohorts

Some studies also show a reduction in prevalence of functional limitations with increasing birth year [280-288] particularly for women [282-284, 288, 289]. There is little research explicitly examining determinants of these trends in sex differences by birth cohort, though many of these studies posit reductions in socioeconomic inequalities between men and women and improvements in management of chronic conditions as contributing to reductions in sex inequalities in functional limitations in successive birth cohorts.

One study examined the effect of education via income compared to occupation on functional limitations in successive birth cohorts. The authors found that educational inequalities in functional limitations were increasing, and that education acted increasingly through occupation rather than income in successive birth cohorts [264]. The implication is that in more recent birth cohorts, it is more difficult for those who are less educated to obtain higher skilled jobs, negatively impacting their health [264].

2.4.3 Other factors

Other contributors to sex differences in cognitive function and functional limitations in old age may not arise from biological sex differences in longevity nor from gender differences in social and economic conditions. These factors may relate to behaviours that are gendered but occur somewhat independently of social and economic position, including gender differences in health-seeking behaviour, or from differences in symptom recognition and treatment. Some of these factors are covered in brief in the following section.

It has been hypothesised that some of the sex differences in functional limitations occur due to sex differences in reporting. Under this condition, differences in functional limitations that are observed might not reflect actual functional capacity, but rather the tendency of men and women to accurately report functional limitations [290]. Women may be more likely to report physical discomfort as a symptom [10, 291-293] and are more likely to be attentive to their health care needs than men; by contrast men are socialised to dismiss physical discomfort [290, 294]. This may lead to sex differences in functional limitations that reflect actual sex differences in functional capacity when it causes women to seek out treatment for chronic conditions earlier on, and thus have better prognoses, leading women to live longer with functional limitations. However, it leads to incorrectly estimated sex differences when men simply do not report their functional limitations accurately when asked. Men have been found to underreport limitations while women overreported limitations when objective measures were used compared to self-report [290].

Despite the evidence that some reported sex differences in functional limitations may not reflect sex differences in functional capacity, studies have found that adjusting for comorbidities explains sex differences in functioning [170, 295]. This suggests at the very least conditions that impact functioning also have an impact on sex differences and sex differences are not solely due to underreporting of limitations among men. Sex differences are also pervasive in objective measures of physical functioning such as gait speed, grip strength, and chair stands, also suggesting that sex differences are not purely due to artefact [177, 295].

Other sex differences in both functional limitations and cognitive function may occur because medical knowledge is predominantly based on men. Women may be less likely to receive appropriate treatment for cardiovascular disease, such as coronary artery disease, due to differences in presentation of these diseases between men and women [296]. When women present with 'male-typical' coronary artery disease patterns, they are more likely to receive more aggressive treatment and experience fewer adverse outcomes [296]. Common knowledge of other cardiovascular conditions such as myocardial infarction is also based on male-typical symptoms, meaning that women may be less likely to recognise their symptoms and receive early treatment [297] to minimise impact on functioning thereafter.

Another determinant of sex differences in cognitive function and functional limitations is behaviours that may tend to differ between genders [233] to an extent independently of social and economic position. Men are more likely to engage in risk-taking behaviours including smoking, alcohol use, use of psychoactive substances, and unsafe driving [9, 298, 299]. Traditionally, women may be more responsible for health in the family and knowledgeable about illness and thus more likely to use healthcare services than men [9, 294]. Stereotypical ideas about gender may also make it more socially acceptable for women to be ill, report health-problems, and seek out advice about illness [9, 294]. Findings from one study of the national Danish Registry suggested that Danish men delayed seeking treatment for disease, requiring more complex interventions that were less effective for long-term survival than women [9, 300]. This potentially contributes to longevity differences between men and women and also the amount of time men and women spend living with functional limitations.

3 Summary of literature, knowledge gaps, and thesis rationale

3.1 Summary of literature review on sex differences in cognitive function during ageing

Sex differences in cognitive function in older adults differ by cognitive domain, with women outperforming men on tests of memory, men outperforming women on tests of visuospatial ability, and mixed results for sex differences in tests of other cognitive domains [51]. There are inconsistent sex differences in cognitive decline with ageing, however the bulk of evidence points toward similar rates of cognitive decline in men and women [161].

Biological determinants of cognitive sex differences are thought to act through genetic and neuroendocrine pathways. XY and XX chromosomes give rise to male- and female-typical distributions of sex hormones respectively. The balance of these sex hormones influences the volume and density of brain structures, likely contributing to sex differences in cognitive function [185]. Sex differences in brain structure volume and density also potentially inform sex differences in resiliency to neurodegeneration with ageing or pathology [184]. Sex differences in cognitive function in old age may occur as a result of sex differences in susceptibility to neurocognitive disease. Oestrogen is broadly neuroprotective, and as a result decreasing oestrogen concentration following menopause and sex differences in genetic risk factors for Alzheimer's disease may result in greater susceptibility to Alzheimer's disease among older women compared to men [184].

Social factors are thought to contribute to sex differences in cognitive function due to their influence on cognitive reserve [250]. Factors such as education and occupation may play a role in sex differences in cognitive function in older adults when women are less likely to be educated or have intellectually-demanding occupations and lifestyles, and therefore have fewer opportunities to build and maintain reserve. Of the social factors associated with cognitive function, there is evidence of a causal association with education [104, 251, 252], and evidence that sex inequalities in education contribute to sex differences in cognitive function [19, 151, 256-260]. There is evidence of improvements in cognitive function with increasing year of birth cohort [270], however how reductions in socioeconomic inequalities

between men and women have impacted sex differences in cognitive function in old age has not been systematically examined.

Sex differences in cognitive function vary between countries at different levels of economic development, with some evidence that men in middle-income countries outperform women, even in cognitive domains such as memory where women outperform men in high-income countries [151, 257]. Comparisons of sex inequalities in cognitive function in high- and lower-income countries and the factors that contribute to differences in sex inequalities between high- and lower-income countries are not well described in the literature.

3.2 Summary of literature review on sex differences in functional limitations during ageing

Older women are more likely to have functional limitations than men [168-174], and there is evidence that this is not due solely to increased longevity among women [169, 182, 183], nor differences in reporting of functional limitations between men and women [170, 295]. In the literature, functional limitations are most commonly examined dichotomously, and characterising sex differences in severity of functional limitations requires further examination.

Sex differences in longevity and type and severity of chronic disease contribute to sex differences in functional limitations. Women live longer due to neuroendocrine and genetic advantages that increase longevity [11]. Women also seem more likely to be diagnosed with disabling though non-fatal chronic conditions, while men are more likely to have conditions that are fatal [211], in part due to hormonal differences between males and females. These factors combine to make women more likely to live longer, albeit more likely to experience disabling chronic conditions, and thus more likely to experience functional limitations in older age.

There is also evidence that sex inequalities in social and economic factors such as education, employment, and income contribute to sex differences in functional limitations [124], possibly due to the influence of these factors on access to healthcare and exposure to health risks as well as behavioural norms associated with social and economic strata. There

is evidence of reductions in sex differences in functional limitations with increasing year of birth cohort, particularly for women [282-284, 289].

The finding that women have a higher prevalence of functional limitations is consistent across high- and lower income countries, though sex differences seemed to be larger in some middle-income countries [176]. Examining differences between countries in sex inequalities in functional limitations and the factors that contribute remains an area for further research.

3.3 Thesis rationale

The literature shows that sex differences in cognitive function and functional limitations in older adults have both biological and social drivers, both of which warrant further investigation. Nonetheless, this thesis will focus on the role of social factors for two reasons. First, social factors—as opposed to biological factors arising out of genetic or epigenetic influences—are perhaps more easily amenable to intervention during the life course. Second, addressing social determinants of health has the potential to affect broad population-wide shifts in cognitive and functional health in old age.

3.3.1 Measuring social position in the thesis

There are several considerations that guide the choice of indicator of social position in this thesis. Among markers of social position, education and occupation are the most widely available in the HRS family of cohort studies. However, until the mid-late 20th century, many women did not enter the paid workforce, making occupation an unsuitable indicator of social position. Furthermore, the thesis uses data from several countries and measures of occupational class are highly context-dependent, while the measure of social position used in this thesis must be comparable between countries.

With these considerations in mind, education is the measure of social position that was chosen for use in this thesis for several reasons. First and most importantly, education is repeatedly identified as a particularly salient driver of sex differences in cognitive function and functional limitations in older adults, with a proposed causal link to cognitive function. Second, education may capture elements of childhood social position, from access to

healthcare to parental involvement to social deprivation, all of which can influence health throughout the life course. Education may also predict and reflect adult social position by opening up occupational pathways and social strata. Finally, there is an international classification system that allows comparison of educational categorisation between countries and is widely available in the HRS family studies.

3.3.2 Knowledge gaps and objectives

Within the body of evidence of the role of education in sex differences in cognitive function and functional limitations in old age, there are two distinct knowledge gaps which this thesis will address. First, despite well-documented historical disadvantages in education for women, gender disparities in access to education and degree attainment have decreased significantly over the 20th century, with little research into how these changes in gender disparities have impacted sex differences in cognitive function and functional limitations in old age. Further, functional limitations are commonly examined dichotomously, while sex differences in severity of functional limitations are not as well-explored. Second, gender disparities in education vary widely between high-income and low- and middle-income countries, as economic development is highly related to gender equity [266]. There are few studies that compare differences in sex inequalities in cognitive function between middle- and high-income countries, and none undertaken in nationally representative samples that examine determinants of differences in sex inequalities between countries. Therefore, the objectives of the thesis fulfil the knowledge gaps identified in the literature:

Objective 1: Cognitive function

a. Examine the role of education in sex differences in cognitive ageing with attention to decreases in sex inequalities in education over time.
b. Examine and compare the role of education in sex differences in cognitive function in older adults in middle- and high-income countries.

Objective 2: Functional limitations

> Examine the role of education in sex differences in functional limitations in older adults with attention to decreases in sex inequalities in education over time and severity of limitations.

Following the methods overview in Chapter 4, Chapter 5 covers in detail the investigations concerning the role of education in sex differences in cognitive function in sections 5.1 (objective 1a) and 5.2 (objective 1b) and in functional limitations in Section 5.3 (objective 2).

4 Methods overview

4.1 Data sources

This thesis uses the HRS family of longitudinal health and ageing studies to examine sex differences in cognitive function and functional limitations in older adults. The HRS-family studies included in the thesis are the Survey of Health, Ageing and Retirement in Europe (SHARE) [301], the English Longitudinal Study of Ageing (ELSA) [302], the Irish Longitudinal Study on Ageing (TILDA) [303], the Health and Retirement Study (HRS) [304], the Mexican Health and Aging Study (MHAS) [305], the Brazilian Longitudinal Study on Ageing (ELSI) [306], the China Health and Retirement Longitudinal Study (CHARLS) [307], and the Longitudinal Ageing Study in India (LASI) [308]. An overview of the countries covered by each of the studies as well as the studies used in each paper are shown in the Table 4.1.1.

The HRS-family studies use a similar combination of computer assisted personal interviews and self-completed questionnaires for survey completion, have a core of analogous questions, and have datasets freely available for the use of researchers. Many HRS-family studies also include cross-sectional survey weights so that population parameters can be estimated using the cohort data.

Table 4.1.1. Countries included in HRS-family studies.

Europe		**Included in paper**
Survey of Health Ageing and Retirement in Europe (SHARE)	Denmark, Sweden, Austria, Belgium France, Germany, Netherlands, Switzerland, Greece, Italy, Spain	3
English Longitudinal Study on Ageing (ELSA)	England	1, 3
Irish Longitudinal Study on Ageing (TILDA)	Ireland	3
Americas		
Health and Retirement Study (HRS)	United States	2
Mexican Health and Aging Study (MHAS)	Mexico	2
The Brazilian Longitudinal Study on Aging (ELSI)	Brazil	2
Asia		
Chinese Health and Retirement Longitudinal Study (CHARLS)	China	2
Longitudinal Ageing Study in India (LASI)	India	2

In addition to HRS, the thesis makes use of three HRS-family European cohort studies. SHARE was created as part of a European Commission initiative to understand population ageing in member states [301]. SHARE includes 8 waves of data collection (2004-06, 2006-07, 2011-12, 2013, 2015, 2017, 2019-2020). For each included country in SHARE wave 1, the target population includes all persons born in 1954 or earlier, excluding those who are incarcerated or hospitalised, and those who lived abroad during the entire period of data collection [301]. As SHARE includes many European countries, the sampling frames are chosen according to the resources available in the respective country, and sampling weights are included to account for survey design [301]. As such, analyses undertaken using SHARE data can produce unbiased estimates of population parameters [301].

The English Longitudinal Study of Ageing (ELSA) is a nationally representative ageing study based on the English population aged 50 years and older, recruited from the 1998-2001 Health Survey for England (HSE). Data collection began in 2002 with follow up every two years until 2018 for a total of 9 waves of data, with an additional wave of data collection currently in progress. Individual weights are available to produce population estimates of parameters.

The Irish Longitudinal Study on Ageing is a nationally representative study of the Irish population aged 50 years and older. The sampling frame is based on the Irish Geodirectory which includes all residential addresses in the Republic of Ireland [309]. TILDA includes 4 waves of data collection, every two years from 2010 to 2016.

The thesis uses data from two other studies from the Americas in addition to HRS. MHAS is a representative study of adults over 50 in Mexico. The sample was selected from the National Employment survey, including participants from all 32 states of Mexico in both urban and rural settings [305]. Participants were initially surveyed in 2001, and then again in 2003, 2012, and 2018. The thesis also uses ELSI, a 2015 nationally representative survey of the Brazilian population aged 50 years and older [306]. As there is no population wide register in Brazil, the national household surveys used the Brazilian Institute of Geography and Statistics geographic operational base and stratified multistage sampling to select households to survey [306]. Individual weights that account for survey design are provided in both MHAS and ELSI to enable estimates of population parameters.

Two Asian studies were used in the thesis. CHARLS is a nationally representative survey of the Chinese population. No sampling frame of residents existed in China at the time of survey inception, so stratified multistage sampling and then village-level mapping and listing was used to determine which households should be surveyed to select the representative sample [307]. CHARLS includes 2011, 2012, 2014, and 2018 waves. LASI is a nationally representative Indian survey of health and ageing, with one wave of data collection taking place between 2017 and 2019 and further waves of data collection planned in the future [308]. LASI is representative for the Indian population aged 45 and older [308]. LASI sampled sub-districts within states, and villages and wards within sub-districts and then carried out mapping and listing to determine which households to sample within these strata [308]. Both CHARLS and LASI include weights to account for survey design.

In addition to the HRS-family studies, data were used from the Whitehall II study. The Whitehall II study is a long-running longitudinal study of British civil servants who worked in the Whitehall neighbourhood of London. The Whitehall II study includes a comprehensive health assessment and spans multiple decades with high retention of participants, making it ideal for examining ageing outcomes. Data collection in Whitehall II began in 1985, with the

first wave taking place from 1985-88, the most recent wave of data collection in 2015-16, and a 2019-22 wave currently in progress. Participants undergo clinical examination every 4-5 years.

4.2 Outcomes

4.2.1 Cognitive function

Cognitive function is examined using scores on neuropsychological tests, administered by an interviewer to the respondent in the HRS-family studies, and self-administered in the Whitehall II study. Cognitive ageing is examined using change in scores with age. The tests administered in each paper are shown in Table 4.2.1. Details of cognitive testing protocol are shown in the respective sections for each study.

Table 4.2.1. Cognitive tests included in each paper.

Cognitive domain	Cognitive test	Included in paper
Episodic memory	Immediate/delayed recall	1, 2
Verbal fluency	Animal naming	1, 2
Orientation	Date naming	2
Sustained attention	Serial 7s	2

There is a battery of cognitive tests called the Harmonized Cognitive Assessment Protocol (HCAP) available in several of the HRS-family studies. HCAP is intended to provide a more detailed cognitive dataset that is comparable between countries. However, HCAP is only administered to a small proportion of study participants. For this reason, this thesis uses the neuropsychological tests that were administered to the entire study population, and that are included in multiple cohorts.

4.2.2 Functional limitations

Functional limitations were assessed using limitation in three categories of activities: ADL, IADL, and mobility activities. The ADL, IADL, and mobility activities used in the examination of functional limitations are described in Table 4.2.2. Participants were asked whether they experienced difficulty performing these activities for longer than three months due to a

physical, mental, emotional, or memory problem. They were considered limited for a given activity if they answered "yes" for that activity.

Table 4.2.2. Activities assessed for each functional measure.

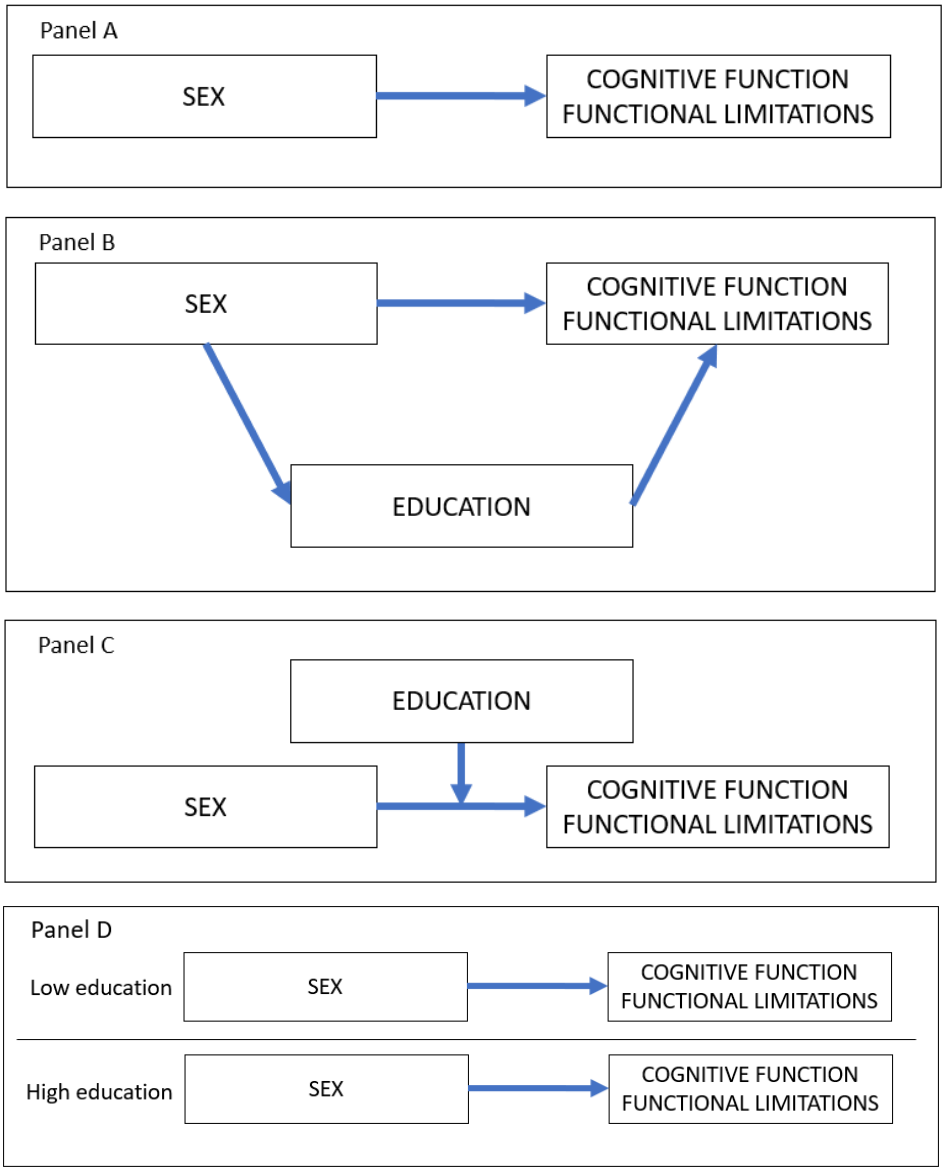
Mobility activities	IADL	ADL
Getting up from a chair	Managing money	Walking across the room
Climbing 1 flight of stairs	Taking medications	Dressing
Stooping, kneeling, or crouching	Grocery shopping	Bathing
Reaching/extending the arms	Preparing meals	Eating
Lifting/carrying weights over 10 lbs	Using the telephone	Getting in/out of bed
Walking 1 block/100 yds/100 m	House/garden work	Using the toilet

4.3 Statistical methods

Although each paper differs in its statistical methods, there is a general form that each of the analyses in this thesis take:

1. Estimate sex differences in the outcome adjusted for appropriate sociodemographic covariates (Figure 4.3.1, Panel A)
2. Adjust for education to examine the effect of education on sex differences (Figure 4.3.1, Panel B)
3. Include an interaction term between education and sex to evaluate education as an effect modifier (Figure 4.3.1, Panel C)
4. Stratify by education level to determine whether sex differences vary by education level (Figure 4.3.1, Panel D)

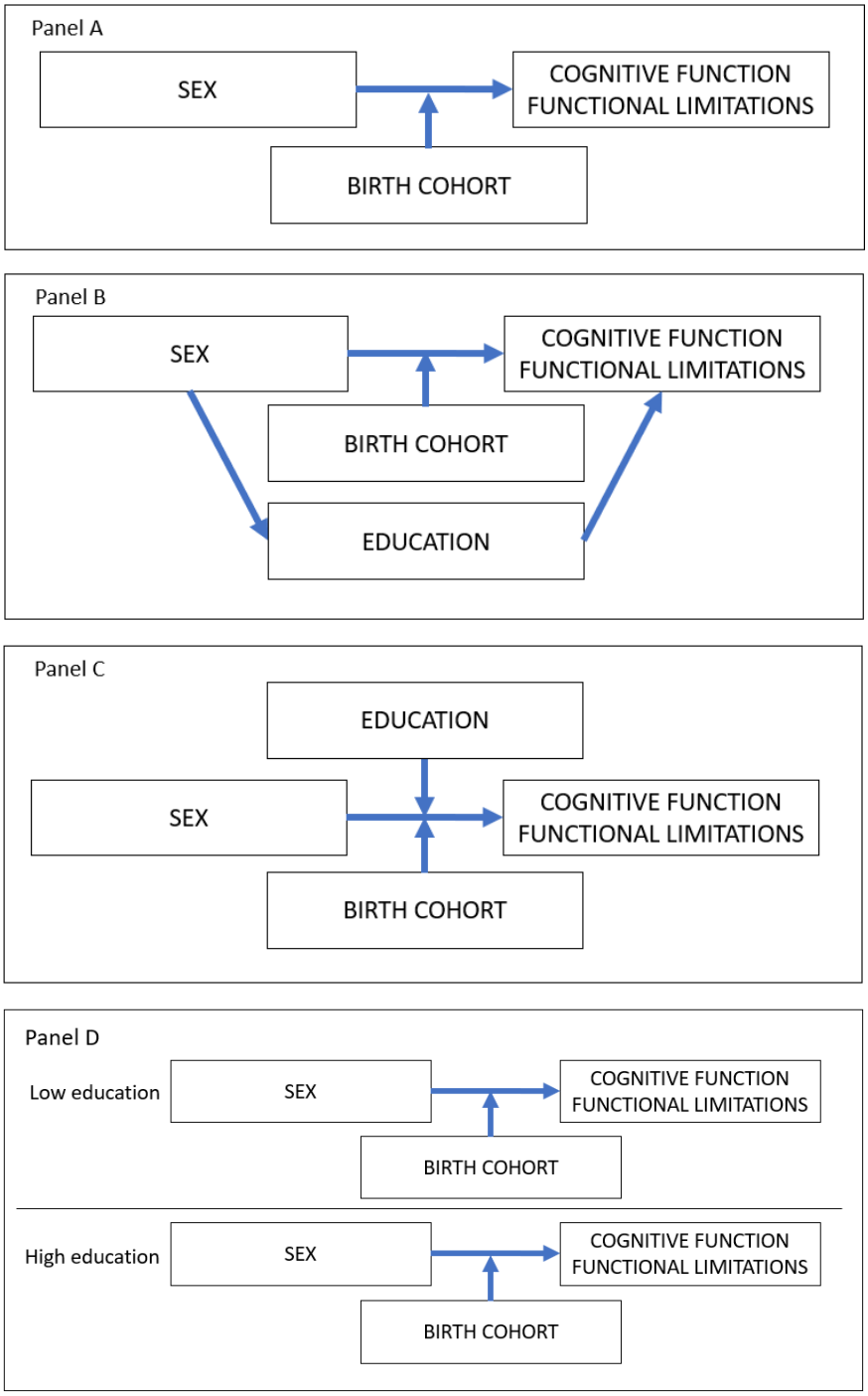
Figure 4.3.1. Analytic framework for examination of sex differences in cognitive function and functional limitations and the role of education.



The analyses also include examination of how reductions in educational sex disparities over time have impacted sex differences in cognitive function and functional limitations. In order to do this, birth cohort is included as an effect modifier, to first examine the sex difference in each outcome in each birth cohort, then the effect of adjustment for education on the sex differences in each birth cohort (Figure 4.3.2). This also allows examination of whether adjustment for education attenuates the variation in sex differences between birth cohorts. Where this is the case, this suggests that differences in education between birth cohorts underlie the birth cohort differences in sex inequalities in the outcome, indicating that reductions in sex inequalities in education play a role in reductions in sex inequalities in the

outcomes. Papers 1 and 3 used longitudinal data with sufficient overlap of ages between birth cohorts to examine birth cohort effects separately from age effects.

Figure 4.3.2. Analytic framework for examination of sex differences in cognitive function and functional limitations and the role of education with inclusion of birth cohort.



5 Investigations in detail

5.1 Paper 1: Sex differences and the role of education in cognitive ageing: analysis of two UK-based prospective cohort studies

Text adapted from *'Sex differences and the role of education in cognitive ageing: analysis of two UK-based prospective cohort studies'* published in the Lancet Public Health (2021). Full publication included in the Appendix (page 220).

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Author contributions: Conceptualisation: SS, AD, JD, AS-M. Methodology: SS, AD, AF. Investigation: MK, ASM, AS, AB. Validation: SS, AD. Formal analysis: MB, AD, SS. Data curation: MB, AD, AF, SS. Writing –original draft preparation: MB, SS. Writing –review and editing: All authors. Visualisation: MB, AD, SS. Supervision: SS, ASM. Funding acquisition: ASM, MK, AS.

5.1.1 Rationale

Previous studies indicate that there are sex differences in cognitive function during ageing, including female advantages on tasks of memory [143], male advantages on tasks of visuospatial ability, and mixed results for other cognitive domains and for sex differences in cognitive decline with age [51]. Sex differences in cognitive function during ageing are thought to be partially attributable to sex inequalities in education [19, 151, 256-260]. Though some studies suggest that secular changes in access to education across birth cohorts affect sex differences in cognitive function [80, 151, 256, 278], the one study that explicitly examines this question does not take into account how sex differences in cognitive function change from midlife to old age [151].

5.1.2 Objective

We used longitudinal data on men and women born between 1930 and 1955 in analyses stratified by birth cohort to examine the role of education in sex differences in memory and fluency performance and decline, and how secular changes in sex disparities in education

impacted sex differences in cognitive function during ageing. We undertook analyses first adjusting for education and then within education groups using pooled data on 15,924 participants from two British prospective cohort studies, followed for up to 19 years.

5.1.3 Methods

5.1.3.1 Data sources

Paper 1 required a study sample sufficiently large to examine variation in sex differences by birth cohort and in education groups. In order to undertake these analyses, it was necessary to pool cohort studies together, meaning that study populations had to be adequately comparable with each other. For this reason, paper 1 used ELSA and Whitehall II, two British longitudinal studies of older adults with participants who were born and educated during the same time period.

ELSA waves from 1 to 7 were used (survey years 2000 to 2014), comprising participants born in 1930 and thereafter. ELSA participants were surveyed every 2 years during this period. ELSA participants born before 1930 were excluded in order to harmonise the range in year of birth cohorts between ELSA and Whitehall II.

Paper 1 also used five waves of Whitehall II data. A battery of cognitive tests was introduced to the Whitehall II study in the 1997-99 wave, the baseline of the present analysis. In addition to this first wave of cognitive data, paper 1 also used waves from 2002-04, 2007-09, 2012-13, and 2015-16. Table 5.1.1 and Table 5.1.2 detail waves and years of inclusion for paper 1.

Table 5.1.1 Overview of studies included in paper 1.

Country	Study	Dates	Number of waves	Birth years	Age range (years)
England	ELSA	2002-2015	7	1930-1953	50-85
England	Whitehall II	1997-2015	5	1930-1952	45-86

Table 5.1.2. Summary of waves and years in paper 1.

Year	*Study*	
	ELSA	**Whitehall II**
1997		Wave 4
1998		
1999		
2000		
2001		
2002	Wave 1	Wave 5
2003		
2004	Wave 2	
2005		
2006	Wave 3	
2007		Wave 6
2008	Wave 4	
2009		
2010	Wave 5	
2011		
2012	Wave 6	Wave 7
2013		
2014	Wave 7	
2015		Wave 8
2016		

5.1.3.2 Sex and covariates

The exposure of interest was sex. Sex was self-reported as male or female in ELSA and was based on British civil service data in Whitehall II.

In addition to sex, paper 1 included age, ethnicity (white/non-white), and birth cohort as sociodemographic covariates. Birth cohorts were defined based on socio-historical events

[165] as follows: the Depression-era birth cohort (1930-1938), the War cohort (1939-1945) and the post-War cohort (1946-1955).

As both included studies comprised English participants educated during similar time periods, we used the English degree classifications in order to categorise education as follows: below O-level, O-level, A-level, and university degree and above. For 8.4% (703/8396) of ELSA participants and 4.9% (370/7528) of Whitehall participants education was imputed using single imputation based on sex, birth cohort, and social class. In order to later perform analyses that were stratified by education, we also classified education into 'low' and 'high' groups, where the low education group included those with no qualifications and O-level qualifications, and the high education group included those with A-level qualifications and above (Table 5.1.3). The final covariate that we included in the analyses was a dichotomous indicator for practice effect. This variable indicated whether or not the measure of cognitive function was the first assessment for that participant.

Table 5.1.3. Education categories available in Whitehall II and ELSA.

<table>
<tr><th>Approx. years of Schooling</th><th>Whitehall II</th><th>ELSA</th><th>4-category education</th><th>2-category education</th></tr>
<tr><td>0-9</td><td>No qualification</td><td>No qualification</td><td>Less than secondary</td><td rowspan="2">Low education</td></tr>
<tr><td>10</td><td>O-level</td><td>O-level</td><td>O-level</td></tr>
<tr><td rowspan="2">11-14</td><td rowspan="2">A-level</td><td>A-level</td><td rowspan="2">A-level</td><td rowspan="4">High education</td></tr>
<tr><td>Higher education below degree level</td></tr>
<tr><td>15</td><td>BA/BSc</td><td rowspan="2">University degree and above</td><td rowspan="2">University degree and above</td></tr>
<tr><td>16+</td><td>Higher degree</td></tr>
</table>

5.1.3.3 Outcomes

The cognitive domains examined in paper 1 included episodic memory and verbal fluency. Memory was assessed using immediate recall. In ELSA, participants were read a 10-word list

at two second intervals by an interviewer. The respondent was asked to recall aloud as many words as possible within two minutes. In Whitehall, participants were read a list of 20 words at two-second intervals by a tape and asked to recall in writing as many as possible within two minutes. Memory was available at all waves of ELSA (2002-2014) and Whitehall (1997-2015).

Fluency was assessed using the animal naming task. In ELSA, participants had one minute to name as many animals as possible aloud to an interviewer. In Whitehall, participants were given one minute to write as many animals as possible. Fluency was available at all waves of Whitehall and waves 1-5 (2002-2010) and 7 (2014) of ELSA.

In order to harmonise cognitive tests between studies and allow comparison between cognitive domains, cognitive scores were standardised separately in each study based on the mean and standard deviation (SD) of the corresponding test among participants aged 50-59 with secondary education (O-level or A-level qualifications).

5.1.3.4 Statistical analysis

Participant characteristics by sex and birth cohort were first described separately for ELSA and the Whitehall II study, as well as in the pooled database. Pearson's x^2 test and the t test were used to assess sex differences in categorical and continuous variables respectively. The x^2 trend test was used to assess birth cohort differences in participant characteristics separately in men and women.

The data were pooled from both cohorts for the following analyses. Linear mixed models were used to assess sex differences in cognitive performance and decline. These models use all available data over the follow-up, handle differences in length of follow-up, and account for the correlation of the measures in each study (ELSA or Whitehall) as well as the correlation of the repeated measures on the same individual [80]. Both the intercept (at the study and individual level) and slope (at the individual level) were fitted as random effects with an unstructured covariance matrix at the individual level, allowing study-specific and individual differences in cognitive performance at baseline and individual differences in rate of cognitive decline. Age was used as the time scale and analyses centred at age 60.

Initial models for memory and fluency included sex, age, age^2, age^3, interaction between sex and age, ethnicity, birth cohort, and practice effect. To these initial models, we added the following terms: 1) interactions between sex and birth cohort, birth cohort and age, and the three way interaction between sex, birth cohort, and age. For all of these interactions with age, we also examined interactions with age^2 and age^3, and retained these interactions if the p-value for these terms based on the Wald test was less than 0.05; and 2) interactions between covariates in the initial model and practice effect, retained if $p < 0.05$ on the basis of the Wald test. As such, the model for fluency additionally included interactions between sex and the dichotomous indicator for practice effect. In addition to covariates included in the initial model, the final birth-cohort adjusted model for memory included all interactions of birth cohort, age, age^2, and age^3, and for fluency, all interactions of birth cohort, sex, age, and age^2.

Next, we examined the impact of education on sex differences in cognitive performance and decline by adding education (4-categories) and the interaction of education and age into the initial and birth-cohort adjusted models, as well as interactions of education and age^2, and age^3 when $p < 0.05$ for the interaction term. We then examined whether the associations of sex with cognitive performance and decline differed by education level by adding interactions between sex, education, and age (included age^2 and age^3 where significant) to the birth-cohort adjusted models. We reported a p-value based on the Wald test that summarised all interaction terms between sex, education, and age. Education was treated as an ordinal variable in this analysis and fit continuously to improve statistical power, as the underlying hypothesis of linearity held with the observed data. Finally, sex differences in cognitive performance and decline were analysed separately in participants with less than A-level education and those with A-level or more education.

In order to facilitate interpretation of results, sex differences in cognitive performance were estimated at ages 50, 60, and 70 years. Sex difference in cognitive decline over 13 years (maximum follow-up period for ELSA; mean follow-up period for Whitehall) from age 60 was based on predicted values for each birth cohort. P-values for change in sex differences in cognitive performance and decline as a function of birth cohort were determined using the Wald test. Based on the models, we also estimated and plotted average cognitive scores between ages 50 and 85 in each birth cohort with and without adjustment for education,

and after stratification by education first for men and women, and then to show the sex difference in scores.

Four sets of sensitivity analyses were conducted. Analyses were undertaken: 1) separately in each study; 2) excluding participants with dementia (ascertained in ELSA using participant/proxy report [302] and in Whitehall using linkage to electronic health records) [310]; 3) restricting the period of follow-up to the same period (2002-2015) in both studies; and 4) using multiple (20 imputations) rather than single imputation for missing data on education in models adjusted for education. All analyses were undertaken in Stata 15 and a two-sided p-value < 0.05 was considered statistically significant.

5.1.4 Results

5.1.4.1 Sample characteristics

Figures 5.1.1 and 5.1.2 show flow charts of sample selection for ELSA and the Whitehall II study respectively. There were 11391 participants in the core cohort of ELSA in 2002. Of these 11391, 2883 (25.3%) were born before 1930, 96 (0.8%) had missing cognitive data at all waves between 2002 and 2014, and 16 (0.1%) were missing covariates for all waves. This resulted in 8396 (73.7%) participants of the core ELSA cohort included in the analyses.

There were 10308 Whitehall II participants at study inception in 1985-1988. Of these 10308, 306 (3.0%) died and 880 (8.5%) withdrew before the 1997-1999 wave at which cognitive function was assessed for the first time. Of the remaining 9122, 1594 (17.5%) had missing cognitive data at all waves of data collection. In total, 7528 (82.5%) of Whitehall II participants were retained in the analysis. The pooled sample comprised 15924 participants.

Sample characteristics are shown in Table 5.1.4. ELSA was 46.5% male, while Whitehall II was 70.3% male. In both studies, education level increased in participants born more recently ($p < 0.001$ for trend across birth cohorts). ELSA participants were slightly older than Whitehall II participants while Whitehall II participants were more likely than ELSA participants to be educated to A-level and above ($p < 0.001$ for difference between ELSA and Whitehall). In the pooled cohort, men were more likely to be educated to A-level and above across all birth cohorts ($p < 0.001$ for sex difference in each birth cohort): 46% of men and

24% of women were educated to A-level and above. Education level also increased with each successive birth cohort ($p < 0.001$ for trend across birth cohorts). At their first wave of participation, respondents with higher education levels had higher cognitive scores ($p < 0.001$ for linear trend in both memory and fluency scores). In order from lowest to highest education level (no qualifications, O-level, A-level, above A-level), the mean standardised memory score in each category was -0.65, -0.18, -0.05, and 0.19 standard deviations (SDs) respectively. The corresponding mean scores for fluency were -0.66, -0.21, 0.04, and 0.33 SDs. In order to further examine the association of education with cognitive score, observed mean cognitive scores for memory and fluency in each age group were plotted (Figure 5.1.3). Those with above A-level education had the highest cognitive scores at all ages, while those with no qualifications had the lowest.

In the pooled cohort, men had on average more years of follow up than women. Men had a mean follow up period of 11.0 years (SD = 6.2) compared to women who had a mean of 9.6 years (SD = 5.7). This was due to the fact that there was a greater proportion of men in Whitehall II, where the follow-up was longer than in ELSA (mean follow up in Whitehall = 12.9 [SD = 6.3] years versus 8.1 [SD = 4.8] years in ELSA; $p < 0.001$ for difference between ELSA and Whitehall).

Figure 5.1.1. Flowchart of sample selection in ELSA.

