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Rozdíly mezi muži a ženami ve vlivu rizikových faktorů na kognitivní stárnutí

Sex differences in risk factors for cognitive aging

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Foreword

In the contemporary world, a new patient is diagnosed with dementia every three seconds, most commonly with dementia due to Alzheimer´s disease. Most of these patients are females. As advanced age is the strongest risk factor, many believe that females receive the diagnosis of dementia simply because they live longer. However, recent literature suggests this explanation oversimplifies the problem.

Research has emphasized the importance of adopting a life course perspective when examining the social and biological determinants of dementia and accelerated cognitive aging. Throughout their lives, females and males encounter distinct experiences related to education, occupation, reproduction, and mental health. It raises the question whether the adverse effects of socioeconomic adversity during upbringing might have a greater impact on females' brains compared to males, as subsequent opportunities may not have mitigated childhood disadvantages. Or whether sex-specific effects of reproductive histories, such as the number of children one has parented, help explain the unequal rate of cognitive decline between females and males. Or perhaps whether sex differences in the occurrence of affective and behavioral problems in later life (recently framed as mild behavioral impairment) might shed light on the different patterns of cognitive aging.

I explore these questions in the present thesis, taking the perspective of the discipline of epidemiology, being interested in the potential to prevent cognitive decline while targeting risk factors earlier in life. As high sample sizes are necessary to discover small effects and long-term follow-up is needed to detect changes in the patterns of cognitive aging, I perform my investigations using established large international epidemiological cohorts with already collected data and long follow-up.

In all samples used in this thesis, respondents were asked to report their sex. However, I acknowledge limitations related to self-reported sex as it is difficult to disentangle if the participants reported their sex (male, female) or their gender (man, woman). Throughout this thesis, I use the terms sex, males, and females, taking into account the limitation that with the current methodology, I am not able to distinguish well between sex and gender.

This thesis is a commentary to five individual studies. At the time of the thesis submission, three have been published and two were under review. I have performed my studies jointly with my colleagues in the US, particularly at Columbia University, and in the UK, especially

Recent studies are optimistically pointing out that the incidence of dementia is declining, at least in high income countries. To achieve even a greater decrease in the incidence, I believe we need greater understanding of what drives the inequalities in cognitive aging between males and females to design efficient preventive strategies.

Abbreviations

AD	Alzheimer's disease
ACT	Adult Changes in Thought
APOE4	Apolipoprotein ε4
BMI	Body mass index
CI	Confidence interval
CES-D	Center for Epidemiological Studies-Depression Scale
CSF	Cerebrospinal fluid
HR	Hazard ratio
HRS	Health and Retirement Study
IADL	Instrumental activities of daily living
IQR	Interquartile range
LR	Likelihood ratio
MBI	Mild behavioral impairment
NPS	Neuropsychiatric symptoms
PET	Positron emission tomography
PROTECT	Platform for Research Online to Investigate Genetics and Cognition in Aging
SD	Standard deviation
SEP	Socioeconomic position
SHARE	Survey of Health, Ageing and Retirement in Europe
UK	United Kingdom
US	United States

WHO   World Health Organization

Abstract

Background: The unequal distribution of social and health-related factors throughout the life course may lead to sex differences in dementia risk and cognitive aging. The aim of this thesis is to provide greater understanding of what drives the inequalities in cognitive aging between males and females. Specifically, we aimed to investigate sex differences in the rate of cognitive decline in European older adults (Study 1), in the association between childhood socioeconomic position and cognition (Study 2), number of children and risk of dementia (Study 3a), offspring sex and cognitive decline (Study 3b), and mild behavioral impairment and cognition (Study 4).

Methods: We performed five cohort studies using four cohorts of middle-aged and older adults residing in 21 countries across Europe, in Israel, and the United States. We sourced our data from the Survey of Health, Ageing and Retirement in Europe in Study 1 and Study 2, from the US Health and Retirement Study in Study 3a, from the US Adult Changes in Thought Study in Study 3b, and from the British Platform for Research Online to Investigate Genetics and Cognition in Aging in Study 4. Cognition was measured by tests on immediate recall, delayed recall and verbal fluency in Study 1 and Study 2, by immediate recall, delayed recall, serial 7s subtraction, and backwards counting tests in Study 3b, and by digit span, paired associate learning, self-ordered search, and verbal reasoning tests in Study 4. Dementia was diagnosed by a panel consensus based on DSM IV criteria in Study 3a. We used linear regression models, linear mixed-effects models, and Cox models in our analyses.

Results: In Study 1, the rate of cognitive decline in immediate recall (interaction sex × time: B=0.002; 95% CI -0.001 to 0.006), delayed recall (interaction sex × time: B=0.000; 95% CI -0.004 to 0.004), or verbal fluency (interaction sex × time: B=0.007; 95% CI -0.005 to 0.020) was similar for males and females. However, when birth cohort and regional differences were considered, the rate of cognitive decline varied by sex. In Study 2, higher childhood socioeconomic position was associated with higher baseline cognition in both sexes, but to a larger extent in females (B=0.238; 95% CI 0.203 to 0.271) compared to males (B=0.208; 95% CI 0.180 to 0.235). Childhood socioeconomic disadvantage was associated with a higher rate of decline in delayed recall to a greater extent in females (B=-0.023; 95% CI -0.035 to -0.011) compared to males (B=-0.018; 95% CI -0.032 to -0.005). In Study 3a, fathers of four or more children had higher rates of dementia compared to fathers of two children (HR=1.317; 95% CI 1.014 to 1.710), while we did not find any differences in rates of dementia in females. In Study 3b, we found a faster rate of cognitive decline in parents of at least one son (B= -0.015; 95% CI -0.029 to -0.002) compared to those without any sons, without any notable differences between sexes. In Study 4, mild behavioral impairment syndrome was associated with a lower level of paired associate learning score only in males (B=-0.158; 95% CI -0.245 to -0.072).

Discussion: Our findings suggest that there are nuanced variations in cognitive aging across different populations and birth cohorts, with potential differences between males and females. Our studies show that females and males are differentially impacted by early-life, midlife

and later life risk factors. Future studies should not omit the importance of sex variations in the relationship between risk factors and cognitive aging.

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1   Background

1.1   Population aging and cognitive aging

Life expectancy is projected to increase in many countries across the world. Estimates suggest that female's life expectancy in well-developed countries might reach the 90-year threshold by 2050 (Kontis, Bennett et al. 2017). Even though increased expected lifespan is a major success of public health efforts, population aging brings new challenges. One of the most important consequences is increasing prevalence of age-related diseases and syndromes, including declining cognitive functions, which may in some individuals result in the syndrome of dementia. It is estimated that there will be 152 million people living with dementia worldwide by 2050 (GBD 2019 Dementia Forecasting Collaborators 2022). These public health projections highlight the need to better understand the risk and protective factors related to dementia.

It is important to note that the projected increase in dementia prevalence is due to population aging, as advancing age is the most important risk factors for dementia (Niccoli and Partridge 2012). However, epidemiologic studies from the United States (US) and Western Europe suggest that incidence of dementia across successive birth cohorts has been declining (Rocca, Petersen et al. 2011, Schrijvers, Verhaaren et al. 2012, Satizabal, Beiser et al. 2016, Wu, Fratiglioni et al. 2016, Wu, Beiser et al. 2017, Seblova, Quiroga et al. 2018). It is not fully elucidated, which changes in societal and health-related factors this decreasing trend reflects. Researchers have hypothesized that decreasing dementia incidence might be driven by improvements in cardiovascular health, education or early-life conditions, but studies that accounted for these factors failed to fully explain the declining trend (Derby, Katz et al. 2017, Tom, Phadke et al. 2020).

Cognitive aging is characterized by decline in cognitive functions that encompass several cognitive domains, such as attention, verbal reasoning, memory, processing speed or visuospatial abilities (Harada, Natelson Love et al. 2013). When the cognitive decline reaches a point severe enough to interfere with a person's daily life and activities, a diagnosis of dementia can be made (Arvanitakis, Shah et al. 2019). Dementia is an umbrella term describing the clinical syndrome of cognitive impairment that may be caused by a wide range of distinct underlying pathologies. There is an ongoing scientific debate on whether cognitive decline related to age and cognitive impairment are two separate entities, with the first one

being a part of normal aging and the second one a result of a disease, or whether they represent one process along a continuum over time (Crimmins, Kim et al. 2011).

1.2 Dementia and underlying pathologies

Alzheimer's disease (AD), the leading cause of dementia, is estimated to account for 50% to 70% of dementia cases, two-thirds of which are females (Qiu, Kivipelto et al. 2009). Originally, when Alois Alzheimer described AD for the first time, AD diagnosis was based purely on neuropathological findings of amyloid plaques and neurofibrillary tangles, which are a result of accumulation of abnormally folded amyloid β protein and of hyperphosphorylated tau protein, respectively (Scheltens, De Strooper et al. 2021). Later, in clinical research settings, the diagnosis of AD shifted from a pathological to a clinical to a combined clinical and biological approach (Scheltens, Blennow et al. 2016). In 2018, the National Institute on Aging and Alzheimer's Association created a new research framework that defines AD solely based on biological biomarkers grouped into three categories: 1) aggregated amyloid β or associated pathologic state, such as concentration of cerebrospinal fluid amyloid (CSF) β42 or amyloid β42/amyloid β40 ratio (markers of amyloidosis) and amyloid positron emission tomography (PET), 2) aggregated tau or associated pathologic state such as concentrations of CSF phosphorylated tau and tau PET, and 3) signs of neurodegeneration detected by anatomic magnetic resonance imaging, and CSF total tau (Jack, Bennett et al. 2018).

The original amyloid hypothesis of AD etiology proposed a linear disease model, implying that amyloid β is the key cause of neurodegeneration, which leads to clinical symptomatology, and assuming that the occurrence of neurofibrillary tangles and vascular damage is a result of amyloid β deposition (Hardy and Higgins 1992). This hypothesis of a simple linear pathway between amyloid β and AD has been challenged as the complexity of multiple causes of dementia is becoming more apparent (Schneider, Arvanitakis et al. 2007, Herrup 2015, Scheltens, Blennow et al. 2016, Selkoe and Hardy 2016). Despite an ongoing debate about the etiology of AD, it is well established that many social, behavioral and health-related factors contribute to increased lifetime AD risk.

According to the current estimates, risk factors such as hypertension, diabetes, obesity, physical and mental inactivity, depression, smoking, alcohol consumption, low educational attainment, and poor diet together have the potential to decrease the risk of dementia by 40% (Livingston, Huntley et al. 2020). Even though AD is more frequent among females, little research has

focused on sex differences in the association between these factors and risk of dementia (Mielke 2018). The most important genetic risk factor of AD is apolipoprotein ε4 (APOE4) allele, with APOE4 homozygotes having 50% lifetime risk for AD. Interestingly, females with APOE4 alleles are at greater risk of AD than males that are carriers of this allele (Altmann, Tian et al. 2014). One possible explanation is that APOE4 is regulated by sex hormones, which might lead to a stronger effect of APOE4 on cellular processes related to neurodegeneration in females (Gamache, Yun et al. 2020).

The second most common type of dementia is vascular dementia (Iadecola, Duering et al. 2019). Vascular dementia is caused by diverse conditions that affect cerebral blood vessels and result in a wide range of underlying pathologies, including multiple lacunar infarcts, white matter lesions, strategic infarcts, hypoperfusion with watershed infarcts, and hemorrhagic lesions, (O'Brien and Thomas 2015). The combination of amyloid plaques and neurofibrillary tangles with vascular pathologies is often referred to as AD with cardiovascular disease (O'Brien and Thomas 2015). Some researchers have been arguing that this type of dementia, also called mixed dementia, is the most common type, especially among the oldest adults (Schneider, Arvanitakis et al. 2007). Although vascular risk factors, such as hypertension or myocardial infarction, occur more frequently among males, consequences of cerebrovascular disease tend to be more severe in females, which might be due to longer survival of females or due to differences in the distribution and management of risk factors resulting in different underlying pathologies (Appelros, Stegmayr et al. 2009). For example, some studies suggest that the prevalence of atrial fibrillation, a modifiable risk factor for cerebrovascular diseases, is higher in females with stroke than in males with stroke (Roquer, Campello et al. 2003, Schnabel and Benjamin 2018).

Other types of dementia are frontotemporal dementia, and Lewy bodies dementia. Frontotemporal dementia is estimated to be the second or third most common type of dementia in patients with early onset (age < 65 years) (Vieira, Caixeta et al. 2013). Frontotemporal dementia encompasses several neurodegenerative diseases that share the main clinical features, especially deficits in behavior, executive function, and language (Bang, Spina et al. 2015). Clinical classification distinguishes between three variants: behavioral-variant frontotemporal dementia, non-fluent variant primary progressive aphasia, and semantic-variant primary progressive aphasia. Neuropathologically, frontotemporal dementia is characterized by neuronal loss, gliosis, and microvacuolar changes, and the predominantly affected brain areas are frontal lobes, anterior temporal lobes, anterior cingulate cortex, and insular cortex

(Bang, Spina et al. 2015). Previous studies have reported higher prevalence of behavioral-variant frontotemporal dementia in males than females, and possibly better ability of females to cope with neuropathological changes related to frontotemporal dementia (Illán-Gala, Casaletto et al. 2021).

Many researchers now consider Lewy bodies dementia as an umbrella term that encompasses two clinical syndromes - dementia with Lewy bodies and Parkinson´s disease dementia (Walker, Possin et al. 2015). These two entities share the same pathophysiology but differ in the sequence of the onset of clinical symptoms of dementia and parkinsonism. Both dementia with Lewy bodies and Parkinson´s disease dementia are more common among older patients, but their onset before the age of 65 is not rare. The prevalence of dementia among patients with Parkinson's disease is estimated to be around 25% (Aarsland, Zaccai et al. 2005), and most patients with Parkinson's disease with longer survival will eventually develop dementia (Williams-Gray, Mason et al. 2013). Both dementia with Lewy bodies and Parkinson´s disease dementia are more prevalent in males than females (Walker, Possin et al. 2015).

Other less frequent causes of dementia are Huntington disease, multisystem atrophy, and Creutzfeldt-Jakob disease (Arvanitakis, Shah et al. 2019). Even though most of the cases of dementia are caused by a disease affecting primarily the brain, dementia might also develop secondarily because of another condition, such as infections, metabolic and endocrine conditions or vitamin deficiencies (Arvanitakis, Shah et al. 2019).

1.3   Treatment and prevention

Dementia is one of the major causes of disability among older adults worldwide and, although currently no cure exists, the increasing prevalence leads to financial burden related to direct as well as indirect costs for treatment and care (Deb, Thornton et al. 2017). Only until recently, the only available treatment of AD consisted of acetylcholinesterase inhibitors donepezil, rivastigmine and galantamine, and the antagonist of glutamate N-methyl-D-aspartate receptors memantine (Scheltens, De Strooper et al. 2021). In 2022, The Food and Drug Administration in the US approved for the treatment of AD an amyloid β-directed antibody called aducanumab (manufactured by Biogen under the brand name Aduhelm) (Budd Haeberlein, Aisen et al. 2022). Nevertheless, this treatment is only disease modifying, meaning that it might slow down the progression of the disease, but it does not lead to clinical improvements beyond the cognitive level at the time of the start of the treatment (Yang and Sun 2021).

On the other hand, the existence of potentially modifiable risk factors has raised a question whether the onset of cognitive decline and dementia can be delayed. There is consensus that the most common dementia types are likely preventable (Ranson, Rittman et al. 2021). Perhaps due to the improvements of cardiovascular health and better socioeconomic conditions (Livingston, Huntley et al. 2020), the incidence of dementia is declining in high income countries (Wu, Fratiglioni et al. 2016, Wu, Beiser et al. 2017). This notion is considered enough to envision global strategies to reduce dementia risk (Altomare, Molinuevo et al. 2021). In 2019, World Health Organization (WHO) published guidelines for the "*Risk reduction of cognitive decline and dementia*" (World Health Organization 2019). However, the quality of evidence in the WHO guidelines was deemed from very low to moderate for most proposed interventions (World Health Organization 2019).

Overall, there is a lack of experimental evidence that cognitive decline and dementia are indeed preventable. Specifically, among all randomized controlled trials on multi-domain interventions, which target multiple risk factors simultaneously, only the FINGER study met its primary outcome, showing greater cognitive improvement in participants of the experimental group versus controls (Ngandu, Lehtisalo et al. 2015). On the contrary, other trials such as MAPT, preDIVA, Look AHEAD, and DO-HEALTH failed to meet their primary outcomes (Altomare, Molinuevo et al. 2021). These trials have three main limitations: possible reverse causation, unmeasured confounding, and wrong target population. Thus, research of underlying pathways that lead to cognitive impairment and their preventive potential is much needed. These pathways might be primarily biological in nature but also might be driven by a wide range of social factors.

1.4   Cognitive reserve

In the late 1980, several studies described post-mortem presence of AD pathology in brains of individuals who had not exhibited any symptoms of dementia during their lives (Crystal, Dickson et al. 1988, Katzman, Terry et al. 1988). To explain these seemingly discrepant findings, concepts of brain reserve, cognitive reserve, and brain maintenance were proposed (Stern, Arenaza-Urquijo et al. 2020). These frameworks aim to describe possible mechanisms of resilience against neuropathological changes. Brain reserve is a macroscopic construct that refers to the number of neurons or synapses at any point in time, while brain maintenance

refers to the relative absence of changes in these quantitative neural resources (Stern, Arenaza-Urquijo et al. 2020).

On the other hand, cognitive reserve depends more on the ability of the brain to function properly regardless of morphological resources. It is defined as a property of human brain that allows for higher cognitive performance than what is expected considering the degree of brain neuropathological changes (Stern, Arenaza-Urquijo et al. 2020).The potential underlying mechanism might operate on molecular, cellular and/or network levels (Stern, Arenaza-Urquijo et al. 2020). The concept of cognitive reserve explains how social factors, such as socioeconomic or family constellations, which operate throughout the life course, might influence an individual's ability to cope with brain injury. It is hypothesized that cognitive reserve can be increased by environmental enrichment and various cognitively stimulating experiences (Stern 2009).

For example, many epidemiologic studies have observed that individuals with higher educational attainment are better able to cope with brain pathologies (Stern 2009). Similarly, individuals with intellectually stimulating occupations or those who participate in more cognitively stimulating leisure activities have more robust cognitive reserve that allows them to better tolerate brain damage (Stern 2012). These factors that enhance cognitive reserve are attained at various stages of life and their distribution across individual population groups is uneven. This variability in social, economic, and cultural structures has been suggested to contribute to inequalities in cognitive aging across countries, socioeconomic groups and sexes (Prince, Acosta et al. 2012, Subramaniapillai, Almey et al. 2021).

1.5 Sex differences in dementia and cognitive decline

Distribution of dementia in the population is unequal, affecting females to a much larger extent than males (Gao, Hendrie et al. 1998, Winblad, Amouyel et al. 2016). Almost two-thirds of patients living with AD are females, but the higher burden of cognitive disorders in females cannot be explained only by females' longer survival (van der Flier and Scheltens 2005). Some studies conducted on European cohorts suggest that females have also higher incidence of AD, particularly at very old ages (Fratiglioni, Viitanen et al. 1997, Andersen, Launer et al. 1999, Beam, Kaneshiro et al. 2018). On the other hand, studies conducted in the US mostly report no sex differences in incidence of AD and dementia (Edland, Rocca et al. 2002, Manly, Jones et al. 2022). Evidence from developing countries is largely lacking, as well as cross-country

comparisons that would explore the role of differential selective survival and variance in sex-related risk factors.

While evidence on sex differences in the level of cognitive function observed in cross-sectional studies is relatively consistent, the differences in the rate of cognitive decline are less clear. Most of the previous literature shows that females outperform males in verbal tasks at baseline, whereas males perform better in visuospatial domains (Kramer, Yaffe et al. 2003, Siedlecki, Falzarano et al. 2019). While a systematic review of prospective studies published between 2001 and 2011 found no sex differences in cognitive decline in the period between 60 to 80 years of age (Ferreira, Ferreira Santos-Galduróz et al. 2014), some more recent studies show a faster cognitive decline in females than males (McCarrey, An et al. 2016, Levine, Gross et al. 2021, Nooyens, Wijnhoven et al. 2022). However, these findings are contradicted by two studies from the United Kingdom (UK), which show slower decline in memory, executive function, and global cognition in females than males (Zaninotto, Batty et al. 2018, Bloomberg, Dugravot et al. 2021).

It should be noted that sex differences in cognition are not a case of sexual dimorphism, meaning that these differences have been observed in group averages and do not apply to all studied individuals. Furthermore, some studies suggest that the magnitude of differences is not consistent across countries and there might be a temporal effect. For example, sex differences in cognitive functions varied systematically across birth cohorts and European regions and were influenced by changes in living conditions and greater educational opportunities for males (Weber, Skirbekk et al. 2014).

Moreover, reported inconsistencies might be a result of methodological differences, selection into individual studies, use of different measures of cognition or length of follow up. Furthermore, the impact of birth cohort and regions on sex differences in cognitive decline suggests that the relationship between sex and cognition is likely complex, and a multitude of modifiable risk and protective factors operating throughout the whole life course may contribute to these differences. These factors may 1) not be equally distributed among sexes, 2) be sex-specific, or 3) have a stronger effect in one sex (Mielke 2018). In other words, sex may act as a confounder when sex is associated with both the risk or protective factor and dementia, or sex may play role as an effect modifier, meaning that the effect of an individual risk factor on dementia varies across strata of sex (Vander Weele 2012).

1.6   Childhood socioeconomic position and cognition

To better understand the beginning of the process of aging, researchers have proposed to study early life experiences. A growing body of evidence suggests that the roots of non-communicable diseases in older age may lie in childhood social and economic circumstances. For example, a wide range of indicators of poor socioeconomic position (SEP), such as low income, poor housing conditions or low parental educational attainment, have been found to be associated with unfavorable later life health outcomes including increased mortality and worse cardiovascular health (Claussen, Davey Smith et al. 2003, Lehman, Taylor et al. 2009). Similarly, cognitive health in older adulthood might be shaped by early childhood experiences.

Findings from a large population-based study from Europe show that older people who were growing up in disadvantaged socioeconomic circumstances had faster cognitive decline in comparison to those with better childhood socioeconomic circumstances (Aartsen, Cheval et al. 2019). Another European study did not find an association with steeper cognitive decline, but lower childhood socioeconomic status was related to lower cognitive functions measured at baseline (Cermakova, Formanek et al. 2018). These studies differed in methodology, particularly in the inclusion of participants from different countries and in the way SEP was operationalized. Another study from the United States (US) reported a positive association between disadvantaged early life conditions and increased risk of subsequent AD (Moceri, Kukull et al. 2000).

Studies of other health outcomes suggest that experiencing socioeconomic adversity in childhood might impose disproportionately stronger consequences on the health of females than males. For example, females who were growing up in disadvantaged conditions during childhood have been found to be at higher risk of obesity and to have steeper systolic and diastolic blood pressure slopes in middle age in comparison to males (Janicki-Deverts, Cohen et al. 2012, Wagner, Bastos et al. 2018). Several researchers have hypothesized that sex acts as an effect modifier also in the relationship between early life experiences and brain health outcomes.

While findings from some studies on how early life stress impacts cognition in animal models support this hypothesis, evidence from human studies is mixed (Marco, Valero et al. 2013, Wang, Ma et al. 2016). In previous literature, researchers have consistently reported that exposure to early-life stressors, including socioeconomic hardship, causes a dysregulation of hypothalamic-pituitary-adrenal axis (Winchester, Sullivan et al. 2016). Importantly,

exposure to increased stress hormone levels disrupts maturation of the brain and this effect varies by sex. Sandman et al. found that exposure to stress was more strongly associated with less cortical thickness in girls than boys (Sandman, Curran et al. 2018). It is plausible that the relationship between early life stress and neural correlates translates to cognitive functioning.

On the other hand, a few studies of older adults show an opposite direction of effect modification by sex. Hurst et al. investigated the influence of childhood SEP on nine markers of physical and cognitive functioning in a cohort of British older adults (Hurst, Stafford et al. 2013). Although the reported difference between sexes was small in magnitude, they found that the effect of lower childhood socioeconomic status on longer reaction time was stronger in males than females. Other study from the US found a similar relationship. Poor childhood SEP was more strongly associated with lower level of memory in males than females (Lyu 2015). While the mechanisms thus far examined suggest that sex is an effect modifier in the relationship between early socioeconomic adversity and later life cognition, the underlying pathways are likely complex and evidence from previous studies is inconclusive.