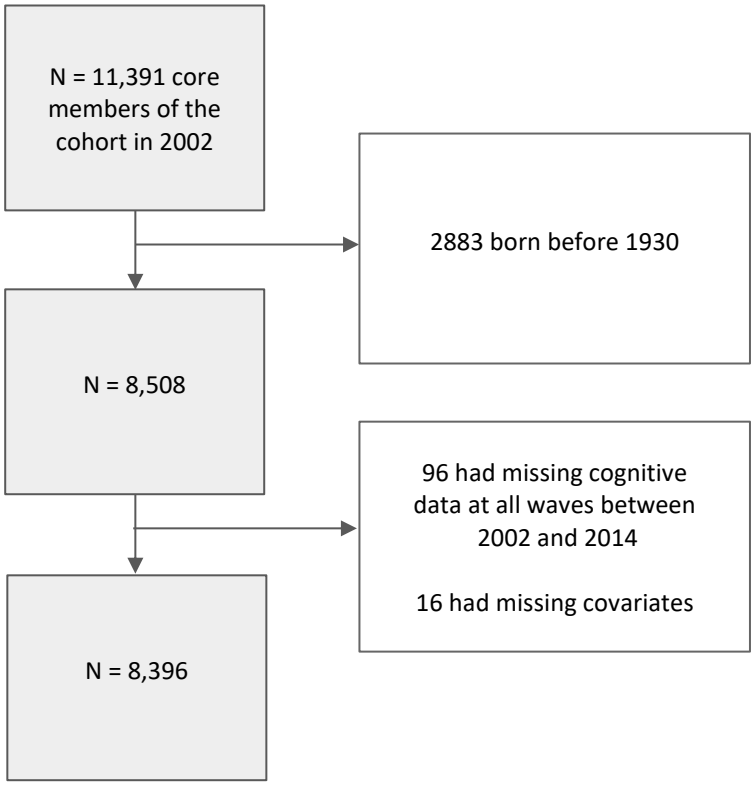


Figure 5.1.2. Flowchart of sample selection in the Whitehall II Study.

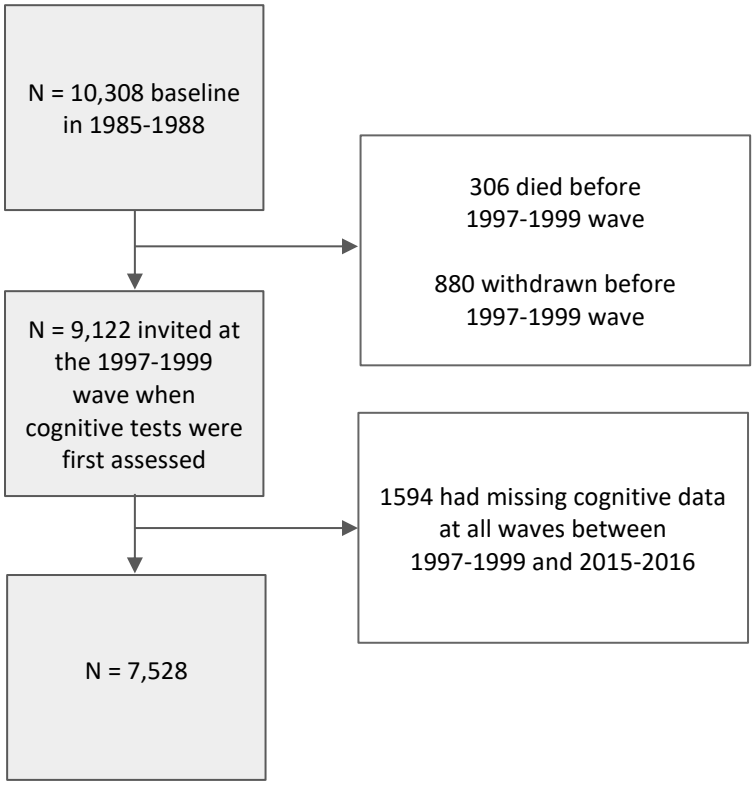
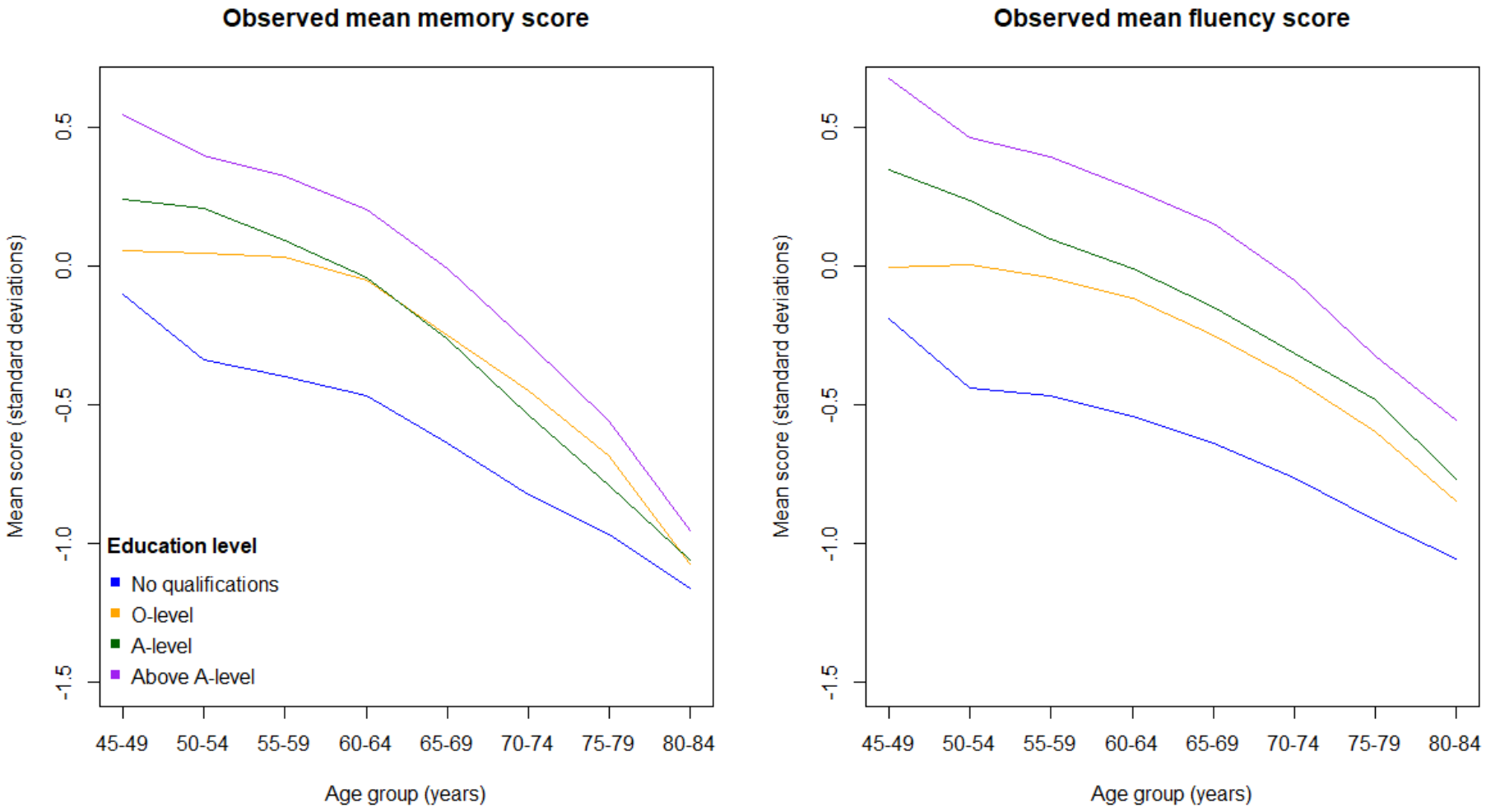


Table 5.1.4. Characteristics of participants included in the analyses from ELSA and the Whitehall II study.

	1930-1938			1939-1945			1946-1955			P trend	P trend
	Men	Women	P-value	Men	Women	P-value	Men	Women	P-value	Men	Women
ELSA	**N = 1377**	**N = 1525**		**N = 1153**	**N = 1338**		**N = 1376**	**N = 1627**			
Baseline Age, M(SD)	67.9 (2.6)	68.1 (2.6)	0.20	60.1 (2.1)	60.0 (2.1)	0.18	53.5 (2.0)	53.4 (2.0)	0.40	<0.001	<0.001
Ethnicity, N (%)											
White	1322 (96.0)	1487 (97.5)	0.02	1116 (96.8)	1308 (97.8)	0.14	1325 (96.3)	1570 (96.5)	0.76	0.69	0.08
Non-white	55 (4.0)	38 (2.5)		37 (3.2)	30 (2.2)		51 (3.7)	57 (3.5)			
Education, N (%)											
Below A-level	1133 (82.3)	1401 (91.9)	<0.001	863 (74.8)	1130 (84.5)	<0.001	928 (67.4)	1299 (79.8)	<0.001	<0.001	<0.001
A-level and above	244 (17.7)	124 (8.1)		290 (25.2)	208 (15.5)		448 (32.6)	328 (20.2)			
Whitehall II	**N = 1599**	**N = 793**		**N = 1704**	**N = 722**		**N = 1992**	**N = 718**			
Baseline Age, M(SD)	64.2 (3.6)	64.8 (4.3)	<0.001	56.9 (3.9)	57.2 (3.9)	0.12	51.0 (3.9)	50.9 (3.9)	0.49	<0.001	<0.001
Ethnicity, N (%)											
White	1455 (91.0)	693 (87.4)	0.01	1587 (93.1)	590 (81.7)	<0.001	1912 (96.0)	638 (88.9)	<0.001	<0.001	0.48
Non-white	144 (9.0)	100 (12.6)		117 (6.9)	132 (18.3)		80 (4.0)	80 (11.1)			
Education, N (%)											
Below A-level	777 (48.6)	588 (74.1)	<0.001	661 (38.8)	410 (56.8)	<0.001	610 (30.6)	281 (39.1)	<0.001	<0.001	<0.001
A-level and above	822 (51.4)	205 (25.9)		1043 (61.2)	312 (43.2)		1382 (69.4)	437 (60.9)			
ELSA & Whitehall II	**N = 2976**	**N = 2318**		**N = 2857**	**N = 2060**		**N = 3368**	**N = 2345**			
Baseline Age, M(SD)	65.9 (3.7)	66.9 (3.6)	<0.001	58.2 (3.6)	59.0 (3.2)	<0.001	52.0 (3.5)	52.6 (2.9)	<0.001	<0.001	<0.001
Ethnicity, N (%)											
White	2777 (93.3)	2180 (94.0)	0.28	2703 (94.6)	1898 (92.1)	<0.001	3237 (96.1)	2208 (94.2)	<0.001	<0.001	0.87
Non-white	199 (6.7)	138 (6.0)		154 (5.4)	162 (7.9)		131 (3.9)	137 (5.8)			
Education, N (%)											
Below A-level	1910 (64.2)	1989 (85.8)	<0.001	1524 (53.3)	1540 (74.8)	<0.001	1538 (45.7)	1580 (67.4)	<0.001	<0.001	<0.001
A-level and above	1066 (35.8)	329 (14.2)		1333 (46.7)	520 (25.2)		1830 (54.3)	765 (32.6)			

Figure 5.1.3. Observed mean memory and fluency scores by education level plotted in each age group.



5.1.4.2 Cognitive performance

Memory

In general, women had better memory scores than men. At ages 50, 60, and 70 years, the mean sex differences in memory scores (male – female) were -0.10 (95% confidence interval: -0.15, -0.05), -0.14 (-0.18, -0.11), and -0.19 (-0.22, -0.16) standard deviations respectively in analyses adjusted for age, ethnicity, birth cohort, and practice effect (data not tabulated). After adjustment for education, these female advantages were even larger. At age 50 years, the sex difference in memory after adjustment for education was -0.17 (-0.21, -0.13), at age 60 years -0.22 (-0.25, -0.20), and at age 70 years -0.28 (-0.31, -0.25) standard deviations.

The female advantage in memory was evident in each birth cohort, before and after adjustment for education (Table 5.1.5, Figure 5.1.4). Before adjustment for education, at age 50, better memory performance was seen in women in the 1946-1955 birth cohort (no data were available in earlier birth cohorts at age 50) and all three birth cohorts at age 60. At age 60, there was a trend toward a larger female advantage in younger birth cohorts, though this did not reach statistical significance ($p = 0.07$ for difference across birth cohorts). At age 70, estimated sex differences in memory performance were also larger in participants born more recently ($p < 0.001$ for difference across birth cohorts).

After adjustment for education, female advantages in all birth cohorts for all ages increased. There was still a trend toward larger female advantages in younger birth cohorts at age 70: in the 1930-1938 birth cohort, the sex difference was 0.26 (0.30, 0.21) compared to 0.29 (0.34, 0.24) in the 1939-1945 birth cohort and 0.36 (0.42, 0.29) in the 1946-1955 birth cohort. However, overall, differences between birth cohorts were attenuated after adjustment for education: at age 60, the p-value indicating whether sex differences differed across birth cohorts was 0.07 before adjustment for education and 0.47 after. The corresponding p-values at age 70 were $p < 0.001$ compared to $p = 0.03$.

When we examined sex differences in memory scores in analyses stratified by education level into less than A-level (low education) and A-level and above (high education) groups, there was robust evidence of a female advantage in both education groups (Table 5.1.6,

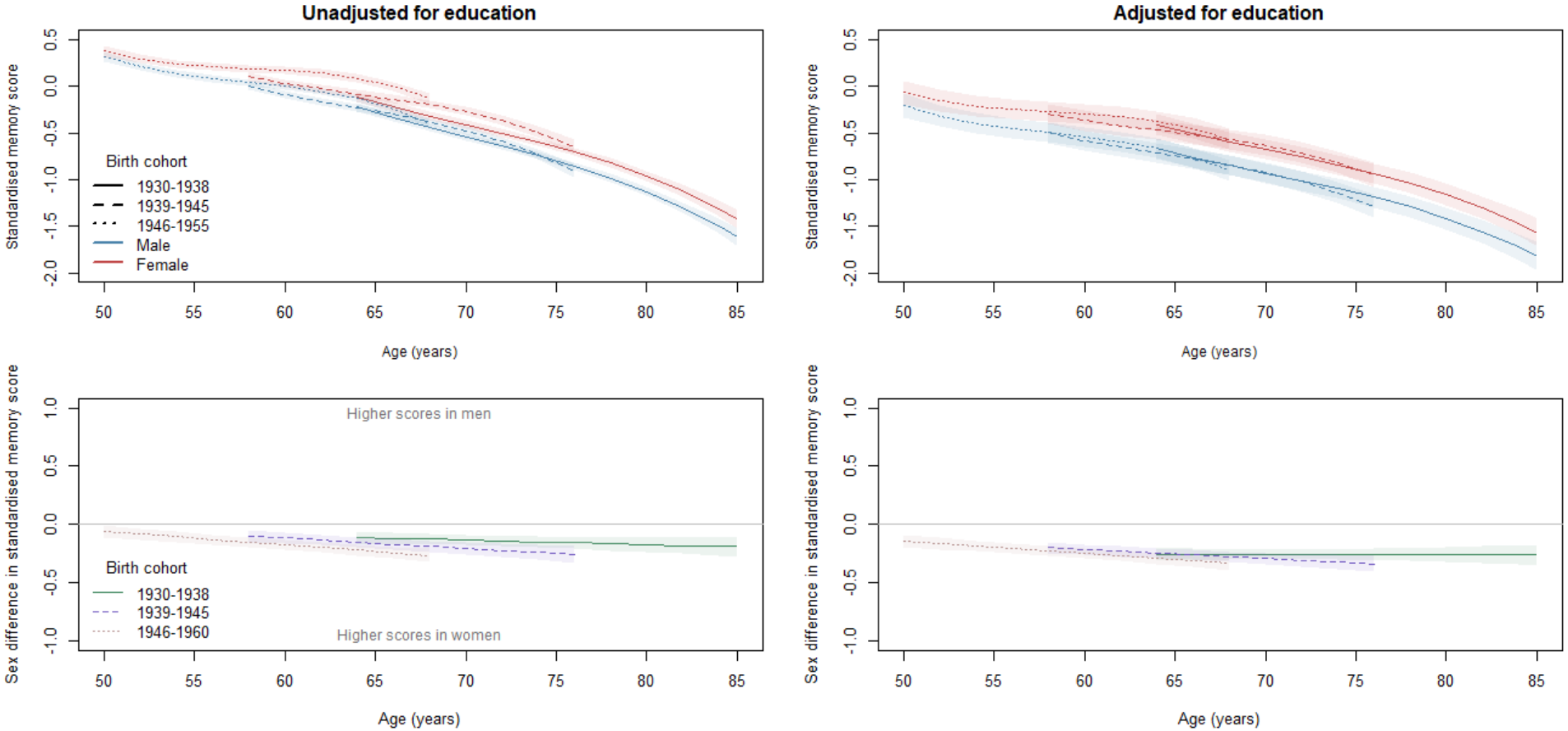
Figure 5.1.5). The female advantage was greater at age 70 than at age 50 in both the low and high education groups (p-value < 0.001 for the difference across ages in the low education group; p = 0.04 for the high education group). The general pattern of results was similar in both education groups. At age 50, the female advantage was greater in those with high (-0.18 [-0.27, -0.10]) compared to low (-0.09 [-0.16, -0.01]) education in the 1946-1955 birth cohort, Table 5.1.6). In the low education group, the female advantage was progressively greater in the younger birth cohorts at age 70 (p = 0.01 for difference across birth cohorts; the sex difference in the 1930-1938 birth cohort was -0.19 [-0.24, -0.14] compared with -0.34 [-0.43, -0.25] in the 1946-1955 birth cohort).

Table 5.1.5. Role of education in sex differences in memory performance: analyses stratified by birth cohort and undertaken in data pooled from ELSA & the Whitehall II study.

	At age 50 years		At age 60 years		At age 70 years	
	Basic Model[a]	Basic Model[a] + Education	Basic Model[a]	Basic Model[a] + Education	Basic Model[a]	Basic Model[a] + Education
ELSA & Whitehall	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**
Memory						
Birth cohort						
1930-1938	No data	No data	-0.10 (-0.16, -0.03)	-0.25 (-0.32, -0.19)	-0.13 (-0.18, -0.09)	-0.26 (-0.30, -0.21)
1939-1945	No data	No data	-0.12 (-0.16, -0.07)	-0.21 (-0.26, -0.17)	-0.20 (-0.26, -0.15)	-0.29 (-0.34, -0.24)
1946-1955	-0.06 (-0.12, -0.01)	-0.14 (-0.20, -0.09)	-0.17 (-0.22, -0.13)	-0.25 (-0.29, -0.21)	-0.29 (-0.35, -0.23)	-0.36 (-0.42, -0.29)
P sex difference by birth cohort			*0.07*	*0.47*	*< 0.001*	*0.03*

[a]Basic models include sex, age^2, age^3, birth cohort, ethnicity, practice effect, and interactions of: sex and birth cohort; birth cohort and age; sex, birth cohort and age. Memory models additionally include all interactions of birth cohort, age^2, and age^3.
Positive value indicates male advantage in performance.

Figure 5.1.4. Memory trajectories and sex differences in memory scores before (left panel) and after (right panel) adjustment for education; undertaken in data pooled from ELSA & the Whitehall II study.



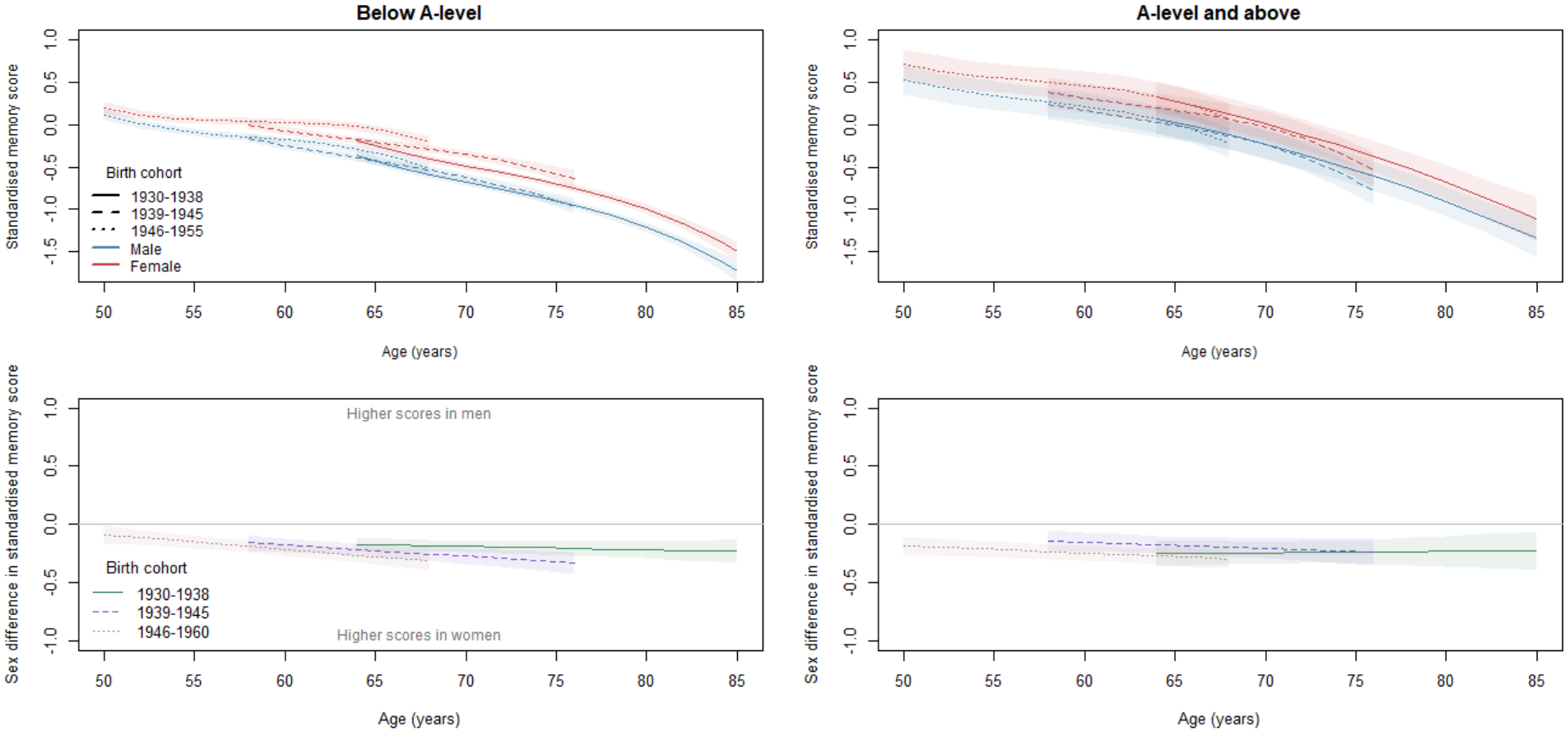
Left panel adjusted for ethnicity, practice effect, and interactions with age. Results are shown for ethnicity (white) and practice effect (no practice effect) reference categories. Right panel additionally adjusted for education and interactions with age and shown for education reference category (no qualifications). Estimates shown for age ranges covered in both ELSA and Whitehall II. Positive value indicates higher score among men.

Table 5.1.6. Sex differences in memory performance: analyses stratified by birth cohort and education level and undertaken in data pooled from ELSA & the Whitehall II study.

	At age 50 years	**At age 60 years**	**At age 70 years**
ELSA & Whitehall	Sex difference (95% CI)	Sex difference (95% CI)	Sex difference (95% CI)
Memory			
Education: Below A-level			
1930-1938	No data	-0.16 (-0.24, -0.08)	-0.19 (-0.24, -0.14)
1939-1945	No data	-0.18 (-0.24, -0.12)	-0.27 (-0.34, -0.21)
1946-1955	-0.09 (-0.16, -0.01)	-0.21 (-0.27, -0.16)	-0.34 (-0.43, -0.25)
P sex difference by birth cohort		*0.49*	*0.01*
Education: A-level and above			
1930-1938	No data	-0.26 (-0.40, -0.12)	-0.24 (-0.34, -0.15)
1939-1945	No data	-0.15 (-0.23, -0.07)	-0.21 (-0.29, -0.12)
1946-1955	-0.18 (-0.27, -0.10)	-0.24 (-0.31, -0.18)	-0.31 (-0.40, -0.22)
P sex difference by birth cohort		*0.17*	*0.28*

[a]Basic models include sex, age^2, age^3, birth cohort, ethnicity, practice effect, and interactions of: sex and birth cohort; birth cohort and age; sex, birth cohort and age. Memory models additionally include all interactions of birth cohort, age^2, and age^3.
Positive value indicates male advantage in performance.

Figure 5.1.5. Memory trajectories and sex differences in memory scores stratified by education level; undertaken in data pooled from ELSA & the Whitehall II study.



Adjusted for ethnicity, practice effect, and interactions with age. Results are shown for ethnicity (white) and practice effect (no practice effect) reference categories. Results shown for birth cohorts 1930-1938, 1939-1945, and 1946-1955. Estimates shown for age ranges covered in both ELSA and Whitehall II. Positive value indicates higher score among men.

Fluency

Men had higher average fluency scores at ages 50, 60, and 70 which were 0.07 (0.00, 0.13), 0.07 (0.04, 0.11), and 0.06 (0.03, 0.09) standard deviations higher than women respectively in analyses accounting for age, ethnicity, birth cohort, practice effect, and interaction between practice effect and sex. This advantage was attenuated after adjustment for education. At ages 50, 60, and 70, after adjustment for education, the average sex differences in fluency were -0.04 (-0.11, 0.02), -0.04 (-0.07, -0.01), and -0.04 (-0.07, -0.01) standard deviations respectively.

Before adjustment for education, the male advantage in fluency was smaller in birth cohorts born later for ages 60 and 70 ($p \leq 0.002$ for difference across birth cohorts at ages 60 and 70, Table 5.1.7, Figure 5.1.6), and the male advantage in later-born birth cohorts was further attenuated or reversed after adjustment for education. For example, at age 50 in the 1946-1955 birth cohort, the sex difference before adjustment for education was 0.06 (-0.01, 0.13) and after adjustment was -0.04 (-0.11, 0.03). At age 60 in the 1946-1955 birth cohort, the sex difference was 0.00 (-0.05, 0.05) before adjustment for education, and -0.09 (-0.14, -0.05) after. Adjustment for education also attenuated differences between birth cohorts: before adjustment for education, the p value for difference in sex differences across birth cohorts was 0.002 at age 60 and <0.001 at age 70. After adjustment for education, the corresponding p-values were 0.03 and 0.002 respectively.

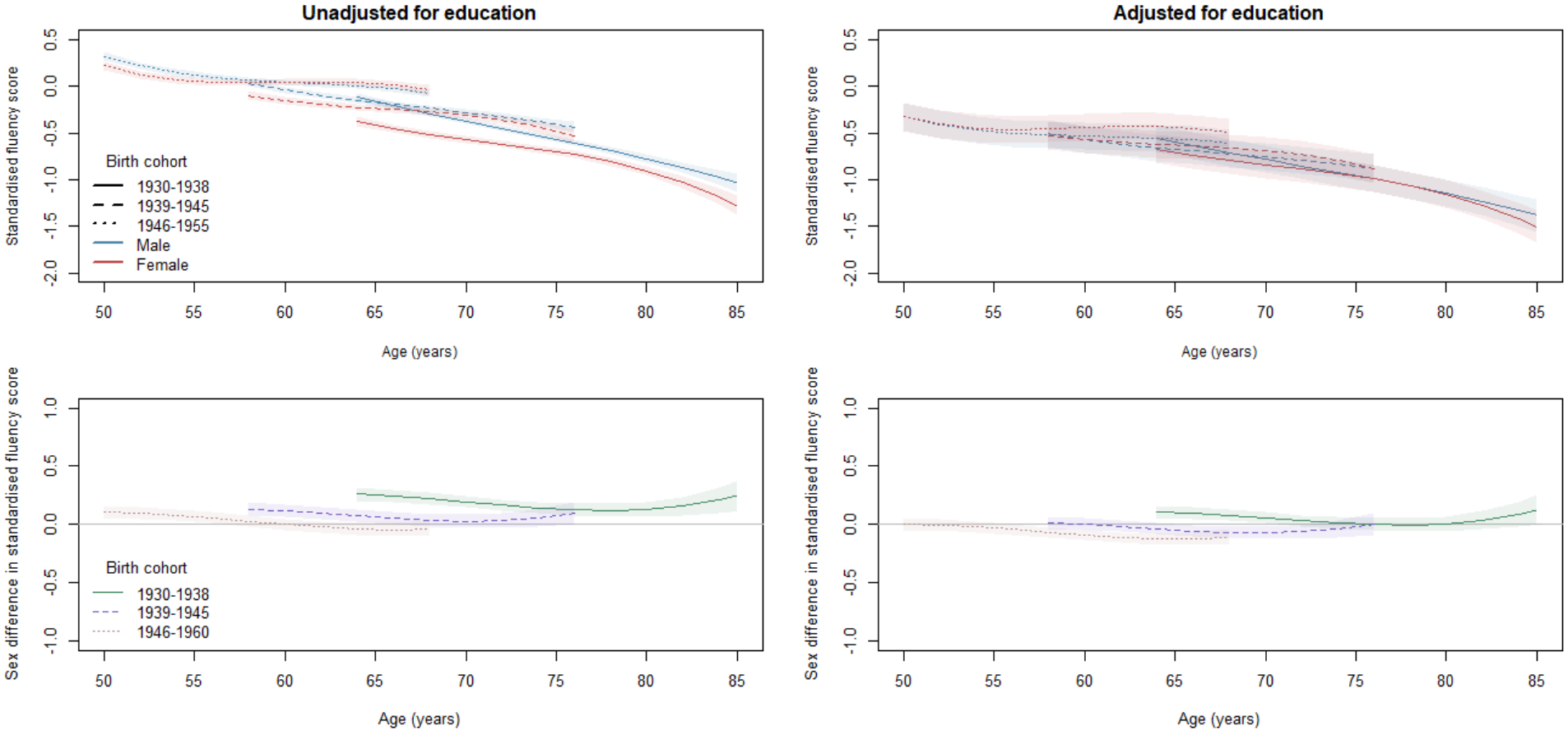
Analyses stratified by education (Table 5.1.8, Figure 5.1.7) showed a male advantage in fluency scores only in the low education group ($p < 0.001$ for sex and education interaction). In the high education group, there was evidence of female advantages, particularly for those in the 1946-1955 birth cohort at age 50 (-0.20 [-0.31, -0.09]) and at age 60 (-0.17 [-0.24, -0.10]).

Table 5.1.7. Role of education in sex differences in fluency performance: analyses stratified by birth cohort and undertaken in data pooled from ELSA & the Whitehall II study.

	At age 50 years		At age 60 years		At age 70 years	
	Basic Model[a]	Basic Model[a] + Education	Basic Model[a]	Basic Model[a] + Education	Basic Model[a]	Basic Model[a] + Education
ELSA & Whitehall	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**
Fluency						
Birth cohort						
1930-1938	No data	No data	0.19 (0.08, 0.31)	0.03 (-0.09, 0.15)	0.18 (0.13, 0.23)	0.04 (-0.01, 0.09)
1939-1945	No data	No data	0.10 (0.04, 0.15)	-0.02 (-0.07, 0.03)	0.03 (-0.02, 0.08)	-0.07 (-0.12, -0.02)
1946-1955	0.06 (-0.01, 0.13)	-0.04 (-0.11, 0.03)	0.00 (-0.05, 0.05)	-0.09 (-0.14, -0.05)	-0.01 (-0.11, 0.08)	-0.08 (-0.18, 0.01)
P sex difference by birth cohort			*0.002*	*0.03*	*< 0.001*	*0.002*

[a]Basic models include sex, age^2, age^3, birth cohort, ethnicity, practice effect, and interactions of: sex and birth cohort; birth cohort and age; sex, birth cohort and age. Fluency models additionally include: interaction of sex and practice effect; and interaction of birth cohort, sex, and age^2.
Positive value indicates male advantage in performance.

Figure 5.1.6. Fluency trajectories and sex differences in fluency scores before (left panel) and after (right panel) adjustment for education; undertaken in data pooled from ELSA & the Whitehall II study.



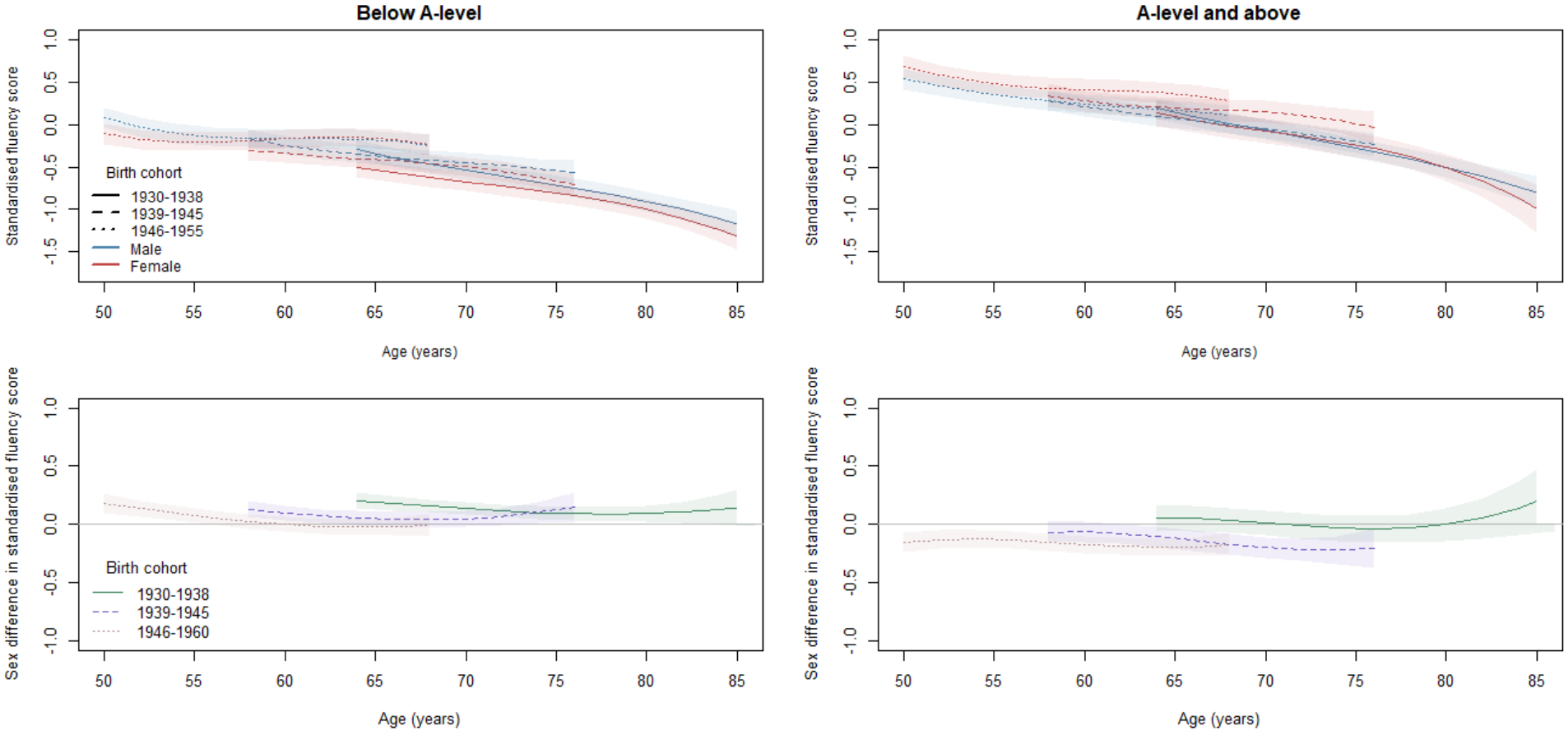
Left panel adjusted for ethnicity, practice effect, and interactions with age. Results are shown for ethnicity (white) and practice effect (no practice effect) reference categories. Right panel additionally adjusted for education and interactions with age and shown for education reference category (no qualifications). Estimates shown for age ranges covered in both ELSA and Whitehall II. Positive value indicates higher score among men.

Table 5.1.8. Sex differences in fluency performance: analyses stratified by birth cohort and education level and undertaken in data pooled from ELSA & the Whitehall II study.

	At age 50 years	**At age 60 years**	**At age 70 years**
ELSA & Whitehall	Sex difference (95% CI)	Sex difference (95% CI)	Sex difference (95% CI)
Fluency			
Education: Below A-level			
1930-1938	No data	0.20 (0.05, 0.36)	0.13 (0.07, 0.18)
1939-1945	No data	0.08 (0.01, 0.15)	0.05 (-0.02, 0.12)
1946-1955	0.15 (0.05, 0.25)	0.00 (-0.06, 0.06)	0.02 (-0.11, 0.15)
P sex difference by birth cohort		*0.03*	*0.12*
Education: A-level and above			
1930-1938	No data	-0.05 (-0.26, 0.15)	0.00 (-0.11, 0.11)
1939-1945	No data	-0.09 (-0.18, 0.01)	-0.20 (-0.29, -0.11)
1946-1955	-0.20 (-0.31, -0.09)	-0.17 (-0.24, -0.10)	-0.13 (-0.27, 0.01)
P sex difference by birth cohort		*0.27*	*0.02*

[a]Basic models include sex, age^2, age^3, birth cohort, ethnicity, practice effect, and interactions of: sex and birth cohort; birth cohort and age; sex, birth cohort and age. Fluency models additionally include: interaction of sex and practice effect; and interaction of birth cohort, sex, and age^2.
Positive value indicates male advantage in performance.

Figure 5.1.7. Fluency trajectories and sex differences in fluency scores stratified by education level; undertaken in data pooled from ELSA & the Whitehall II study.



Adjusted for ethnicity, practice effect, and interactions with age. Results are shown for ethnicity (white) and practice effect (no practice effect) reference categories. Results shown for birth cohorts 1930-1938, 1939-1945, and 1946-1955. Estimates shown for age ranges covered in both ELSA and Whitehall II. Positive value indicates higher score among men.

5.1.4.3 Cognitive decline

In analyses adjusted for age, ethnicity, birth cohort, education, and practice effect, the mean 13-year change in memory among men and women was -0.76 (-0.85, -0.71) and -0.69 (-0.75, -0.63) standard deviations respectively ($p < 0.001$ for sex difference in 13-year change). Table 5.1.9 shows that 13-year memory decline was slower in women than in men. The sex difference in the 1939-1945 cohort was -0.12 (-0.18, -0.05) and in 1946-1955 cohort was -0.15 (-0.20, -0.09) standard deviations, with no sex difference in the 1930-1938 birth cohort. Adjustment for education did not affect these estimates.