1.7   Reproductive history

1.7.1   *Number of children*

A growing body of evidence suggests that males' and females' reproductive history may influence post-reproductive health outcomes. Many previous studies have documented a consistent J- or U- shaped relationship between number of children and later life health outcomes such as mortality or cardiovascular diseases in both females and males (Lv, Wu et al. 2015, Zeng, Ni et al. 2016), showing that childless individuals and parents of many children have worse health outcomes in comparison to parents of two children. Several more recent studies have shown a similar pattern in the relationship between measures of reproductive history and cognitive outcomes, although the results are inconsistent (Read and Grundy 2017, Keenan and Grundy 2019, Bae, Lipnicki et al. 2020, Harville, Guralnik et al. 2020, Ning, Zhao et al. 2020, Saenz, Díaz-Venegas et al. 2021, Zhang and Fletcher 2021, Gemmill and Weiss 2022). Many of the studies have focused solely on females (Bae, Lipnicki et al. 2020, Bae, Lipnicki et al. 2020, Harville, Guralnik et al. 2020, Jung, Lee et al. 2020, Yoo, Shin et al. 2020), but some have examined the relationship between number of children and cognition also

in males (Read and Grundy 2017, Saenz, Díaz-Venegas et al. 2021, Gemmill and Weiss 2022). In addition, studies of females often examine parity, i.e., the number of children ever born to a female, rather than number of children regardless of whether they are biological, adopted or stepchildren, thus potentially missing an important social aspect of parenting.

These studies on reproductive history and cognition that have to a large extent focused only on females argue that the biological effects of the number of pregnancies a female experiences might impose long-lasting effects on maternal cognition. For example, physiological decrease in vascular resistance during pregnancy induces a drop in blood pressure level that lasts for decades after delivery and might have protective effect on cognition (Haug, Horn et al. 2018). On the other hand, many pregnancies are complicated by hypertensive disorders of pregnancy or gestational diabetes, conditions that are more prevalent in multiparas likely due to advanced maternal age, and that may negatively influence later-life cognition (Adank, Hussainali et al. 2021, Yee, Miller et al. 2022). Another hypothesis is that lifelong exposure to endogenous estrogens, a factor that is influenced by the number of pregnancies, might have beneficial effects on maternal cognition (Matyi, Rattinger et al. 2019). It is important to note that other factors, such as socioeconomic circumstances, are related to indicators of reproductive history as well as to cognitive outcomes, and previous studies mostly don't account for these potential confounders (Peterson and Tom 2021).

Research using data on females aged 60 years or older from 11 countries from Europe, Asia and South America found that grand multiparity (giving birth to five or more children) was associated with increased risk of dementia, when compared to primiparity (giving birth to one child) (Bae, Lipnicki et al. 2020). This prospective study examined the relationship only among females and their biological children and showed no association with nulliparity (not giving birth to any children) and risk of dementia. Gemmill & Weiss reported similar findings based on data from a population-based cohort in the US. They have documented that having three or more children was associated with higher risk of dementia in both males and females, but this association diminished after adjustment for sociodemographic and health-related covariates in both sexes (Gemmill and Weiss 2022). Another prospective study of females based on registry data from Korea came to a different conclusion. Compared to females who have no children, females with one child had lower risk of dementia, while females with two children had higher risk of dementia (Yoo, Shin et al. 2020).

In addition, studies that examined cognitive functions measured by validated tests also show some inconsistencies. Findings from a cross-sectional Bogalusa Heart Study of relatively younger females (mean age 48 years) observed that nulliparous females scored lower on cognitive tests that measure memory and attention, while higher parity was not associated with any of the measures (Harville, Guralnik et al. 2020). A multinational population-based study of both males and females enrolled in the Survey of Health, Aging and Retirement in Europe (SHARE) found that, compared to parents of two children, both mothers and fathers of four or more children and childless females and males score lower in cognitive tests such as verbal fluency, immediate recall, delayed recall, orientation and numeracy (Bordone and Weber 2012, Keenan and Grundy 2019). Another cross-sectional study of males and females from the UK Biobank found that being childless was associated with worse visual memory and slower response time in both females and males. In addition, parents of two or three children had reduced brain age relative to those who were childless, with greater effects observed in males (Ning, Zhao et al. 2020).

Utilizing data from the US National Health and Aging Trends Study, Zhang & Fletcher found that having at least one living adult child was associated with lower risk of cognitive impairment for older males and females. Those who had three and more children, who had adult daughter(s), and who had biological/adopted adult children had significantly lower risk of cognitive impairment (Zhang and Fletcher 2021). Another study from the UK provides somewhat contrary findings. Read & Grundy reported that parents of three or more children, regardless of parental sex, had poorer cognitive functioning in immediate recall, delayed recall, and verbal fluency compared to parents of two children, but this relationship ceased to exist after adjustment for socioeconomic variables (Read and Grundy 2017). They have also found that while childlessness in males was related to lower SEP in males, but not in females, both childless males and females had worse cognition in comparison to parents of two children. This association weakened in males but strengthened in females after adjustment for additional covariates.

While most previous studies come from Western countries, a few have examined this relationship in less developed regions and suggest the importance of country-specific context. Results from the Mexican Health and Aging show that, regardless of sex, having six or more children (compared to having two-three children) is associated with poorer cognitive functioning, even after adjustment for socioeconomic, health, employment, and psychosocial factors, but childlessness was associated with worse cognition only among females (Saenz,

Díaz-Venegas et al. 2021). Grand multiparity was found to be associated with worse cognition also among older adults from China, with a stronger effect in females (Yang, Zhang et al. 2022). Findings of worse cognitive outcomes among grand multiparous females are further supported by studies of neurobiological correlates. For example, Jung et al. has documented reduced adjusted hippocampal volume, spatial pattern of atrophy for recognition of AD volume and spatial pattern of atrophy for recognition of brain aging volume in grand multiparous females. Neuropathological hallmarks of AD were found in females with more children, but not in males.

These inconsistencies might be due to many reasons, including differences in methodology and data sources. For example, some studies include only biological children, while other don't differentiate between biological, adopted and stepchildren. Inconsistencies might arise when dementia diagnosed by a physician is used as the outcome in comparison to cognition measured by tests. Also, the set of covariates differs substantially, with some studies accounting for a wide range of socioeconomic factors and other studies focusing on health-related covariates. In addition, findings might depend on socioeconomic and cultural context of the country of origin and on timing of data collection. While some regions are more egalitarian and provide relatively equal opportunities for males and females, educational and occupational opportunities for females in many countries might be sparser. Educational attainment and financial stability are closely related to fertility as well as later-life cognitive health.

1.7.2 *Offspring sex*

Another aspect of parenting that might further influence cognition is offspring sex. Previous studies that have focused on mortality and cardiovascular health have found that parents of sons have worse later-life outcomes (Hurt, Ronsmans et al. 2006, Næss, Mortensen et al. 2017). Some studies of offspring sex and brain health outcomes are limited by inclusion of only females. For example, a study of pregnant mothers found that those with male foetuses score higher in working memory and spatial ability tests in comparison to mothers pregnant with female foetuses (Vanston and Watson 2005). It is not known for how long after delivery this effect persists and whether the effect of parenting boys versus daughters is the same in both males and females.

Similar reasoning has been proposed in studies of offspring sex and maternal health outcomes. Some studies suggest sexually dimorphic reactions of maternal placenta, which leads to greater maternal microvascular vasodilatation in pregnancies with boys (Gabory, Roseboom et al. 2013). However, long-term persistence of the differences in cardiovascular reactivity between mothers of sons and daughters has not been studied. Another possible pathway that links pregnancy and brain health outcomes might operate through microchimerism of foetal origin. A small number of foetal cells, genetically distinct from maternal cells, are incorporated in maternal tissues, including brain, and can be found in these tissues decades after delivery (Johnson, Ehli et al. 2020). Exposure to antigens from foetal male cells have been suggested to be associated with longer maternal survival, decreased risk of cancer, and reduced rate of maternal ischemic heart disease (Gadi and Nelson 2007, Cirello and Fugazzola 2014, Kamper-Jørgensen, Hjalgrim et al. 2014, Hallum, Gerds et al. 2020). Chan et al. found decreased prevalence of dementia related pathology in females with present male microchimerism in their brains (Chan, Gurnot et al. 2012).

Although males have received much less attention, some studies have included females as well as males in their analytic sample and show that also childless males and males with many children have worse cognitive outcomes in comparison to fathers of two children. These findings suggest that social aspects of parenting may play a role in later-life cognitive outcomes. Furthermore, parenting boys versus girls might shape parents' lives in different ways. For example, previous studies suggest that parents of boys are less likely to divorce and being married has a protective effect on later-life cognition (Liu, Zhang et al. 2019, Kabátek and Ribar 2020). On the other hand, daughters become informal caregivers more often than sons, thus they provide more social support to their parents in later life, which might protect them from cognitive decline (Friedman, Shih et al. 2015, Cascella Carbó and García-Orellán 2020, Costa-Cordella, Arevalo-Romero et al. 2021). Also, parents of daughters were found to be less often smokers and consumers of alcohol or drugs (Powdthavee, Wu et al. 2009). Parenting experiences likely differ between males and females, but studies that would examine these differences and the effect on parental health behavior are lacking.

The mechanism, by which childbearing and childrearing influences cognition, are likely complex, may consist of both biological and social pathways, and may have different implications for males and females. Replicating previous findings across populations with inclusion of indicators of both socioeconomic and health related factors may provide

a better understanding of the extent to which reproductive history is associated with cognition in later life.

1.8 Neuropsychiatric symptoms in later life

Males and females differ not only in the prevalence and incidence of dementia, but also in severity and presentation of symptoms (Mielke, Vemuri et al. 2014). Sex differences are not limited only to cognitive aspects of the disease but are present also in neuropsychiatric symptoms (NPS), including apathy, depression, hallucinations, delusions, agitation, or aggression. Even though NPS are waxing and waning, they represent a source of burden for caregivers and are often a reason for institutionalization (Okura, Plassman et al. 2011). Current guidelines largely emphasize the importance of non-pharmacologic managements such as avoidance of triggers, treatment of underlying medical conditions, or discontinuation of certain medicine (Kales, Gitlin et al. 2014, Reus, Fochtmann et al. 2016).

Distribution of types of dementia is not equal across sexes, but also individual NPS associated with different types of dementia are not distributed equally between sexes. For example, a recent meta-analysis reported higher prevalence and severity of depression among females with AD, a type of dementia more common in females than males, whereas males with AD experienced more severe forms of apathy (Eikelboom, Pan et al. 2022). While psychotic symptoms are present in around 30% of patients with AD, they occur in around 50% of patients with Parkinson's disease dementia and dementia with Lewy bodies, types of dementia more prevalent in males (Nelson, Schmitt et al. 2010, Smith and Dahodwala 2014, Martin and Velayudhan 2020). While several prior studies have focused on sex differences in frequency, type, and severity of NPS among patients with dementia, less attention has been paid to behavioral and psychiatric symptoms that precede cognitive decline.

Because NPS have been increasingly recognized as an important consequence of neuropathologic changes, researchers developed a concept of mild behavioral impairment (MBI). MBI helps to detect cognitively healthy individuals who are at higher risk of developing subsequent dementia based on a persistent personality and behavior change. MBI is a syndrome characterized by the emergence of new NPS later in life, namely apathy, anxiety, mood disturbances, agitation, disinhibition, lack of empathy, loss of insight, or psychosis in individuals who have not developed dementia (Ismail, Smith et al. 2016). Occurrence of MBI as well as individual NPS has been found to be associated with subsequent faster

cognitive and functional decline (Leoutsakos, Forrester et al. 2015, Creese, Brooker et al. 2019, Burhanullah, Tschanz et al. 2020, Ismail, McGirr et al. 2021). In addition, MBI correlates with several biological markers of neurodegenerative processes, such as higher β-amyloid deposition, lower plasma amyloid β42/amyloid β40, tau pathology in a pre-dementia population, which further supports its role as a promising indicator of a population at risk (Lussier, Pascoal et al. 2020, Naude, Gill et al. 2020, Johansson, Stomrud et al. 2021, Miao, Chen et al. 2021).

However, existing literature on sex differences in NPS and their relationship to subsequent risk of cognitive decline is limited. Some studies indicate that males exhibit symptoms of MBI more often than females. Specifically, researchers have reported findings of higher prevalence of impulse dyscontrol, decreased motivation, apathy, agitation, and irritability among males in comparison to females (Hölttä, Laakkonen et al. 2012, Geda, Roberts et al. 2014, Mortby, Ismail et al. 2018).

2   Aims and hypotheses

2.1   Study 1: Sex differences in cognitive decline among older Europeans

We aim to investigate sex differences in the rate of cognitive decline measured by immediate recall, delayed recall and verbal fluency. Considering the inconsistent results from previous longitudinal studies, we do not specify a hypothesis. Secondarily, we will explore whether cognitive decline in males and females differs across European regions and birth cohorts.