Mean 13-year change in fluency was similar in men (-0.41 [-0.46, -0.36] standard deviations) and women (-0.40 [-0.45, -0.34] standard deviations; $p = 0.61$ for sex difference in 13-year change in analyses adjusted for age, ethnicity, birth cohort, education, practice effect, and interaction of practice effect and sex). This was also the case in analyses within each birth cohort (Table 5.1.9) even after adjustment for education.

Sex differences in memory and fluency decline in low and high education groups are shown in Table 5.1.10. For memory, the estimates were similar ($p = 0.08$ for interaction between sex, education, and age), in that women experienced slower decline in memory compared to men both in the low and high education groups. For decline in fluency, the interaction term between sex, education, and age suggested differences in patterns in the low and high education groups ($p < 0.001$). Table 5.1.10 shows this was due to the 1939-1945 birth cohort where there was no sex difference in 13-year decline (sex difference 0.00 [-0.08, 0.09]) in the low education group and a female advantage (sex difference: -0.13 [-0.24, -0.03]) in the high education group.

Table 5.1.9. Role of education in sex differences in 13-year cognitive decline: analyses stratified by birth cohort and undertaken in data pooled from ELSA & the Whitehall II study.

	Basic Model[a]	Basic Model[a] + Education
ELSA & Whitehall	**Sex difference (95% CI)**	**Sex difference (95% CI)**
Memory		
Birth cohort		
1930-1938	-0.05 (-0.11, 0.01)	0.00 (-0.07, 0.06)
1939-1945	-0.12 (-0.18, -0.05)	-0.10 (-0.16, -0.04)
1946-1955	-0.15 (-0.20, -0.09)	-0.14 (-0.20, -0.08)
P sex difference by birth cohort	*0.07*	*0.01*
Fluency		
Birth cohort		
1930-1938	-0.05 (-0.17, 0.08)	-0.01 (-0.13, 0.11)
1939-1945	-0.05 (-0.12, 0.01)	-0.03 (-0.10, 0.03)
1946-1955	0.06 (-0.11, 0.24)	0.10 (-0.08, 0.27)
P sex difference by birth cohort	*0.48*	*0.41*

[a]Basic models include sex, age^2, age^3, birth cohort, ethnicity, practice effect, and interactions of: sex and birth cohort; birth cohort and age; sex, birth cohort and age. Memory models additionally include all interactions of birth cohort, age^2, and age^3. Fluency models additionally include: interaction of sex and practice effect; and interaction of birth cohort, sex, and age^2. Results are shown for the reference category: participants aged 60 years. Positive value indicates slower cognitive decline in men.

Table 5.1.10. Sex differences in 13-year cognitive decline: analyses stratified by birth cohort and education level and undertaken in data pooled from ELSA & the Whitehall II study.

ELSA & Whitehall	Sex difference (95% CI)
Memory	
Education: Below A-level	
1930-1938	-0.04 (-0.11, 0.04)
1939-1945	-0.12 (-0.21, -0.04)
1946-1955	-0.17 (-0.24, -0.09)
P sex difference by birth cohort	*0.06*
Education: A-level and above	
1930-1938	0.02 (-0.11, 0.14)
1939-1945	-0.07 (-0.17, 0.02)
1946-1955	-0.08 (-0.16, -0.00)
P sex difference by birth cohort	*0.41*
Fluency	
Education: Below A-level	
1930-1938	-0.10 (-0.25, 0.06)
1939-1945	0.00 (-0.08, 0.09)
1946-1955	0.08 (-0.16, 0.32)
P sex difference by birth cohort	*0.29*
Education: A-level and above	
1930-1938	0.03 (-0.18, 0.24)
1939-1945	-0.13 (-0.24, -0.03)
1946-1955	0.16 (-0.11, 0.44)
P sex difference by birth cohort	*0.11*

[a]Basic models include sex, age^2, age^3, birth cohort, ethnicity, practice effect, and interactions of: sex and birth cohort; birth cohort and age; sex, birth cohort and age. Memory models additionally include all interactions of birth cohort, age^2, and age^3. Fluency models additionally include: interaction of sex and practice effect; and interaction of birth cohort, sex, and age^2. Results are shown for the reference category: participants aged 60 years. Positive value indicates slower cognitive decline in men.

5.1.4.4 Supplementary analyses

The analyses conducted separately in ELSA and Whitehall showed results broadly similar to those in the pooled analyses for cognitive performance (Appendix Tables 8.1.1-8.1.2) and decline (Appendix Table 8.1.3) although differences in education level in these studies were reflected in the estimates. In ELSA, results were similar to those in the low education group in the pooled analyses and in Whitehall, similar to the high education group. Neither omitting respondents with dementia (Appendix Tables 8.1.4-8.1.6), limiting years of follow-up from 2002-2015 (Appendix tables 8.1.7-8.1.10), nor using multiple rather than single imputation for missing data on education (Appendix Tables 8.1.11-8.1.12) substantively impacted results.

5.1.5 Discussion

In this analysis of 15,924 men and women born between 1930 and 1955, with longitudinal data on memory and fluency spanning up to 19 years, there was no evidence of a cognitive disadvantage in women after accounting for education. On the contrary, women performed better than men on the memory test, and this difference was more marked at older age and in the youngest birth cohort. For fluency performance, there was evidence of an effect of education and birth cohort. Women in the high education group and those in the youngest birth cohort performed better than men; men in the low education group and those born in the oldest birth cohort performed better than women. Adjustment for education attenuated the difference in sex inequalities between birth cohorts for both memory and fluency. For cognitive decline, women experienced a slower rate of memory decline than men, while there was no strong evidence of sex differences in fluency decline. Adjustment for education had a negligible impact on memory and fluency decline. Taken together, these findings suggest a role of education over successive birth cohorts in shaping improved cognitive performance in women.

5.1.5.1 Comparison with previous studies

Our results are consistent with previous studies that found domain-specific sex differences in cognitive performance and decline [51]. As in previous studies [143, 311, 312], women consistently outperformed men in memory regardless of education level and birth cohort.

The underlying mechanisms of observed sex differences in memory are not well understood [313], though the neuroprotective effect of oestradiol has been identified as a possible explanation [314]. However, consistent with de Frias and colleagues [314], our results do not support this hypothesis as we observe a smaller female advantage at peri and pre-menopausal age (50 years) compared to menopausal age groups (60 and 70 years). Another possible explanation for better memory performance and slower age-related decline among women is larger average volume of the hippocampal gyrus in females compared to males [186].

Previous studies of sex differences in verbal fluency are inconsistent, with some showing male [163] or female [162] advantages, and others showing no sex differences [256, 311, 312]. The findings of our analysis offer one possible explanation for these mixed results, as male advantages in fluency were observed among older birth cohorts and fewer sex differences were observed among younger birth cohorts. Furthermore, stratification by education level showed no sex differences or female advantages in the high education group and male advantages in the low education group. Taken together, these results suggest sex differences in fluency vary by education level and birth cohort.

Some studies found women experienced slower cognitive decline than men across multiple cognitive domains [158, 162], however others did not find sex differences in age-related cognitive decline [161, 162, 314]. Our data show slower rate of memory decline in women compared to men, while there was little evidence of sex differences in fluency decline. We also found that accounting for education level did not affect sex differences in decline for either memory or fluency. This is consistent with two previous studies, one undertaken in a sample of 2225 adults aged 31 years and older over 27 years of follow up [163], and the other a study of 368 adults older than 70 years at baseline and followed up for 13 years [256]. Our study is based on a larger sample size and has the advantage of explicit consideration of birth cohort effects to reflect the changes in access to education, particularly in women. We found that education played an important role in shaping performance but not decline in memory and fluency.

Our findings were in accordance with previous studies that suggested changing sex inequalities in education contributed to differences in sex inequalities in cognitive function

across birth cohorts [80, 256, 278]. We found that overall education level increased in the study population in successive birth cohorts, while sex inequalities in education level decreased. Before accounting for education, this translated into worse performance in memory and fluency among women in older birth cohorts compared to women in younger birth cohorts. Accounting for sex inequalities in education level reduced birth cohort differences in sex inequalities for both cognitive domains. This finding suggests that the larger sex inequalities in education level in the older birth cohorts contribute to women performing worse in older birth cohorts than in younger birth cohorts. This was in contrast with one previous study, which used economics methods to conclude that education did not underlie birth cohort trends in sex differences in cognitive function [151]. However, this paper did not allow sex differences to change with age, but rather produced point estimates for sex differences in each birth cohort adjusting for age.

5.1.5.2 Strengths and limitations

A major strength of our study is its large sample size compared to previous longitudinal studies on the role of education in sex differences in cognitive function. Pooling data from two large studies allowed sufficient statistical power to examine the role of education on sex differences in cognitive ageing. Differences in target population and study design—including between-study differences due to written versus orally conducted cognitive tests—were addressed by standardising cognitive measures within each study, including a random effect for study, and performing sensitivity analyses separately in each study. Our analytical approach considered both the role of birth cohort and education in sex differences in cognitive trajectories, allowing secular changes in educational level in the mid-20th century to be taken into consideration. Another strength is the long follow-up period which allowed us to examine cognitive trajectories from midlife to older ages.

There are a number of limitations of our study. The ability of linear mixed models to handle incomplete data is dependent on the assumption that data are missing-at-random, which might not hold completely in the present case [165]. The impact of attrition on memory in ELSA was previously examined using joint models and estimates were comparable to those using linear mixed models [165]. A recent paper from the Whitehall II study also found a similar association of socioeconomic factors with cognitive performance and decline when

estimates from mixed models were compared to simulations with a missing-not-at-random assumption [315]. Another paper found that sex differences in cognitive trajectories were not affected by attrition in the Whitehall II study [167]. In the present study, differences in mean follow-up between men and women in each cohort were small compared to the mean follow-up duration—1.3 years in Whitehall and 0.5 years in ELSA—representing at most 10% of the mean follow-up duration of the respective studies. Thus, the impact of attrition on our findings is likely to be small. Participants in ELSA and Whitehall are primarily white and the extent to which these results are generalisable to other racial and ethnic groups is unknown. However, the ethnic composition of both studies reflects the population in England for the birth years included in the analyses [316]. Sex in both studies was measured as declared in administrative documents rather than gender identity. It is likely that the effect of education on cognitive function arises through expectations of gender roles rather than effects of biological sex, but lack of data on gender leads us to refer to sex rather than gender differences. Fine-grained analysis of education using years of schooling or more categories than our 4-category measure is likely to affect findings, perhaps strengthening the attenuation in sex differences after adjustment for education. The use of single rather than multiple imputation can underestimate standard errors, but in the present case it did not appear to substantively impact findings, as a relatively small proportion (1073/15924; 6.7%) of participants had missing data. Finally, we could examine only two cognitive tests as these were the tests available in both cohorts. The extent to which our findings extend to other cognitive domains remains to be examined.

5.1.5.3 Conclusion

Our analysis of education and birth cohort shows sex differences in cognitive function are in a dynamic state, whereby women born later increasingly have better memory scores and the deficit in fluency has progressively been eliminated. We found that reductions in sex disparities in education may play a role in these progressive reductions in female disadvantages in cognitive function in successive birth cohorts. These findings highlight the importance of education as a contributing factor for sex differences in cognitive function and point to the necessity of considering sex-specific effects when evaluating modifiable factors for cognitive outcomes.

5.2 Paper 2: Comparison of sex differences in cognitive function between high- and middle-income countries and the role of education: a population-based multicohort study

Text adapted from *'Comparison of sex differences in cognitive function between high- and middle-income countries and the role of education: a population-based multi-cohort study'*. Currently under review with Age and ageing.

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5.2.1 Rationale

Findings from high-income countries suggest that on average men outperform women on tests of visuospatial ability and attention, while women outperform men on episodic memory and some verbal tasks [51, 143]. Sex differences in cognitive function are likely due to a combination of biological differences [317], as well as social and economic factors. Women have had limited access to education historically [12], which may contribute to sex differences in cognitive function as education confers a cognitive advantage that persists throughout life [101, 105]. Sex inequalities in education may therefore partly explain sex differences in cognitive function in high [19, 256] and middle-income countries [151, 257-260], with larger female cognitive disadvantages in middle-income countries [318], even in cognitive domains such as memory where women outperform men in high-income countries [260]. Studies that used data from both high- and middle-income countries to examine the role of education in sex differences in cognitive function were based on non-representative samples [151, 257] that are prone to selection bias, precluding cross-national comparison and generalisation.

5.2.2 Objective

We used weighted data on persons 60 years and older in five population-based cohort studies to undertake a nationally representative comparison of sex differences in four cognitive domains (orientation, episodic memory, attention, and verbal fluency) between a high-income country (United States [US]) and four middle-income countries (Mexico, Brazil, China, and India). A further objective was to examine the role of education in these sex differences.

5.2.3 Methods

5.2.3.1 Data sources

We chose to use cross-sectional data for this paper as several middle-income countries only had single waves of data, to make use of available cross-sectional weights, and to reduce period effects. In addition, for each respondent, a longitudinal weight was only available for a wave if the respondent had participated in all previous waves of data collection. As such, we would be limited in the waves we could include, as the majority of participants have intermittent drop out patterns. We first chose our reference high-income country. ELSA and HRS were both evaluated and sex differences in cognitive function were similar in both cohorts. We chose to use HRS as a reference for a high-income country as it was the largest cohort with data on the most cognitive tests.

Paper 2 also includes data from four middle-income countries: Mexico (MHAS), Brazil (ELSI), China (CHARLS), and India (LASI). These countries were selected as they were the HRS-family cohorts that were both classified by the World Bank as upper- (Mexico, Brazil, China) or lower- (India) middle income countries and also had the most cognitive tests available with nationally representative samples from similar survey years.

Paper 2 included participants over age 60 from wave 13 of HRS (2016-18), wave 5 of MHAS (2018-19), wave 1 of ELSI (2015-16), wave 4 of CHARLS (2018), and wave 1 of LASI (2017-19). These waves were chosen to make survey years comparable between studies and to attenuate period effects. Core cohort members and younger spouses with survey weights were included. Analyses were restricted to participants over age 60 in order to reduce bias

due to birth cohort effects, which are indistinguishable from age effects for cross-sectional studies. Included studies in paper 2 are summarised in Tables 5.2.1 and 5.2.2.

Table 5.2.1. Overview of studies included in paper 2.

Country	Cohort name	Years	Age range	Birth years	World bank classification
United States	HRS	2016-18	50-107	1901-1968	high income
Mexico	MHAS	2018-19	50-101	1916-1971	upper-middle
Brazil	ELSI	2015-16	50-105	1910-1966	upper-middle
China	CHARLS	2018	50-118	1900-1968	upper-middle
India	LASI	2017-19	50-116	1902-1969	lower-middle

Table 5.2.2. Summary of waves and years in paper 2.

Year	*Country (study)*				
	US (HRS)	**Brazil (ELSI)**	**Mexico (MHAS)**	**China (CHARLS)**	**India (LASI)**
2015		Wave 1			
2016	Wave 13				
2017					Wave1
2018			Wave 5	Wave 4	
2019					

5.2.3.2 Sex and covariates

Sex was based on self-report, recorded as male or female. In addition to sex, paper 2 included marital status (not married/partnered, married/partnered) and age as sociodemographic covariates.

Because the educational distributions in HRS and the included middle income cohorts were very different, with the majority having no or less than secondary educational qualifications in the middle income cohorts, classification using categorisation based on degree cut offs would not give meaningful results. Instead, we chose to examine relative education level by creating education levels in each country that had a distribution similar to that in HRS. First, we categorised education in HRS based on degree level. Low education in HRS included those with less than a high school degree, intermediate included those with a high school degree or GED, and high included any education above high school degree or GED. Education was then categorised in the other cohorts based on the frequencies of each

category in HRS. This yielded education categories where, for example, high education referred to be highly educated relative to the population in that country. The approximate years of schooling included in each educational category and their frequencies in the analytic sample are shown in Table 5.2.3.

Table 5.2.3. Education categories in the five countries.

Education category	Country (cohort)									
	US (HRS)		Mexico (MHAS)		Brazil (ELSI)		China (CHARLS)		India (LASI)	
	Approximate years of schooling	%[a]	Approximate years of schooling	%[a]	Approximate years of schooling	%[a]	Approximate years of schooling	%[a]	Approximate years of schooling	%[a]
Low	<12	13.4	<6	22.0	<2	27.6	<6	30.1	0	60.3
Intermediate	12	50.8	6-11	51.2	2-8	51.7	6-8	42.1	1-7	20.3
High	>12	35.8	>11	26.8	>8	20.7	>8	27.8	>7	19.4

[a]Data are percentages in the weighted, imputed dataset. Imputation described in Section 5.2.3.4.
Abbreviations: HRS, Health and Retirement Study; MHAS, Mexican Health and Aging Study; ELSI, Brazilian Longitudinal Study of Aging; CHARLS, Chinese Health and Retirement Longitudinal Study; LASI, Longitudinal Aging Study in India

5.2.3.3 Outcomes

There were four cognitive tests included in paper 2: date naming, immediate and delayed recall, serial 7s, and the animal naming task. Date naming, recall, serial 7s, and animal naming tasks were used to measure the cognitive domains orientation, episodic memory, attention, and verbal fluency respectively. Date naming and recall were available in all cohorts. Animal naming was available in all studies except CHARLS and serial 7s in all studies except ELSI.

The date naming task required participants to correctly name the day, month, and year that the interview took place. Participants were scored out of 3 points. For immediate and delayed recall, participants were asked to recall either 8 (MHAS) or 10 (all other cohorts) word lists, once immediately after hearing the list and then again after several questions. The animal naming task required participants to recall out loud as many animals as possible within a minute period. The serial 7s task required counting backward from 100 by 7s five times. Participants were scored out of 5 points. If they incorrectly calculated one step, but then successfully subtracted 7 from the incorrect value in the subsequent step, they

received full points for the step where they subtracted correctly. Though serial 7s was devised at a task of attention and is not intentionally a numeracy test, it does require a degree of basic numeracy.

5.2.3.4 Statistical methods

Imputation

Before running analyses for paper 2, I first imputed the missing data. In order to retain as many respondents as possible so that survey weights could be applied and national representativeness of the sample could be maintained, missing data in any included covariate or outcome was imputed using multiple imputation with chained equations (MICE). Predictive mean matching (PMM) was used to impute missing values. PMM is a method that does not assume an underlying distribution of the variables to be imputed, but instead uses a linear model to predict an imputed value and then identifies the k nearest neighbours and randomly selects one of these neighbours' values to impute for the missing value. Predictive mean matching is a suitable alternative when the imputed variables would otherwise require ordinal or multinomial logistic models—for example, in modelling discrete scores—as these models are frequently unstable when performing MICE. Values between $k = 5, \ldots, 10$ have been found to yield the best results [319]. This paper used $k = 10$ neighbours.

The number of imputations was determined using the 'linear rule of thumb' which is appropriate up to 50% missingness [319, 320]: the number of imputations was equal to 100 minus the percentage of complete cases, plus an additional 10 imputations to be conservative. So that we could pool the cohorts for analyses, all of the cohorts required the same number of imputations. As such, the number of imputations was determined based on the cohort with the greatest proportion of missing information. In total, 50 imputations were run for each cohort.

All imputation models were run separately in men and women and in each cohort so that sex and cohort interactions were compatible with the main models in the analysis. Imputation models must include at minimum two types of variables: 1) all variables that will be included in the main analysis; 2) auxiliary variables that are not included in the main

analysis but nonetheless are informative for missingness patterns or are highly correlated with missing variables. These variables are included in order to strengthen the missing at random assumption that underlies the imputation. As such, all imputation models included 1) all cognitive tests, age, age^2, marital status, education, and interactions of education with age and age^2; and 2) number of limitations in basic/instrumental activities of daily living and mobility activities, and labour force status (employed, unemployed, retired, homemaker). We also included survey weights as a covariate in the imputation model and interaction terms between survey weight and all other covariates in the imputation model. Survey weights were included because there was an association between survey weights and missingness in the imputed variables, so it was insufficient to simply weight the imputation model; doing so would have resulted in an incorrectly specified imputation model that would not be compatible with the final weighted models used in the main analysis [321]. The imputed outcome variables are summarised in Tables 5.2.4 and 5.2.5.

Table 5.2.4. The number and percentage of imputed data on covariates in each cohort.

Cohort (Total N, % complete cases)	**The number (%) of imputed covariates**		
	Age	*Marital status*	*Education*
HRS (13590, 61.0)	0 (0.0)	0 (0.0)	4 (0.0)
MHAS (10121, 81.9)	1 (0.0)	0 (0.0)	468 (4.6)
ELSI (5432, 95.7)	0 (0.0)	0 (0.0)	51 (0.9)
CHARLS (10226, 58.4)	46 (0.5)	0 (0.0)	0 (0.0)
LASI (31477, 57.7)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: HRS, Health and Retirement Study; MHAS, Mexican Health and Aging Study; ELSI, Brazilian Longitudinal Study of Aging; CHARLS, Chinese Health and Retirement Longitudinal Study; LASI, Longitudinal Aging Study in India

Table 5.2.5. The number and percentage of imputed data on cognitive scores in each cohort.

Cohort (Total N, % complete cases)	**The number (%) of imputed cognitive scores**				
	Orientation	*Immediate recall*	*Delayed recall*	*Serial 7s*	*Verbal fluency*
HRS (13590, 61.0)	4372 (32.1)	905 (6.7)	906 (6.7)	1607 (11.8)	4659 (34.3)
MHAS (10121, 81.9)	1019 (10.0)	1172 (11.6)	1172 (11.6)	1154 (11.4)	1323 (13.1)
ELSI (5432, 95.7)	290 (5.3)	290 (5.3)	290 (5.3)	No data	303 (5.6)
CHARLS (10226, 58.4)	1093 (10.7)	2189 (21.4)	2619 (25.6)	3665 (35.8)	No data
LASI (31477, 57.7)	747 (2.4)	1122 (3.6)	3528 (11.2)	12022 (38.2)	887 (2.8)

Abbreviations: HRS, Health and Retirement Study; MHAS, Mexican Health and Aging Study; ELSI, Brazilian Longitudinal Study of Aging; CHARLS, Chinese Health and Retirement Longitudinal Study; LASI, Longitudinal Aging Study in India

Analysis

Sex differences in education in each country were examined using a weighted ordinal logistic model with education level (1 = low, 2 = intermediate, 3 = high) as the outcome. To examine whether sex differences in education in middle-income countries were larger than in the US (HRS), we pooled data from all cohort studies and included sex, age, country, and interaction between sex and country as predictors, with HRS as the reference.

We used weighted linear regression to examine sex differences in each cognitive domain. The interaction between sex and age terms (age, age^2) suggested no robust change in sex differences with age ($p > 0.05$, apart for memory in India), allowing us to exclude these interaction terms and conduct analyses on the entire study population without stratification by age or inclusion of interaction terms of sex and age.

Sex differences in the four cognitive domains in each country were examined by first pooling data from all cohorts. These models included sex, age (centred at 65 years), age^2, marital status, country (US [HRS] as the reference category, Mexico [MHAS], Brazil [ELSI], China [CHARLS], and India [LASI]) and interactions of country with sex, age, age^2, and marital status to generate estimates of sex differences in each cognitive domain for each country. These analyses were then further adjusted for education, interactions between education and age (age, age^2), and education and country. Sex differences in each of the middle-income countries were compared to the US, with p-values for interactions between sex and country reported in the results. In supplementary analyses, we reran these analyses without weighting or imputation in order to determine the effect of weighting and imputation.

To further investigate the role of education, we examined whether sex differences varied by education group in each country. Analyses were undertaken separately in each country and included sex, age, age^2, marital status, education, interactions between education and age (age, age^2), and between education and sex. Then, analyses were stratified by education in order to report sex differences in each education group.

We finally examined whether sex differences in cognitive function in each education group differed between countries, using the pooled dataset. Analyses were stratified by education and included sex, age, age^2, marital status, country, and interactions between country and each of the other covariates. For each education category, we reported the p-values for the

interactions between sex and country to examine whether sex differences in the middle-income countries differed from the US. All analyses were undertaken using Stata 17 with a two-sided $p < 0.05$ considered statistically significant.

5.2.4 Results

5.2.4.1 Sample characteristics

Analyses were based on 70846 participants aged 60 and older, including 13590 participants from the US, 10121 from Mexico, 5432 from Brazil, 10226 from China, and 31477 from India. Characteristics of participants in each country based on weighted, imputed data are shown in Table 5.2.6, with corresponding observed data shown in Table 5.2.7. There were negligible sex differences (< 1.5 years) in mean age across the five countries. Women were less likely than men to be married/partnered and less likely to have received a high level of education in all five cohorts ($p < 0.001$ for sex differences). The latter disadvantage was considerably larger in China and India ($p < 0.001$ for interaction between sex and country for both) compared to the US (Table 5.2.8). Figure 5.2.1 shows the mean standardised cognitive scores in each education level for each country in the weighted, imputed dataset. Higher education level generally corresponded to higher mean cognitive score for all countries, age groups, and cognitive domains.

Table 5.2.6. Characteristics of men and women in five countries after imputation of missing data and weighting to obtain national representativeness.

	United States (HRS)			Mexico (MHAS)			Brazil (ELSI)			China (CHARLS)			India (LASI)		
	Men	Women	P-value	Men	Women	P-value	Men	Women	P-value	Men	Women	P-value	Men	Women	P-value
	45.4%	54.6%		45.8%	54.2%		44.2%	55.8%		49.3%	50.7%		49.2%	50.8%	
Age, Mean	70.4	71.7	<0.001	70.5	70.1	0.23	69.4	70.3	0.01	69.7	70.1	0.05	68.7	68.7	0.71
Age group															
60-69	54.0	50.1		53.1	56.4		59.0	54.7		57.4	56.8		62.0	61.5	
70-79	30.4	29.4	<0.001	31.0	28.9	0.25	29.3	30.3	0.004	30.2	28.7	0.08	28.2	27.5	0.01
80+	15.6	20.5		15.9	14.7		11.7	15.0		12.4	14.5		9.8	11.0	
Married/partnered															
Yes	74.1	53.0	<0.001	79.3	50.8	<0.001	75.0	44.3	<0.001	85.7	67.8	<0.001	82.4	46.0	<0.001
No	25.9	47.0		20.7	49.2		25.0	55.7		14.3	32.2		17.6	54.0	
Education															
Low	12.5	14.1		18.7	24.9		25.7	29.0		14.0	45.6		44.4	75.7	
Intermediate	47.5	53.7	<0.001	52.8	49.8	<0.001	53.0	50.7	0.08	48.9	35.6	<0.001	25.5	15.3	<0.001
High	40.0	32.2		28.5	25.3		21.3	20.3		37.1	18.8		30.1	9.0	

Data shown are percentages unless otherwise indicated.

Abbreviations: HRS, Health and Retirement Study; MHAS, Mexican Health and Aging Study; ELSI, Brazilian Longitudinal Study of Aging; CHARLS, Chinese Health and Retirement Longitudinal Study; LASI, Longitudinal Aging Study in India

Table 5.2.7. Characteristics of men and women in the five countries: observed data.

	US (HRS) N = 13590			Mexico (MHAS) N = 10121			Brazil (ELSI) N = 5432			China (CHARLS) N = 10226			India (LASI) N = 31477		
	Men	Women	P-value	Men	Women	P-value	Men	Women	P-value	Men	Women	P-value	Men	Women	P-value
	41.6%	58.4%		44.1%	55.9%		40.0%	60.0%		48.7%	51.3%		48.0%	52.0%	
Age, Mean	72.2	73.0	<0.001	72.0	71.6	0.01	70.1	70.5	0.05	69.1	69.3	0.28	69.0	68.7	<0.001
Age group															
60-69	45.7	43.4		41.7	45.6		54.4	52.0		59.9	59.6		59.3	61.2	
70-79	31.1	30.9	0.002	40.1	36.2	<0.001	31.9	33.4	0.22	30.2	29.2	0.23	30.1	27.8	<0.001
80+	23.2	25.7		18.2	18.2		13.8	14.6		9.7	10.6		10.5	11.0	
Married/partnered															
Yes	75.0	46.8	<0.001	78.0	48.5	<0.001	71.8	37.7	<0.001	86.2	70.5	<0.001	82.8	46.4	<0.001
No	25.0	53.2		22.0	51.5		28.2	62.3		13.8	29.5		17.2	53.6	
Education															
Low	18.4	19.0		15.8	20.3		30.2	31.1		15.1	49.6		36.3	69.7	
Intermediate	48.6	54.7	<0.001	50.9	52.0	<0.001	50.1	49.7	0.77	50.9	35.7	<0.001	29.7	18.8	<0.001
High	32.9	26.3		28.0	23.6		18.7	18.3		34.0	14.6		34.1	11.5	

Data shown are percentages unless otherwise indicated.

Abbreviations: HRS, Health and Retirement Study; MHAS, Mexican Health and Aging Study; ELSI, Brazilian Longitudinal Study of Aging; CHARLS, Chinese Health and Retirement Longitudinal Study; LASI, Longitudinal Aging Study in India

Table 5.2.8. Odds ratio of being in higher education group for women compared to men.

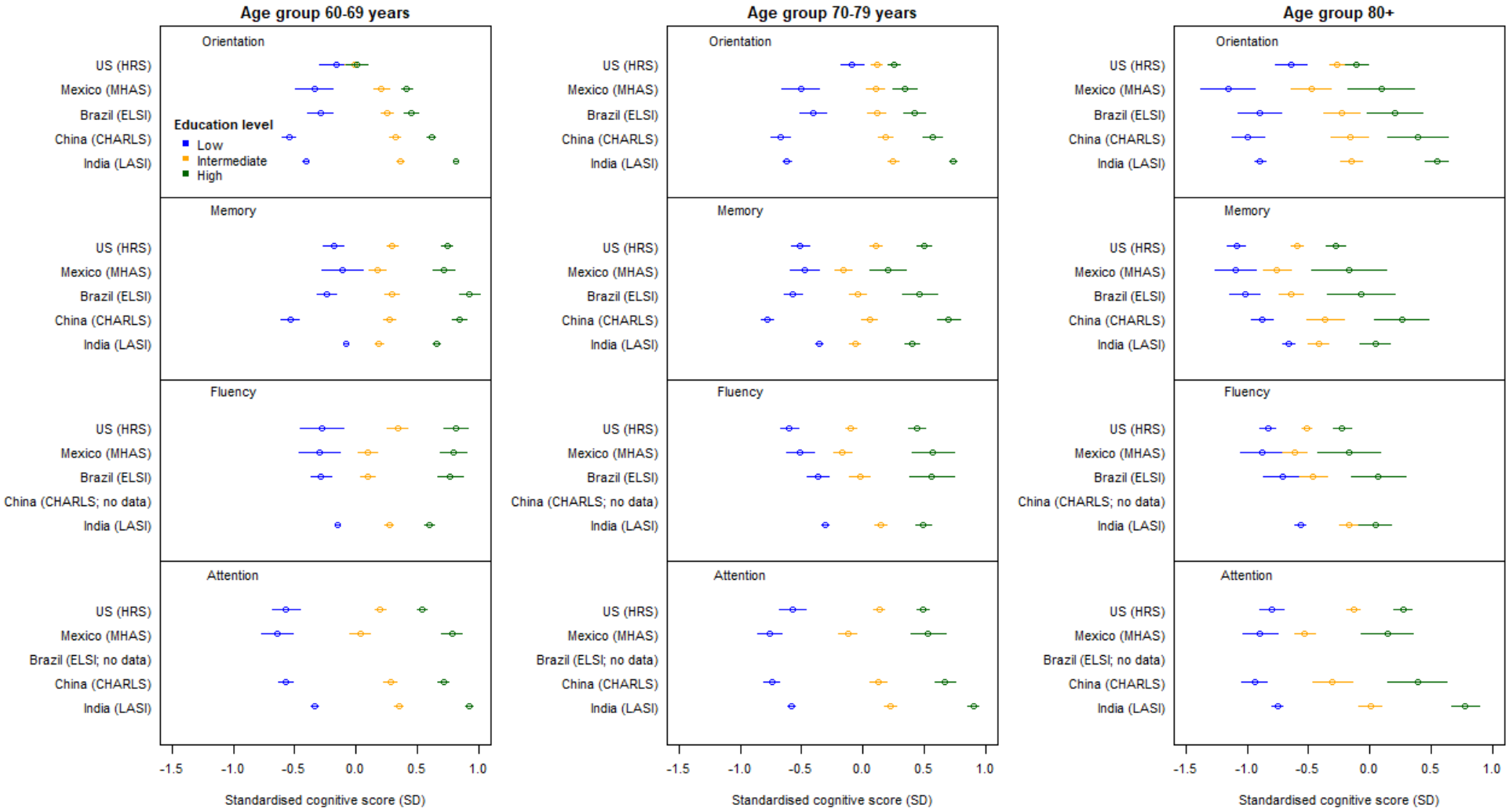
Country (cohort)	Odds ratio (95% CI)[a]	P-value[b]
United States (HRS)	0.83 (0.77, 0.90)	Ref.
Mexico (MHAS)	0.77 (0.66, 0.89)	0.36
Brazil (ELSI)	0.94 (0.83, 1.05)	0.10
China (CHARLS)	0.26 (0.23, 0.29)	<0.001
India (LASI)	0.17 (0.16, 0.19)	<0.001

[a]Odds ratio below 1 indicates women are less likely to be in higher education group compared to men, estimated using weighted ordinal logistic models with education level (1 = low, 2 = intermediate, 3 = high) as the outcome.

[b]P-value < 0.05 indicates that sex difference in education level for the given country differs from that in the US.

Abbreviations: HRS, Health and Retirement Study; MHAS, Mexican Health and Aging Study; ELSI, Brazilian Longitudinal Study of Aging; CHARLS, Chinese Health and Retirement Longitudinal Study; LASI, Longitudinal Aging Study in India

Figure 5.2.1. Mean standardised cognitive scores by education level in each country after weighting and imputation, stratified by age group.



5.2.4.2 *Comparison of sex differences in cognitive function between countries before and after adjustment for education*

Sex differences in cognitive scores in each country before and after adjustment for education are shown in Figure 5.2.2 in panels A and B respectively and in Table 5.2.9; the figures and table also show p-values for the comparison of sex differences between countries using the US as the reference country. Before adjustment for education, women had higher scores on orientation than men in the US (the male – female sex difference in standardised score [95% confidence interval] was -0.08 [-0.15, 0.00] standard deviations), while men outperformed women in Mexico (0.09 [0.00, 0.17]), Brazil (0.07 [0.00, 0.13]), China (0.39 [0.33, 0.44]), and India (0.55 [0.52, 0.58]). After adjustment for education, the female disadvantage persisted only in China (0.12 [0.07, 0.17]) and India (0.27 [0.24, 0.29]). Pooled data showed sex differences in middle-income countries differed from those in the US both before ($p < 0.01$ for all comparisons) and after adjustment for education ($p < 0.04$ for all).

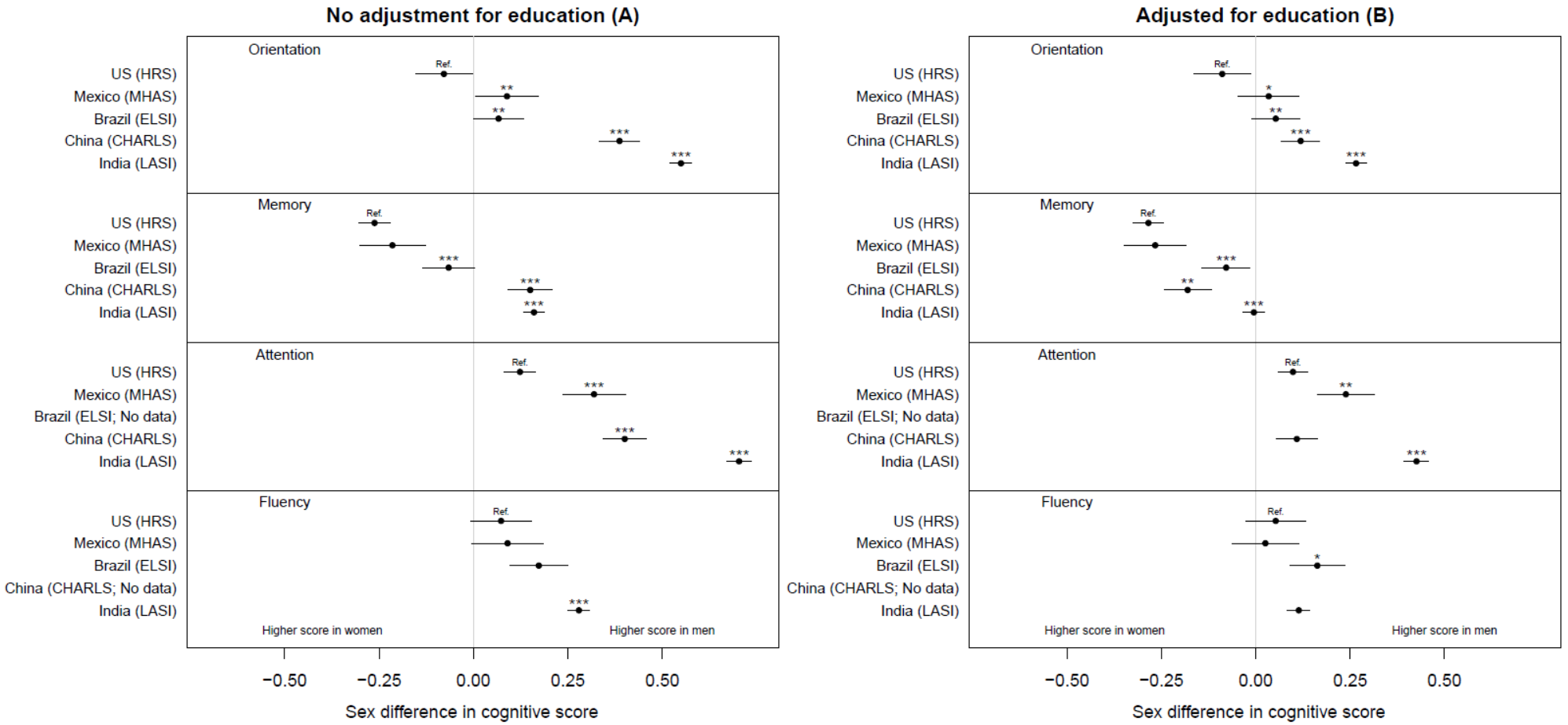
For memory, before adjustment for education, sex differences in Brazil, China, and India differed from the US ($p < 0.001$ for all). Women performed better than men in the US (-0.26 [-0.30, -0.22]), Mexico (-0.21 [-0.30, -0.13]), and Brazil (-0.07 [-0.13, 0.00]), but worse in China (0.15 [0.09, 0.21]) and India (0.16 [0.13, 0.19]). After adjustment for education, there was no sex difference in memory in India, and a female advantage in all other countries, although the female advantage in the US remained larger than in Brazil ($p < 0.001$), China ($p = 0.01$), and India ($p < 0.001$).

For attention, men outperformed women before adjustment for education in all countries, but the magnitude of the female disadvantage was larger in the middle-income countries (0.32 [0.24, 0.40] in Mexico, 0.40 [0.34, 0.46] in China, and 0.70 [0.67, 0.74] in India), than in the US (0.12 [0.08, 0.17]; $p < 0.001$ for all). After adjustment for education, the female disadvantage in attention was attenuated in all countries, but remained larger in Mexico (0.24 [0.16, 0.31]) and India (0.43 [0.39, 0.46]) than in the US (0.10 [0.06, 0.14]; $p < 0.01$ for both comparisons).

For fluency, there was a female disadvantage before adjustment for education in the US (0.07 [-0.01, 0.15]) and Mexico (0.09 [-0.01, 0.19]) though these sex differences did not

reach statistical significance. A female disadvantage was found in Brazil (0.17 [0.10, 0.25]) and India (0.28 [0.25, 0.31]), with the sex difference in India differing from that in the US ($p < 0.001$). After adjustment for education, the female disadvantage in Brazil (0.16 [0.09, 0.24]) was larger than that in the US ($p = 0.04$ for comparison between US and Brazil) while the female disadvantage in India (0.11 [0.08, 0.14]) was attenuated such that it no longer differed from the US (0.05 [-0.03, 0.13]).

Figure 5.2.2. Sex differences in standardised cognitive scores in each country.



Left panel (A) shows sex differences in standardised cognitive scores in each country. Right panel (B) shows analyses further adjusted for education. Tests for difference with the US (HRS) were based on pooled data and *denotes significance at $\alpha < 0.05$, **$\alpha < 0.01$, and *** $\alpha < 0.001$.

Table 5.2.9. Comparison of sex differences in cognitive performance between education groups in each country.

	Before adjustment for education		After adjustment for education	
	Sex difference (95% CI)[a]	*P for interaction sex and cohort*	Sex difference (95% CI)[a]	*P for interaction sex and cohort*
Orientation				
United States (HRS)	-0.08 (-0.15, 0.00)	Ref.	-0.09 (-0.16, -0.01)	Ref.
Mexico (MHAS)	0.09 (0.00, 0.17)	0.01	0.03 (-0.05, 0.12)	0.04
Brazil (ELSI)	0.07 (0.00, 0.13)	0.01	0.05 (-0.01, 0.12)	0.01
China (CHARLS)	0.39 (0.33, 0.44)	<0.001	0.12 (0.07, 0.17)	<0.001
India (LASI)	0.55 (0.52, 0.58)	<0.001	0.27 (0.24, 0.29)	<0.001
Memory				
United States (HRS)	-0.26 (-0.30, -0.22)	Ref.	-0.28 (-0.32, -0.24)	Ref.
Mexico (MHAS)	-0.21 (-0.30, -0.13)	0.34	-0.27 (-0.35, -0.18)	0.70
Brazil (ELSI)	-0.07 (-0.13, 0.00)	<0.001	-0.08 (-0.14, -0.01)	<0.001
China (CHARLS)	0.15 (0.09, 0.21)	<0.001	-0.18 (-0.24, -0.12)	0.01
India (LASI)	0.16 (0.13, 0.19)	<0.001	-0.01 (-0.03, 0.02)	<0.001
Attention				
United States (HRS)	0.12 (0.08, 0.17)	Ref.	0.10 (0.06, 0.14)	Ref.
Mexico (MHAS)	0.32 (0.24, 0.40)	<0.001	0.24 (0.16, 0.31)	0.001
Brazil (ELSI)	No data	No data	No data	No data
China (CHARLS)	0.40 (0.34, 0.46)	<0.001	0.11 (0.05, 0.16)	0.77
India (LASI)	0.70 (0.67, 0.74)	<0.001	0.43 (0.39, 0.46)	<0.0001
Fluency				
United States (HRS)	0.07 (-0.01, 0.15)	Ref.	0.05 (-0.03, 0.13)	Ref.
Mexico (MHAS)	0.09 (-0.01, 0.19)	0.78	0.03 (-0.06, 0.11)	0.65
Brazil (ELSI)	0.17 (0.10, 0.25)	0.07	0.16 (0.09, 0.24)	0.04
China (CHARLS)	No data	No data	No data	No data
India (LASI)	0.28 (0.25, 0.31)	<0.001	0.11 (0.08, 0.14)	0.16

[a]Estimated using weighted linear regression models adjusted for sex, marital status, age, and age^2; positive values indicate men had higher cognitive scores, negative values indicate women had higher cognitive scores.
Abbreviations: CI, confidence interval; HRS, Health and Retirement Study; MHAS, Mexican Health and Aging Study; ELSI, Brazilian Longitudinal Study of Aging; CHARLS, Chinese Health and Retirement Longitudinal Study; LASI, Longitudinal Aging Study in India.

5.2.4.3 *Comparison of sex differences in cognitive function between education groups in each country*

In the US and Mexico, sex differences in all cognitive scores were similar in the three education groups, although a qualitative trend towards smaller differences in the high education category was observed (Table 5.2.10). The interaction terms between sex and education showed sex differences in all cognitive scores were largest in the low education group and smallest in the high education group in China and India ($p < 0.001$ for all cognitive domains). This was also the case for orientation ($p = 0.001$) and memory ($p = 0.02$) but not fluency ($p = 0.23$) in Brazil.

Table 5.2.10. Comparison of sex differences in cognitive performance between education groups in each country.

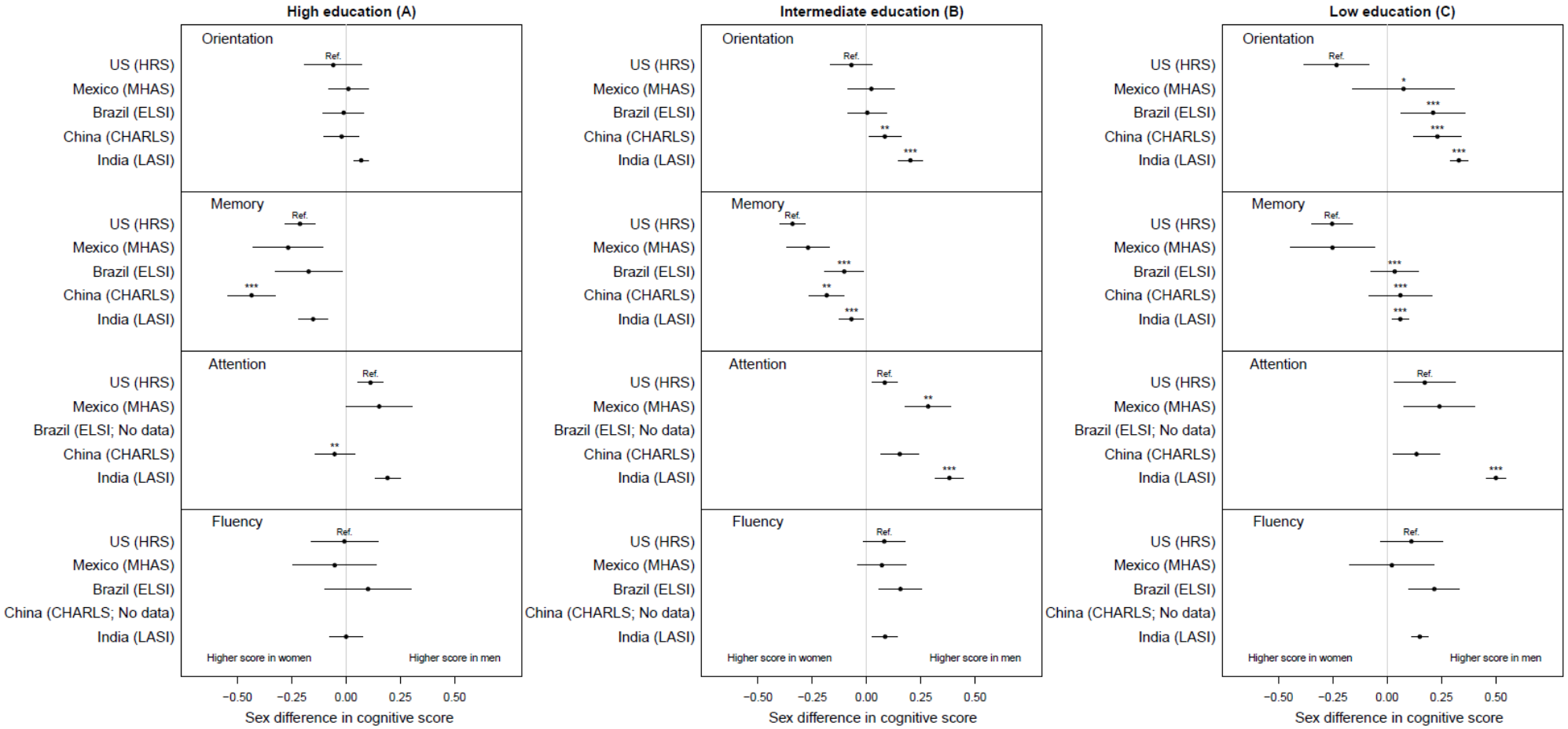
	Sex difference (95% CI)[a]			*P-value for interaction between sex and education*
	High education	Intermediate education	Low education	
United States *(N = 13590)*				
Orientation	-0.06 (-0.19, 0.07)	-0.07 (-0.17, 0.03)	-0.23 (-0.38, -0.08)	0.18
Memory	-0.21 (-0.28, -0.14)	-0.34 (-0.40, -0.28)	-0.25 (-0.35, -0.16)	0.17
Attention	0.11 (0.06, 0.17)	0.08 (0.03, 0.14)	0.17 (0.03, 0.31)	0.29
Fluency	-0.01 (-0.16, 0.15)	0.08 (-0.01, 0.18)	0.11 (-0.03, 0.25)	0.21
Mexico *(N = 10121)*				
Orientation	0.01 (-0.08, 0.10)	0.02 (-0.08, 0.13)	0.08 (-0.16, 0.31)	0.23
Memory	-0.27 (-0.43, -0.11)	-0.27 (-0.37, -0.17)	-0.25 (-0.45, -0.06)	0.99
Attention	0.15 (0.00, 0.30)	0.28 (0.18, 0.39)	0.24 (0.08, 0.40)	0.41
Fluency	-0.05 (-0.25, 0.14)	0.07 (-0.04, 0.18)	0.02 (-0.17, 0.22)	0.98
Brazil (N = 5432)				
Orientation	-0.01 (-0.10, 0.08)	0.00 (-0.09, 0.09)	0.21 (0.06, 0.36)	0.001
Memory	-0.17 (-0.32, -0.02)	-0.10 (-0.19, -0.01)	0.04 (-0.07, 0.14)	0.02
Attention	No data	No data	No data	No data
Fluency	0.10 (-0.10, 0.30)	0.16 (0.06, 0.25)	0.22 (0.10, 0.33)	0.23
China (N = 10226)				
Orientation	-0.02 (-0.10, 0.06)	0.08 (0.01, 0.16)	0.23 (0.12, 0.34)	<0.001
Memory	-0.43 (-0.54, -0.32)	-0.18 (-0.26, -0.10)	0.06 (-0.08, 0.21)	<0.001
Attention	-0.05 (-0.14, 0.04)	0.15 (0.07, 0.24)	0.14 (0.03, 0.24)	<0.001
Fluency	No data	No data	No data	No data
India (N = 31477)				
Orientation	0.07 (0.03, 0.10)	0.20 (0.15, 0.26)	0.33 (0.29, 0.37)	<0.001
Memory	-0.15 (-0.22, -0.09)	-0.07 (-0.13, -0.01)	0.06 (0.02, 0.10)	<0.001
Attention	0.19 (0.13, 0.25)	0.38 (0.32, 0.45)	0.50 (0.46, 0.55)	<0.001
Fluency	0.00 (-0.07, 0.08)	0.09 (0.03, 0.14)	0.15 (0.11, 0.19)	<0.001

[a]Estimated using weighted linear regression models adjusted for sex, marital status, age, and age^2; positive values indicate men had higher cognitive scores, negative values indicate women had higher cognitive scores. Abbreviations: CI, confidence interval; HRS, Health and Retirement Study; MHAS, Mexican Health and Aging Study; ELSI, Brazilian Longitudinal Study of Aging; CHARLS, Chinese Health and Retirement Longitudinal Study; LASI, Longitudinal Aging Study in India.

5.2.4.4 *Comparison of sex differences in cognitive function between countries within each education group*

Figure 5.2.3. shows results from the comparison of sex differences in cognitive function between countries within each education group. The smallest between-country differences in sex differences in cognitive function were in the high education group (Figure 5.2.3, Panel A), particularly in orientation and fluency where sex differences were similar in all countries. Compared to the US, sex differences in memory ($p < 0.001$) and attention ($p = 0.003$) in China were more favourable to women. In the intermediate education category (Figure 5.2.3, Panel B), sex differences were similar for fluency in all countries. Compared to the US, there was a female disadvantage in orientation and attention in the middle-income countries and the female advantage in memory was smaller in these countries. In the low education category (Figure 5.2.3, Panel C), the between-country patterns in sex differences were similar to those in the intermediate group but the female disadvantage was more pronounced. The p-values for the interaction between sex and cohort shown in Figure 5.2.3 are tabulated in Table 5.2.11.

Figure 5.2.3. Sex differences in standardised cognitive scores by education level in each country.



Left panel (A) shows sex differences in standardised cognitive scores in each country in the high education group. Centre panel (B) shows sex differences in the intermediate education group. Right panel (C) shows sex differences in the low education group. Tests for difference with the US (HRS) were based on pooled data and *denotes significance at $\alpha < 0.05$, **$\alpha < 0.01$, and *** $\alpha < 0.001$.

Table 5.2.11. P-values for the comparison of sex differences in middle-income countries to the US in each education group.

	High education	**Intermediate education**	**Low education**
	P for interaction between sex and cohort	*P for interaction between sex and cohort*	*P for interaction between sex and cohort*
Orientation			
United States (HRS)	Ref.	Ref.	Ref.
Mexico (MHAS)	0.41	0.21	0.04
Brazil (ELSI)	0.56	0.29	<0.001
China (CHARLS)	0.63	0.01	<0.001
India (LASI)	0.07	<0.001	<0.001
Memory			
United States (HRS)	Ref.	Ref.	Ref.
Mexico (MHAS)	0.55	0.22	0.99
Brazil (ELSI)	0.64	<0.001	<0.001
China (CHARLS)	<0.001	0.002	<0.001
India (LASI)	0.22	<0.001	<0.001
Attention			
United States (HRS)	Ref.	Ref.	Ref.
Mexico (MHAS)	0.63	0.001	0.52
Brazil (ELSI)	No data	No data	No data
China (CHARLS)	0.003	0.2	0.66
India (LASI)	0.06	<0.001	<0.001
Fluency			
United States (HRS)	Ref.	Ref.	Ref.
Mexico (MHAS)	0.72	0.88	0.44
Brazil (ELSI)	0.39	0.28	0.26
China (CHARLS)	No data	No data	No data
India (LASI)	0.93	0.94	0.61

[a]Estimated using weighted linear regression models adjusted for sex, marital status, age, and age2; positive values indicate men had higher cognitive scores, negative values indicate women had higher cognitive scores. Abbreviations: CI, confidence interval; HRS, Health and Retirement Study; MHAS, Mexican Health and Aging Study; ELSI, Brazilian Longitudinal Study of Aging; CHARLS, Chinese Health and Retirement Longitudinal Study;

5.2.4.5 Supplementary analyses

Rerunning the results without weighting or imputation resulted in overestimated sex differences for orientation and fluency, and overestimated female advantages in memory before and after adjustment for education (Appendix Figures 8.2.1-8.2.2). For fluency, sex differences also varied from the US for Mexico, Brazil, and India before and after adjustment for education. This was in contrast with the main results, where sex inequalities differed from the US in India only (before adjustment for education) and in Brazil (after adjustment for education). The results without imputation or weighting after stratification by education level were more similar to the main results, however there were still several instances where sex differences differed from the US without weighting or imputation but not in the main analysis (e.g. orientation in India in the high education group) or male advantages were overestimated (e.g. fluency for Mexico in the high education group).

5.2.5 Discussion

In this multicohort study of 70,846 men and women aged 60 and older from five countries, we found education, usually correlated with the economic development of a country, to play an important role in sex differences in cognitive function. Compared to the US—the high-income country in our analyses—poorer cognitive performance in women was more pronounced in middle-income countries. Women had higher scores on orientation and memory in the US, but this was not the case in the middle-income countries where there was either no sex difference, a smaller female advantage, or a female disadvantage. Adjustment for education attenuated sex differences in all cognitive domains, highlighting its importance. In further analyses where sex differences were examined separately in each education group, the larger cognitive disadvantages in women in the middle-income countries compared to the US were not seen in the high education group. These findings suggest that disparities in education play an important role in the cognitive disadvantage observed in women compared to men, particularly in comparisons of high- and middle-income countries.

5.2.5.1 Comparison with previous studies

Education is thought to confer a lifelong cognitive benefit, increasing cognitive function in early adulthood, and thus providing a buffer against cognitive impairment at older ages [101]. Therefore, education is seen to be a marker of cognitive reserve, or the ability of the brain to maintain adequate cognitive function in the presence of age-related or pathological neurodegeneration [250]. Sex differences in cognitive reserve are thought to contribute to sex differences in cognitive function [250]. Our findings are consistent with this hypothesis as before adjustment for education, the female disadvantage in cognitive function was particularly large in countries with the largest sex inequalities in education: India and China. This disadvantage was substantially attenuated when education was taken into account in the analysis. Mexico and Brazil had smaller sex differences in education and accordingly, sex differences in cognitive function were smaller than those in India and China and did not substantively change after adjustment for education. Concerted investment in education in Mexico has been a priority since the 1920s, resulting in a substantial increase in education levels in the population in both men and women [259, 322]. Enrolment of Brazilian women in schooling has also increased consistently, beginning early in the 20th century, although the overall levels of education in the population remain low [323].

The results from this study are in accordance with previous studies that show sex differences in orientation vary in magnitude and direction by country [151], a consistent female advantage in memory in high-income countries [143] that is reversed in middle-income countries [260], and a female disadvantage on tasks of sustained attention [51] including serial 7s [151]. Previous studies undertaken in high income countries also indicated no sex differences in fluency after taking education into account [51], or in our study, a female disadvantage only in the low education group and a female advantage or no sex differences among those who were more educated [19]. Consistent with these studies, we found that female disadvantage in fluency was eliminated in all countries in the high education group. We build on the existing evidence by showing that attenuation of female disadvantage in cognitive function among those who were most educated occurred across cognitive domains and in middle- and high-income countries. Sex differences tended to be largest and the least favourable to women in the low education group, with the biggest difference between middle-income countries and the US. By contrast, in the high education

group there were either no or few sex differences in cognitive domains. In this group, sex differences in the middle-income countries were mostly similar to those in the US. These findings suggest that the greater female disadvantage in cognitive function in the middle-income countries compared to the US is likely to be mainly driven by those in the low education group.

5.2.5.2 Strengths and limitations

The major strength of the present study is the use of nationally representative estimates from a diverse group of countries over a narrow time period, minimising the impact of selection bias and period effect. Some cognitive tests, such as attention measured using serial 7s, may not be appropriate for participants in settings where a considerable proportion of the study participants have no formal education. The use of multiple imputation allowed us to include all participants in the analysis, including those who did not perform the serial 7s task, minimising selection bias while maintaining national representativeness in all five cohort studies. In addition, we show absolute rather than relative measures of sex differences in cognitive function, allowing better interpretation of the size and comparison of sex differences between countries.

There are several limitations in this study. The cross-sectional design does not allow inferences on sex differences in the rate of cognitive decline with age. Nonetheless there is little evidence of sex differences in cognitive decline with age in adults aged 60 and above [161], findings that were confirmed in our data which showed that sex differences in cognitive function were similar across the age span in our analyses. There were large differences in education between high- and middle-income countries, with no formal education in a large proportion of participants in some of the middle-income countries. This precluded use of similar education categories, leading us to use numbers in the education categories in the US to create education groups of similar proportions in all countries in the analyses. Availability of more detailed education data in all cohorts, such as years of schooling, might have allowed more fine-grained analyses. The serial 7s task may be more likely to measure numeracy rather than attention in the middle-income countries where the lower education level may have meant individuals were less likely to have the numeracy skills needed to perform the test. This may have contributed to the magnitude of the male

advantages found in the serial 7s task in the middle-income countries. It is likely that the effect of education is due to gender roles rather than biological factors, but we did not have data on gender to allow us to separate the effects of sex and gender. Further studies are needed to elucidate the role of gender and biological sex in a wider range of countries, ideally with nationally representative longitudinal data.

5.2.5.3 Conclusion

Our findings suggest that improving education could eliminate the female disadvantage in cognitive function. In middle-income countries, 8-9 years of schooling was sufficient to see the same pattern of sex differences as in the high education category in the US, which was composed of participants with college/university education. Being highly educated compared to the rest of the population may open up otherwise inaccessible occupational and lifestyle pathways that further contribute to cognitive reserve [254], compounding the effect of education on cognitive function in old age. Furthermore, inequalities in education between men and women have decreased in many middle- and high-income countries over the 20th century [324]. These changes may eventually result in smaller disparities in cognitive function between men and women in middle- and high-income countries. This study reiterates the role of education in cognitive function and further shows that larger sex disparities in education in middle-income countries may account for the larger female cognitive disadvantage seen in middle- compared to high-income countries, pointing to the importance of gender equity in education as a target for improving cognitive health in old age.

5.3 Paper 3: Sex differences in functional limitations and the role of socioeconomic factors: a multi-cohort analysis

Adapted from *'Sex differences in functional limitations and the role of socioeconomic factors: a multi-cohort analysis'* published in the Lancet Healthy Longevity (2022). Full publication included in the Appendix (page 230).

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Author contributions: Conceptualisation: MB, SS, AD, ASM. Methodology: MB, BL, SS, AD. Investigation: ASM, AS, AB. Validation: SS, AD. Formal analysis: MB, AD, SS. Data curation: MB, SS. Writing –original draft preparation: MB, SS. Writing –review and editing: All authors. Visualisation: MB, AD, SS. Supervision: SS, ASM. Funding acquisition: AS, ASM, AB.

5.3.1 Rationale

There is a consistent finding in the literature that women are more likely than men to have functional limitations in ADL, IADL, and mobility activities [11]. There is also evidence that these sex differences in functional limitations may be decreasing in successive birth cohorts [282-284, 289], as women have had progressively more access to education and are more likely to participate in the labour force. Though social factors such as education are likely to contribute to differences in sex inequalities in functional limitations across birth cohorts, the role of education is not well-explored in this context.

There are limitations in the current body of knowledge. First, studies of sex differences in functional limitations by birth cohort are based on small samples [280, 282, 283, 289, 325] and cover a limited range of birth years [280, 282, 283, 286, 289, 326]. Second, functional limitations are often examined dichotomously [282, 285, 327] or combined into indices [286] that do not necessarily translate into easily interpretable measures of functional capacity. Dichotomous categorisation of functional limitations includes individuals with one or several limitations in the same category, thus failing to take into account potential variation in sex differences by severity of limitations.

5.3.2 Objective

In order to gain further understanding of sex differences in functional limitations in old age, we used longitudinal data pooled from four cohort studies of individuals aged 50-107 years from 14 countries to investigate the role of education in sex differences in mobility, IADL, and ADL limitations across birth cohorts including years from 1895-1960 and examine how sex differences vary by severity of limitations for each of the three measures (mobility, IADL, and ADL).

5.3.3 Methods

5.3.3.1 Data sources

The objectives of paper 3 necessitated a large dataset with ages represented in multiple birth cohorts. Given the availability of comparable data on functional limitations in the HRS-family of studies, we chose to use ELSA (England), TILDA (Ireland), SHARE (multiple European countries), and HRS (United States). Paper 3 included waves 1-9 of ELSA (surveyed every two years from 2002/03-2018/19), waves 1, 3, and 4 of TILDA (2009/11, 2014/15, 2016), waves 1, 2, and 4-7 of SHARE (2004/05, 2006/07, 2010/11, 2013, 2015, 2017), and waves 5-13 of HRS (2000, 2002/03-2016/17). Though data collection began in 1992 for HRS, earlier waves of HRS were excluded so that years of follow up were comparable between studies. Data from participants in these studies over age 50 at the baseline wave of the present study were pooled for analysis. As participants in ELSA and TILDA older than 80 or 90 years respectively at wave 1 had their age coded as 80 or 90 years without further precision, they were excluded from the analyses. Tables 5.3.1-5.3.3 summarise the studies used in paper 3.

Table 5.3.1. Countries in each study included in paper 3.

Study	Region	Country
ELSA	Western Europe	England
TILDA	Western Europe	Ireland
SHARE	Northern Europe	Denmark
		Sweden
	Western Europe	Austria
		Belgium
		France
		Germany
		Netherlands
		Switzerland
	Southern Europe	Greece
		Italy
		Spain
HRS	North America	United States

Abbreviations: ELSA: English Longitudinal Study of Ageing; TILDA: The Irish Longitudinal Study on Ageing; SHARE: Survey of Health, Ageing and Retirement in Europe; HRS: Health and Retirement Study

Table 5.3.2. Overview of studies included in paper 3.

Study	Dates	Number of waves	Birth years	Age range (years)
ELSA	2002-2019	9	1912-1952	50-103
TILDA	2010-2016	3	1931-1960	50-85
SHARE	2004-2017	6	1901-1955	50-105
HRS	2000-2017	9	1895-1950	50-107

Abbreviations: ELSA: English Longitudinal Study of Ageing; TILDA: The Irish Longitudinal Study on Ageing; SHARE: Survey of Health, Ageing and Retirement in Europe; HRS: Health and Retirement Study

Table 5.3.3. Summary of waves and years included in paper 3.

Year	*Study*			
	ELSA	**TILDA**	**SHARE**	**HRS**
2000				Wave 5
2001				
2002	Wave 1			Wave 6
2003				
2004	Wave 2		Wave 1	Wave 7
2005				
2006	Wave 3		Wave 2	Wave 8
2007				
2008	Wave 4			Wave 9
2009				
2010	Wave 5	Wave 1		Wave 10
2011			Wave 4	
2012	Wave 6			Wave 11
2013			Wave 5	
2014	Wave 7	Wave 3		Wave 12
2015			Wave 6	
2016	Wave 8	Wave 4		Wave 13
2017			Wave 7	
2018	Wave 9			
2019				

Abbreviations: ELSA: English Longitudinal Study of Ageing; TILDA: The Irish Longitudinal Study on Ageing; SHARE: Survey of Health, Ageing and Retirement in Europe; HRS: Health and Retirement Study

5.3.3.2 Sex and covariates

Sex was based on self-report (male or female). In addition to sex, sociodemographic characteristics in paper 3 included age, region (Western Europe, Northern Europe, Southern Europe, North America), study (SHARE, ELSA, TILDA, HRS [equivalent to North America region category]), and marital status (married/partnered, not married/partnered). Birth cohorts included pre-depression era (1895-1929), Depression era (1930-1938), World War II (1939-1945) and post-War (1946-1960) cohorts.

As the third paper included several countries, we used the HRS-family harmonised education category derived from the International Standard Classification of Education 1997 (ISCED 97). Educational categorisations are summarised in Table 5.3.4 as well as approximate years of schooling in each category. Participants were grouped into "less than upper secondary", "upper secondary and vocational training", and "university degree and above." The "less than upper secondary" group included ISCED 97 categories 0 (early childhood education, primary education), 1 (primary education) and 2 (lower secondary education). "Upper secondary and vocational training" included ISCED 97 categories 3 (upper secondary education) and 4 (post-secondary non-tertiary education). Tertiary education included ISCED 97 categories 5 (first stage of tertiary education) and 6 (second stage of tertiary education leading to advanced research qualification). Classification varied slightly between countries due to differences in educational systems, however the harmonised education variable used was intended for cross-national comparisons.

Table 5.3.4. Educational categorisation in paper 3.

Approx. years of schooling*	**ISCED 97**	**Harmonised education variable**
0-11	Early childhood	Less than upper secondary
	Primary	
	Lower secondary	
12-15	Upper secondary education	Upper secondary and vocational training
	Post-secondary non-tertiary	
16+	First stage of tertiary	University degree and above
	Second stage of tertiary education leading to advanced research degree qualification	

*Approximate years of schooling varies by educational system in each country.

In additional analyses, we included labour force status and chronic conditions as covariates in order to examine their impact on remaining sex differences in functional limitations. Labour force status was derived in each study based on questions about employment history and retirement status and harmonised into the following categories: employed/self-employed, retired, unemployed, homemaker. Chronic conditions were self-reported at the time of each interview and included high blood pressure, diabetes, cancer, lung disease, psychiatric illness, arthritis, and cardiovascular disease (heart attack and stroke).

5.3.3.3 Outcomes

Functional limitations were assessed using limitation in three categories of activities (mobility activities, IADL, and ADL). Each of the three measures (mobility activities, IADL, ADL) were composed of 6 activities. Mobility activities included getting up from a chair, climbing 1 flight of stairs, stooping/kneeling/crouching, reaching/extending the arms, lifting/carrying weights over 10 lbs, and walking 1 block/100 yards/100 metres. IADL included managing money, taking medications, grocery shopping, preparing meals, using the telephone, and house or garden work. ADL included walking across the room, dressing, bathing, eating, getting in and out of bed, and using the toilet. These activities were selected as they were available in all studies and are commonly used in the literature to examine functional limitations. Participants were asked whether they experienced "some difficulty" performing these activities for longer than three months due to a physical, mental, emotional, or memory problem. They were considered limited for a given activity if they answered "yes" for that activity. For house/garden work, HRS participants were asked whether their health limited their ability to perform housework (yes/no).

For each functional measure, the number of limited activities was summed to yield a score from 0-6. Participants with a score ≥1 were considered limited for the given functional measure. Severity of limitations for each functional measure (mobility activities, IADL, ADL) was examined using 0, 1, 2, or ≥3 limited activities.

5.3.3.4 Statistical analysis

Participant characteristics were described for all studies by birth cohort. Differences between men and women were examined using Pearson's x^2 test for categorical variables

and *t* test for continuous variables. To examine differences in each study separately, the observed proportion with at least one mobility, IADL, and ADL limitation for each 5-year age group was plotted in HRS, SHARE, TILDA, and ELSA.

Mixed effects ordinal logistic models were used to examine sex differences in functional limitation severity. The mixed models included a random intercept and slope at the individual level with an unstructured covariance matrix to account for intraindividual clustering. We also assessed including a random intercept at study level in order to account for clustering by study, however we determined that including this additional random effect did not impact results, and instead included study as a fixed covariate. We used an age time scale. The basic model included sex, age, birth cohort, and interactions between sex and age, and between birth cohort and age, region, study, and time-varying marital status. We then included interactions with age^2, and age^3 for each of these covariates and retained those in the model that were significant on the basis of the Wald test if $p < 0.05$. We then adjusted the model for education and interactions between education and higher-order age terms (age^2, age^3) where significant. We evaluated the interaction terms between sex, education, and age for inclusion in the models, but we ultimately omitted these terms as sex differences did not substantively vary between education levels.

In post hoc analyses, we examined whether time-varying labour force status and self-reported chronic conditions further explained the sex differences in functional limitations that remained after adjustment for education. We also undertook analyses including interaction terms between sex, region, and age, and then stratified results by region to examine region-specific variation in sex differences. Lastly, in order to ensure that no one activity was driving the findings for sex differences, as certain activities are more likely to be performed by women than by men such as housekeeping and food preparation [328], we examined sex differences in the distribution of mobility activities, IADL, and ADL in order to ensure that no one activity was driving the overall findings for sex differences in each functional outcome.

The sex difference in probability of each limitation number (0, 1, 2 or ≥3 limitations) was then derived from the ordinal models, estimated every 5 years from ages 50-100 years. We also calculated the probability of having ≥1 limitation as 1 minus the probability of having 0

limitations. All statistical analyses were undertaken in Stata 16.1 and 17.0 with a p-value < 0.05 considered statistically significant.

5.3.4 Results

5.3.4.1 Sample characteristics

There were 11391 eligible participants at the baseline wave of ELSA in 2002. Of these eligible participants, 95 (0.8%) had their age coded as 90 years at baseline and were therefore omitted from the analytic sample. Of the remaining 11296, 75 (0.6%) were missing at least 1 ADL, IADL, or mobility activity for all waves and 582 were missing other covariates. In total 10639 (93.3%) of 11391 ELSA participants were included in the analyses (Figure 5.3.1).

There were 8504 eligible participants at wave 1 of TILDA in 2010. Of the 8504, 329 (3.8%) were aged less than 50 years at baseline. A further 626 (7.4%) had their ages coded as 80 years at baseline, and 12 (0.1%) were missing age and birth year for all waves of data collection. Of the remaining 7537, 24 were missing covariates, leading to 7513 (88.3%) of 8504 TILDA participants retained in the analyses (Figure 5.3.2).

At the baseline wave of SHARE in 2004, there were 27975 eligible participants. Of these participants, 1153 (4.1%) were aged less than 50 years at baseline and 3 were missing age and birth year for all waves. Of the remaining 26819, 82 were missing at least 1 ADL, IADL, or mobility activity for all waves and 230 were missing other covariates, leading to 26507 SHARE participants retained in the analyses (Figure 5.3.3).

The 2000 wave of HRS included 19578 participants, of which 554 were excluded as they were aged less than 50 years. Of the remaining 19024, 1247 were missing at least 1 ADL, IADL, or mobility activity at all waves and 61 were missing other covariates. This resulted in 17,716 of 19,578 HRS participants retained in the analyses (Figure 5.3.4).

In total, there were 62,375 participants in the pooled sample. Of the participants in the pooled sample, 375 (0.6%) were resident in institutions at the baseline of the present study. Follow-up ran from January 2000 to January 2019 with a median follow up of 7 years and an interquartile range of 2 to 13 years.

Figure 5.3.1. Flowchart of sample selection in ELSA.

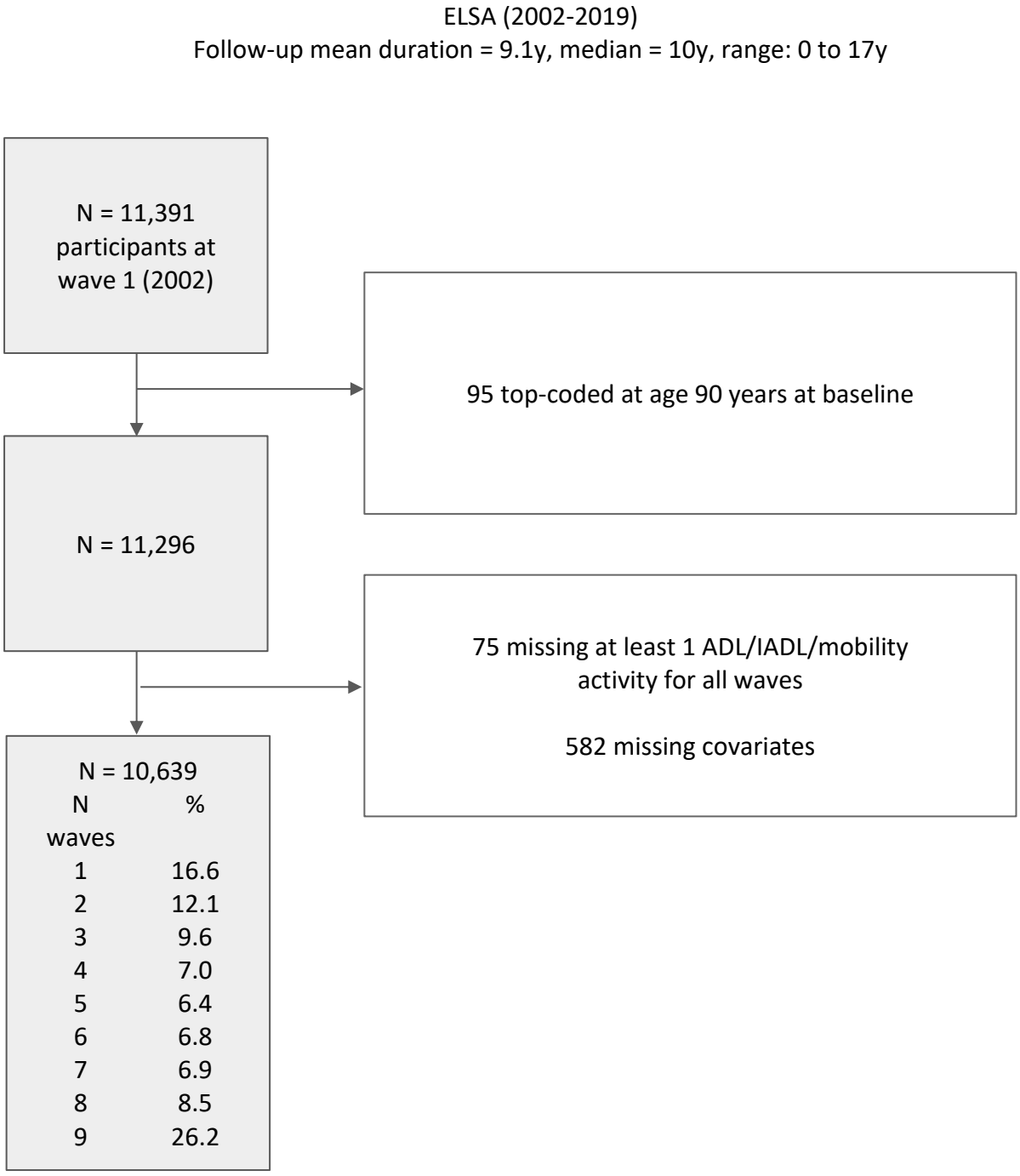

Figure 5.3.2. Flowchart of sample selection in TILDA.