2.2   Study 2: Roots in childhood socioeconomic position

We will investigate sex differences in the relationship between childhood SEP, operationalized as a composite variable of household characteristics when the child was growing up, and the level of cognitive functions and the rate of cognitive decline measured by immediate recall, delayed recall and verbal fluency. We hypothesize that experiencing worse childhood SEP would be more strongly associated with worse cognitive outcomes in females than males. We will secondarily explore mediators in the relationship between childhood SEP and baseline level of cognition.

2.3   Study 3: Midlife reproductive history

Study 3a: As biological mechanisms related to pregnancy are specific to mothers and the social pathways linked to parenthood differ for males and females, we will explore sex differences in the relationship between number of children and risk of dementia. We hypothesize that high parity individuals would have higher risk of dementia in comparison to parents of two children. We don't specify a hypothesis for the sex difference in the relationship.

Study 3b: We will investigate sex differences in the relationship between having at least one son and the rate of cognitive decline measured by immediate recall and delayed recall. Previous studies are inconsistent and don't allow for generation of a hypothesis with a specific direction of this relationship. We will secondarily explore whether the magnitude of the relationship increases with each additional son and whether the relationship differs by cognitive domain.

2.4   Study 4: Mild behavioral impairment in later life

We will investigate sex differences in the relationship between MBI and the level of baseline cognitive performance and the rate of cognitive decline measured by digit span, paired associate learning, verbal reasoning and spatial working memory tests. We hypothesize that MBI syndrome would be more strongly associated with lower level of cognition and with faster cognitive decline in males than females. When exploring this relationship in individual MBI domains, we expect depressive symptoms to be more strongly associated with worse cognitive functioning in females, whereas the association between other MBI domains and cognition would be stronger in males.

3 Methods

We performed a total of five cohort studies using four cohorts of middle-aged and older adults residing in 21 countries across Europe, Israel and America. We sourced our data from the Survey of Health, Ageing and Retirement in Europe (SHARE) in Study 1 and Study 2, from the Health and Retirement Study (HRS) in Study 3a, from the Adult Changes in Thought Study (ACT) in Study 3b, and from the Platform for Research Online to Investigate Genetics and Cognition in Aging (PROTECT) in Study 4. First, the sources of data for the cohort studies are presented, followed by information about how the data on sex in each cohort was collected. In the end, details about study participants, measurements of cognitive outcomes and main variables and statistical analysis are summarized.

3.1 Sources of data

SHARE is a longitudinal, cross-national study that provides information about demographic, social, economic, and health-related aspects of the ageing populations in Europe (Börsch-Supan, Brandt et al. 2013). Eligible participants were community-dwelling individuals who were at least 50 years old at the time of recruitment. SHARE collects data from 28 European countries and Israel. Participants were interviewed using computer-assisted personal interviewing in the first wave in 2004 (response rate = 62%) and then in seven subsequent waves biennially up until 2020 (wave 8). To mitigate the effect of dropouts and maintain a consistent sample size, refresher samples were added.

ACT is a large longitudinal US cohort study that collects information about health-related and socioeconomic conditions of adults who are at least 65 years old and who are members of Kaiser Permanente Washington, an integrated health care system organization in the greater Seattle area (Kukull, Higdon et al. 2002). The first participants were enrolled between 1994 and 1996 (n=2,581) and then an additional enrollment was conducted between 2000 and 2002 (n=811). From 2005 onwards, the study enrolls 120 to 180 participants every year to account for attrition and maintain a consistent sample size. All participants were free from dementia at the time of enrollment.

HRS is a population-based longitudinal study in the US that collects data on more than 30 000 adults aged 50+ years and their spouses of any age. Data is collected through a combination of surveys and standardized interviews (Sonnega, Faul et al. 2014). The study was founded in 1992 and assessments are conducted biennially. The response rate in each wave

is greater than 85%. To keep the sample size steady and representative, new participants are enrolled every 6 years. All participants were free from dementia at the time of enrollment.

PROTECT is an online prospective study that collects data from approximately 25,000 healthy participants in the UK (Creese, Griffiths et al. 2020). The project began in November 2015, and subsequent assessments have been conducted on an annual basis. To ensure a steady sample size, new eligible participants are added each year. To be eligible to participate, individuals must be based in the UK, have a good understanding of English, be at least 50 years old, have regular access to the internet, and not have been diagnosed with dementia. Participants who receive a dementia diagnosis during the follow-up are withdrawn from the study.

3.2 Definition of sex

Participants in English speaking countries (i.e., participants in ACT and HRS in the US, in PROTECT in Britain, and in SHARE in Ireland) were asked whether they are female or male, thus, they self-reported their sex. In SHARE, the precise questions used vary between countries participating in SHARE based on their official language. Some countries don't have terminology that would distinguish sex and gender, while other countries do. For more specific details about how data on sex and gender are collected in individual countries participating in SHARE, please see documentation available at www.share-project.org. All studies primarily focus on the traditional concept of sex as a binary variable and no other options were included. As the concepts of sex and gender are closely related, it is not possible to differentiate whether the self-reported data indicate sex or gender (Clayton and Tannenbaum 2016). Sex refers to an individual's biological and genetic characteristics, while gender represents an individual's sociocultural self-perception of their identity. We acknowledge that our findings on sex differences might relate to social and cultural norms as well as to biological differences. To improve readability of this thesis, we use the terms sex, female, and male to describe participants' sex/gender. Keeping in mind that these concepts are not interchangeable, we don't expect that our results would change with self-reported gender.

3.3 Effect modification

Where appropriate, when investigating sex differences, effect modification by sex is tested. Effect modification refers to a situation where the association between an exposure

and an outcome varies depending on the level of another factor. We assess whether sex is an effect modifier using a statistical method called interaction testing. This analysis is important because it helps us to determine the statistical significance of the difference between males and females in the effect of an exposure to an outcome. Therefore, we use interaction testing in linear regression models and linear mixed-effects models as an indicator of a presence of meaningful sex difference. In the Cox model, interaction testing is less commonly recommended due to its inherent limitations and challenges (VanderWeele 2011). Thus, analyses that use the Cox models are stratified by sex without prior interaction testing.

3.4   Note on statistical analysis

Primary and secondary analyses are described in the chapter Methods and the corresponding findings in the chapter Results. For each study, we conducted several sets of sensitivity analyses to test the robustness of our findings. For better readability of the thesis, I present only methods and results related to the main and secondary aims and details concerning the sensitivity analyses are included in Annex 1. Further details concerning Study 2, 3b and 4 can be found in published full texts. The references for published studies are listed in Annex 2. Analyses were conducted using R Studio and R statistical programming language (version 4.2.0), Stata (version 16.1) and Mplus (version 8).

3.5   Study 1: Sex differences in cognitive decline among older Europeans

Participants

Data on participants comes from four European regions (Figure **1**) and was sourced from the SHARE study. Our final analytic sample for the main analysis was based on data collected in wave 1 to 8 and included 66,607 participants who had a total of 219,143 cognitive assessments over a maximum of 17 years of follow-up (sample selection in Figure 2).
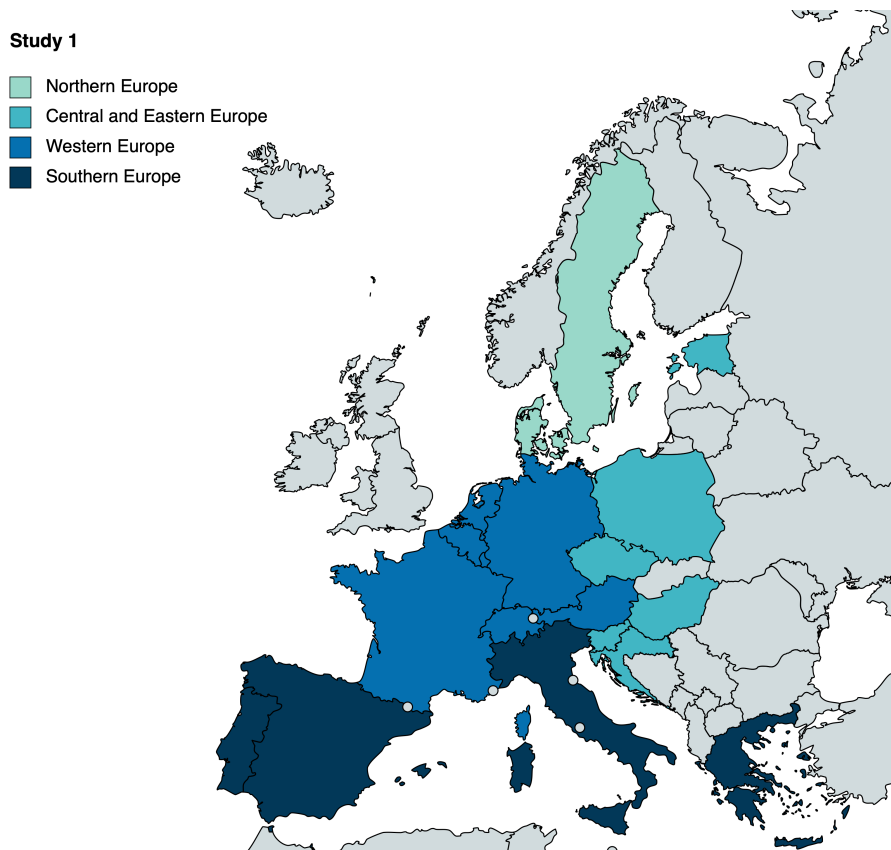
Figure 1 Geographical area represented in Study 1
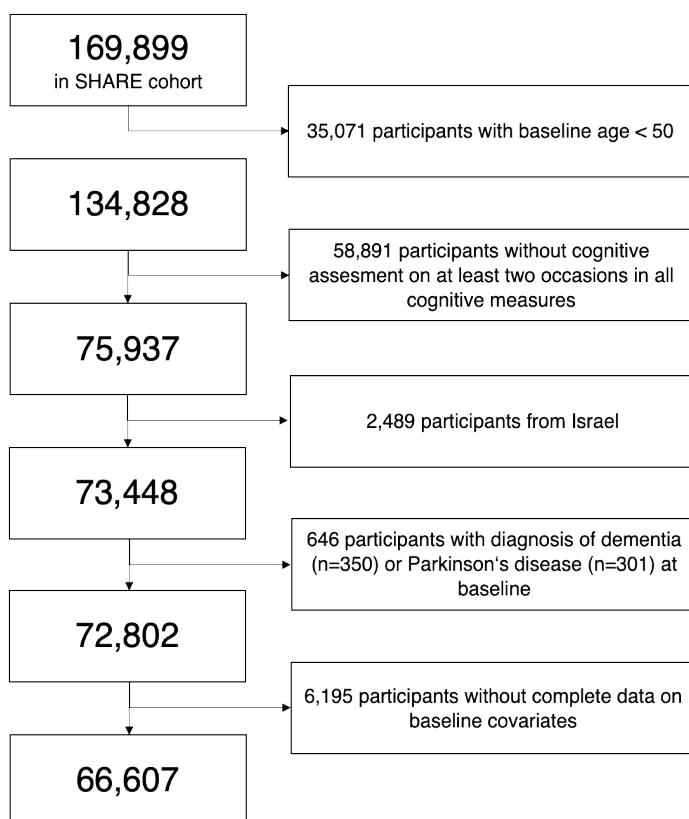
Figure 2 Sample selection in Study 1

Cognition

Cognition was assessed over 7 waves (1, 2, 4, 5, 6, 7, 8) using tests on verbal fluency, immediate recall, and delayed recall. Verbal fluency score, which ranged from 0 to 100, was measured using the animal fluency test (Henley and Behavior 1969), which involved naming as many animals as possible within one minute and reflects participant's executive functions. Immediate and delayed recall scores were obtained from the adapted 10-word delay recall test (Harris and Dowson 1982) and reflect participant's episodic memory. The immediate recall score, which ranged from 0 to 10, was determined by counting the number of words that participants could recall after an interviewer read a list of 10 words to them. Upon completion the cognitive testing session, participants were asked by the interviewer to recall the words from the earlier list, which was recorded as the delayed recall score, also ranging from 0 to 10.

Other covariates

Time was treated as a continuous variable measured in years since study enrolment. Participants self-reported information on their sociodemographic and health-related characteristics at baseline (Table 1).