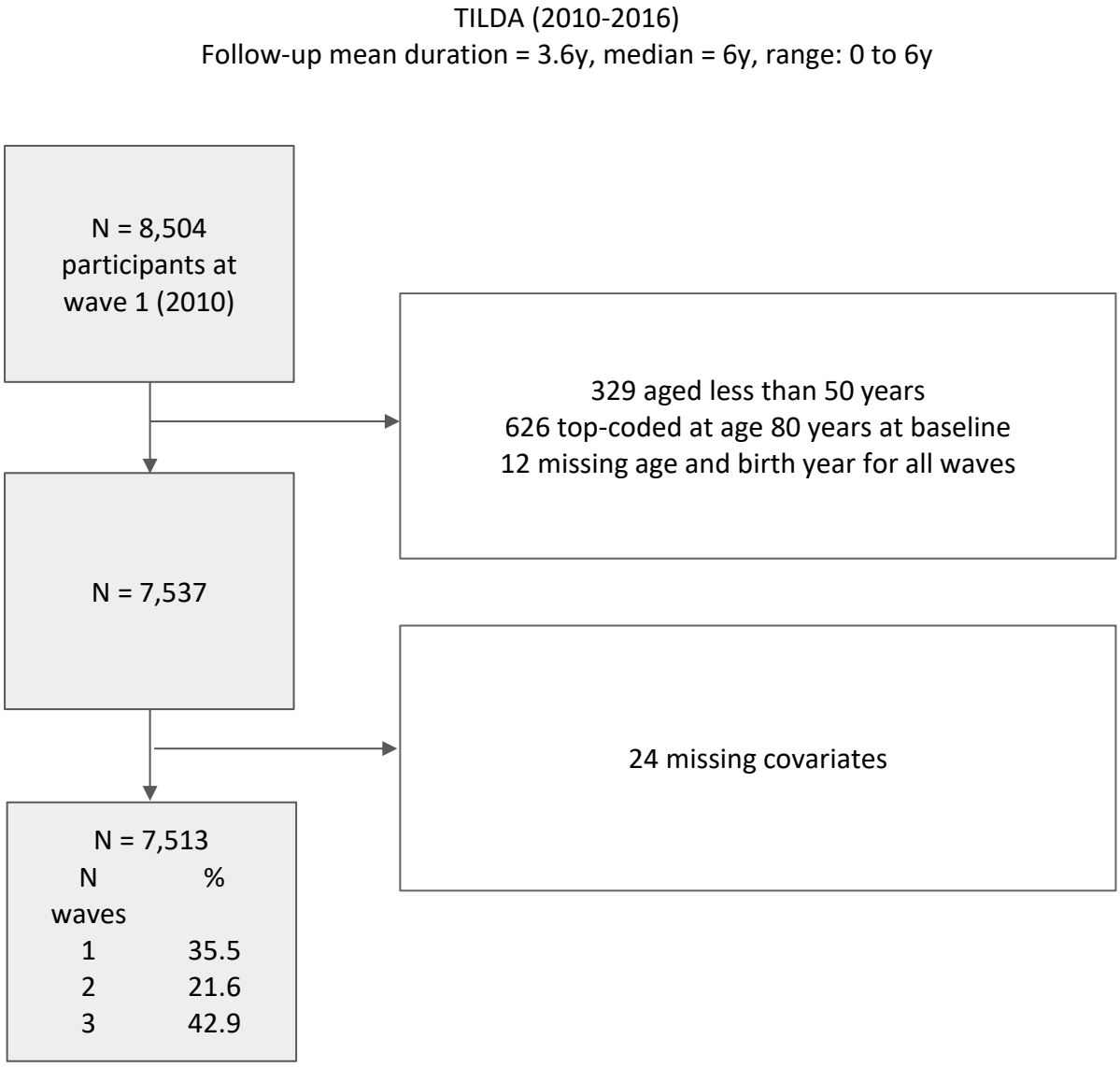

Figure 5.3.3. Flowchart of sample selection in SHARE.

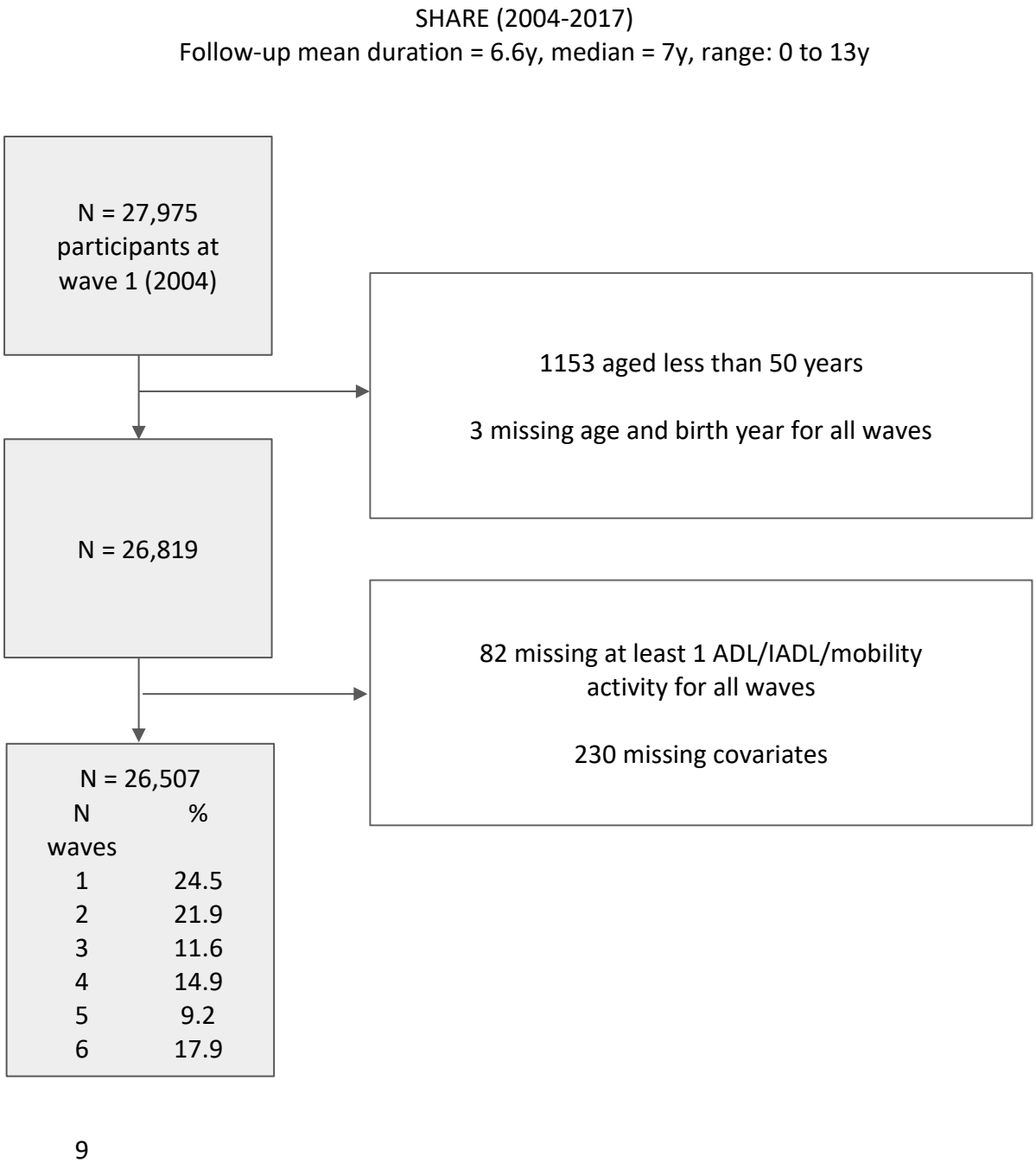

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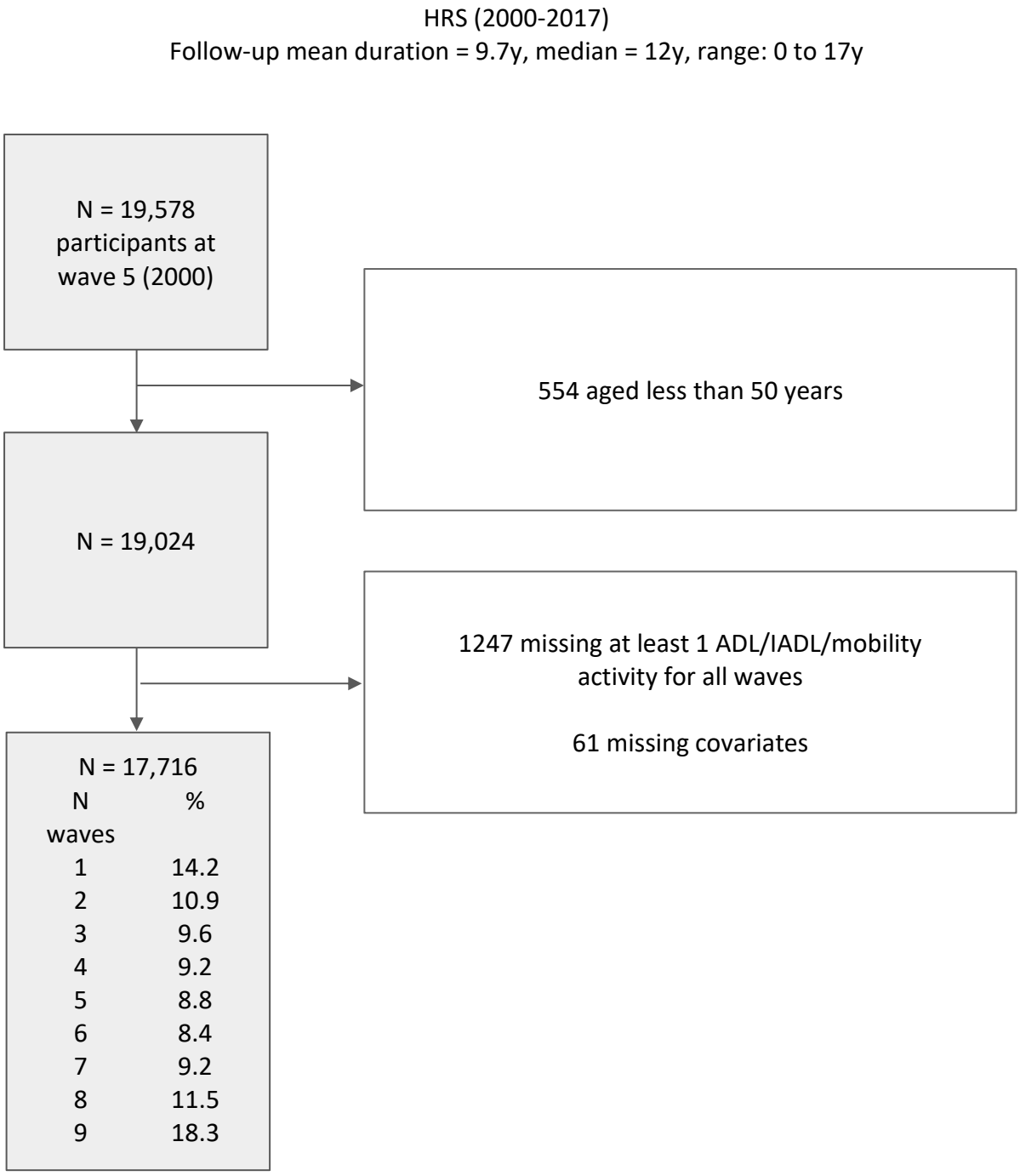
Figure 5.3.4. Flowchart of sample selection in HRS.



In the pooled analytic sample, women were slightly older (mean age = 65.2 [SD = 10.2] years in women compared to 64.8 [SD = 9.5] years in men; $p < 0.001$), less likely to be married, have above secondary level education, and be employed than men at baseline ($p < 0.001$ for all). Characteristics by sex in each birth cohort are shown in Table 5.3.5. The proportion of participants with education above secondary level increased in the later birth cohorts (p for trend < 0.001), particularly among women (from 8.2% in the 1895-1929 birth cohort to 19.7% in the 1946-1960 birth cohort, in men the corresponding numbers were 16.8% and 23.9%). Among participants who were not retired (employed/self-employed, unemployed/unable to work, homemakers), women born in more recent birth cohorts were more likely to be employed while no such change was seen in men: 25.8% women and 80.8% men were employed in 1930-1938 birth cohort compared to 62.5% women and 86.1% men in the 1946-1960 birth cohort.

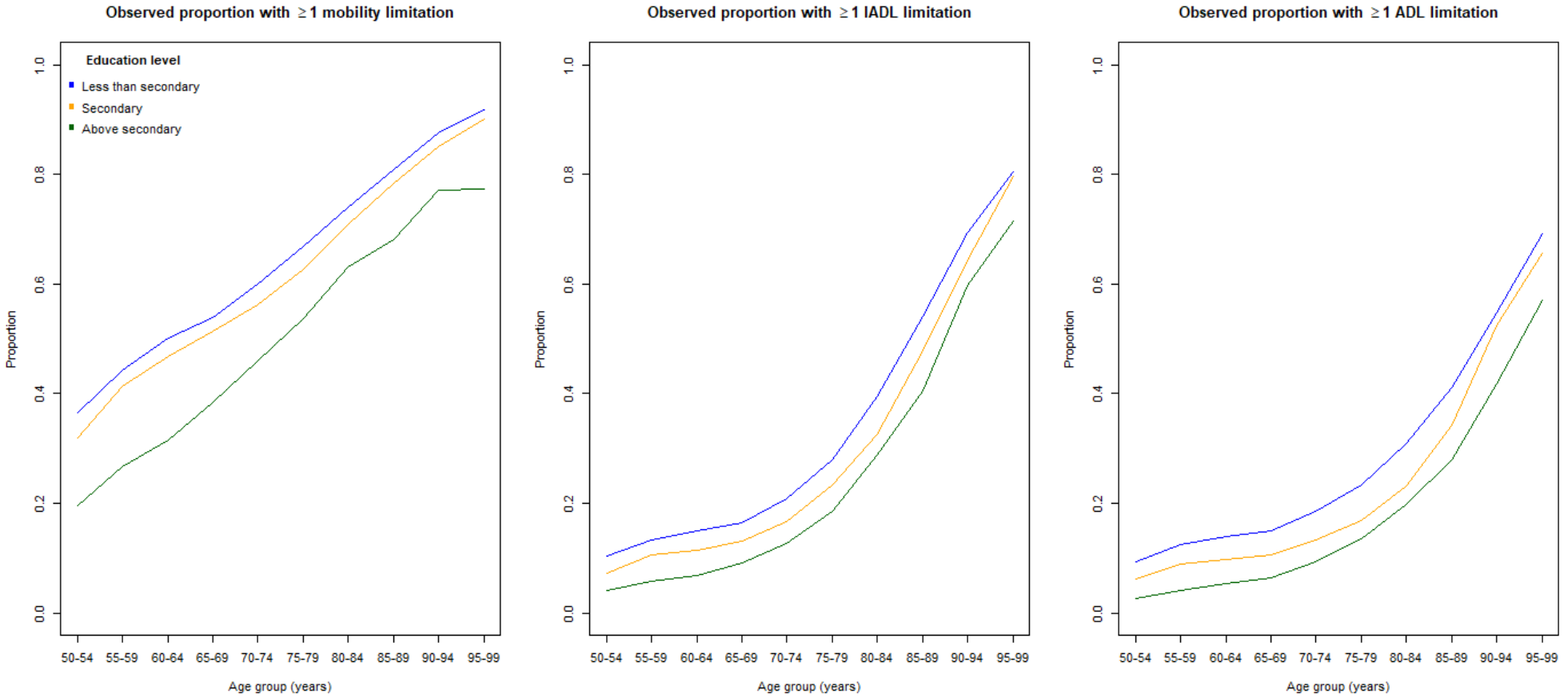
At the baseline of the present study, those with higher education levels were less likely to have limitations in mobility activities, IADL, and ADL ($p < 0.001$ for test of trend for all outcomes). In order to examine the crude association between education and functional limitations, the observed proportion of those with at least one mobility, IADL, and ADL limitation was plotted in each age group and education level (Figure 5.3.5). In all age groups for all outcomes, the observed proportion of participants with at least one limitation was lower in the above secondary education group.

Table 5.3.5. Baseline population characteristics in men and women as a function of cohort.

	Overall		**1895-1929 birth cohort**		**1930-1938 birth cohort**		**1939-1945 birth cohort**		**1946-1960 birth cohort**	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
	N = 27923	**N = 34452**	**N = 5818**	**N = 8257**	**N = 7602**	**N = 8648**	**N = 6651**	**N = 7807**	**N = 7852**	**N = 9740**
Age at baseline, Mean (SD)	64.8 (9.5)	65.2 (10.2)	78.5 (5.1)	79.3 (5.4)	68.1 (3.8)	68 (3.8)	61.1 (3.6)	60.8 (3.6)	54.6 (3.2)	54.4 (3.3)
Cohort, N (%)										
ELSA	4957 (17.8)	5682 (16.5)	1190 (20.5)	1557 (18.9)	1362 (17.9)	1435 (16.6)	1164 (17.5)	1258 (16.1)	1241 (15.8)	1432 (14.7)
TILDA	3461 (12.4)	4052 (11.8)	No data	No data	587 (7.7)	660 (7.6)	806 (12.1)	819 (10.5)	2068 (26.3)	2573 (26.4)
SHARE	12140 (43.5)	14367 (41.7)	2082 (35.8)	2904 (35.2)	3055 (40.2)	3363 (38.9)	2909 (43.7)	3293 (42.2)	4094 (52.1)	4807 (49.4)
HRS	7365 (26.4)	10351 (30.0)	2546 (43.8)	3796 (46.0)	2598 (34.2)	3190 (36.9)	1772 (26.6)	2437 (31.2)	449 (5.7)	928 (9.5)
Region, N (%)										
Northern Europe	2130 (7.6)	2412 (7.0)	405 (7.0)	490 (5.9)	501 (6.6)	527 (6.1)	527 (7.9)	600 (7.7)	697 (8.9)	795 (8.2)
Western Europe	15146 (54.2)	17643 (51.2)	2299 (39.5)	3130 (37.9)	3595 (47.3)	3923 (45.4)	3564 (53.6)	3850 (49.3)	5688 (72.4)	6740 (69.2)
Southern Europe	3282 (11.8)	4046 (11.7)	568 (9.8)	841 (10.2)	908 (11.9)	1008 (11.7)	788 (11.8)	920 (11.8)	1018 (13)	1277 (13.1)
North America	7365 (26.4)	10351 (30.0)	2546 (43.8)	3796 (46.0)	2598 (34.2)	3190 (36.9)	1772 (26.6)	2437 (31.2)	449 (5.7)	928 (9.5)
Marital status, N (%)										
Not married/partnered	5340 (19.1)	12983 (37.7)	1590 (27.3)	5337 (64.6)	1318 (17.3)	3372 (39.0)	1094 (16.4)	2136 (27.4)	1338 (17.0)	2138 (22.0)
Married/partnered	22583 (80.9)	21469 (62.3)	4228 (72.7)	2920 (35.4)	6284 (82.7)	5276 (61.0)	5557 (83.6)	5671 (72.6)	6514 (83.0)	7602 (78.0)
Education, N (%)										
Below secondary	10507 (37.6)	15240 (44.2)	2784 (47.9)	4675 (56.6)	3156 (41.5)	4272 (49.4)	2345 (35.3)	3159 (40.5)	2222 (28.3)	3134 (32.2)
Secondary	11719 (42.0)	14527 (42.2)	2056 (35.3)	2904 (35.2)	3081 (40.5)	3461 (40.0)	2828 (42.5)	3472 (44.5)	3754 (47.8)	4690 (48.2)
Above secondary	5697 (20.4)	4685 (13.6)	978 (16.8)	678 (8.2)	1365 (18)	915 (10.6)	1478 (22.2)	1176 (15.1)	1876 (23.9)	1916 (19.7)
Labour force status, N (%)										
Employed/self-employed	9800 (35.1)	8890 (25.8)	176 (3.0)	139 (1.7)	1017 (13.4)	788 (9.1)	2835 (42.6)	2513 (32.2)	5772 (73.5)	5450 (56.0)
Unemployed/unable to work	1804 (6.5)	1976 (5.7)	62 (1.1)	243 (2.9)	204 (2.7)	233 (2.7)	664 (10.0)	538 (6.9)	874 (11.1)	962 (9.9)
Retired/semi-retired	16159 (57.9)	15165 (44.0)	5554 (95.5)	5707 (69.1)	6344 (83.5)	5590 (64.6)	3114 (46.8)	2854 (36.6)	1147 (14.6)	1014 (10.4)
Homemaker	160 (0.6)	8421 (24.4)	26 (0.4)	2168 (26.3)	37 (0.5)	2037 (23.6)	38 (0.6)	1902 (24.4)	59 (0.8)	2314 (23.8)
Number of morbidities, Median (IQR)	1 (0-2)	1 (0-2)	2 (1-3)	2 (1-3)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	0 (0-1)	1 (0-1)

Abbreviations: SD: standard deviation; IQR: interquartile range

Figure 5.3.5. Observed proportion with ≥1 mobility, IADL, or ADL limitation in each education level.



5.3.4.2 Sex differences in functional limitations

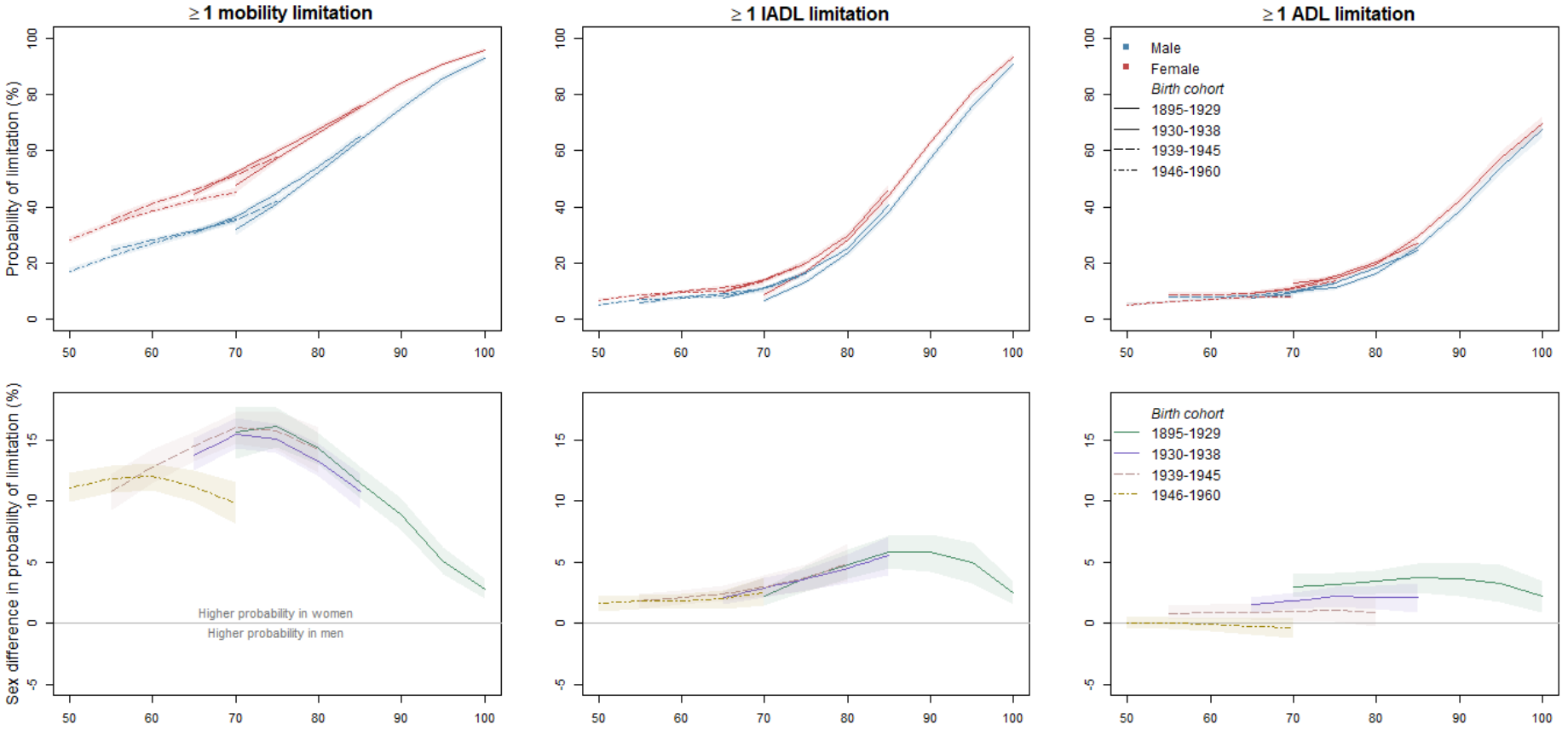
Functional limitations increased with age for all three outcomes (Figure 5.3.6, top panel). Mobility limitations increased consistently from age 50, while IADL and ADL limitations increased slowly between ages 50 and 70 and then rapidly thereafter. Plots of observed data in each cohort study separately yielded results broadly similar to those in the pooled analyses (Appendix, Figure 8.3.1).

At age 50, the probability of mobility limitations was 17.1% (95% CI 16.1, 18.2) in men and 28.2% (27.0, 29.5) in women, increasing to 93.1% (91.7, 94.4) and 95.8% (95.0, 96.7) respectively at age 100. Between ages 50 and 100, IADL limitations increased from 5.1% (4.6, 5.7) to 90.8% (89.4, 91.2) in men and from 6.7% (6.1, 7.3) to 93.2% (92.2, 94.4) in women. ADL limitations increased from 5.1% (4.6, 5.7) to 67.5% (64.9, 70.0) in men and from 5.2% (4.6, 5.7) to 69.6% (67.2, 72.0) in women over the same age period.

Women were more likely to have IADL and mobility limitations, irrespective of birth cohort and age (Figure 5.3.6, bottom panel). Sex differences in mobility increased until age 70 and in IADL until age 90 and decreased thereafter. Sex differences in ADL limitations remained substantially similar with age but varied by birth cohort ($p < 0.001$ for interaction of sex and birth cohort). The sex difference in ADL limitations—where women were more likely to be limited—decreased in recent birth cohorts: at age 75, it was 3.2% (2.3, 4.1) in the 1895-1929 birth cohort, 2.2% (1.3, 3.0) in the 1930-1938 birth cohort, and 1.1% (0.1, 2.1) in the 1939-1945 birth cohort (Table 5.3.6). No sex differences were observed in ADL limitations in the 1946-1960 birth cohort between age 50 and 70 (ages where data were available). This decrease in sex differences reflects a larger decrease in ADL limitations among women in more recent birth cohorts.

In analyses adjusted for age, birth cohort, region, and country, sex differences for each mobility activities, IADL, and ADL were consistent for all but two activities (Appendix Table 8.3.1). Women were more likely to report limitations for all activities except using the telephone, where men were more likely to report activities, and dressing, for which there was no sex difference.

Figure 5.3.6. Sex differences in probability of ≥ 1 mobility, IADL, and ADL limitation.



Top panel shows the probability of having ≥1 functional limitation plotted by age for men and women in each birth cohort. Bottom panel shows the sex difference in probability of ≥1 functional limitation: positive value indicates women have greater probability than men of ≥1 functional limitation. Predicted probabilities based on models adjusted for sex, age, birth cohort, and their interactions, marital status, study, and region and plotted for reference categories for all covariates (married/partnered, SHARE, Western Europe).

Table 5.3.6. Role of education in sex differences in mobility, IADL, and ADL limitations in each birth cohort.

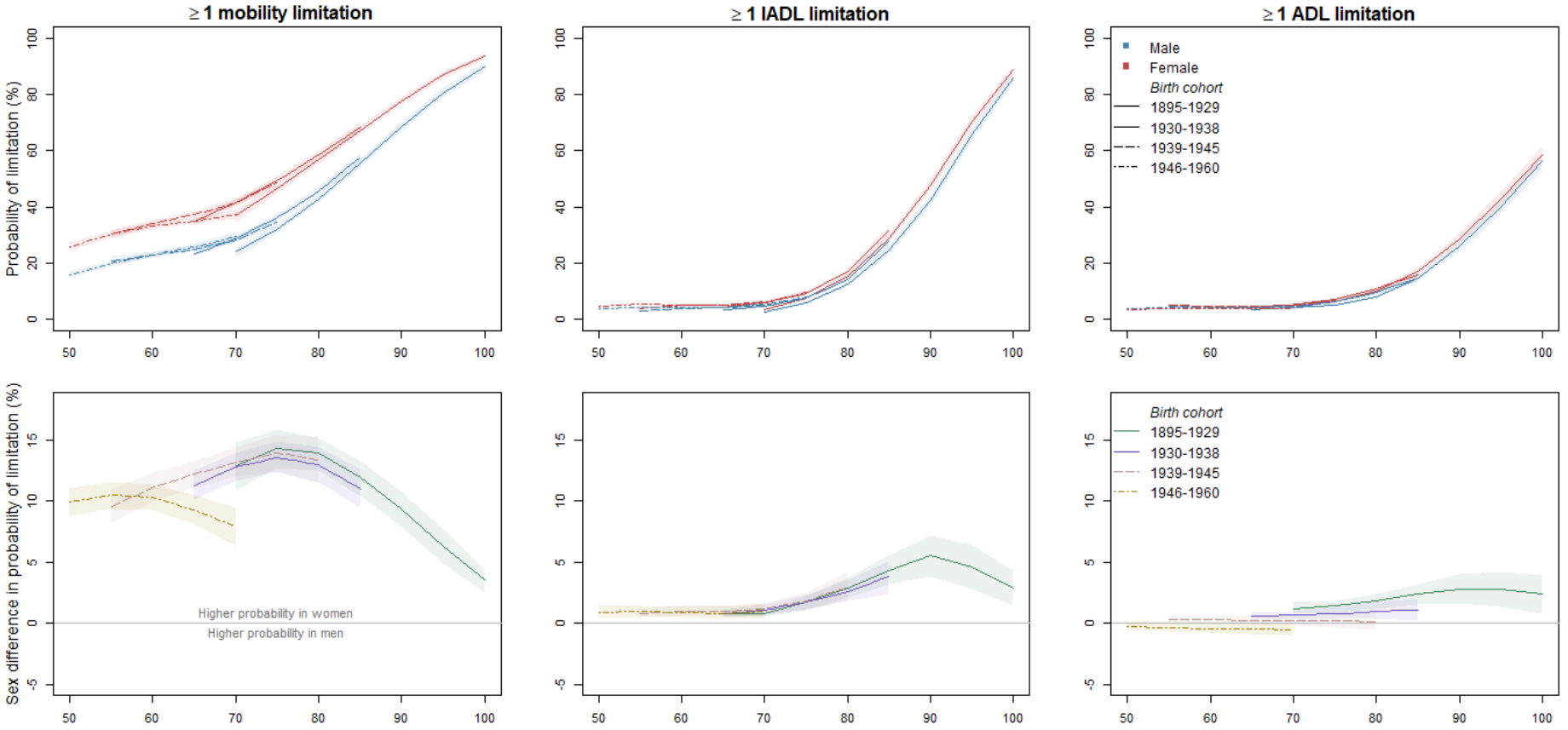
	Percent sex difference (95% CI) in probability of functional limitations					
	At age 65		**At age 75**		**At age 85**	
	Minimally adjusted[a]	Additionally adjusted for education	Minimally adjusted[a]	Additionally adjusted for education	Minimally adjusted[a]	Additionally adjusted for education
≥1 mobility limitation						
1895-1929	No data	No data	16.1 (14.4, 17.7)	14.6 (13.0, 16.3)	11.5 (10.2, 12.8)	11.1 (9.8, 12.5)
1930-1938	13.8 (12.5, 15.2)	12.1 (10.8, 13.4)	15.1 (13.9, 16.3)	14.0 (12.7, 15.2)	10.8 (9.4, 12.2)	10.4 (9.0, 11.9)
1939-1945	14.5 (13.3, 15.7)	13.1 (12.0, 14.3)	15.8 (14.2, 17.4)	14.8 (13.2, 16.4)	No data	No data
1946-1960	11.2 (9.9, 12.5)	10.5 (9.2, 11.7)	No data	No data	No data	No data
P sex difference by birth cohort	*<0.001*	*0.01*	*0.63*	*0.68*	*0.47*	*0.48*
≥1 IADL limitation						
1895-1929	No data	No data	3.7 (2.6, 4.7)	2.6 (1.6, 3.5)	5.8 (4.5, 7.2)	4.8 (3.5, 6.1)
1930-1938	2.1 (1.5, 2.6)	1.4 (0.9, 1.8)	3.6 (2.7, 4.4)	2.6 (1.8, 3.4)	5.5 (3.9, 7.1)	4.5 (3.0, 6.0)
1939-1945	2.4 (1.8, 3.1)	1.8 (1.2, 2.4)	3.7 (2.6, 4.8)	2.9 (1.9, 4.0)	No data	No data
1946-1960	2.0 (1.2, 2.7)	1.5 (0.8, 2.2)	No data	No data	No data	No data
P sex difference by birth cohort	*0.57*	*0.53*	*0.97*	*0.87*	*0.71*	*0.77*
≥1 ADL limitation						
1895-1929	No data	No data	3.2 (2.3, 4.1)	2.1 (1.3, 2.9)	3.7 (2.5, 4.9)	2.9 (1.8, 4.0)
1930-1938	1.5 (0.9, 2.1)	0.9 (0.4, 1.4)	2.2 (1.3, 3.0)	1.3 (0.6, 2.0)	2.1 (0.9, 3.3)	1.4 (0.2, 2.6)
1939-1945	0.9 (0.3, 1.5)	0.4 (-0.2, 0.9)	1.1 (0.1, 2.1)	0.4 (-0.5, 1.3)	No data	No data
1946-1960	-0.3 (-0.9, 0.4)	-0.6 (-1.2, 0.1)	No data	No data	No data	No data
P sex difference by birth cohort	*<0.001*	*0.003*	*0.01*	*0.03*	*0.05*	*0.05*

Abbreviations: IADL: Instrumental Activities of Daily Living; ADL: Activities of Daily Living.
[a]Estimates extracted at age 65, 75, and 85 with age analysed as a continuous term; analyses adjusted for sex, birth cohort, and their interactions, marital status, study, and region. Positive value indicates women are more likely than men to be limited.

5.3.4.3 Effect of adjustment for education on sex differences in functional limitations

The higher probability of mobility and IADL limitations in women in all birth cohorts and ADL limitations in the oldest three birth cohorts was attenuated after adjustment for education (Table 5.3.6, Figure 5.3.7), however attenuation was minor (<1% reduction after adjustment for education) for most ages. For example, for ADL limitation at age 75 in the 1930-1938 birth cohort, before adjustment for education the sex difference was 2.2 (1.3, 3.0) and after adjustment the sex difference was 1.3 (0.6, 2.0). There was also no reduction in the sex difference at age 85 for mobility limitations after adjustment for education. The observed variation in sex differences between birth cohorts for ADL limitations where older women born in earlier birth cohorts were more likely to have ADL limitations than younger women in later birth cohorts appeared to be slightly attenuated by adjustment for education, however the impact was minor.

Figure 5.3.7. Sex differences in probability of ≥ 1 mobility, IADL, and ADL limitation after adjustment for education.



Top panel shows the probability of having ≥1 functional limitation plotted by age for men and women in each birth cohort. Bottom panel shows the sex difference in probability of ≥1 functional limitation: positive value indicates women have greater probability than men of ≥1 functional limitation. Predicted probabilities based on models adjusted for sex, age, birth cohort, and their interactions, marital status, study, region, and education and plotted for reference categories for all covariates (below secondary education, married/partnered, SHARE, Western Europe).

5.3.4.4 Supplementary analyses

Though the primary interest of this investigation was the role of education on sex differences in functional limitations, given that sex differences in functional limitations were only modestly reduced after adjustment for education, we also examined the effect of adjustment for labour force status and chronic conditions on sex differences in the probability of having ≥1 functional limitation. Further adjustment for labour force status attenuated sex differences more than adjustment for education alone (Appendix Figure 8.3.2 and Table 8.3.2).

As there were still sex differences in probability of limitations for all three functional outcomes after additional adjustment for labour force status, we also adjusted for presence of self-reported chronic conditions, as we observed sex differences in prevalence of chronic conditions in the study population at the baseline wave. The distribution of chronic conditions in men and women at baseline is shown in Appendix Table 8.3.3. Women were more likely than men to report high blood pressure, cancer, psychiatric illness, and arthritis ($p < 0.001$ for all sex differences). Men were more likely than women to report diabetes, lung disease, and cardiovascular disease including heart attack and stroke ($p < 0.001$ for all). Additional adjustment for self-reported chronic conditions (Appendix Table 8.3.4) further attenuated sex differences in IADL and ADL limitations but only to a small extent for mobility limitations.

We also undertook analyses to examine regional variation in sex differences in functional limitations. In order to carry out these analyses, we repeated the main analyses separately in each of the four geographical regions (Northern Europe, Southern Europe, Western Europe, and North America). These analyses indicated that there was some regional variation in sex differences in functional limitation (Appendix Figures 8.3.3-8.3.5), particularly for ADL in Northern Europe where men were more likely to have limitations than women, unlike in other regions and in the main results.