Table 1 Covariates in Study 1

Covariate	Definition
Sociodemographic characteristics	
Sex	Female; male.
Baseline age	In years centered at median [62 years].
Birth cohort	Up until 1939 [pre-World War II]; 1939–1945 [World War II]; and 1945 and after [post-World War II].
Region	Central and Eastern Europe [Czech Republic, Poland, Hungary, Slovenia, Estonia, Croatia]; Western Europe [Austria, Germany, Netherlands, France, Switzerland, Belgium, Luxembourg]; Northern Europe [Sweden, Denmark]; Southern Europe [Italy, Spain, Portugal, Greece].
Marital status	Married/registered partnership; divorced/separated; never married; widowed.
Health-related characteristics	
Depressive symptoms	Score ≥ 4 measured by EURO-D scale [ranging from 0 to 12].

Covariate	Definition
IADL	Number of limitations in instrumental activities of daily living (IADL, 0-9).
Physical inactivity	Never vigorous nor moderate physical activity; other.
Myocardial infarction	Yes; no. Self-reported.
Stroke	Yes; no. Self-reported.
Diabetes	Yes; no. Self-reported.
Hypertension	Yes; no. Self-reported.
Dyslipidemia	Yes; no. Self-reported.
Body mass index	Underweight/normal [below 24.9 kg/m^2]; overweight [25 – 29.9 kg/m^2]; obese [30 kg/m^2 and above].

Abbreviations: EURO-D = EURO-depression scale, IADL = instrumental activities of daily living.

Statistical analysis

In the primary analysis, we used linear mixed-effects models to study the relationship between sex and the rate of cognitive decline. We analyzed all three cognitive measures (verbal fluency, immediate recall and delayed recall) in separate models. Models included time, sex and their interaction term (time × sex), which allows to estimate sex differences in rate of cognitive decline. Model 1 was adjusted for age, Model 2 for other sociodemographic characteristics (region, birth cohort, education, employment status, marital status), and Model 3 for health-related characteristics (depressive symptoms, IADL, physical inactivity, heart disease, stroke, diabetes, hypertension, dyslipidemia, body mass index [BMI]).

In the secondary analyses, as prior research shows that later born cohorts have better cognitive functioning, regardless of the effect of age, we stratified the analysis by birth cohort (Brailean, Huisman et al. 2018). In addition, because previous studies identified differences in the rate of cognitive decline across European countries (Skirbekk, Loichinger et al. 2012), we stratified our analysis by region.

3.6 Study 2: Roots in childhood socioeconomic position

Participants

We utilized data from SHARE. In the present study, we used data from wave 1 to wave 7 encompassing participants from up to 19 countries (Figure 33). Our final analytic sample for the main analysis was based on data collected in 7 waves of SHARE and included 84,059 participants in the cross-sectional sample and 74,279 participants in the longitudinal sample (sample selection in Figure 4).
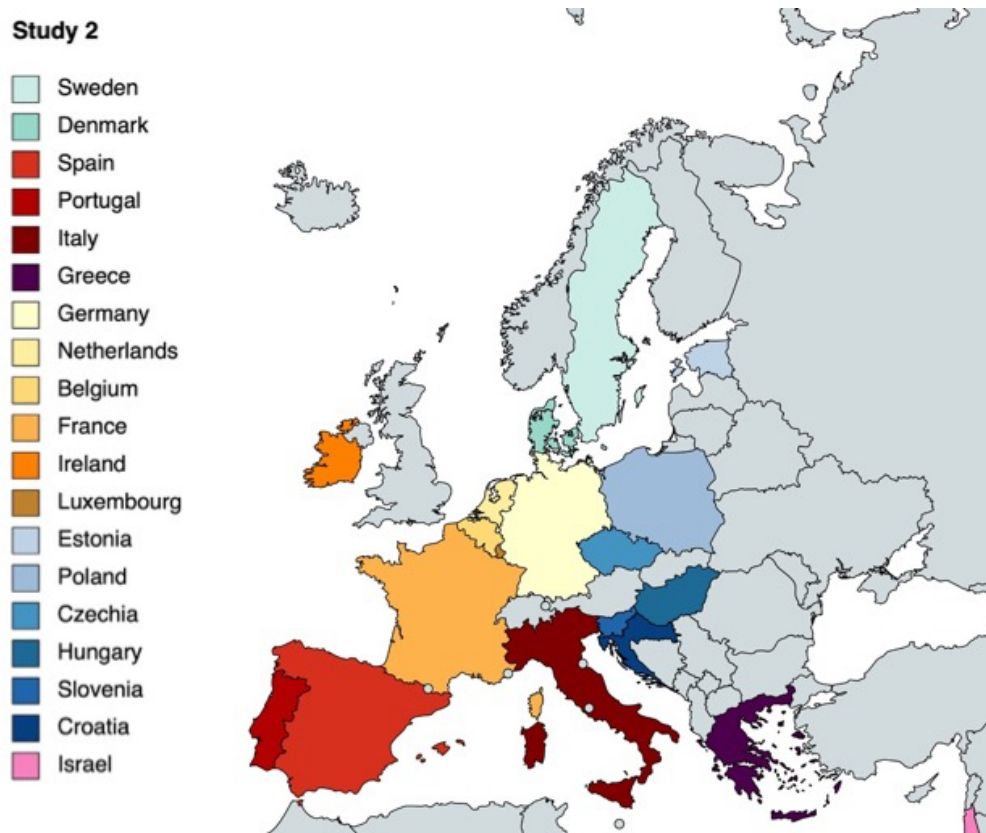
Figure 3 Geographical area represented in Study 2
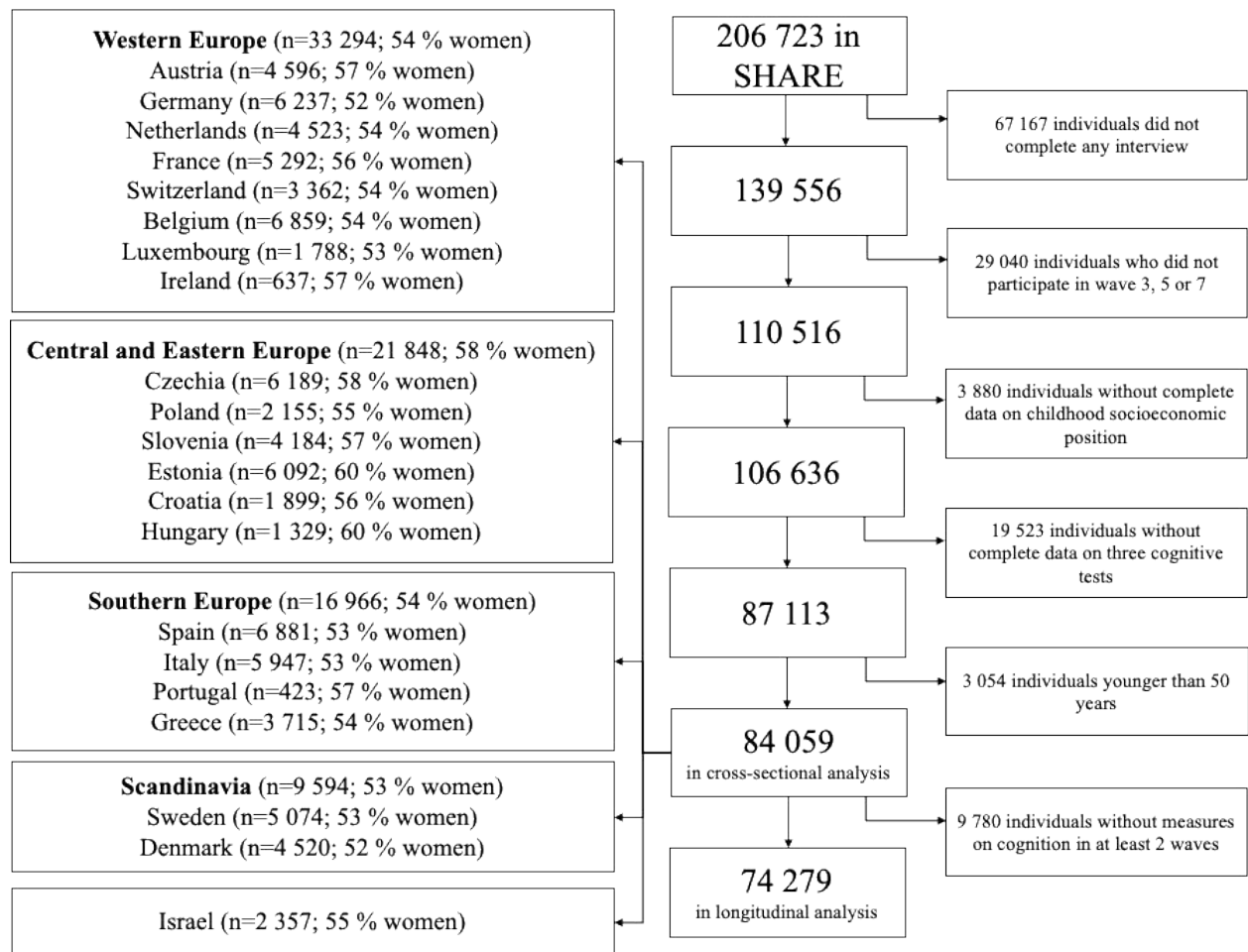
Figure 4 Sample selection in Study 2

Childhood SEP

A part of SHARE was devoted to collecting data about the past experiences of the participants. Data about participants' life histories were gathered in wave 3 and 5 using the "Life History Calendar", an instrument designed to improve memory recollection (Freedman, Thornton et al. 1988). We created a composite variable "childhood SEP" using two household characteristics, which represent key components of wealth at the age of 10 (Galobardes, Shaw et al. 2006, Galobardes, Shaw et al. 2006, Niedzwiedz, Katikireddi et al. 2014): overcrowding, which, in particular, indicates socioeconomic disadvantage, and the number of books at home, representing the intellectual dimension of SEP (Galobardes, Shaw et al. 2006, Galobardes, Shaw et al. 2006, Winkler, Formánek et al. 2018). First, to establish a measure of household overcrowding, we divided the number of rooms by the number of household members, creating a "household ratio", in which larger values indicate less crowding in the household. Next, the variable "number of books" (none or very few [0-10 books] / enough to fill one shelf [11-25 books] / enough to fill one bookcase [26-100 books] / enough to fill two bookcases [101-

40

200 books] / enough to fill two or more bookcases [more than 200 books]) was converted into a scale ranging from 0 to 4. Then, we transformed the variables "household ratio" and "number of books" into z-scores and calculated their average to create a composite measure of "childhood SEP", where lower values indicate a more disadvantaged SEP.

For longitudinal analysis, we created a country-specific binary variable "childhood socioeconomic disadvantage" that indicated the most extreme distribution of childhood SEP and corresponded to 1) not achieving the household ratio above the 5th percentile in participants' respective countries and 2) being in the most unfavorable category of number of books.

Cognition

Cognition was assessed over six waves (1, 2, 4, 5, 6, and 7) using tests on verbal fluency, immediate recall, and delayed recall, as described above in Study 1. For the cross-sectional analysis, we used data on cognition from the wave, in which all three measures were available for the first time, meaning that the wave varies for each participant. For the longitudinal analysis, we utilized all available data on cognition.

Because the association between SEP and level of cognitive performance was comparable across the three cognitive measures, we transformed the measures into z-scores and calculated their average for the cross-sectional analysis to create a composite measure of cognitive performance. On the other hand, the rate of cognitive decline in participants with childhood socioeconomic disadvantage was different for each cognitive measure. Thus, we created separate models for each cognitive measure in the longitudinal analysis. As participants who are repeatedly tested may become familiar with the content of the cognitive tests, which may result in underestimation of the rate of cognitive decline, we controlled for practice effect (Weuve, Proust-Lima et al. 2015, Vivot, Power et al. 2016).

Covariates

We selected a set of covariates based on previously established evidence on the association of sociodemographic and health-related factors with childhood SEP and cognitive outcomes (Cermakova, Formanek et al. 2018, Formanek, Kagstrom et al. 2019). We used data on covariates from the same wave as when cognition was assessed or from the closest one (Table 2).

Table 2 Covariates in Study 2

Covariate	Definition
Sociodemographic characteristics	
Baseline age	In years.
Sex	Females; males.
Education	In years.
Household net worth	Standardized difference between household gross financial assets and financial liabilities.
Current working status	Working; not working.
Cohabitation status	Living with a partner; living alone.
Number of children	Continuous variable. Self-reported.
Number of grandchildren	Continuous variable. Self-reported.
Health-related characteristics	
Depressive symptoms	Score $\geq$ 4 measured by EURO-D scale [ranging from 0 to 12] (Co-operation and Development 1999)).
IADL	Number of limitations in IADL (0-9).
Cardiovascular disease	Defined as ever diagnosed or treated for coronary heart disease, stroke, diabetes, high blood pressure or high blood cholesterol.
Number of chronic diseases	Continuous variable. Self-reported.
Physical inactivity	Never vigorous nor moderate physical activity; other.
Body mass index	In kg/m^2. Calculated as weight in kilograms divided by height in meters squared.
Smoking	Ever smoked daily; never smoked daily.
Alcohol use	Drinking more than 2 glasses of alcohol almost every day; drinking less.
Maximal grip strength	Continuous variable.

Abbreviations: EURO-D = EURO-depression scale, IADL = instrumental activities of daily living.

We used component analysis to examine whether physical health measures (i.e., number of chronic diseases, cardiovascular disease, number of limitations in IADL, physical inactivity, and maximal grip strength) represent an overall composite variable "physical state". This composite variable was used as a mediating latent factor in the structural equation model.

Statistical analysis

In the primary analysis, to assess the associations between childhood SEP and the level of cognitive performance, we used multilevel linear regression with participants nested within countries and with a random slope for SEP on a country level. We constructed four sets of models, stepwise adjusting for covariates. The association between childhood SEP and the level of cognitive performance was similar in all three cognitive measures, thus the final analysis was conducted only for the composite cognitive score. We assessed an interaction between sex and childhood SEP using likelihood ratio (LR) test (p from LR test < 0.001) and stratified all models by sex. We adjusted Model 1 for age; Model 2 additionally for education; Model 3 additionally for depressive symptoms and sociodemographic characteristics; and Model 4 additionally for health-related characteristics.

Next, to study the relationship between childhood SEP and the rate of cognitive decline, we used linear mixed-effects models with unstructured covariance. We analyzed all three cognitive measures (verbal fluency, immediate recall and delayed recall) separately in non-standardized format. Preliminary models included time (in years since baseline centered around grand mean), time squared, childhood SEP, an interaction term between time, childhood SEP and sex (childhood SEP × time × sex), baseline age, sex and practice effect. We found differences between males and females in the rate of decline in all the three cognitive measures (p from likelihood ratio test < 0.001 for all three measures) and stratified all analyses by sex. To better interpret the effect of childhood SEP, we used a binary variables childhood socioeconomic disadvantage as the primary exposure. The model in the primary analysis included the primary exposure variable (childhood socioeconomic disadvantage) and the interaction term (childhood socioeconomic disadvantage × time), controlling for baseline age and practice effect. We set participants, time in years and countries as random intercepts, the time squared as random slope at participant level and also as fixed effect, childhood socioeconomic disadvantage as random slope at country level and also fixed effect, and baseline age and practice effect as fixed effect in Model 1. We added additional covariates as fixed effects: education in Model 2; depressive symptoms and sociodemographic characteristics in Model 3; health-related characteristics in Model 4.

In the secondary analysis, we constructed a structural equation model with multiple mediations using the strongest predictors of the level of cognitive performance. Childhood SEP was a predictor of the baseline level of cognitive performance. This relationship was mediated by education, depressive symptoms, and the latent factor "physical state". Age was a predictor of

depressive symptoms, "physical state", and cognitive performance and correlated with childhood SEP and education.

3.7   Study 3: Midlife reproductive history

3.7.1   *Study 3a: Number of children and dementia*

Participants

We used data from the ACT Study. Participants were recruited in the Greater Seattle area in the US state of Washington (Figure 5). Final analytic sample included 4,743 participants (sample selection in Figure 6).
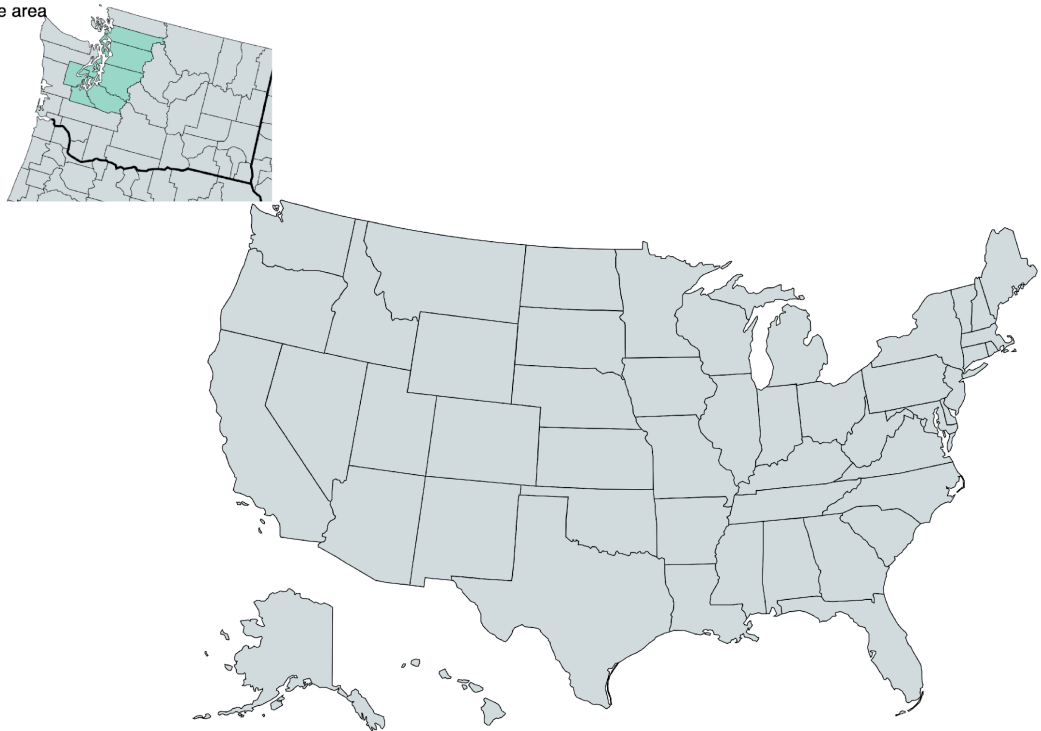
Figure 5 Geographical area represented in Study 3a