5.3.4.5 Sex differences in severity of functional limitations

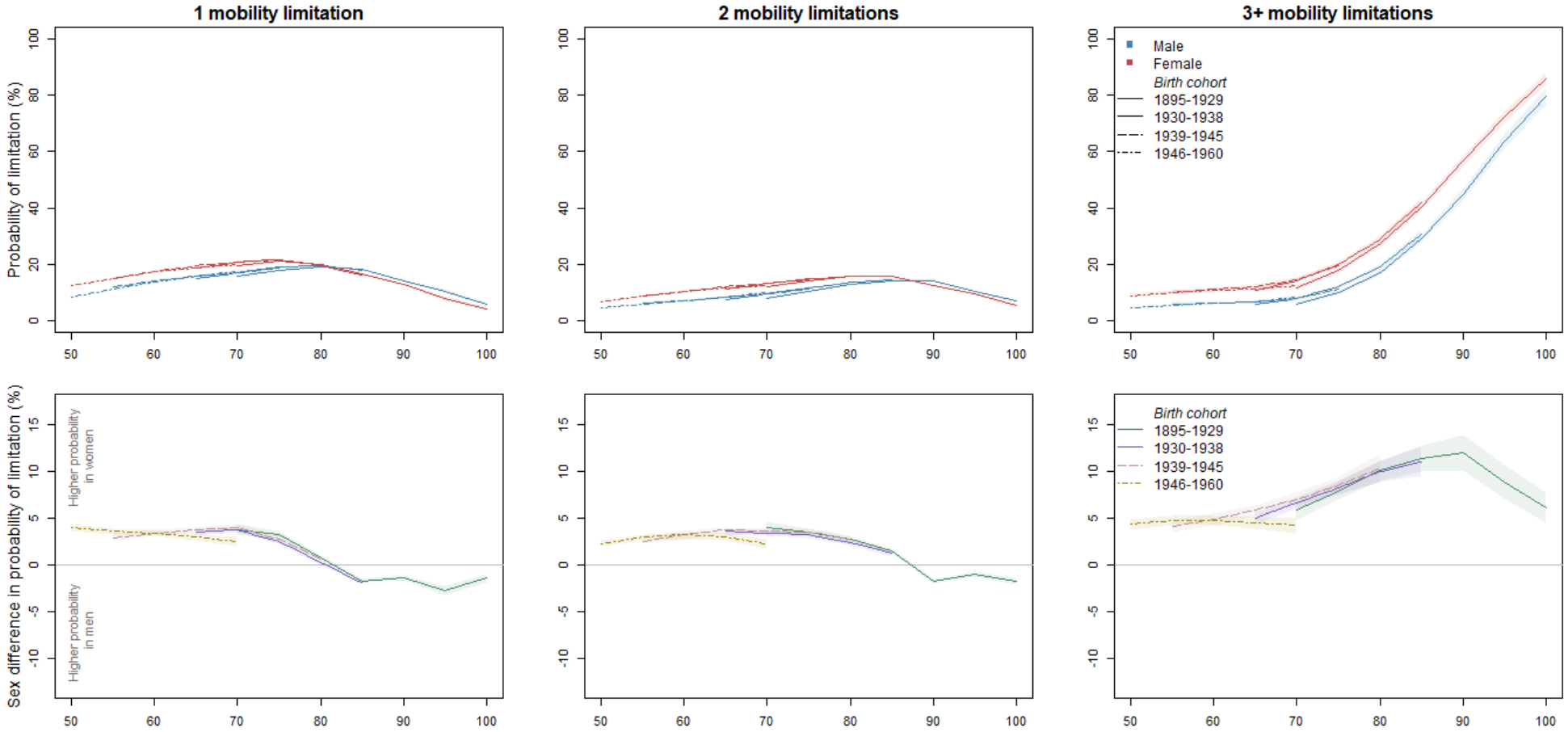
Participants with mobility limitations (Figure 5.3.8) were most likely to have 1 mobility limitation until age 75 in women and age 85 in men. By age 80 in women and 85 in men,

participants with mobility limitations were most likely to have ≥3 mobility limitations. Analyses adjusted for education showed that between ages 50 to 80 years, women were more likely than men to have mobility limitations irrespective of the number of limitations (Figure 5.3.8, Table 5.3.7). Between ages 70 and 90, the sex difference in having ≥3 limitations increased markedly (at age 70 [1895-1929 birth cohort] the sex difference was 5.8% (4.8, 6.8); at age 90 it was 11.9% [10.1, 13.8]) and sex differences in 1 and 2 limitations decreased such that men were more likely than women to report 1 limitation from age 80 and more likely than women to report 2 limitations from age 85.

Participants with IADL limitations were most likely to have 1 limitation until age 80, and ≥3 limitations by age 90 (Figure 5.3.9). IADL limitations increased from age 70 and sex differences in 1 and 2 limitations increased progressively, peaking at around age 85 (1895-1929 birth cohort sex difference in 1 limitation = 0.9% [0.6, 1.1] and in 2 limitations = 1.2% [0.8, 1.5]; Table 5.3.8). Sex differences in 1 and 2 limitations decreased thereafter and by age 90 men were more likely to have 1 or 2 limitations. From age 75, women were increasingly more likely than men to have ≥3 IADL limitations (1895-1929 birth cohort sex difference at age 75 = 0.5% [0.3, 0.7] and at age 90 = 4.5% [3.1, 5.9]).

For ADL limitations, there were no sex differences in the 1938-1945 and 1946-1960 birth cohorts but women were more likely than men to have of 1, 2, or ≥ 3 ADL limitations in the 1895-1929 (age 85, sex difference in ≥3 limitations = 1.4% [0.9, 1.9]) and the 1930-1938 (0.7% [0.1, 1.2]) birth cohorts (Figure 5.3.10; Table 5.3.9). Sex differences in ADL limitations were stable with age except in the oldest birth cohort.

Figure 5.3.8. Sex differences in probability of mobility limitations by number of limitations.



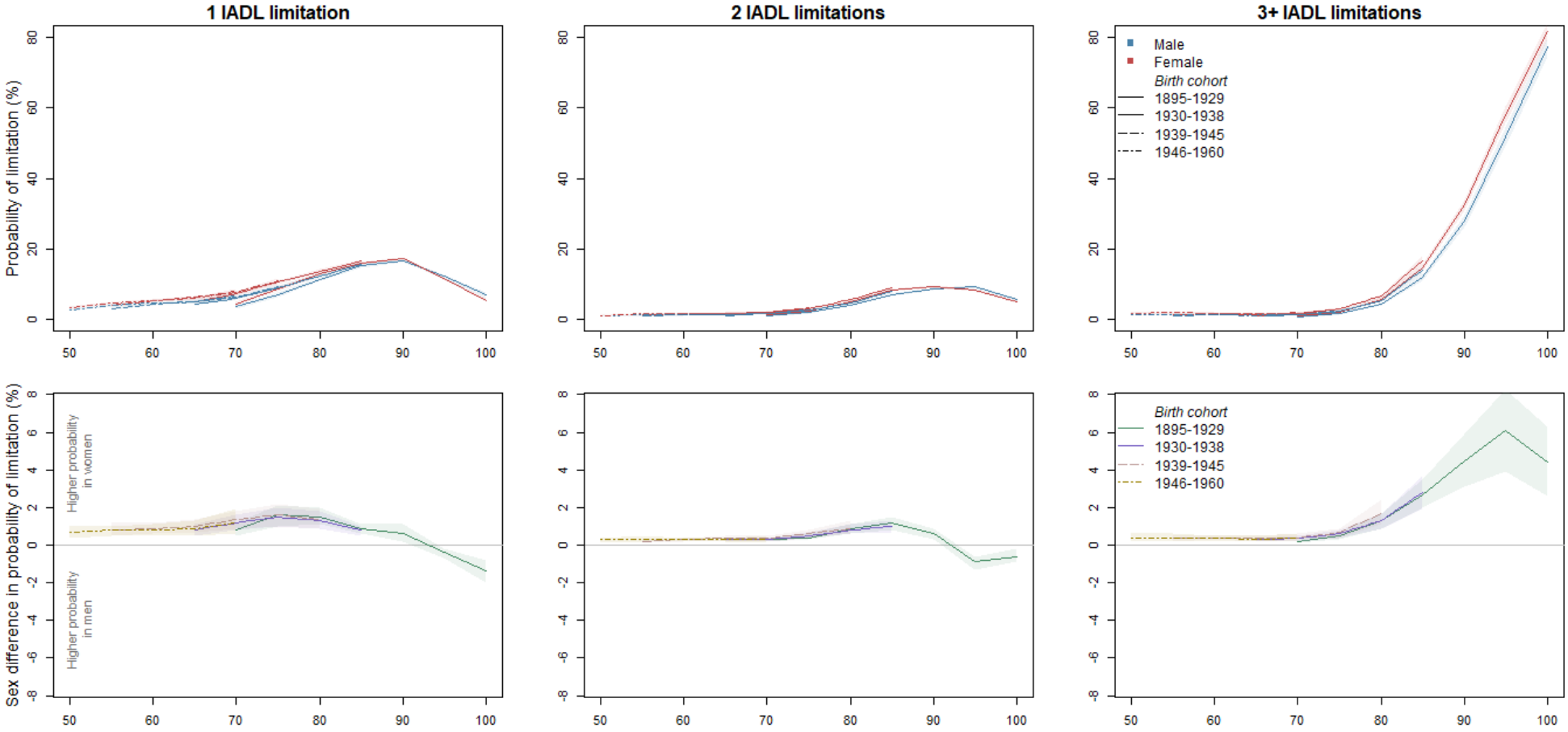
Top panel shows the probability of the given number of mobility limitations plotted by age for men and women in each birth cohort. Bottom panel shows the sex difference in probability of limitation: positive values indicates women have greater probability than men of given number of limitations. Predicted probabilities based on models adjusted for sex, age, birth cohort, and their interactions, marital status, study, region, and education, and plotted for reference categories for all covariates (below secondary education, Western Europe, SHARE, married/partnered).

Table 5.3.7. Sex differences in probability of mobility limitations by number of limitations.

	Percent sex difference (95% CI) in probability of number of mobility limitations		
	At age 65	**At age 75**	**At age 85**
1 limitation			
1895-1929	No data	3.2 (2.8, 3.6)	-1.7 (-1.9, -1.5)
1930-1938	3.5 (3.1, 3.9)	2.5 (2.2, 2.8)	-1.8 (-2.0, -1.6)
1939-1945	3.7 (3.4, 4.0)	2.8 (2.5, 3.2)	No data
1946-1960	3.0 (2.6, 3.3)	No data	No data
P sex difference by birth cohort	*0.01*	*0.01*	*0.46*
2 limitations			
1895-1929	No data	3.5 (3.1, 3.9)	1.5 (1.3, 1.7)
1930-1938	3.6 (3.2, 3.9)	3.2 (2.9, 3.5)	1.2 (0.9, 1.5)
1939-1945	3.7 (3.4, 4.0)	3.5 (3.1, 3.9)	No data
1946-1960	3.0 (2.6, 3.4)	No data	No data
P sex difference by birth cohort	*0.01*	*0.44*	*0.05*
≥3 limitations			
1895-1929	No data	7.9 (7.0, 8.8)	11.3 (10.0, 12.7)
1930-1938	5.0 (4.4, 5.6)	8.2 (7.5, 9.0)	11.0 (9.5, 12.6)
1939-1945	5.8 (5.2, 6.3)	8.5 (7.6, 9.4)	No data
1946-1960	4.5 (3.9, 5.1)	No data	No data
P sex difference by birth cohort	*0.01*	*0.68*	*0.76*

Estimates extracted at age 65, 75, and 85 with age analysed as a continuous term; analyses further adjusted for sex, birth cohort, and their interactions, marital status, study, region, and education. Positive value indicates women have greater probability than men of having given number of limitations.

Figure 5.3.9. Sex differences in probability of IADL limitations by number of limitations.



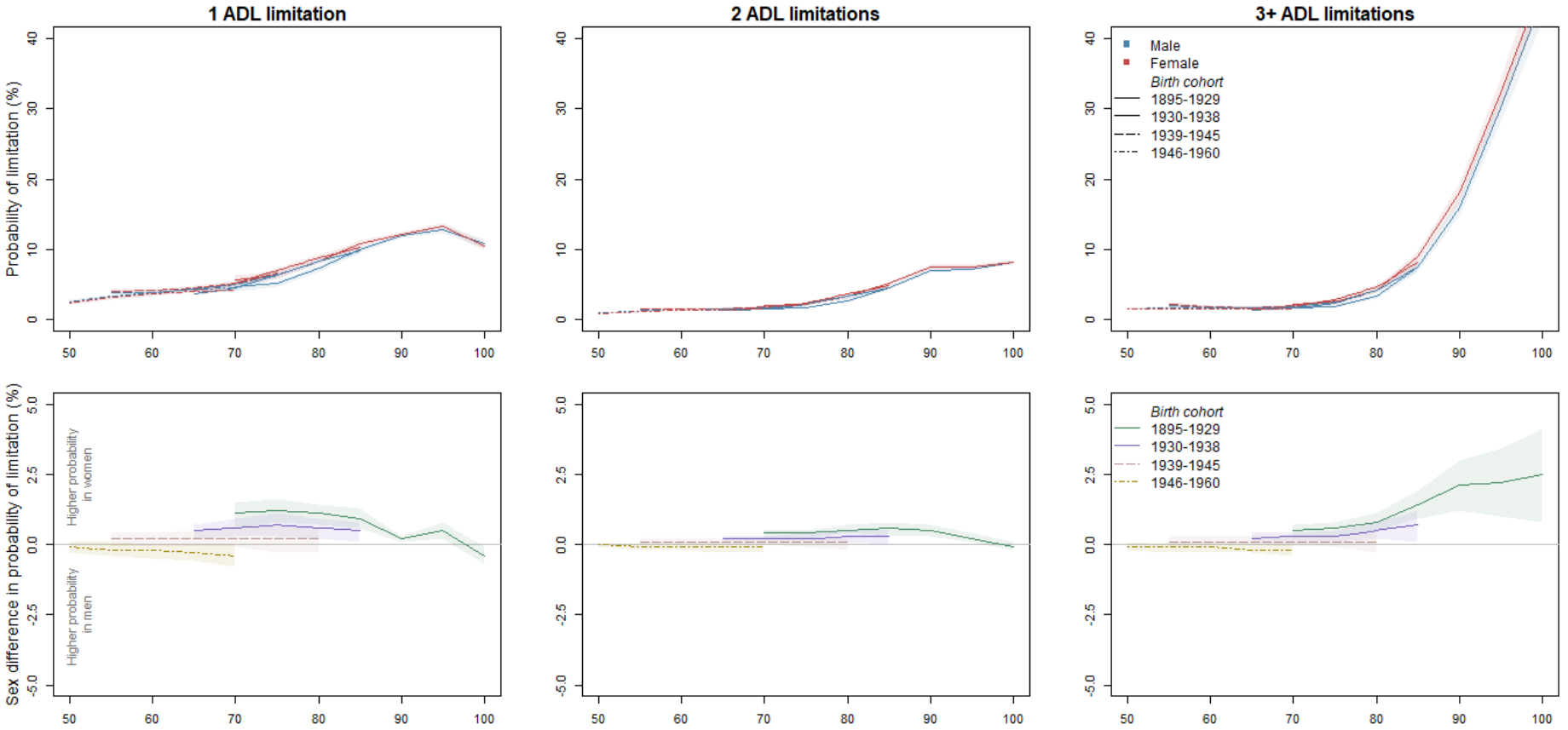
Top panel shows the probability of the given number of IADL limitations plotted by age for men and women in each birth cohort. Bottom panel shows the sex difference in probability of limitations: positive values indicates women have greater probability than men of given number of limitations. Predicted probabilities based on models adjusted for sex, age, birth cohort, and their interactions, marital status, study, region and education and plotted for reference categories for all covariates (below secondary education, Western Europe, SHARE, married/partnered).

Table 5.3.8. Sex differences in probability of instrumental activity of daily living (IADL) limitations by number of limitations.

	Percent sex difference (95% CI) in probability of number of IADL limitations		
	At age 65	**At age 75**	**At age 85**
1 limitation			
1895-1929	No data	1.6 (1.0, 2.1)	0.9 (0.6, 1.1)
1930-1938	0.8 (0.5, 1.1)	1.5 (1.0, 2.0)	0.8 (0.5, 1.0)
1939-1945	1.0 (0.7, 1.4)	1.6 (1.0, 2.2)	No data
1946-1960	0.9 (0.5, 1.3)	No data	No data
P sex difference by birth cohort	*0.62*	*0.92*	*0.54*
2 limitations			
1895-1929	No data	0.4 (0.3, 0.6)	1.2 (0.8, 1.5)
1930-1938	0.3 (0.2, 0.4)	0.5 (0.4, 0.7)	1.0 (0.6, 1.3)
1939-1945	0.4 (0.2, 0.5)	0.6 (0.4, 0.8)	No data
1946-1960	0.3 (0.2, 0.4)	No data	No data
P sex difference by birth cohort	*0.47*	*0.53*	*0.31*
≥3 limitations			
1895-1929	No data	0.5 (0.3, 0.7)	2.7 (2.0, 3.5)
1930-1938	0.3 (0.2, 0.4)	0.6 (0.4, 0.8)	2.8 (1.9, 3.7)
1939-1945	0.4 (0.2, 0.5)	0.7 (0.4, 0.9)	No data
1946-1960	0.3 (0.2, 0.5)	No data	No data
P sex difference by birth cohort	*0.35*	*0.66*	*0.92*

Estimates extracted at age 65, 75, and 85 with age analysed as a continuous term; analyses further adjusted for sex, birth cohort, and their interactions, marital status, study, region, and education. Positive value indicates women have greater probability than men of having given number of limitations.

Figure 5.3.10. Sex differences in probability of ADL limitations by number of limitations.



Top panel shows the probability of the given number of ADL limitations plotted by age for men and women in each birth cohort. Bottom panel shows the sex difference in probability of limitations: positive values indicates women have greater probability than men of given number of limitations. Predicted probabilities based on models adjusted for sex, age, birth cohort, and their interactions, marital status, study, region, and education and plotted for reference categories for all covariates (below secondary education, Western Europe, SHARE, married/partnered).

Table 5.3.9. Sex differences in probability of activity of daily living (ADL) limitations by number of limitations.

	Percent sex difference (95% CI) in probability of number of ADL limitations		
	At age 65	**At age 75**	**At age 85**
1 limitation			
1895-1929	No data	1.2 (0.8, 1.6)	0.9 (0.6, 1.3)
1930-1938	0.5 (0.2, 0.7)	0.7 (0.3, 1.1)	0.5 (0.1, 0.8)
1939-1945	0.2 (-0.1, 0.5)	0.2 (-0.3, 0.7)	No data
1946-1960	-0.3 (-0.6, 0.0)	No data	No data
P sex difference by birth cohort	*0.003*	*0.03*	*0.06*
2 limitations			
1895-1929	No data	0.4 (0.2, 0.5)	0.6 (0.3, 0.8)
1930-1938	0.2 (0.1, 0.3)	0.2 (0.1, 0.4)	0.3 (0.0, 0.5)
1939-1945	0.1 (-0.0, 0.2)	0.1 (-0.1, 0.2)	No data
1946-1960	-0.1 (-0.3, 0.0)	No data	No data
P sex difference by birth cohort	*0.003*	*0.04*	*0.05*
≥3 limitations			
1895-1929	No data	0.6 (0.3, 0.8)	1.4 (0.9, 1.9)
1930-1938	0.2 (0.1, 0.4)	0.3 (0.1, 0.5)	0.7 (0.1, 1.2)
1939-1945	0.1 (-0.0, 0.3)	0.1 (-0.1, 0.3)	No data
1946-1960	-0.2 (-0.3, 0.0)	No data	No data
P sex difference by birth cohort	*0.004*	*0.03*	*0.04*

Estimates extracted at age 65, 75, and 85 with age analysed as a continuous term; analyses further adjusted for sex, birth cohort, and their interactions, marital status, study, region, and education. Positive value indicates women have greater probability than men of having given number of limitations.

5.3.5 Discussion

This study of 62,375 participants born between 1895 and 1960 in 14 countries with data on functional limitations spanning up to 17 years presents three key findings. First, sex differences in ADL and IADL limitations were small, particularly before age 80. When education was considered these differences were attenuated, and for ADL were eliminated in the more recent birth cohorts. Second, women were more likely to have mobility limitations, even after adjustment for education and further adjustment for labour force status and self-reported chronic conditions. Third, consideration of the number of limitations suggested that at the oldest ages women were more likely to have 3 or more mobility and IADL limitations and men were more likely to have 1 or 2 limitations. These findings highlight the importance of considering age, birth cohort, type, and number of limitations in understanding sex differences in functional limitations during ageing.

5.3.5.1 Comparison with previous studies

In line with previous evidence [177], we found women were more likely than men to report functional limitations, however we found that absolute sex differences in functional limitations were minor for IADL and ADL. This suggests that previous evidence using relative measures to examine sex differences in IADL and ADL limitations may have overestimated the impact of sex differences in IADL and ADL, where the sex difference in probability of being limited is less than 5% for ADL and 7% for IADL even at the most advanced ages when limitations are most prevalent. In accordance with previous studies [124, 228], we also found that sex inequalities in education, where women were less educated than men, played a role in sex differences in functional limitations, with the female disadvantage attenuated after accounting for education. At least two decomposition analyses have examined the effect of education on sex differences in functional limitations to find that the distribution of education between men and women was among the most important social factors contributing to sex differences in prevalence of ADL limitations [124, 228]. However, while social factors overall may explain as much as 45% of the sex differences in prevalence of functional limitations [124], consistent with previous evidence [124, 228], we found that education on its own only explained a small proportion of sex differences in IADL and ADL

limitations, and attenuation of the sex differences in mobility limitations in particular after accounting for education was negligible.

Other social and economic factors that have been found to contribute to sex differences in functional limitations include labour force participation, type of employment, marital status, and household economic status [124]. Women are more likely to be unemployed or in low paid or domestic labour, and unemployment is associated with functional limitations [329], as it can lead to material deprivation and increased exposure to health risk factors [177]. Our findings were consistent with studies that showed sex inequalities in labour force participation to be a contributor to sex differences in functional limitations [124, 228]. After further adjustment for labour force status in addition to education, we saw a further attenuation of sex differences in functional limitations for IADL, ADL, and to a lesser extent mobility activities.

Sex differences in chronic conditions might also play a role in sex differences in functional limitations. Consistent with evidence showing women are more likely to have disabling though non-lethal chronic conditions including musculoskeletal and autoimmune disorders while men may be more likely to have cardiovascular diseases [9, 214, 215], we found that women were more likely to report arthritis and psychiatric illnesses, while men were more likely to report heart attack and stroke. Adjustment for self-reported chronic conditions further attenuated sex differences in functional limitations for all three functional outcomes.

We added to the previous evidence by showing that the sex difference in longevity, where women live longer albeit with more disabilities, is unlikely to be the sole driver of sex differences in functional limitations. Our findings showed that sex differences in functional limitations were attenuated after adjustment for education, labour force status, and self-reported chronic conditions, suggesting that these factors also play a role in sex differences in functional limitations. Further, our finding that at older ages, where limitations were highly prevalent, women were more likely than men to have 3 or more IADL and mobility limitations while men were more likely to have 1 or 2 limitations is a refinement of previous findings using composite scores of limitations in ADL/IADL [178, 179], and/or mobility activities [179] that reported faster decline with age in ability to perform these activities in women compared to men.

Higher prevalence of mobility limitations in women were not explained by either education, labour force status, or self-reported chronic conditions. More research is needed to examine whether objective measures of chronic conditions and consideration of other disability-causing conditions such as dementia would have further attenuated sex differences. It has been proposed that remaining sex differences in mobility are due to differences in body composition such as body mass and skeletal muscle index [330].

Previous studies examining sex differences in severity of limitations in Danish centenarians born between 1895 and 1915 with sample sizes of 500 or less have shown reductions in ADL limitations in women in recent birth cohorts [283, 289]. Another study of 3846 participants born in 1905 and 1915 did not find any change in sex differences in ADL limitations across birth cohorts [280]. Our study extends these findings to a broader range of birth cohorts and age groups in a larger study sample. We found no evidence of sex differences in ADL limitations in more recent birth cohorts. While we did observe that birth cohort differences in sex inequalities in ADL limitations were attenuated after accounting for education, suggesting that reductions in sex inequalities in education may contribute to differences in sex inequalities in ADL limitations between birth cohorts, the effect was minor. This would suggest that birth cohort differences in sex inequalities in ADL limitations are more likely to be due to other factors in addition to education, for example improvements in housing and working conditions, environmental accommodations, access to assistive devices, increased access to healthcare, and reductions in unpaid labour [289]. Our finding of negligible variation between birth cohorts for sex differences in IADL and mobility limitations also agrees with previous evidence [280, 326].

5.3.5.2 Strengths and limitations

A primary strength of our study is consideration of sex differences in mobility, IADL, and ADL limitations along with severity of these limitations. Dichotomous categorisation (0 and 1 or more limitations) of measures of functional limitations results in loss of information by grouping together individuals with different limitation severity, as limitation in a single ADL has different implications for quality of life than limitation in 3 or more ADLs. Another strength of this analysis is the use of multi-cohort data, providing a large sample size that covers a broad range of birth years and age groups. This allows sufficient numbers in the

analyses to identify trends in sex differences in functional limitations by birth cohort. Results reflecting absolute rather than relative measures of sex differences is a further strength as it provides a more realistic measure of sex differences. Difference in probability of limitations of 1% or less as found in many instances may appear large when assessed using relative measures.

There are several limitations to consider. First, results using self-reported measures of functional limitations may differ from objective measures, although sex differences have also been reported in objective measures of physical functioning such as grip strength and walking speed [177]. Second, the role of education in sex differences in functional limitations might partly arise out of gender roles rather than biological sex; lack of data on gender did not allow me to explore this issue further. Third, a more detailed measure of education such as number of years of schooling might better capture sex and between-country differences. Fourth, mixed effects models account for missing data for which the underlying mechanism is missing-at-random. It is possible that individuals with the most functional limitations were also most likely to be lost to follow-up. Nonetheless, individuals with limitations at baseline, including those in the oldest age group, were included in the analysis and the duration of follow-up was similar between men and women (mean follow-up (SD) for men = 7.2 (5.7) years; for women = 7.8 (5.8)), suggesting attrition is unlikely to have seriously impacted findings for sex differences. Fifth, lack of information on dementia precludes us from considering it in the analysis; this may have overestimated sex differences at the oldest ages due to higher dementia rates among women [188]. Sixth, certain activities may be more likely to be performed by women than by men, influencing findings for sex differences. Nonetheless, we found that sex differences were overwhelmingly consistent across individual activities for each functional measure, suggesting that single activities were unlikely to have overly influenced overall findings for sex differences. Finally, analyses by region were intended to examine variation in sex differences between regions. However, systematic comparisons between regions requires sufficient sample size and weighting analyses to yield nationally representative estimates of sex differences. As such, lack of longitudinal weights and insufficient sample size in some regions meant that power and selection bias precluded us from explicitly comparing sex differences in functional limitations between countries or geographical regions. For these reasons, we were unable

to draw robust conclusions for regional comparisons in paper 3. Lack of longitudinal data from middle-income countries meant that we could only consider high-income countries in this analysis. Also, lack of information on race/ethnicity meant that we could not consider it in our analyses. Further analyses are thus required to examine whether the sex differences in functional limitations differ by race/ethnicity and region.

5.3.5.3 Conclusion

Functional limitations tend to follow a hierarchical progression from mobility limitations to IADL and ADL limitations, which occur as a culmination of the disablement process at advanced age [120]. Our finding of minor sex differences for ADL and IADL in midlife accompanied by notable sex differences in mobility limitations suggests that mobility limitations could be an important prevention target in order to reduce sex differences in disability at older ages. Mobility limitations precede IADL and ADL limitations and may be milder at onset, while IADL and ADL limitations occur at older age when it might be too late to intervene. Further research is needed to identify modifiable risk factors of mobility limitations in midlife.

Our study confirmed the previously observed higher prevalence of functional limitations among women and showed that at older ages when limitations are most prevalent, women were more likely to be more severely limited than men. Our findings suggest sex inequalities in education may to an extent contribute to sex inequalities in functional limitations particularly for IADL and ADL limitations. However, sex differences in IADL and ADL limitations were small in absolute terms. Further, there are likely to be other more salient contributors to sex inequalities in functional limitations other than education such as labour force participation and chronic disease. Efforts to reduce sex differences in functional limitations in old age should therefore focus on identifying and targeting drivers of sex disparities in mobility limitations from midlife onward, as mobility limitations might signify the beginning of a progressive process leading to disability.

6 Summary of findings and conclusion

6.1 Summary of findings

6.1.1 Cognitive function

Objective 1a: Examine the role of education in sex differences in cognitive ageing with attention to decreases in sex inequalities in education over time.

The first analysis of this thesis examined sex differences in episodic memory and verbal fluency performance from mid- to late life and 13-year memory and fluency decline in 15,924 participants in two British cohort studies. Before taking education into account, women performed better than men on tasks of memory. Women also had slower memory decline than men. The female advantage in memory also tended to be larger in the younger birth cohorts. For fluency, men outperformed women in the older birth cohorts but not the youngest. There were no sex differences in fluency decline.

Accounting for sex inequalities in education increased the female advantage in memory performance, while the male advantage in fluency performance was eliminated. Accounting for education also reduced differences in sex inequalities between birth cohorts for memory and fluency. Stratifying by education level showed that only less educated women performed worse than men in fluency. Among those who were highly educated, there was no male advantage in fluency. The observed sex differences in memory decline were not affected by accounting for education.

Objective 1b: Examine and compare the role of education in sex differences in cognitive function in older adults in middle- and high-income countries.

The second investigation of the thesis was undertaken using data from 70,846 older adults from four middle-income countries and the US as a high-income reference country. The investigation comprised nationally representative analyses of sex differences in orientation in time, episodic memory, sustained attention, and verbal fluency. Before taking sex inequalities in education into account, the sex differences in middle-income countries were larger and less favourable to women than in the US. In orientation and memory, where

women outperformed men in the US, women performed worse than men in the middle-income countries. Women performed worse than men in all countries in attention, but the female disadvantages were considerably larger in the middle-income countries compared to the US. Where there was a modest male advantage in fluency in the US before accounting for education, there were substantial male advantages in the middle-income countries.

Consistent with the results from the British cohort studies, the findings showed that male advantages were attenuated or female advantages were increased after accounting for sex differences in education level. Further, differences in sex inequalities in education contributed to differences between the US and the middle-income countries in sex inequalities in cognitive function. After stratifying by education level, sex differences among those who were highly educated relative to the rest of the population in the respective country were smaller with negligible differences in sex inequalities in cognitive function between the US and the middle-income countries.

Summary of findings on sex inequalities in cognitive function

Taken together, these results provide robust evidence that sex inequalities in education play a role in sex inequalities in cognitive function in older adults. The findings indicate that larger sex inequalities in education in older birth cohorts contributed to poorer cognitive function for women in older birth cohorts compared to those born later in younger birth cohorts. The results also suggest that differences in educational sex inequalities between high- and middle-income countries may underlie the differences between countries in sex inequalities in cognitive function, where sex inequalities in middle-income countries were larger and less favourable to women than in high-income countries.

6.1.2 Functional limitations

Objective 2: Examine the role of education in sex differences in functional limitations in older adults with attention to decreases in sex inequalities in education over time and severity of limitations.

In findings from 62,375 older adults in fourteen high-income countries, women were more likely to have functional limitations in mobility activities and IADL. The probability of having

mobility limitations increased steadily from age 50, and women were substantially more likely to have mobility limitations at ages 50-100. IADL and ADL limitations occurred more commonly after ages 70 and 75 respectively, and women were more likely to have IADL limitations at all ages, though in absolute terms, sex differences in IADL limitations were minor. Sex differences in ADL limitations differed between birth cohorts, with no sex differences in the youngest two birth cohorts, even at ages where ADL limitations became more prevalent. By contrast, women were more likely than men to have functional limitations in ADL in the oldest two birth cohorts, though once again in absolute terms sex differences were minor.

In contrast to cognitive function, taking sex differences in education into account did not have a substantive attenuating effect on sex differences in functional limitations. Accounting for education did slightly attenuate the female disadvantage so that sex differences were reduced. It also reduced the birth cohort effect seen in sex differences in ADL limitations, suggesting reductions in sex inequalities in education over time may have contributed to birth cohort trends in ADL limitations where women in older birth cohorts were more likely to be limited than women in younger birth cohorts, however the effect was minor. As such, two main findings of the analysis were that sex differences in IADL and ADL limitations may be somewhat less impactful than they appear in relative terms, and that sex inequalities in education may contribute to sex differences in functional limitations to an extent, but on its own, education has a relatively minor effect. There are likely to be other factors that act in combination with education to influence sex differences in functional limitations. In additional analyses, I examined two such factors and found that accounting for labour force participation and chronic conditions in addition to education had a more substantial attenuating effect on sex differences in functional limitations. Nonetheless, sex differences in mobility limitations persisted even after accounting for labour force status and chronic conditions.

Summary of findings on sex differences in functional limitations

Older women were more likely to have functional limitations in mobility activities and IADL than older men, and in ADL activities in older birth cohorts. To an extent, sex inequalities in education played a role in sex differences in functional limitations, however other factors

such as sex differences in labour force participation and distribution of chronic disease are likely to contribute more to sex differences in functional limitations than education alone. Further, as sex inequalities in IADL and ADL limitations were small in absolute terms even at the oldest ages where limitations were most prevalent, efforts to reduce sex differences in functional limitations should focus on identifying drivers of sex differences in mobility limitations. Sex differences in mobility limitations were present from midlife onward even after accounting for education, labour force status, and self-reported chronic disease, and can signify the beginning of a progressive process of disablement.

6.2 Key findings

- Women were not cognitively disadvantaged when education was taken into account. Lower education level among women contributed to worse midlife cognitive function among women compared to men, over the midlife to old age period, though education did not effect sex differences in the rate of cognitive decline. Progressive decreases in sex disparities in education level over time contributed to better cognitive function in women born later.
- Sex differences in cognitive function in old age were larger in middle-income compared to high-income countries and women performed worse compared to men in middle-income countries where educational sex inequalities were larger. These differences between high- and middle-income countries in sex inequalities in cognitive function were not observed when analyses were restricted to individuals who were highly educated relative to the rest of the population of a given country.
- Women were more likely than men to have functional limitations, however the magnitude of absolute sex differences were small for IADL and ADL, limitations that occurred at the oldest ages. Sex inequalities in education level are likely not the most salient driver of sex differences in functional limitations.

6.3 Strengths and limitations of the thesis

6.3.1 Strengths

The examination of sex differences in healthy ageing is complex for several reasons. First, and most fundamentally, it is difficult to determine a suitable measure for healthy ageing, as

healthy ageing is a broad concept including health, longevity, and wellbeing in old age. One strength of this thesis is that through review of the literature, it parses healthy ageing into components and identifies two components of healthy ageing that are particularly relevant for autonomy, wellbeing, and quality of life for older adults. Narrowing the focus of the thesis to sex differences in two dimensions of healthy ageing allowed for in-depth review of their underlying mechanisms. This examination of determinants of sex differences in cognitive function and functional limitations among older adults is what led to the focus on education. In addition to the evidence that sex inequalities in education level contribute to sex differences in cognitive and functional ageing, gender equity in education is amenable to intervention and better education is also associated with a range of other positive health outcomes during the life course. Focus on the role of education in sex differences in cognitive function and functional limitations allowed for the development of research questions with findings that have clear implications for future research and policy. This is not to say that other pathways underlying sex differences in health or other dimensions of healthy ageing are unimportant; all of these pathways require further research. Furthermore, sex inequalities in health at all stages of the life course, not just old age, require examination in order to address these inequalities. However, the narrow focus of this thesis and its comprehensive analytic framework is what allows its in depth evaluation of the role of education in sex differences across birth cohorts.

Another strength of this thesis is its use of large studies from multiple countries. For the analyses using longitudinal data, this facilitates analysis by birth cohort: age ranges are sufficiently broad in the dataset, with sufficiently large sample size, to have overlapping ages from different birth cohorts. This allows analyses that distinguish between birth cohort and age effects and enables examination of whether education underlies birth cohort effects in sex differences in cognitive function and functional limitations. Because sex inequalities in education have changed substantially during the 20th century, it is particularly important to consider birth cohort effects in the examination of the role of education in sex inequalities in cognitive and functional outcomes in study populations born during this time period.

In addition to the statistical power provided by the large datasets, the inclusion of multiple multi-national cohorts showed how consistent the results for both cognitive function and

functional limitations were across cohorts. Preliminary analyses comparing results for sex differences in cognitive function in HRS and ELSA, and in Whitehall II and ELSA, showed that the results were very similar between studies. Findings for observed sex differences in functional limitations in the cohorts from the high-income countries included in paper 3 were also consistent across cohorts. This indicates that results for papers 1 and 3, which used data from combined cohorts, were unlikely to be driven by a single cohort, and as such, data quality or survey methodology issues with a single cohort are unlikely to have overly influenced the results.

Another strength of this thesis is that it did not limit analyses to the same cohort studies, but used multiple studies from the HRS-family of cohorts as well as the Whitehall II study. This allowed me to use the cohorts that were most suitable and most comparable for the given objective, rather than being confined to using the same cohorts for all three objectives. In the first analysis, this allowed me to combine an occupational cohort with a population-based cohort. As the occupational cohort has higher than average education compared to the national population, this allowed sufficient numbers in each education category to perform analyses stratified by education level and birth cohort. For the second paper, I was able to select those cohorts with the most available cognitive tests and wasn't confined by having to use longitudinal data, allowing me to include more cohorts in the analyses. In the final paper, using different cohorts from the previous papers allowed me to select all of the cohorts from comparable time periods with multiple waves of data on functional limitations, rather than being limited to those cohorts that also had comparable cognitive data. The sample size and objectives of each investigation would not have been possible without using different HRS-family studies in each.

The thesis also benefits from thorough analysis of the effects of attrition and selection bias. These biases are somewhat cushioned by consideration of sex differences in the outcomes: results for overall cognitive function or prevalence of functional limitations may be biased by selection or attrition, however sex differences are only biased if selection or attrition differentially impacts men or women. For the longitudinal studies, I examined sex differences in years of follow-up and found that neither men nor women seemed more likely than the other to drop out of the study. I was also able to draw on previous evidence showing that sex differences in cognitive function were less affected by attrition bias than

cognitive trajectories overall [165, 167]. Though individuals with the lowest cognitive scores may have been more likely to drop out of the study, the differences between sexes were minimal. In the cross-sectional analysis in paper 2, selection bias was minimised by imputing data so that every participant in each cohort could be included, and by incorporating weights into imputation models and the main analyses to yield population estimates for each country.

Lastly, the statistical methods used in this thesis underwent many iterations before they were employed. Inclusion or exclusion of variables and/or random effects in each model was carefully analysed. For example, in the analysis of functional limitations, I examined introducing a random effect on intercept for each cohort in addition to individual intercept and slope and determined that it did not substantively impact the results. Model fit was carefully examined; for example, initial models included functional limitations as a continuous outcome, however it was determined that the results within birth cohorts did not fit the observed data when these models were employed. This led me to use mixed effects ordinal logistic regression, which enabled the modelling of severity of functional limitations in discrete categories. For the between-country comparisons of sex differences in cognitive function, many imputation models and strategies were examined before settling on the given imputation methods and model. The LASI research team had imputed cognitive variables, however as I had to reproduce the imputation in all other cohorts, I was unable to use these imputed values. I performed imputations using a variety of strategies including using a multivariate normal distribution for all variables, or recoding polytomous variables into multiple dichotomous variables so as not to include ordinal and multinomial variables in the imputation model and thus improve stability of the model. For all imputation models, I first ran the imputed values in LASI and compared the results in each sex to the imputation of cognitive outcomes performed by the LASI research team in order to assess their validity. I found the results of my imputation to be comparable to those produced by the LASI team. The fact that the main conclusions of the thesis were unchanged after examination using a variety of statistical methods is another signifier of the robustness of the results.