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┌──────────────────┐
│      5,104       │
│   in ACT cohort  │
└──────────────────┘
         │          ┌─────────────────────────────────────┐
         │─────────▶│ 361 individuals with no information  │
         │          │ on birth year, sex, number of        │
         ▼          │ children, cognition at baseline and  │
┌──────────────────┐│ at a second time point               │
│      4,743       │└─────────────────────────────────────┘
│ in imputed sample│
└──────────────────┘
         │          ┌─────────────────────────────────────┐
         │─────────▶│ 1,075 individuals with missing data  │
         ▼          │ on covariates                        │
┌──────────────────┐└─────────────────────────────────────┘
│      3,668       │
│ in complete case │
│ sample for       │
│ sensitivity      │
│ analysis         │
└──────────────────┘
```
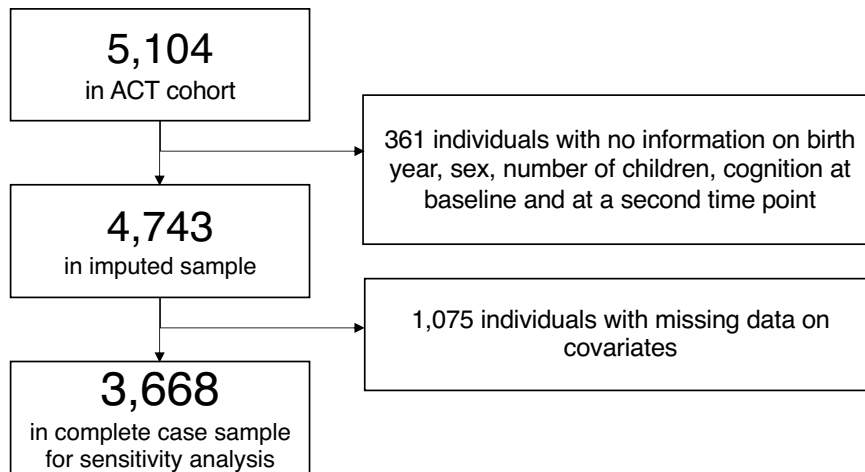
Figure 6 Sample selection in Study 3a

Number of children

At baseline, participants self-reported the number of their biological children. We created a categorical variable number of children with 5 levels (no children; one child; two children; three children; four or more children).

Dementia

The outcome was diagnosis of dementia (dementia, no dementia). Diagnosis of dementia was established during consensus conferences that followed definitions from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. To be assessed by the panel of experts, participants had to meet a threshold in their cognitive scores. Every two years, participants' cognitive abilities were evaluated using the Cognitive Abilities Screening Instrument, which generates a total score ranging between 0 to 100, with lower scores indicating poorer cognitive functions. If a participant scored below 86 points, they underwent standardized physical and neurological examinations, as well as a neuropsychological test battery assessment.

Covariates

We identified covariates based on prior research indicating that sociodemographic, early-life and health-related factors may affect the association between the number of children and dementia. Participants reported their sociodemographic and health-related characteristics during the initial assessment (Table 3). Sociodemographic characteristics were considered as potential confounders. A set of health-related variables were considered as potential

confounders / mediators. These variables might be possible mediators when measured at the time of study enrolment, however, as these conditions may have been developing over time, they could potentially act as confounders as well. Even though it is not possible to adequately distinguish whether the measured variables are confounders or mediators, we controlled for these variables in our analysis test the robustness of our findings (VanderWeele 2019).

Table 3 Covariates in Study 3a

Covariate	Definition
Sociodemographic characteristics	
Baseline age	In years.
Sex	Females; males.
Marital status	Never married; married/living as married; separated/divorced; widowed; other.
Educational level	Less than college; college or higher.
Basic needs and small luxuries	The participants were asked to indicate whether their families were able to fulfill basic needs (food, housing, clothing, and medical care) as well as whether they could afford small luxuries (yes; no). Based on their responses, we created a categorical variable with three levels, which represented whether the family could afford neither basic needs nor small luxuries, only basic needs, or both basic needs and small luxuries.
Paternal education	In years, standardized as z-score.
Maternal education	In years, standardized as z-score.
Health-related characteristics	
Depression	Yes; no (indicated by a score of 10 or on 10-item Center for Epidemiologic Studies Depression Scale).
Systolic blood pressure	In mmHg, obtained by taking two measurements on the participant's left arm while they were seated, with the measurements taken five minutes apart.
Antihypertensive medication	Yes; no. Self-reported.

Smoking	Yes; no. Self-reported.
Diabetes	Yes; no. Self-reported.
Heart disease	Yes; no. Self-reported.
Stroke	Yes; no. Self-reported.
Body mass index	Calculated as weight in kilograms divided by height in meters squared (kg/m^2). Continuous variable.

Statistical analysis

We employed the R package Multivariate Imputation by Chained Equations and conducted a multiple imputation (5 imputations) to impute data on missing covariates. To examine the relationship between the number of children and the risk of dementia, we estimated hazard ratios (HR) obtained from Cox proportional hazards regression models. Age was utilized as the time scale, where the participants' age at study entry was considered the starting point (left truncation), and the end time point was either the age at dementia diagnosis or age at censoring. Censored participants were those who were event-free at the end of the study or those who died during the study. Models with age as the time scale implicitly control for age.

To consider potential differences between males and females in social and biological mechanisms related to number of children, we stratified the analyses by sex. We did not perform interaction testing as the hypothesis test might be underpowered and doesn't allow for the possibility of different baseline hazards between males and females. We created two sets of models: 1) Model 1, which included number of children as the exposure and controlled for potential confounders (father's education, mother's education, basic needs and small luxuries, education, marital status), and 2) Model 2 which additionally controlled for potential confounders / mediators (depression, systolic blood pressure, antihypertensive medication, smoking, diabetes, heart disease, stroke, BMI).

3.7.2 *Study 3b: Offspring sex and cognitive decline*

Participants

We utilized data from the HRS in the US (Figure 7). We restricted the sample to participants who had cognitive assessment conducted in 2000 and onwards. Our final analytic sample includes 13,222 participants who were at least 50 years old at baseline (sample selection in Figure 8).
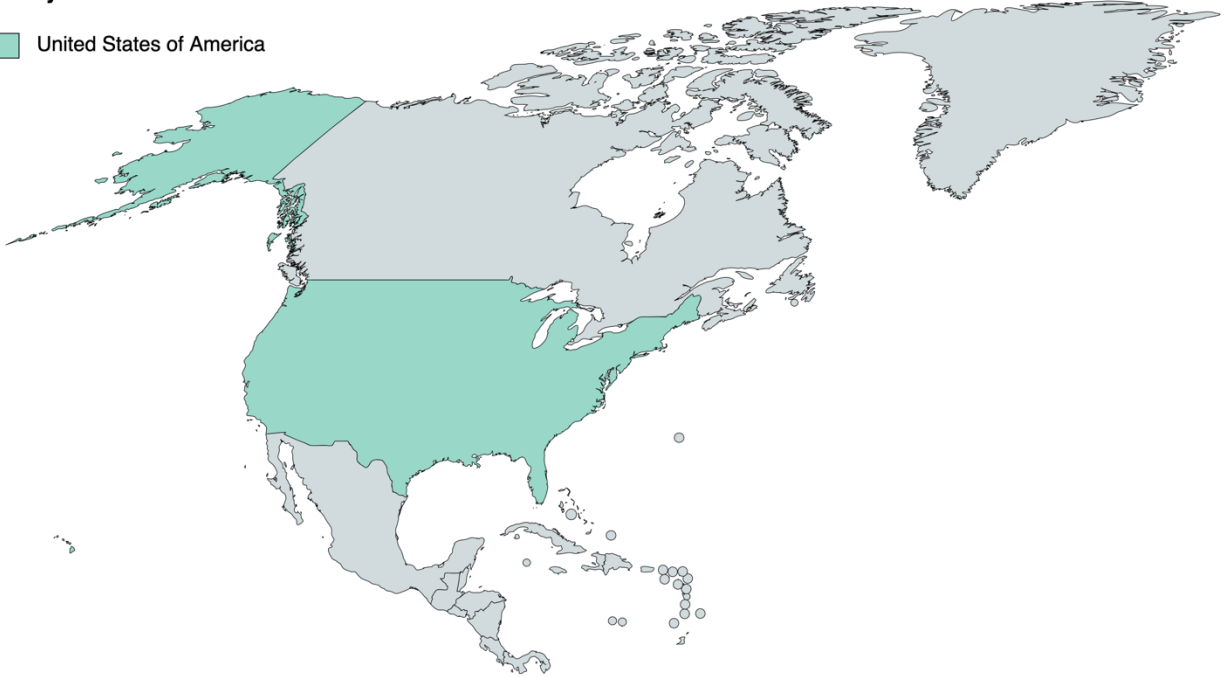
Figure 7 Geographical area represented in Study 3b
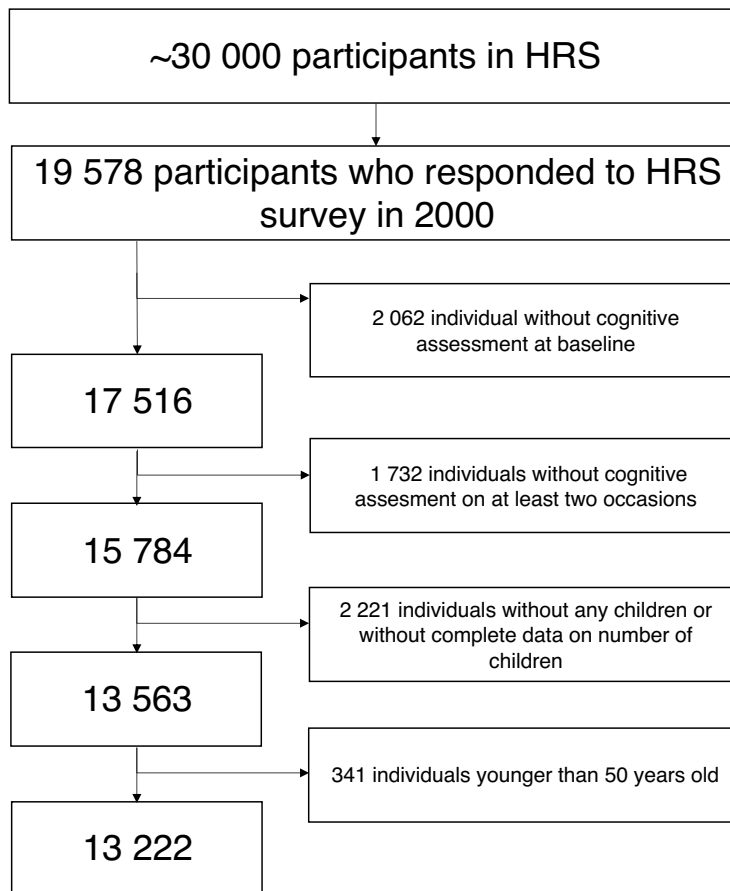
Figure 8 Sample selection in Study 3b

Offspring sex

Offspring sex variable is based on self-reported information of participant's children, including biological, adopted, and stepchildren. Because offspring sex is closely related to the number of children, a potential confounder of the relationship between offspring sex and cognition, we conducted two sets of analysis with different definitions of offspring sex. In the primary analysis, offspring sex was created as a binary indicator defined as no son vs. at least one son. In the secondary analysis, offspring sex was represented by a categorical variable number of sons (no sons, one son, two sons, three or more sons).

Cognition

All study waves included an evaluation of cognitive function, which was measured using a sum of scores of four validated cognitive tests. Cognitive functions were measured by immediate and delayed 10-noun free recall tests, a serial 7s subtraction test, and a backwards counting test. Immediate recall scores were based on the number of words recalled from a list of 10 nouns presented by the interviewer, with a score ranging between 0 and 10. Participants were then asked to recall any of the previously presented nouns after a delay of approximately 5 minutes, with a score ranging between 0 and 10. The serial 7s subtraction scores measured the number of times over 5 trials that the participant was able to subtract 7 from 100 consecutively, with a score ranging between 0 and 15. For the backward counting test, participants were asked to count backwards by 10 continuous numbers from both 20 and 86. The test score, ranging between 0 and 2, was determined by the number of successful trials completed. A total cognition score was then calculated as the sum of scores from all four tests, with a score ranging between 0 and 27. In the primary analysis, we used the total cognition score as the primary outcome. In the secondary analysis, we used each cognitive measure as the alternative outcome and constructed separate models for each outcome.

Covariates

Potential confounders included participant's self-reported sociodemographic characteristics, and potential confounders / mediators included health-related variables (Table 4). Although health-related variables could potentially act as confounders when measured prior to having children, they might be also possible mediators when measured at the time of study enrolment. Thus, we adjusted for this set of variables in a separate model.

Table 4 Covariates in Study 3b

Covariate	Definition
Sociodemographic characteristics	
Baseline age	In years, centered at the median by subtracting the median of 62 years form baseline age.
Sex	Females; males.
Race and ethnicity	Non-Hispanic White; non-Hispanic Black; Hispanic; other
Birth cohort	Pre–World War I, World War I, and Spanish influenza (1899-1920); pre–Great Depression (1921-1928); Great Depression (1929-1939); World War II and postwar (1940-1950)
Number of children	One child; two children; three children; four children; five or more children.
Education	Less than high school; General Educational Development program or high school; college and above.
Paternal education	In years.
Maternal education	In years.
Marital status	Married or partnered; other.
Age at the first birth	< 20 years old; ≥20 years old.
Place of birth	Southern states; other US states; abroad.
Health-related characteristics	
Heart disease	Yes; no. Self-reported.
Stroke	Yes; no. Self-reported.
Diabetes	Yes; no. Self-reported.
Body mass index	In kg/m^2. Calculated from self-reported baseline data as weight in kilograms divided by height in meters squared.
Smoking status	Ever smoked; never smoked.
Depressive symptoms	Measured at baseline by the 8-item Center for Epidemiological Studies-Depression Scale [CES-D], score range: $0 - 8$.

For the secondary analysis, we created a categorical variable number of daughters (no daughters, one daughter, two daughters, three or more daughters).

Statistical analysis

In the primary analysis, the association between offspring sex, baseline cognition and cognitive decline was evaluated using linear mixed-effects models with subject-specific random intercept and slope effects with an unstructured covariance using the R package "nlme". Our primary outcome was total cognition, and the primary exposure variable was offspring sex (no son vs. ≥ one son). To assess differences by offspring sex in the rate of cognitive decline over time we included an interaction between time and offspring sex. The three-way interaction of time, parental sex and offspring sex was not significant (p value from LR test 0.956). Even though the hypothesis testing did not show any sex differences, we stratified the primary analysis by participant's sex.

We considered time as a continuous variable defined as years since baseline. Models were controlled for the following sets of covariates: 1) baseline age (in years, centered at median), participant's sex and race and ethnicity (Model 1); 2) all variables in the previous model plus number of children (Model 2); 3) all variables in the previous model plus potential confounders (birth cohort, education, father's education, mother's education, age at the first birth, place of birth) (Model 3), and 4) all variables in previous model plus potential confounders / mediators (baseline marital status; smoking status; BMI; depressive symptoms; and prevalent diabetes, heart disease, and stroke; Model 4). Variables baseline age and time are concepts related to the effect of aging. The variable birth cohort reflects the effect of being born at a particular point in time, which is distinct from the process of aging (Holford 1991).

In the secondary analysis, we constructed models with an alternative exposure and alternative outcomes. Because we did not find a significant interaction in the primary analysis, we constructed the models for the whole sample. Models with the alternative primary exposure defined as the number of sons also included the interaction of time with the number of sons (time × number of sons) to estimate the differences in the rate of cognitive decline. The primary outcome in these models was total cognition. Models were adjusted for the following sets of covariates: 1) baseline age (in years, centered at median), the number of daughters (no daughters, one daughter, two daughters, three or more daughters), the interaction of time with the number of daughters (time × number of daughters), participant's sex and race and ethnicity (Model 1); 2) additionally for other potential confounders (birth cohort, education, father's education, mother's education, age at the first birth, place of birth; Model 2). Next, we constructed models with an alternative outcome. We fitted separate model for each alternative outcome defined as score from individual cognitive tests (immediate recall, delayed

recall, serial 7s subtraction, and backwards counting). The exposure in these models was having at least one son.

3.8   Study 4: Mild behavioral impairment in later life

Participants

We utilized data from the British PROTECT study (Figure 9). Our final analytical sample comprised 8,181 individuals with a median follow-up of 3.07 years (interquartile range [IQR] 2.02-3.22). Participants with missing data on covariates were included in the descriptive analyses. Only participants with complete data on MBI-C and cognition were included in the analyses (sample selection in Figure 10).