6.3.2 Limitations

One main limitation that underlies the thesis is the inability to distinguish between sex and gender. This limitation is borne out of data limitations, where participants are asked if they are male or female without making a distinction between sex and gender. Despite this oversimplification, the vast majority of persons (for example, estimated greater than 99% of the population of the United States [331]) have a binary gender identity that aligns with their sex assigned at birth, so this conflation of sex and gender is unlikely to have impacted the results. Nonetheless, examination of gender identity and how it effects sex differences in cognitive function and functional limitations in old age is an important question for future research, especially given that gender roles ascribed to women are so key for shaping disparities between men and women in educational and health outcomes.

Though its narrow focus is one of the strengths of the thesis, it also limits the conclusions that can be drawn. Education is just one pathway through which sex inequalities in cognitive function and functional limitations in older adults arise, and other pathways and sex inequalities in other dimensions of healthy ageing should be examined in future research. Indeed, the findings of this thesis indicate that while sex inequalities in education possibly contribute to sex inequalities in functional limitations, education is not likely to be the most relevant factor on its own. In part, this is likely because sex inequalities in ADL and IADL limitations are small in absolute terms, even at the oldest ages where IADL and ADL limitations are more prevalent. This means that even if adjustment for education reduces the sex difference in probability of having functional limitations by half, this might correspond to a less than 1% change in probability. This in itself, however, is an important observation: the sex differences in ADL and IADL limitations noted in the literature in relative terms may translate into relatively small sex differences in probability of being limited in absolute terms. This is useful information for identifying targets for intervention so that health benefits are maximised.

Using data from multiple cohorts brings up issues of differences in data quality and survey methods. Part of the idea underlying the HRS-family of cohort studies is that they are designed to be used together. While this does not entirely negate differences in data quality between countries and even those occurring within studies such as in the case of multi-

country cohorts like SHARE, using similar multi-stage sampling strategies and survey instruments facilitates harmonisation of the data and makes the cohorts more appropriate for comparison. Survey questions may also be received differently in different contexts, leading to systematic differences between cohorts or countries. Here, once again, this potential bias is reduced by examining sex differences in cognitive function and functional limitations rather than cognitive function or prevalence of functional limitations itself. Men and women in the same country or cohort are more likely to be comparable within countries or cohorts. Differences between cohorts were also reduced by standardising cognitive scores.

Another limitation of this thesis was the lack of information about race and ethnicity in the datasets. Race and ethnicity intersect sex inequalities in health, and lack of data, or where information was provided, lack of sufficient power to examine how results varied by race and ethnicity is an important limitation of the thesis. In the first analysis, ethnicity was included. Unfortunately, race/ethnicity information was not available in all cohorts in the subsequent analyses, and therefore could not be included. Even for ELSA and Whitehall II, where data on race/ethnicity were available, the study population was overwhelmingly white, leading to binary classification of race/ethnicity that does not consider differences in racial and ethnic minority groups. Future research should oversample racial and ethnic minority populations in order to facilitate research in these communities.

A comparison of the role of education in sex differences in functional limitations between high- and middle-income countries was not undertaken in this thesis. In part, this was due to the findings of the third analysis of sex differences in functional limitations. Education did not impact sex differences in functional limitations to the same degree that it appeared to play a role in sex differences in cognitive function. Nonetheless, it is possible that education plays more of a role in countries at lower levels of economic development. Furthermore, though there are many published analyses of sex differences in functional limitations using data from multiple countries, these studies usually do not weight analyses to account for non-response, so selection bias may preclude direct comparison between countries. For these reasons, comparisons of sex differences in functional limitations in high- and lower-income settings and the factors that contribute to differences between countries remains an area of future research.

The between-country comparison of sex differences in cognitive function also used cross-sectional rather than longitudinal data, which prevented examination of birth cohort effects as in the other two analyses. This was in part in order to minimise period effects, in part because some countries had only one wave of cognitive data, and to maintain national representativeness of the study: the longitudinal weights in the HRS-family of the studies were only available for a given wave if the respondent participated in all previous waves of data. Due to intermittent drop out of participants, this would have confined the analyses to one or two waves of data for most participants, and so cross-sectional data were used instead.

Other limitations that might have affected the results such as selection and attrition bias are discussed in the strengths section. Methods to reduce these biases have been carefully considered. Nonetheless, neither bias can be completely discounted. However, as was stated previously in the strengths section, length of follow up was similar between men and women in the longitudinal analyses of cognitive ageing and functional limitations (papers 1 and 3), suggesting this is unlikely to have impacted the results. Other common biases in observational research like reverse causation are less of a consideration, as sex must precede cognitive function in the causal pathway, and education was completed well before follow up began.

6.4 Novelty of the findings

Sex differences in cognitive function and functional limitations from middle to old age have been examined in a variety of ways. However, there are several factors that distinguish the findings of this thesis from the previous research. First, combining multiple cohorts together for papers 1 and 3 provided the necessary statistical power to undertake analyses stratified by education level and birth cohort. This allowed me to examine how changing sex inequalities in education contributed to birth cohort trends in sex inequalities in cognitive function and functional limitations. This investigation of birth cohort trends is a novel element of the thesis. There are some studies that have examined the effect of education on sex differences in cognitive function [19, 151, 256-260], some that include at least some consideration of birth cohort [80, 151, 256, 278], and at least one that explicitly examines the effect of education in successive birth cohorts [151]. This study does so using economics

methods and stratifies analyses by country, yielding smaller sample size than that in the thesis. It is also unclear which waves of the studies the authors use, and how the authors address sex differences in cognitive function changing with age, as they present point estimates for sex differences in each birth cohort rather than examining cognitive trajectories. As a result, the authors attribute reductions in sex differences in successive birth cohorts to factors other than education. By contrast, this thesis, which takes into account both age and birth cohort effects and has the benefit of a larger sample size, shows education to be an important contributor to birth cohort trends. Further, though there are some studies that examine birth cohort differences in functional limitations with attention to differences between men and women [282-284, 288, 289], and others that examine determinants of sex differences in functional limitations [124, 228], the analysis in this thesis is among the first to examine the effect of education and changes in sex differences in functional limitations in successive birth cohorts, and to present results for severity of functional limitations.

Another novel element of this thesis is the use of nationally representative data to compare sex differences in cognitive function between countries. To compare sex differences in cognitive function between countries, this thesis uses multiple imputation and weighted analyses in order to retain all participants so that estimates for sex differences are more likely to be directly comparable between countries. In other comparative studies which do not perform weighted analyses [151, 257], selection bias precludes direct comparisons of sex differences between countries. The sensitivity analyses undertaken as part of the analysis of between-country comparisons of cognitive function showed the importance of imputation and weighting, where estimates for sex differences were incorrectly estimated if participants were not retained using imputation and analyses were unweighted. A final novel element of the thesis is its presentation of absolute rather than relative measures of sex differences. This is particularly important when relative measures might lead to overestimating the impact of sex differences, for example, in functional limitations in IADL and ADL.

6.5 Future directions for research

There are several areas for future research posed by the findings of this thesis. First, the use of cross-sectional data for between-country comparisons of cognitive sex differences highlights directions for future research. Subsequent analyses might use longitudinal data in weighted analyses with sufficient overlap of age ranges in order to examine birth cohort effects and how these differ between countries by level of economic development. Another area of interest would be to examine whether determinants of birth cohort differences in sex inequalities in cognitive function are different in different settings. Use of longitudinal data would also allow examination of cognitive decline with ageing, which was not possible in the analysis due to inability to distinguish between age and birth cohort effects in cross-sectional data. Though the literature and the findings of this thesis did not indicate that there were substantial sex differences in the rate of cognitive decline after age 60, it is possible that this varies between countries, and the findings may differ were the analysis expanded to cognitive domains beyond memory and fluency and in a wider age range. Future research could examine more cognitive domains using longitudinal data from more countries.

Formal mediation analysis of factors that explain sex differences in cognitive function and functional limitations would be another possible direction for future research. This thesis focusses on education, however broader and more systematic examination of the mediating effects of modifiable social, biological, and behavioural risk factors for sex differences in both cognitive and functional outcomes would be a useful contribution to the body of evidence. In particular, identifying modifiable contributors to sex differences in mobility limitations is an important question, because of the three functional outcomes, sex differences in mobility limitations were the largest and present from middle age onward. Accounting for education, labour force status, and self-report of chronic conditions also had the least impact on sex differences in mobility limitations. As mobility limitations occur from middle age onward and may eventually progress to IADL and ADL limitations, identifying the determinants of sex differences in mobility limitations, and examining and comparing the progression of mobility limitations to IADL and ADL limitations in men and women is a key

area for future research coming out of the analysis of sex differences in functional limitations.

A further direction for future research arises out of methodological considerations for longitudinal analysis of age-related outcomes. While the effects of attrition are unlikely to have substantially impacted the results of this thesis, systematic examination of attrition effects in sex differences in healthy ageing outcomes in the HRS-family studies would be a valuable direction for future research. Other areas for future analysis touched on in the limitations include in depth examination of gender roles and the effect of gender on sex differences in healthy ageing outcomes, and consideration of race/ethnicity.

6.6 Implications for policy and public health

The main policy and public health implications of this thesis come from the results for the role of education in sex differences in cognitive function in old age. This is because the thesis indicates that there are likely to be other more salient drivers of sex differences in functional limitations in addition to education. Policy aiming to target sex inequalities in functional limitations should therefore focus on addressing a combination of education, labour force entrance, and access to healthcare and treatment, as well as addressing accessibility needs of older adults with functional limitations.

This thesis suggests that sex inequalities in education level, where women are less likely than men to be highly educated, contribute to women performing worse than men on some cognitive tasks. The findings of the thesis indicate that education influences sex inequalities during midlife, rather than sex inequalities in the rate of cognitive decline. This affects sex differences in cognitive function at old age because when women are less educated, cognitive function declines from a lower midlife starting point, though the rate of cognitive decline with age may not be impacted. This means women have worse cognitive function at older ages, and may reach the threshold of cognitive impairment earlier. However, the thesis finds that worse cognitive function among women was only observed in the oldest birth cohorts and that the reductions in sex inequalities in education in the younger birth cohorts have contributed to better cognitive function for women in later-born birth cohorts, such that women no longer perform worse than men in later-born birth cohorts. Declining

from a higher midlife starting point means retaining cognitive abilities later into life for women experiencing normal cognitive ageing.

In addition to better cognitive function for older women experiencing normal age-related cognitive declines, the results also potentially have implications for neurocognitive disease. Alzheimer's disease disproportionately impacts women, with one meta-analysis estimating up to a 50% increased risk in women compared to men [188]. However, this finding is based on studies of persons born in the 1920s and earlier [188], a period during which sex differences in education level were particularly large [332]. Given the increase in mean education level over the last century and the reduction in sex differences in education level in many countries [332, 333], the findings of this thesis suggest that the sex differences in Alzheimer's disease risk may be attenuated in later-born birth cohorts in part due to a secular decrease in sex disparities in education level. This is once again a result of the cognitive buffer afforded by higher education level. Higher education level contributes to better midlife cognitive function, potentially delaying the point at which Alzheimer's disease neuropathology manifests in cognitive impairment.

The findings of this thesis also suggest that sex inequalities in education level underlie differences in sex inequalities in cognitive function between high- and middle-income countries. The thesis shows that the fact that women tend to be less educated in middle-income compared to high-income countries may contribute to larger sex differences in cognitive function that are less favourable to women in middle-income countries. However, this is not the case among those who are highly educated relative to the rest of the population of the given country. This suggests that as countries increase education level overall and increase gender equity in education, disparities in sex inequalities in cognitive function between middle- and high-income countries will be decreased. For this reason, it is important that efforts to improve education level in middle-income countries fundamentally include consideration of gender equity.

WHO publish guidelines on cognitive health and dementia that include areas for intervention as well as the evidence that supports these areas of intervention [334]. These areas currently include physical activity, tobacco cessation, nutrition, alcohol use, cognitive interventions including cognitive training or cognitive stimulation, social activity, and

management of multiple chronic conditions. Education is not included as a recommendation in these guidelines, despite the building evidence that education not only contributes to cognitive health throughout life, but also contributes to sex inequalities in cognitive health. Considering the beneficial effect of education on cognitive function and dementia risk, national and international policies aiming to improve cognitive health should prioritise the promotion of more education for all, with an emphasis on gender equity.

6.7 Concluding statement

This thesis provides evidence that sex inequalities in education contribute to sex inequalities in cognitive function and to a lesser extent to functional limitations. Education has wide-ranging effects on health throughout the life course. It can inform the kind of occupation individuals have, their social circles, habits, and health-related behaviours. High education can indicate early life social and economic advantages and can influence experiences of adulthood. The effects of all of these factors on health are cumulative, and as a result, this early life exposure can have implications for health for the entire life course. Growing evidence shows that lower education level has a negative impact on cognitive health, both in normal cognitive ageing and in neurocognitive disease. It follows that inequalities in education contribute to inequalities in cognitive health. Throughout history, women have been systematically excluded from education and from higher education levels. This thesis shows that historical inequalities in education have likely contributed to worse cognitive function among women in a variety of settings.

However, the findings of this thesis are also encouraging: sex inequalities in cognitive function appear to be decreasing as gender equity in education increases over time. This thesis points to the importance of considering sex inequalities in examination of healthy ageing outcomes, reiterates the importance of policies that underscore education and gender equity in education as targets for improving health in old age, and shows that sex inequalities in cognitive function particularly are not static or rooted in biology alone, but instead can be progressively reduced. The consensus is that women live "longer lives in worse health" than men. This thesis provides evidence that cognitive health may be one dimension of ageing where this idea might not hold true in the future.

7 References

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8 Appendix

8.1 Paper 1 supplementary materials

Table 8.1.1. Role of education in sex differences in cognitive performance in the Whitehall II study.

	Age 50 years		Age 60 years		Age 70 years	
	Base Model[a]	Basic Model[a] + Education	Basic Model[a]	Basic Model[a] + Education	Basic Model[a]	Basic Model[a] + Education
	Sex difference (95% CI)	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**
Memory						
Birth cohort						
1930-1938	No data	No data	-0.06 (-0.16, 0.03)	-0.20 (-0.30, -0.11)	-0.02 (-0.08, 0.05)	-0.12 (-0.19, -0.06)
1939-1945	No data	No data	-0.06 (-0.14, 0.01)	-0.14 (-0.21, -0.07)	-0.06 (-0.13, 0.01)	-0.13 (-0.20, -0.06)
1946-1955	-0.17 (-0.26, -0.09)	-0.21 (-0.29, -0.12)	-0.18 (-0.24, -0.11)	-0.21 (-0.28, -0.15)	-0.18 (-0.27, -0.10)	-0.22 (-0.30, -0.14)
P sex difference by birth cohort			*0.03*	*0.27*	*0.01*	*0.14*
Fluency						
Birth cohort						
1930-1938	No data	No data	0.38 (0.29, 0.47)	0.17 (0.09, 0.25)	0.33 (0.27, 0.40)	0.14 (0.08, 0.21)
1939-1945	No data	No data	0.11 (0.03, 0.18)	-0.02 (-0.09, 0.04)	0.06 (-0.02, 0.13)	-0.06 (-0.13, 0.01)
1946-1955	-0.10 (-0.18, -0.01)	-0.16 (-0.24, -0.09)	-0.11 (-0.17, -0.04)	-0.17 (-0.23, -0.10)	-0.11 (-0.19, -0.03)	-0.17 (-0.25, -0.10)
P sex difference by birth cohort			*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*

[a]Adjusted for ethnicity, practice effect, interactions with age.
Positive value indicates male advantage in performance.

Table 8.1.2. Role of education in sex differences in cognitive performance in ELSA.

	Age 50 years		Age 60 years		Age 70 years	
	Basic Model[a]	Basic Model[a] + Education	Basic Model[a]	Basic Model[a] + Education	Basic Model[a]	Basic Model[a] + Education
	Sex difference (95% CI)	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**
Memory						
Birth cohort						
1930-1938	No data	No data	No data	No data	-0.22 (-0.29, -0.16)	-0.35 (-0.41, -0.29)
1939-1945	No data	No data	-0.18 (-0.25, -0.11)	-0.27 (-0.34, -0.21)	-0.25 (-0.32, -0.17)	-0.36 (-0.43, -0.28)
1946-1955	-0.09 (-0.17, -0.01)	-0.17 (-0.25, -0.09)	-0.16 (-0.21, -0.10)	-0.25 (-0.30, -0.20)	No data	No data
P sex difference by birth cohort			*0.69*	*0.47*	*0.90*	*0.83*
Fluency						
Birth cohort						
1930-1938	No data	No data	No data	No data	0.11 (0.04, 0.17)	0.00 (-0.07, 0.06)
1939-1945	No data	No data	0.07 (-0.00, 0.14)	-0.02 (-0.09, 0.05)	0.07 (-0.01, 0.15)	-0.03 (-0.11, 0.05)
1946-1955	0.17 (0.09, 0.25)	0.08 (-0.00, 0.16)	0.09 (0.03, 0.15)	0.00 (-0.06, 0.06)	No data	No data
P sex difference by birth cohort			*0.57*	*0.65*	*0.27*	*0.47*

[a]Adjusted for ethnicity, practice effect, interactions with age.
Positive value indicates male advantage in performance

Table 8.1.3. Role of education in sex differences in 13-year cognitive decline: Analyses stratified by birth cohort and undertaken separately in Whitehall II and ELSA.

	Basic Model[a]	Basic Model[a] + Education
	Sex difference (95% CI)	**Sex difference (95% CI)**
Whitehall II		
Memory		
Birth cohort		
1930-1938	0.06 (-0.02, 0.14)	0.10 (0.02, 0.19)
1939-1945	0.00 (-0.07, 0.08)	0.01 (-0.06, 0.09)
1946-1955	-0.01 (-0.08, 0.06)	-0.01 (-0.08, 0.06)
P sex difference by birth cohort	*0.43*	*0.10*
Fluency		
Birth cohort		
1930-1938	-0.06 (-0.13, 0.00)	-0.04 (-0.10, 0.03)
1939-1945	-0.06 (-0.12, -0.00)	-0.05 (-0.11, 0.01)
1946-1955	-0.01 (-0.07, 0.05)	-0.01 (-0.06, 0.05)
P sex difference by birth cohort	*0.37*	*0.53*
ELSA		
Memory		
Birth cohort		
1930-1938	-0.02 (-0.12, 0.08)	-0.04 (-0.14, 0.07)
1939-1945	-0.09 (-0.19, 0.02)	-0.11 (-0.22, -0.01)
1946-1955	-0.09 (-0.18, 0.00)	-0.10 (-0.19, -0.00)
P sex difference by birth cohort	*0.54*	*0.57*
Fluency		
Birth cohort		
1930-1938	-0.04 (-0.14, 0.06)	-0.05 (-0.15, 0.05)
1939-1945	0.00 (-0.10, 0.10)	-0.01 (-0.11, 0.09)
1946-1955	-0.10 (-0.19, -0.01)	-0.10 (-0.19, -0.01)
P sex difference by birth cohort	*0.32*	*0.42*

[a]Adjusted for ethnicity, practice effect, interactions with age. Results are shown for the reference category: participants aged 60 years.
Positive value indicates slower cognitive decline in men.

Table 8.1.3. Role of education in sex differences in cognitive performance: analyses stratified by birth cohort and excluding participants with dementia.[a]

	Age 50 years		Age 60 years		Age 70 years	
	Basic Model[b]	Basic Model[b] + Education	Basic Model[b]	Basic Model[b] + Education	Basic Model[b]	Basic Model[b] + Education
ELSA & Whitehall II	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**
Memory						
Birth cohort						
1930-1938	No data	No data	-0.12 (-0.20, -0.04)	-0.27 (-0.34, -0.19)	-0.14 (-0.19, -0.09)	-0.26 (-0.30, -0.21)
1939-1945	No data	No data	-0.13 (-0.18, -0.07)	-0.22 (-0.27, -0.17)	-0.22 (-0.27, -0.16)	-0.30 (-0.35, -0.25)
1946-1955	-0.07 (-0.13, -0.01)	-0.14 (-0.20, -0.09)	-0.18 (-0.22, -0.14)	-0.25 (-0.29, -0.21)	-0.29 (-0.35, -0.22)	-0.36 (-0.42, -0.29)
P sex difference by birth cohort			*0.22*	*0.46*	*0.002*	*0.03*
Fluency						
Birth cohort						
1930-1938	No data	No data	0.19 (0.07, 0.31)	0.03 (-0.09, 0.15)	0.18 (0.13, 0.24)	0.05 (-0.00, 0.10)
1939-1945	No data	No data	0.09 (0.03, 0.14)	-0.02 (-0.08, 0.03)	0.02 (-0.04, 0.07)	-0.08 (-0.14, -0.03)
1946-1955	0.06 (-0.01, 0.13)	-0.04 (-0.11, 0.03)	0.00 (-0.05, 0.04)	-0.10 (-0.14, -0.05)	-0.02 (-0.11, 0.08)	-0.09 (-0.18, 0.01)
P sex difference by birth cohort			*0.002*	*0.04*	*< 0.001*	*< 0.001*

[a]This analysis is conducted on 15,372 participants free of dementia during the follow-up period (N dementia cases excluded: 434 in Whitehall II and 118 in ELSA).
[b]Basic models include sex, sex by age, age^2, age^3, birth cohort, sex by birth cohort, birth cohort by age, sex by birth cohort by age, ethnicity, and practice effect. Memory models additionally include birth cohort by age^3 and lower-order interactions. Fluency models additionally include practice effect by sex and birth cohort by sex by age^2 and lower-order interactions.
Positive value indicates male advantage in performance.

Table 8.1.4. Sex differences in cognitive performance: analyses stratified by birth cohort and education and excluding participants with dementia.[a]

	Age 50 years	**Age 60 years**	**Age 70 years**
ELSA & Whitehall II	Sex difference (95% CI)	Sex difference (95% CI)	Sex difference (95% CI)
Memory			
Education: Below A-level			
1930-1938	No data	-0.18 (-0.27, -0.10)	-0.19 (-0.24, -0.14)
1939-1945	No data	-0.18 (-0.24, -0.12)	-0.29 (-0.35, -0.23)
1946-1955	-0.09 (-0.16, -0.02)	-0.22 (-0.27, -0.16)	-0.34 (-0.43, -0.26)
P sex difference by birth cohort		*0.68*	*0.0042*
Education: A-level and above			
1930-1938	No data	-0.23 (-0.38, -0.09)	-0.24 (-0.33, -0.14)
1939-1945	No data	-0.15 (-0.23, -0.06)	-0.20 (-0.28, -0.11)
1946-1955	-0.18 (-0.26, -0.10)	-0.24 (-0.30, -0.18)	-0.30 (-0.39, -0.21)
P sex difference by birth cohort		*0.19*	*0.25*
Fluency			
Education: Below A-level			
1930-1938	No data	0.23 (0.07, 0.38)	0.13 (0.07, 0.19)
1939-1945	No data	0.08 (0.01, 0.15)	0.03 (-0.03, 0.10)
1946-1955	0.16 (0.06, 0.25)	0.00 (-0.06, 0.06)	0.01 (-0.12, 0.15)
P sex difference by birth cohort		*0.02*	*0.04*
Education: A-level and above			
1930-1938	No data	-0.07 (-0.28, 0.14)	-0.01 (-0.12, 0.11)
1939-1945	No data	-0.10 (-0.19, -0.00)	-0.20 (-0.29, -0.11)
1946-1955	-0.20 (-0.30, -0.09)	-0.18 (-0.25, -0.10)	-0.13 (-0.27, 0.01)
P sex difference by birth cohort		*0.34*	*0.03*

[a]This analysis is conducted on 15,372 participants free of dementia during the follow-up period (N dementia cases excluded: 434 in Whitehall II and 118 in ELSA).

Models include sex, sex by age, age^2, age^3, birth cohort, sex by birth cohort, birth cohort by age, sex by birth cohort by age, ethnicity, and practice effect. Memory models additionally include birth cohort by age^3 and lower-order interactions. Fluency models additionally include practice effect by sex and birth cohort by sex by age^2 and lower-order interactions.

Positive value indicates male advantage in performance.

Table 8.1.5. Role of education in sex differences in 13-year cognitive decline: analyses stratified by birth cohort and excluding participants with dementia.[a]

	Basic Model[b]	**Basic Model[b] + Education**
ELSA & Whitehall II	**Sex difference (95% CI)**	**Sex difference (95% CI)**
Memory		
Birth cohort		
1930-1938	-0.02 (-0.09, 0.05)	0.01 (-0.05, 0.08)
1939-1945	-0.12 (-0.18, -0.05)	-0.11 (-0.17, -0.05)
1946-1955	-0.14 (-0.20, -0.08)	-0.14 (-0.19, -0.08)
P sex difference by birth cohort	*0.02*	*0.002*
Fluency		
Birth cohort		
1930-1938	-0.04 (-0.16, 0.09)	-0.01 (-0.13, 0.11)
1939-1945	-0.06 (-0.13, 0.00)	-0.05 (-0.11, 0.02)
1946-1955	0.06 (-0.11, 0.23)	0.09 (-0.09, 0.26)
P sex difference by birth cohort	*0.46*	*0.38*

[a]This analysis is conducted on 15,372 participants free of dementia during the follow-up period (N dementia cases excluded: 434 in Whitehall II and 118 in ELSA).
[b]Basic models include sex, sex by age, age^2, age^3, birth cohort, sex by birth cohort, birth cohort by age, sex by birth cohort by age, ethnicity, and practice effect. Memory models additionally include birth cohort by age^3 and lower-order interactions. Fluency models additionally include practice effect by sex and birth cohort by sex by age^2 and lower-order interactions. Results are shown for the reference category: participants aged 60 years.
Positive value indicates slower cognitive decline in men.

Table 8.1.6. Sex differences in 13-year cognitive decline: analyses stratified by birth cohort and education, and excluding participants with dementia.[a]

ELSA & Whitehall II	Sex difference (95% CI)
Memory	
Education: Below A-level	
1930-1938	-0.01 (-0.09, 0.07)
1939-1945	-0.14 (-0.22, -0.06)
1946-1955	-0.16 (-0.24, -0.09)
P sex difference by birth cohort	*0.012*
Education: A-level and above	
1930-1938	-0.01 (-0.14, 0.12)
1939-1945	-0.07 (-0.16, 0.03)
1946-1955	-0.08 (-0.16, -0.00)
P sex difference by birth cohort	*0.64*
Fluency	
Education: Below A-level	
1930-1938	-0.11 (-0.28, 0.05)
1939-1945	-0.02 (-0.10, 0.06)
1946-1955	0.07 (-0.17, 0.31)
P sex difference by birth cohort	*0.30*
Education: A-level and above	
1930-1938	0.05 (-0.16, 0.27)
1939-1945	-0.13 (-0.23, -0.02)
1946-1955	0.16 (-0.11, 0.43)
P sex difference by birth cohort	*0.10*

[a]This analysis is conducted on 15,372 participants free of dementia during the follow-up period (N dementia cases excluded: 434 in Whitehall II and 118 in ELSA).
Models include sex, sex by age, age^2, age^3, birth cohort, sex by birth cohort, birth cohort by age, sex by birth cohort by age, ethnicity, and practice effect. Memory models additionally include birth cohort by age^3 and lower-order interactions. Fluency models additionally include practice effect by sex and birth cohort by sex by age^2 and lower-order interactions. Results are shown for the reference category: participants aged 60 years. Positive value indicates slower cognitive decline in men.

Table 8.1.7. Role of education in sex differences in cognitive performance: analyses stratified by birth cohort and restricted to follow-up period 2002 to 2015.[a]

	Age 50 years		Age 60 years		Age 70 years	
	Basic Model[b]	Basic Model[b] + Education	Basic Model[b]	Basic Model[b] + Education	Basic Model[b]	Basic Model[b] + Education
ELSA & Whitehall II	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**
Memory						
Birth cohort						
1930-1938	No data	No data	No data	No data	-0.14 (-0.20, -0.09)	-0.26 (-0.30, -0.21)
1939-1945	No data	No data	-0.14 (-0.19, -0.08)	-0.23 (-0.28, -0.18)	-0.21 (-0.27, -0.16)	-0.30 (-0.35, -0.25)
1946-1955	-0.06 (-0.13, 0.01)	-0.14 (-0.20, -0.07)	-0.17 (-0.22, -0.13)	-0.25 (-0.29, -0.21)	No data	No data
P sex difference by birth cohort			*0.31*	*0.58*	*0.08*	*0.21*
Fluency						
Birth cohort						
1930-1938	No data	No data	No data	No data	0.18 (0.13, 0.23)	0.05 (-0.00, 0.10)
1939-1945	No data	No data	0.10 (0.04, 0.16)	0.00 (-0.06, 0.05)	0.04 (-0.02, 0.10)	-0.06 (-0.11, -0.01)
1946-1955	0.12 (0.01, 0.23)	0.03 (-0.08, 0.14)	-0.01 (-0.06, 0.04)	-0.10 (-0.14, -0.05)	No data	No data
P sex difference by birth cohort			*0.003*	*0.01*	*<0.001*	*0.004*

[a]N = 15,368.

[b]Basic models include sex, sex by age, age^2, age^3, birth cohort, sex by birth cohort, birth cohort by age, sex by birth cohort by age, ethnicity, and practice effect. Memory models additionally include birth cohort by age^3 and lower-order interactions. Fluency models additionally include practice effect by sex and birth cohort by sex by age^2 and lower-order interactions.

Positive value indicates male advantage in performance.

Table 8.1.8. Sex differences in cognitive performance: analyses stratified by birth cohort and education, and restricted to follow-up period 2002 to 2015.[a]

	Age 50 years	**Age 60 years**	**Age 70 years**
ELSA & Whitehall II	Sex difference (95% CI)	Sex difference (95% CI)	Sex difference (95% CI)
Memory			
Education: Below A-level			
1930-1938	No data	No data	-0.20 (-0.26, -0.15)
1939-1945	No data	-0.18 (-0.25, -0.12)	-0.28 (-0.35, -0.21)
1946-1955	-0.10 (-0.18, -0.02)	-0.21 (-0.27, -0.16)	No data
P sex difference by birth cohort		*0.47*	*0.08*
Education: A-level and above			
1930-1938	No data	No data	-0.24 (-0.34, -0.13)
1939-1945	No data	-0.18 (-0.28, -0.09)	-0.22 (-0.31, -0.13)
1946-1955	-0.14 (-0.24, -0.04)	-0.24 (-0.30, -0.18)	No data
P sex difference by birth cohort		*0.31*	*0.83*
Fluency			
Education: Below A-level			
1930-1938	No data	No data	0.12 (0.07, 0.18)
1939-1945	No data	0.09 (0.02, 0.16)	0.06 (-0.01, 0.13)
1946-1955	0.17 (0.02, 0.31)	0.00 (-0.06, 0.06)	No data
P sex difference by birth cohort		*0.05*	*0.18*
Education: A-level and above			
1930-1938	No data	No data	0.03 (-0.08, 0.14)
1939-1945	No data	-0.08 (-0.18, 0.02)	-0.20 (-0.29, -0.10)
1946-1955	-0.18 (-0.36, 0.00)	-0.17 (-0.24, -0.09)	No data
P sex difference by birth cohort		*0.18*	*0.003*

[a]N = 15,368.

Models include sex, sex by age, age^2, age^3, birth cohort, sex by birth cohort, birth cohort by age, sex by birth cohort by age, ethnicity, and practice effect. Memory models additionally include birth cohort by age^3 and lower-order interactions. Fluency models additionally include practice effect by sex and birth cohort by sex by age^2 and lower-order interactions.

Positive value indicates male advantage in performance.

Table 8.1.9. Role of education in sex differences in 13-year cognitive decline: analyses stratified by birth cohort and restricted to follow-up period 2002 to 2015.[a]

	Basic Model[b]	**Basic Model[b] + Education**
ELSA & Whitehall II	**Sex difference (95% CI)**	**Sex difference (95% CI)**
Memory		
Birth cohort		
1930-1938	No data	No data
1939-1945	-0.09 (-0.18, -0.01)	-0.09 (-0.17, -0.02)
1946-1955	-0.15 (-0.23, -0.08)	-0.14 (-0.21, -0.07)
P sex difference by birth cohort	*0.28*	*0.33*
Fluency		
Birth cohort		
1930-1938	No data	No data
1939-1945	-0.03 (-0.11, 0.04)	-0.02 (-0.10, 0.05)
1946-1955	0.14 (-0.11, 0.39)	0.16 (-0.09, 0.41)
P sex difference by birth cohort	*0.20*	*0.17*

[a]N = 15,368.

[b]Basic models include sex, sex by age, age^2, age^3, birth cohort, sex by birth cohort, birth cohort by age, sex by birth cohort by age, ethnicity, and practice effect. Memory models additionally include birth cohort by age^3 and lower-order interactions. Fluency models additionally include practice effect by sex and birth cohort by sex by age^2 and lower-order interactions. Results are shown for the reference category: participants aged 60 years.
Positive value indicates slower cognitive decline in men.

Table 8.1.10. Sex differences in 13-year cognitive decline: analyses stratified by birth cohort and education, and restricted to follow-up period 2002 to 2015.[a]

ELSA & Whitehall II	Sex difference (95% CI)
Memory	
Education: Below A-level	
1930-1938	No data
1939-1945	-0.13 (-0.23, -0.03)
1946-1955	-0.14 (-0.24, -0.05)
P sex difference by birth cohort	*0.84*
Education: A-level and above	
1930-1938	No data
1939-1945	-0.05 (-0.18, 0.08)
1946-1955	-0.13 (-0.24, -0.02)
P sex difference by birth cohort	*0.37*
Fluency	
Education: Below A-level	
1930-1938	No data
1939-1945	0.02 (-0.07, 0.11)
1946-1955	0.09 (-0.23, 0.42)
P sex difference by birth cohort	*0.68*
Education: A-level and above	
1930-1938	No data
1939-1945	-0.12 (-0.25, 0.00)
1946-1955	0.23 (-0.20, 0.66)
P sex difference by birth cohort	*0.12*

[a]N = 15,368.

Basic models include sex, sex by age, age^2, age^3, birth cohort, sex by birth cohort, birth cohort by age, sex by birth cohort by age, ethnicity, and practice effect. Memory models additionally include birth cohort by age^3 and lower-order interactions. Fluency models additionally include practice effect by sex and birth cohort by sex by age^2 and lower-order interactions. Results are shown for the reference category: participants aged 60 years. Positive value indicates slower cognitive decline in men.

Table 8.1.11. Role of education in sex differences in cognitive performance: analyses stratified by birth cohort using multiple imputation to account for missing education data.

	At age 50 years		At age 60 years		At age 70 years	
	Basic Model[a]	Basic Model[a] + Education	Basic Model[a]	Basic Model[a] + Education	Basic Model[a]	Basic Model[a] + Education
ELSA & Whitehall II	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**	**Sex difference (95% CI)**
Memory						
Birth cohort						
1930-1938	No data	No data	-0.10 (-0.16, -0.03)	-0.24 (-0.31, -0.17)	-0.13 (-0.18, -0.09)	-0.25 (-0.29, -0.20)
1939-1945	No data	No data	-0.12 (-0.16, -0.07)	-0.21 (-0.26, -0.17)	-0.20 (-0.26, -0.15)	-0.29 (-0.34, -0.24)
1946-1955	-0.06 (-0.12, -0.01)	-0.14 (-0.19, -0.08)	-0.17 (-0.22, -0.13)	-0.25 (-0.28, -0.21)	-0.29 (-0.35, -0.23)	-0.35 (-0.41, -0.29)
P sex difference by birth cohort			*0.07*	*0.57*	*<0.001*	*0.01*
Fluency						
Birth cohort						
1930-1938	No data	No data	0.19 (0.08, 0.31)	0.04 (-0.08, 0.16)	0.18 (0.13, 0.23)	0.06 (0.01, 0.10)
1939-1945	No data	No data	0.10 (0.04, 0.15)	-0.02 (-0.07, 0.04)	0.03 (-0.02, 0.08)	-0.07 (-0.12, -0.02)
1946-1955	0.06 (-0.01, 0.13)	-0.03 (-0.10, 0.04)	0.00 (-0.05, 0.05)	-0.09 (-0.13, -0.04)	-0.01 (-0.11, 0.08)	-0.08 (-0.17, 0.02)
P sex difference by birth cohort			*0.002*	*0.03*	*<0.001*	*<0.001*

[a]Basic models include sex, sex by age, age^2, age^3, birth cohort, sex by birth cohort, birth cohort by age, sex by birth cohort by age, ethnicity, and practice effect. Memory models additionally include birth cohort by age^3 and lower-order interactions. Fluency models additionally include practice effect by sex and birth cohort by sex by age^2 and lower-order interactions.
Positive value indicates male advantage in performance.

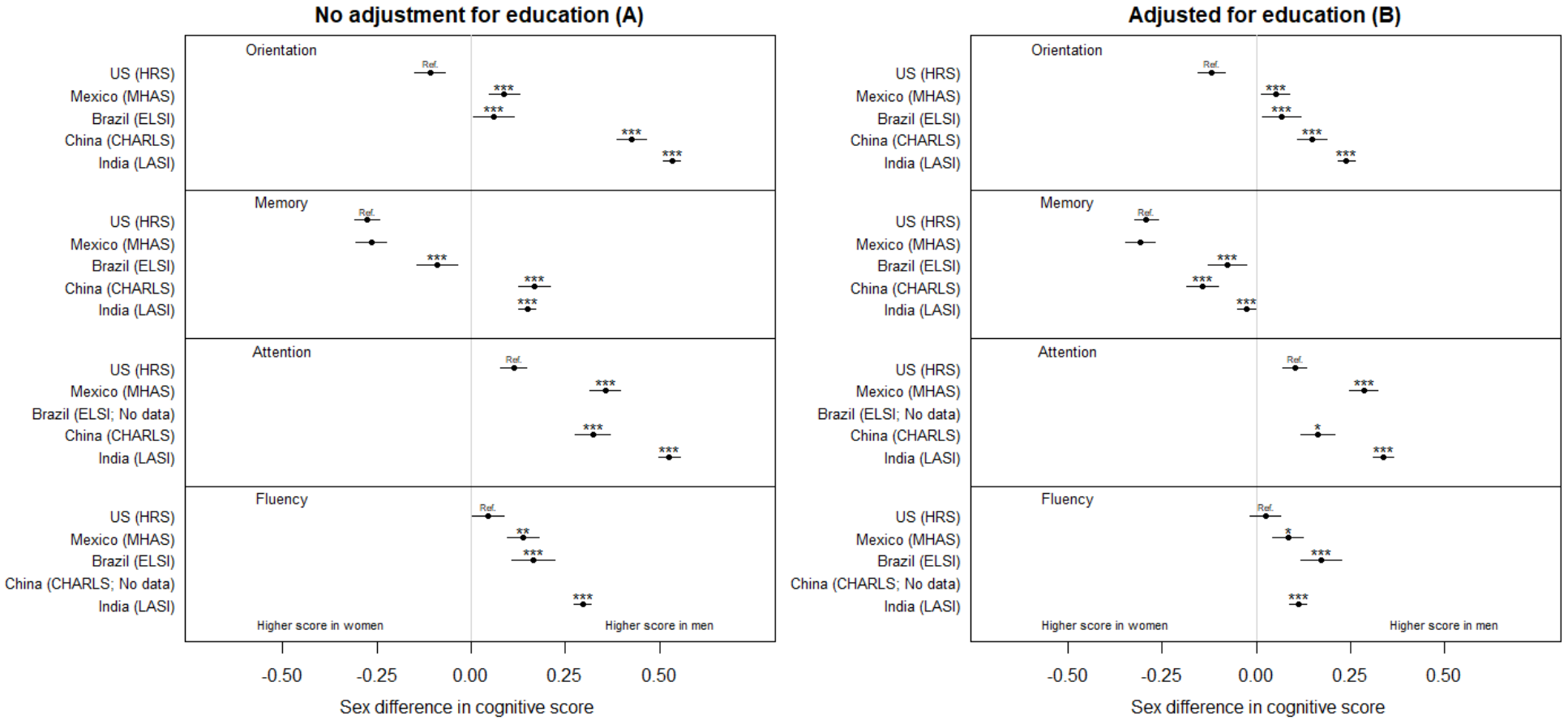
Table 8.1.12. Role of education in sex differences in 13-year cognitive decline: analyses stratified by birth cohort using multiple imputation to account for missing education data.

	Basic Model[a]	Basic Model[a] + Education
ELSA & Whitehall II	**Sex difference (95% CI)**	**Sex difference (95% CI)**
Memory		
Birth cohort		
1930-1938	-0.05 (-0.11, 0.01)	-0.01 (-0.07, 0.06)
1939-1945	-0.12 (-0.18, -0.05)	-0.10 (-0.17, -0.04)
1946-1955	-0.15 (-0.20, -0.09)	-0.14 (-0.20, -0.09)
P sex difference by birth cohort	*0.07*	*0.01*
Fluency		
Birth cohort		
1930-1938	-0.05 (-0.17, 0.08)	-0.01 (-0.13, 0.11)
1939-1945	-0.05 (-0.12, 0.01)	-0.04 (-0.10, 0.03)
1946-1955	0.06 (-0.11, 0.24)	0.09 (-0.08, 0.27)
P sex difference by birth cohort	*0.48*	*0.41*

[a]Basic models include sex, sex by age, age^2, age^3, birth cohort, sex by birth cohort, birth cohort by age, sex by birth cohort by age, ethnicity, and practice effect. Memory models additionally include birth cohort by age^3 and lower-order interactions. Fluency models additionally include practice effect by sex and birth cohort by sex by age^2 and lower-order interactions. Results are shown for the reference category: participants aged 60 years. Positive value indicates slower cognitive decline in men.

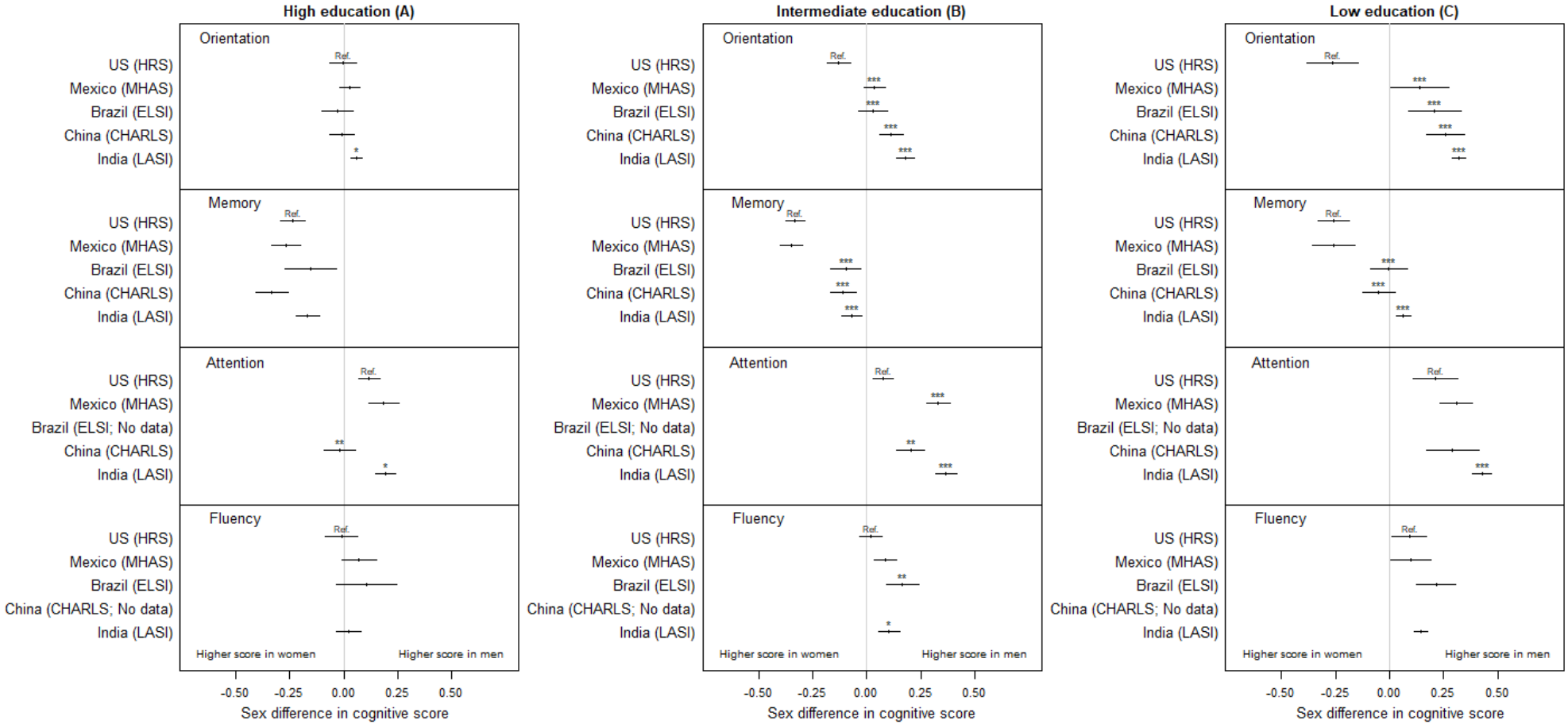
8.2 Paper 2 supplementary materials

Figure 8.2.1. Sex differences in standardised cognitive scores in each country without weighting or imputation.



Left panel (A) shows sex differences in standardised cognitive scores in each country. Right panel (B) shows analyses further adjusted for education. Tests for difference with the US (HRS) were based on pooled data and *denotes significance at $\alpha < 0.05$, **$\alpha < 0.01$, and *** $\alpha < 0.001$.

Figure 8.2.2. Sex differences in standardised cognitive scores by education level in each country without weighting or imputation.



Left panel (A) shows sex differences in standardised cognitive scores in each country in the high education group. Centre panel (B) shows sex differences in the intermediate education group. Right panel (C) shows sex differences in the low education group. Tests for difference with the US (HRS) were based on pooled data and *denotes significance at $\alpha < 0.05$, **$\alpha < 0.01$, and *** $\alpha < 0.001$.

8.3 Paper 3 supplementary materials

Figure 8.3.1. Observed proportion ≥1 mobility, IADL, and ADL limitation in ELSA, TILDA, SHARE, and HRS.

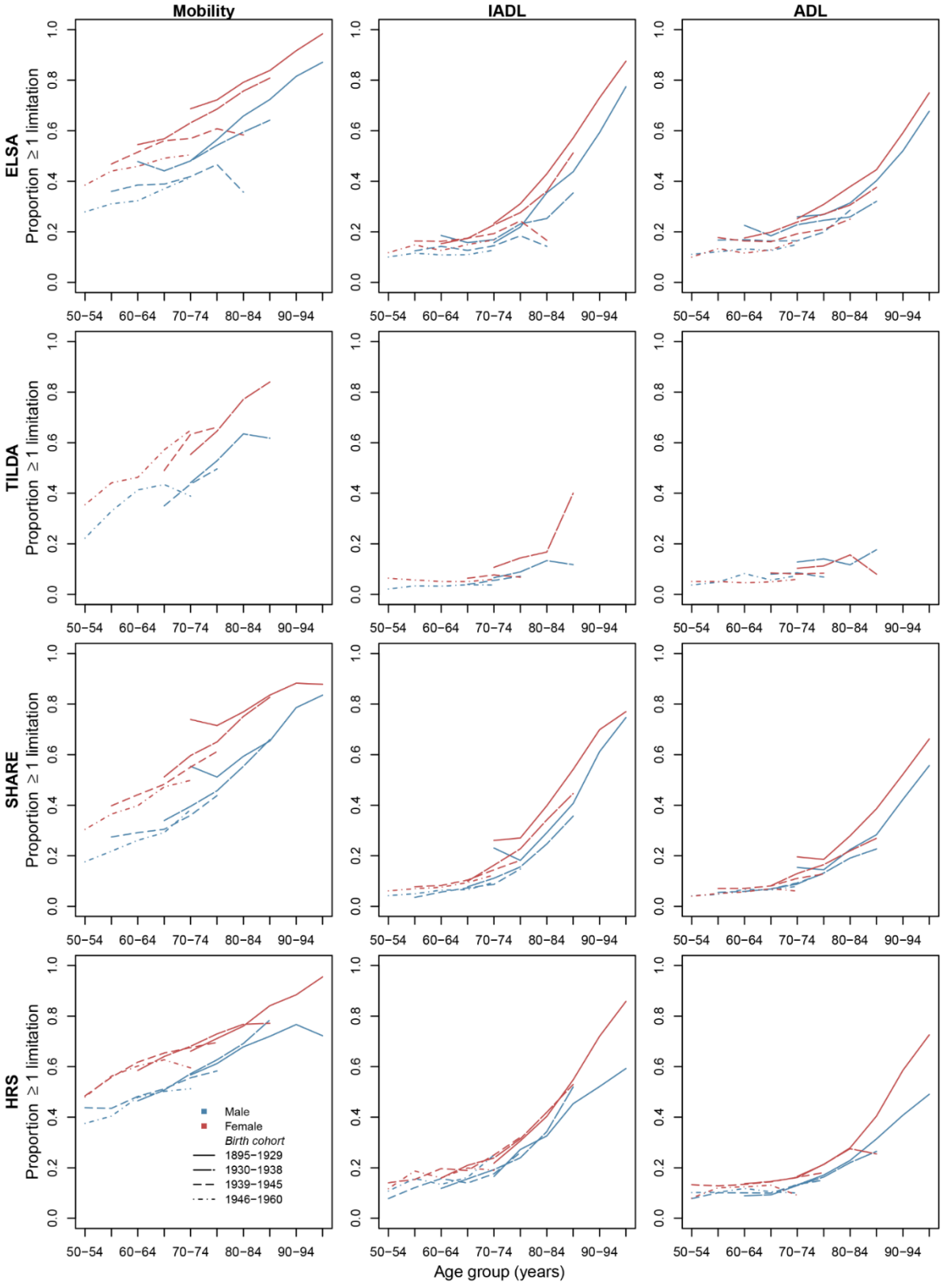


Figure 8.3.2. Comparison of sex differences in probability of ≥ 1 mobility, IADL, and ADL limitation after adjustment for education only versus education and labour force status.

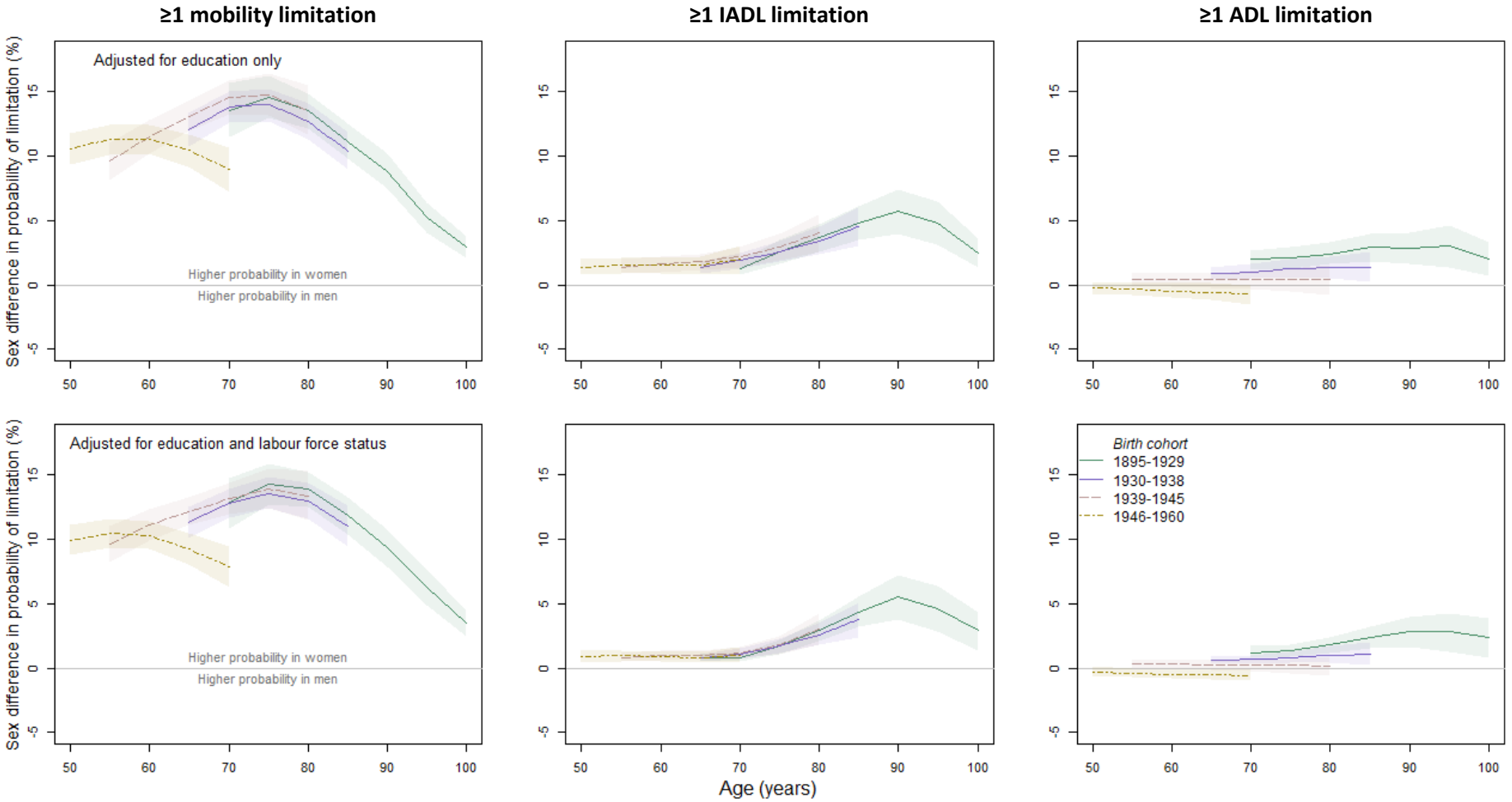
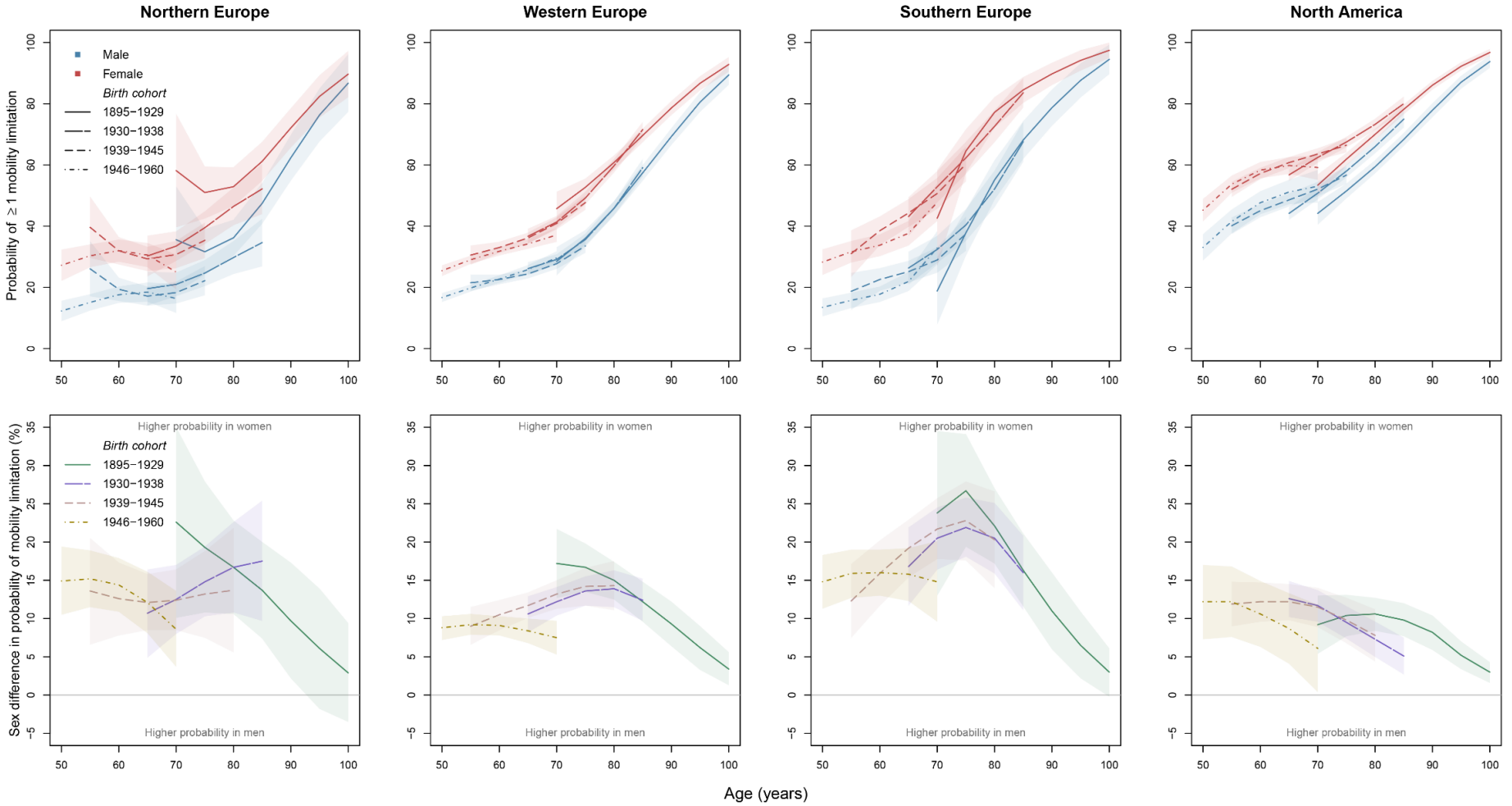
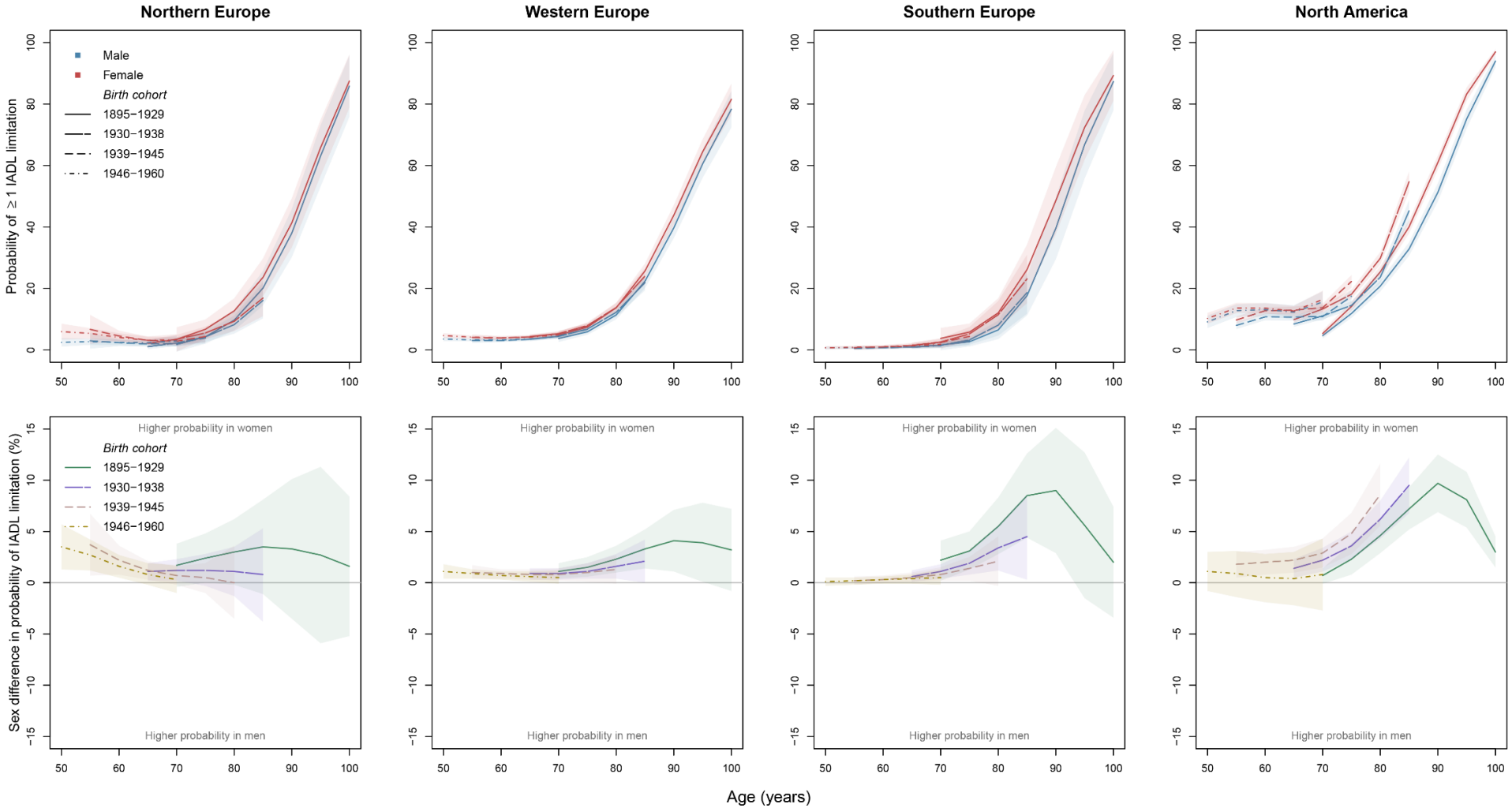


Figure 8.3.3. Sex differences in probability of ≥1 mobility limitation by region.



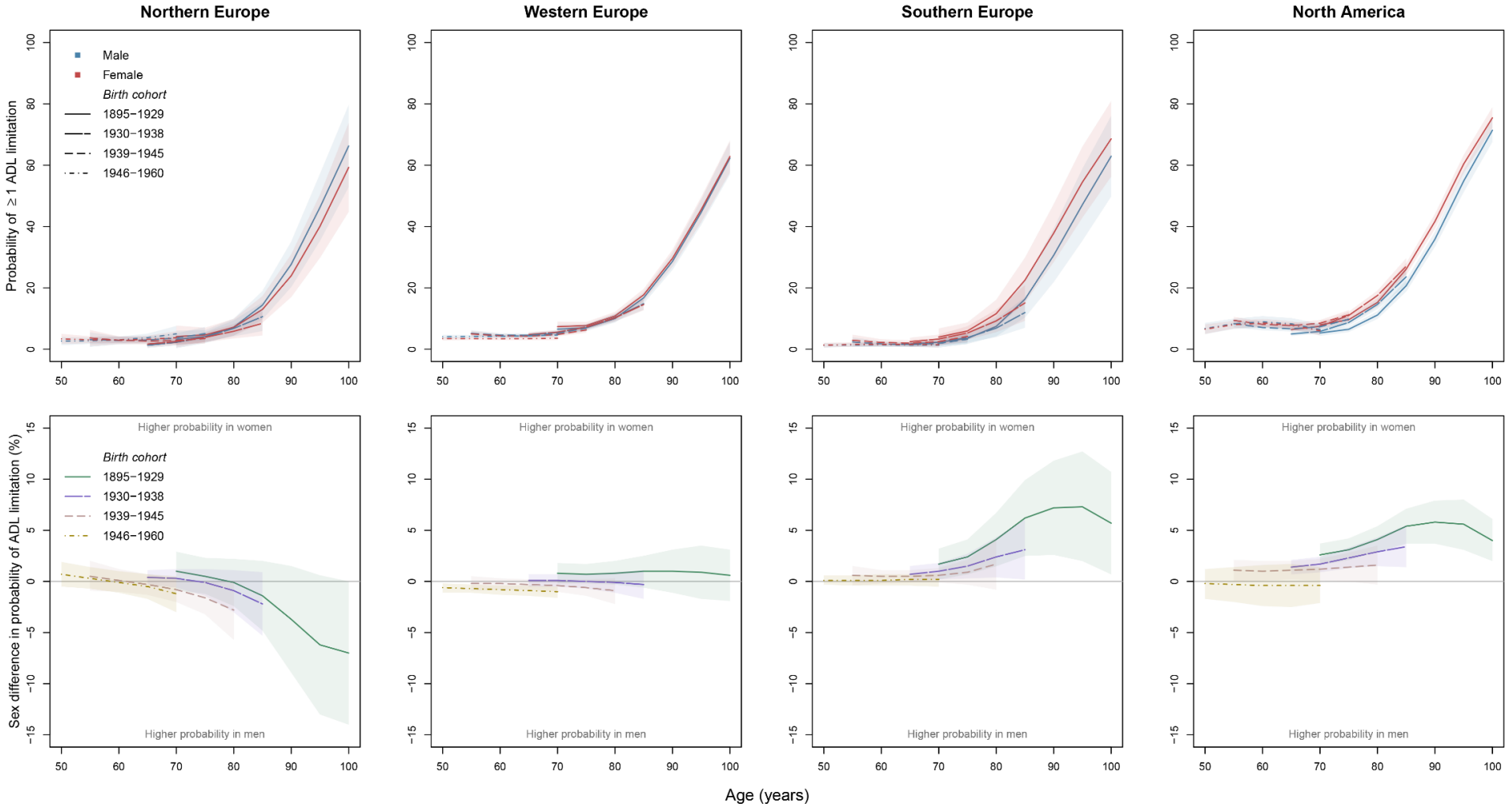
Top panel shows the probability of having ≥1 mobility limitation plotted by age for men and women in each birth cohort. Bottom panel shows the sex difference in probability of ≥1 mobility limitation: positive value indicates women have greater probability than men of ≥1 mobility limitation. Predicted probabilities based on models in each region adjusted for sex, age, birth cohort, and their interactions, marital status, education and labour force status, and plotted for reference categories for all covariates.

Figure 8.3.4. Sex differences in probability of ≥1 IADL limitation by region.



Top panel shows the probability of having ≥1 IADL limitation plotted by age for men and women in each birth cohort. Bottom panel shows the sex difference in probability of ≥1 IADL limitation: positive value indicates women have greater probability than men of ≥1 IADL limitation. Predicted probabilities based on models in each region adjusted for sex, age, birth cohort, and their interactions, marital status, education and labour force status, and plotted for reference categories for all covariates.

Figure 8.3.5. Sex differences in probability of ≥1 ADL limitation by region.



Top panel shows the probability of having ≥1 ADL limitation plotted by age for men and women in each birth cohort. Bottom panel shows the sex difference in probability of ≥1 ADL limitation: positive value indicates women have greater probability than men of ≥1 ADL limitation. Predicted probabilities based on models in each region adjusted for sex, age, birth cohort, and their interactions, marital status, education and labour force status, and plotted for reference categories for all covariates.

Table 8.3.1. Odds ratios of being more likely to be limited for given activity for women compared to men.

Mobility activities	**Odds ratio[a] (95% CI)**	**P-value**
Getting in/out of a chair	1.51 (1.49, 1.54)	<0.001
Climbing 1 flight of stairs	1.72 (1.68, 1.76)	<0.001
Stooping/kneeling/crouching	1.67 (1.64, 1.70)	<0.001
Reaching/extending the arms	1.56 (1.52, 1.60)	<0.001
Lifting/carrying weights over 10 lbs	2.86 (2.80, 2.92)	<0.001
Walking 100m	1.36 (1.33, 1.40)	<0.001
IADL		
Managing money	1.25 (1.20, 1.29)	<0.001
Taking medications	1.13 (1.07, 1.18)	<0.001
Grocery shopping	1.76 (1.71, 1.82)	<0.001
Preparing meals	1.18 (1.14, 1.22)	<0.001
Using the telephone	0.81 (0.78, 0.85)	<0.001
House/garden work	1.57 (1.53, 1.61)	<0.001
ADL		
Walking across the room	1.39 (1.33, 1.44)	<0.001
Dressing	0.98 (0.96, 1.01)	0.22
Bathing	1.47 (1.42, 1.51)	<0.001
Eating	1.28 (1.22, 1.35)	<0.001
Getting in/out of bed	1.39 (1.34, 1.45)	<0.001
Using the toilet	1.62 (1.55, 1.69)	<0.001

[a]Odds ratio derived from logistic models adjusted for sex, age, birth cohort, region, and study. OR > 1 indicates women are more likely than men to report limitation in given activity.

Table 8.3.2. Role of education and labour force status in sex differences in ADL, IADL, and mobility limitations.

	Percent sex difference (95% CI) in probability of functional limitations					
	At age 65		At age 75		At age 85	
	Adjusted for education[a]	Additionally adjusted for labour force status	Adjusted for education[a]	Additionally adjusted for labour force status	Adjusted for education[a]	Additionally adjusted for labour force status
≥1 mobility limitation						
1895-1929	No data	No data	14.6 (13.0, 16.3)	14.3 (12.7, 15.9)	11.1 (9.8, 12.5)	11.9 (10.4, 13.3)
1930-1938	12.1 (10.8, 13.4)	11.3 (10.1, 12.5)	14.0 (12.7, 15.2)	13.6 (12.4, 14.9)	10.4 (9.0, 11.9)	11.0 (9.5, 12.6)
1939-1945	13.1 (12.0, 14.3)	12.2 (11.1, 13.3)	14.8 (13.2, 16.4)	13.9 (12.4, 15.5)	No data	No data
1946-1960	10.5 (9.2, 11.7)	9.3 (8.1, 10.5)	No data	No data	No data	No data
P sex difference by birth cohort	*0.01*	*0.001*	*0.68*	*0.81*	*0.48*	*0.43*
≥1 IADL limitation						
1895-1929	No data	No data	2.6 (1.6, 3.5)	1.7 (1.1, 2.2)	4.8 (3.5, 6.1)	4.3 (3.2, 5.5)
1930-1938	1.4 (0.9, 1.8)	0.8 (0.5, 1.1)	2.6 (1.8, 3.4)	1.7 (1.2, 2.3)	4.5 (3.0, 6.0)	3.8 (2.4, 5.1)
1939-1945	1.8 (1.2, 2.4)	1.0 (0.7, 1.4)	2.9 (1.9, 4.0)	1.8 (1.1, 2.5)	No data	No data
1946-1960	1.5 (0.8, 2.2)	0.8 (0.4, 1.3)	No data	No data	No data	No data
P sex difference by birth cohort	*0.53*	*0.58*	*0.87*	*0.95*	*0.77*	*0.48*
≥1 ADL limitation						
1895-1929	No data	No data	2.1 (1.3, 2.9)	1.4 (0.9, 1.8)	2.9 (1.8, 4.0)	2.4 (1.5, 3.2)
1930-1938	0.9 (0.4, 1.4)	0.6 (0.3, 0.9)	1.3 (0.6, 2.0)	0.8 (0.4, 1.3)	1.4 (0.2, 2.6)	1.1 (0.2, 2.0)
1939-1945	0.4 (-0.2, 0.9)	0.2 (-0.1, 0.6)	0.4 (-0.5, 1.3)	0.2 (-0.4, 0.7)	No data	No data
1946-1960	-0.6 (-1.2, 0.1)	-0.5 (-0.9, -0.1)	No data	No data	No data	No data
P sex difference by birth cohort	*0.003*	*<0.001*	*0.03*	*0.01*	*0.05*	*0.03*

Abbreviations: IADL: Instrumental Activities of Daily Living; ADL: Activities of Daily Living.

[a]Estimates extracted at age 65, 75, and 85 with age analysed as a continuous term; analyses adjusted for sex, birth cohort, and their interactions, marital status, study, region, education. Positive value indicates women are more likely than men to be limited.

Table 8.3.3. Baseline distribution of self-reported chronic conditions in the pooled study population.

	Men	Women	P-value
	N = 27923	**N = 34452**	
High blood pressure, N (%)			
No	17795 (63.7)	21054 (61.1)	*<0.001*
Yes	10128 (36.3)	13398 (38.9)	
Diabetes, N (%)			
No	24674 (88.4)	31140 (90.4)	*<0.001*
Yes	3249 (11.6)	3312 (9.6)	
Cancer, N (%)			
No	26042 (93.3)	31720 (92.1)	*<0.001*
Yes	1881 (6.7)	2732 (7.9)	
Lung disease, N (%)			
No	26162 (93.7)	32564 (94.5)	*<0.001*
Yes	1761 (6.3)	1888 (5.5)	
Psychiatric illness, N (%)			
No	26350 (94.4)	30874 (89.6)	*<0.001*
Yes	1573 (5.6)	3578 (10.4)	
Arthritis, N (%)			
No	20859 (74.7)	21504 (62.4)	*<0.001*
Yes	7064 (25.3)	12948 (37.6)	
Cardiovascular disease,* N (%)			
No	21640 (77.5)	28799 (83.6)	*<0.001*
Yes	6283 (22.5)	5653 (16.4)	

*Heart attack and stroke.

Table 8.3.4. Role of chronic conditions in sex differences in ADL, IADL, and mobility limitations.

	Percent sex difference (95% CI) in probability of functional limitations					
	At age 65		At age 75		At age 85	
	Adjusted for socioeconomic factors[a]	Additionally adjusted for chronic conditions[b]	Adjusted for socioeconomic factors[a]	Additionally adjusted for chronic conditions[b]	Adjusted for socioeconomic factors[a]	Additionally adjusted for chronic conditions[b]
≥1 mobility limitation						
1895-1929	No data	No data	14.3 (12.7, 15.9)	13.5 (12.1, 14.9)	11.9 (10.4, 13.3)	13.2 (11.7, 14.6)
1930-1938	11.3 (10.1, 12.5)	9.8 (8.7, 10.9)	13.6 (12.4, 14.9)	11.0 (10.0, 12.0)	11.0 (9.5, 12.6)	11.4 (9.7, 13.0)
1939-1945	12.2 (11.1, 13.3)	8.9 (8.0, 9.8)	13.9 (12.4, 15.5)	9.7 (8.4, 10.9)	No data	No data
1946-1960	9.3 (8.1, 10.5)	6.1 (5.2, 7.0)	No data	No data	No data	No data
P sex difference by birth cohort	*0.001*	*<0.001*	*0.81*	*<0.001*	*0.43*	*0.11*
≥1 IADL limitation						
1895-1929	No data	No data	1.7 (1.1, 2.2)	1.2 (0.8, 1.6)	4.3 (3.2, 5.5)	3.6 (2.7, 4.5)
1930-1938	0.8 (0.5, 1.1)	0.5 (0.3, 0.6)	1.7 (1.2, 2.3)	0.8 (0.5, 1.0)	3.8 (2.4, 5.1)	2.4 (1.4, 3.3)
1939-1945	1.0 (0.7, 1.4)	0.3 (0.1, 0.5)	1.8 (1.1, 2.5)	0.5 (0.2, 0.7)	No data	No data
1946-1960	0.8 (0.4, 1.3)	0.2 (0.1, 0.4)	No data	No data	No data	No data
P sex difference by birth cohort	*0.58*	*0.28*	*0.95*	*0.01*	*0.48*	*0.02*
≥1 ADL limitation						
1895-1929	No data	No data	1.4 (0.9, 1.8)	0.8 (0.5, 1.1)	2.4 (1.5, 3.2)	1.4 (0.8, 1.9)
1930-1938	0.6 (0.3, 0.9)	0.2 (0.0, 0.4)	0.8 (0.4, 1.3)	0.2 (-0.0, 0.4)	1.1 (0.2, 2.0)	0.2 (-0.2, 0.7)
1939-1945	0.2 (-0.1, 0.6)	-0.2 (-0.3, 0.0)	0.2 (-0.4, 0.7)	-0.2 (-0.4, -0.0)	No data	No data
1946-1960	-0.5 (-0.9, -0.1)	-0.4 (-0.5, -0.2)	No data	No data	No data	No data
P sex difference by birth cohort	*<0.001*	*<0.001*	*0.01*	*<0.001*	*0.03*	*<0.001*

Abbreviations: IADL: Instrumental Activities of Daily Living; ADL: Activities of Daily Living.

[a]Estimates extracted at age 65, 75, and 85 with age analysed as a continuous term; analyses further adjusted for sex, birth cohort, and their interactions, marital status, study, region, education, and labour force status. [b]Additionally adjusted for high blood pressure, diabetes, cancer, lung disease, psychiatric illness, arthritis, and cardiovascular disease (heart attack, stroke). Positive value indicates women are more likely than men to be limited.