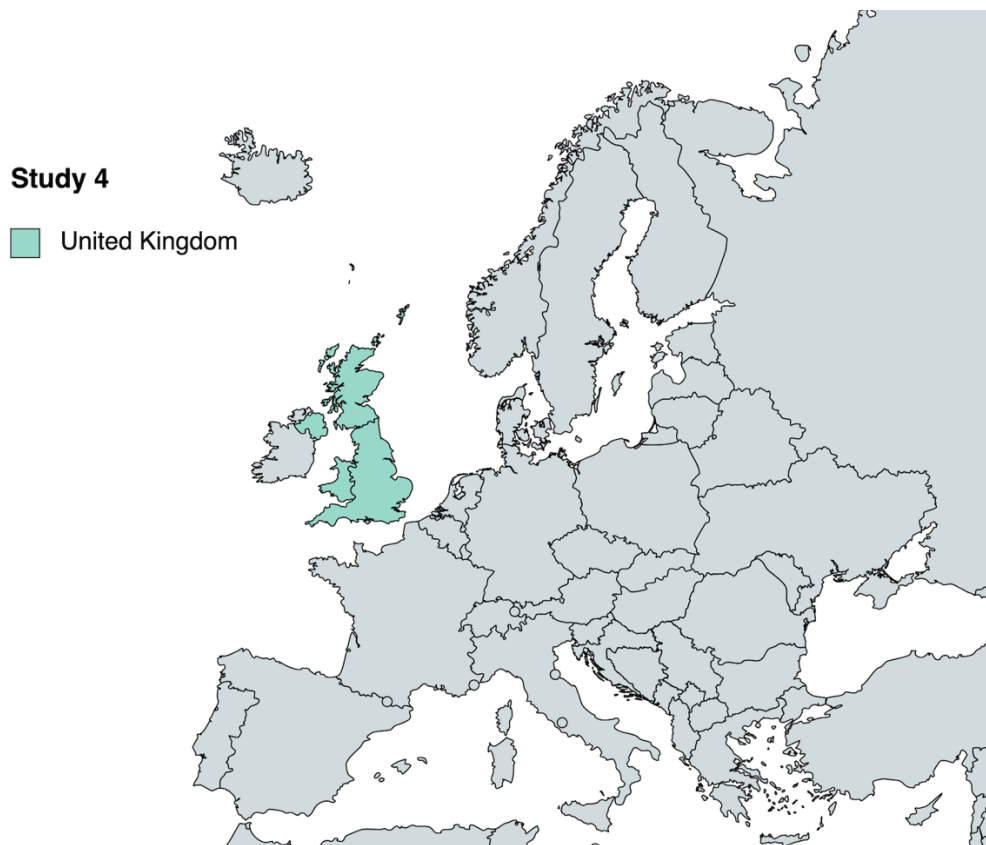
Figure 9 Geographical area represented in Study 4

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┌──────────────────────┐
│       23,632         │
│   in PROTECT cohort  │
└──────────────────────┘
         │      ┌────────────────────────────────────────┐
         │─────▶│  11,397 individuals without assessment │
         │      │        of MBI at baseline or year 1     │
         ▼      └────────────────────────────────────────┘
┌──────────────────────┐
│       12,235         │
└──────────────────────┘
         │      ┌────────────────────────────────────────┐
         │─────▶│  156 individuals without complete data │
         │      │        on all MBI-C questions          │
         ▼      └────────────────────────────────────────┘
┌──────────────────────┐
│       12,080         │
└──────────────────────┘
         │      ┌────────────────────────────────────────┐
         │─────▶│  1,835 individuals without data on     │
         │      │  cognitive measures at baseline and    │
         │      │  at least one follow-up occasion       │
         ▼      └────────────────────────────────────────┘
┌──────────────────────┐
│       10,245         │
└──────────────────────┘
         │      ┌────────────────────────────────────────┐
         │─────▶│  1 individual considered as outlier    │
         │      │        in cognitive tests              │
         ▼      └────────────────────────────────────────┘
┌──────────────────────┐
│       10,244         │
└──────────────────────┘
         │      ┌────────────────────────────────────────┐
         │─────▶│  2,063 individuals who reported        │
         ▼      │  history of stroke ...                 │
┌──────────────────────┐
│        8,181         │
└──────────────────────┘
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2,063 individuals who reported history of stroke (n=149), Parkinson's disease (n=22), mania/bipolar/manic depression (n=48), anxiety/generalized anxiety disorder (n=1,410), social anxiety (n=121), agoraphobia (n=34), panic attacks (n=520), obsessive-compulsive disorder (n=34), anorexia nervosa (n=81), bulimia nervosa (n=54), psychological overeating/binge eating (n=50), schizophrenia (n=5), other psychotic illnesses (n=28), personality disorders (n=13), autism/Asperger's/autistic spectrum disorder (n=13), or attention deficit disorder (n=7). In addition, participants with clinical signs of depression defined by score ≥ 14 at Patient Health Questionnaire-9 (PHQ9) scale were also excluded (n=99)

Figure 10 Sample selection in Study 4

Mild behavioral impairment

The assessment of MBI was conducted by informants using the Mild Behavioral Impairment Checklist (MBI-C). This checklist consists of 34 questions that were specifically designed to evaluate the severity and presence of NPS in pre-dementia and healthy populations (Ismail, Agüera-Ortiz et al. 2017). For the symptom to be considered present, it must persist for at least

six months and represent a change from an individual's typical behavior, whether that change is continuous or intermittent. MBI encompasses six individual domains: 1) decreased motivation, decreased interest and drive, apathy (which will be further on referred as "decreased motivation"); 2) emotional or affective dysregulation, mood and anxiety symptoms ("emotional dysregulation"); 3) impulse dyscontrol, agitation, aggression, and abnormal reward salience ("impulse dyscontrol"); 4) social inappropriateness, impaired social cognition ("social inappropriateness"); and 5) abnormal thoughts and perception, psychotic symptoms ("psychotic symptoms").

Each present symptom is rated for its severity on a scale from 1 to 3, with 1 indicating a mild change that is noticeable but not significant, 2 indicating a moderate change that is significant but not dramatic, and 3 indicating a severe change that is very marked or prominent. We excluded 156 participants who had incomplete data in any of the MBI domains. As the MBI-C has been previously validated using a discretization approach (Creese, Brooker et al. 2019, Creese, Griffiths et al. 2020, Kassam, Chen et al. 2022), we generated a binary variable that indicated presence of MBI syndrome using a cut-off value of more than 8 points ("MBI syndrome"). This approach has been shown to have good sensitivity and specificity for clinically diagnosed MBI based on the ISTAART diagnostic criteria in participants with subjective cognitive decline (Creese, Brooker et al. 2019). Then we created binary variables representing the presence of at least one symptom of any severity in an individual MBI domain, which have also been utilized in previous studies (Creese, Griffiths et al. 2020).

Cognition

At the time of enrollment, participants and their informants reported that they did not have dementia. Cognitive performance was assessed annually using four tests (digit span, paired associate learning, self-ordered search, and verbal reasoning that had been previously adapted and validated for online administration (Owen, Hampshire et al. 2010, Wesnes, Brooker et al. 2017). Participants were given up to three attempts to complete the same test battery within a span of seven days, with a minimum 24-hour break between sessions. The scores for the digit span (ranging from 0 to 20), paired associated learning (ranging from 0 to 11), and self-ordered search (ranging from 0 to 20) tests were based on the total number of correct answers. The score for the verbal reasoning test (ranging from -1 to 70) was represented by the total number of trials answered correctly minus the number answered incorrectly. Our outcome measures were computed by averaging the scores from up to three separate

attempts. Longitudinal analysis operationalized cognitive decline as an annual decrease in the outcome measure by incorporating a variable representing time on study and a two-way interaction between time and exposure.

The digit span test assesses attention and concentration by presenting a sequence of numbers on the screen that the participant is asked to remember (Hebben Nancy et al. 2002). The paired associate learning test presents objects hidden under boxes and requires participants to remember which object is hidden under which box. Deficits in paired associate learning have been linked to worse memory and hippocampal atrophy, an early feature of AD on neuroimaging (Fowler, Saling et al. 1995). The self-ordered search test measures spatial working memory through a task in which participants find a symbol hidden under a box, then search for another symbol while remembering not to search the same box twice. Lower scores on this test are associated with frontal lobe damage (Owen, Downes et al. 1990). The verbal reasoning test is an online version of Baddeley's Grammatical Reasoning test, which is related to fluid intelligence, the ability to reason, analyze, and solve problems (Baddeley 1968). Participants must indicate whether they agree with a statement about a relationship between two shapes (a circle, a square, etc.) by clicking either the "True" or "False" button.

Covariates

Participants self-reported sociodemographic and health-related characteristics (Table 5).

Table 5 Covariates in Study 4

Covariate	Definition
Sociodemographic characteristics	
Baseline age	In years.
Sex	Females; males.
Ethnic origin	White; non-white.
Education level	Low (secondary education); middle (post-secondary education, vocational qualification, undergraduate degree); high (post-graduate degree, doctorate).
Employment status	Employed; other.
Co-habitation status	Married/co-habiting; living alone.
Health-related characteristics	

Hypertension	Yes; no. Self-reported.
Heart disease	Yes; no (history of heart disease, heart attack of angina). Self-reported.
Diabetes	Yes; no. Self-reported.
Hypercholesterolemia	Ever smoked; never smoked.
Body mass index	In kg/m^2. Calculated from self-reported baseline data as weight in kilograms divided by height in meters squared.

Statistical analysis

We applied linear regression to estimate beta coefficients with 95% CIs for the associations of the independent variable MBI (syndrome and individual MBI domains) with the level of cognitive performance at baseline. To evaluate the moderating effect of sex on the association between MBI (syndrome and individual domains) and baseline cognitive performance level, we introduced a two-way interaction term between MBI and sex in a model that was adjusted for age. We tested the interaction effect using the LR test. Sex moderated the association between the MBI syndrome and the level of cognitive performance in paired associate learning (p from LR test <0.05). Thus, we stratified the analysis by sex. We present three sets of models, adjusting for covariates. Model 1 is adjusted for age, Model 2 additionally for sociodemographic factors, and Model 3 additionally for health-related characteristics.

To evaluate the association between MBI (syndrome and individual MBI domains) and the rate of cognitive decline, we used linear mixed-effects models. Participants and time (in years since baseline) were set as random intercepts, time as random slope at participant level, and time, MBI, sex, and baseline age (centered around mean) as fixed effects. To evaluate whether the association between MBI and the rate of cognitive decline varies by sex, we included a three-way interaction term between MBI, time, and sex (MBI × time × sex) in a model that was adjusted for age (Model 1). Sex moderated the association of MBI syndrome as well as all MBI domains with the rate of cognitive decline in verbal reasoning (p from LR test <0.05). With regards to the individual MBI domains, sex moderated the association between impulse dyscontrol and the level of cognitive performance in digit span (p from LR test 0.040) and paired associate learning (p from LR test 0.035). Thus, we stratified the analysis by sex where appropriate. We added additional covariates as fixed effects: sociodemographic characteristics in Model 2, and health-related characteristics in Model 3. As participants who are repeatedly tested may become familiar with the content of the cognitive tests, which may result in

underestimation of the rate of cognitive decline, we controlled for practice effect by adjusting for the root square of the number of prior tests (Weuve, Proust-Lima et al. 2015, Vivot, Power et al. 2016).

4   Results

4.1   Study 1: Sex differences in cognitive decline among older Europeans

Among 66,607 participants (mean age at baseline 63.5 ± standard deviation (SD) 9.4; 55.0% females), females scored higher than males in immediate and delayed recall at baseline (Table 6). Pre-World War II cohort included 16,491 participants, World War II cohort included 13,876 participants, and post-World War II cohort included 36,240 participants. The region of Western Europe comprised 27,090 participants, Southern Europe 14,254 participants, Central and Eastern Europe 17,018 participants, and Northern Europe 8,245 participants. Participants' characteristics are presented in Table 6.

Table 6 Sample characteristics in Study 1

	Females (n=36,602)	Males (n=30,005)
Immediate recall, mean (SD)	5.38 (1.76)	5.15 (1.69)
Delayed recall, mean (SD)	3.97 (2.13)	3.65 (1.99)
Verbal fluency, mean (SD)	20.2 (7.61)	20.4 (7.40)
Baseline age, mean (SD)	63.4 (9.55)	63.5 (9.22)
Birth cohort, n (%)		
pre-WWII	9,112 (24.9)	7,379 (24.6)
WWII	7,437 (20.3)	6,439 (21.5)
post-WWII	20,053 (54.8)	16,187 (53.9)
Region, n (%)		
Western Europe	14,591 (39.9)	12,499 (41.7)
Southern Europe	7,647 (20.9)	6,607 (22.0)
Central and Eastern Europe	10,015 (27.4)	7,003 (23.3)
Northern Europe	4,349 (11.9)	3,896 (13.0)
Education (years), mean (SD)	10.6 (4.18)	11.2 (4.43)
Marital status, n (%)		
Married/registered	24,150 (66.0)	24,266 (80.9)
Divorced/separated	4,034 (11.0)	2,488 (8.3)
Never married	1,883 (5.1)	1,776 (5.9)
Widowed	6,535 (17.9)	1,475 (4.9)
Employment status, n (%)		
Retired	17,152 (46.9)	16,464 (54.9)

	Females (n=36,602)	Males (n=30,005)
Employed	10,589 (28.9)	11,143 (37.1)
Other	8,861 (24.2)	2,398 (8.0)
Physical inactivity, n (%)	3,310 (9.0)	1,963 (6.5)
Limitations in IADL, mean (SD)	0.263 (0.764)	0.148 (0.621)
Depressive symptoms, n (%)	11,817 (32.3)	5,233 (17.4)
Myocardial infarction, n (%)	3,605 (9.8)	4,315 (14.4)
Hypertension, n (%)	13,687 (37.4)	10,587 (35.3)
Dyslipidemia, n (%)	8,335 (22.8)	6,648 (22.2)
Stroke, n (%)	1,098 (3.0)	1,134 (3.8)
Diabetes, n (%)	3,484 (9.5)	3,489 (11.6)
BMI, n (%)		
Underweight / normal	15,341 (41.9)	9,293 (31.0)
Overweight	13,427 (36.7)	14,692 (49.0)
Obese	7,834 (21.4)	6,020 (20.1)

Abbreviations: SD = standard deviation, IADL = instrumental activities of daily living, BMI = body mass index.

The rate of cognitive decline in immediate recall (e.g., B=0.002, 95% confidence interval [CI] -0.001 to 0.006 in Model 3, Table 7), delayed recall (e.g., B=0.000, 95% CI -0.004 to 0.004 in Model 3, Table 7), or verbal fluency (e.g., B=0.007, 95% CI -0.005 to 0.020 in Model 3, Table 7) in the fully adjusted model was the same for males and females. The estimates were similar in models adjusted for age (Model 1) and for sociodemographic covariates (Model 2, tables not presented). Consistently with previous studies (Ahrenfeldt, Scheel-Hincke et al. 2019), being female was associated with higher baseline cognition in all cognitive measures in the whole analytic sample.

Table 7 The relationship between participant's sex and cognition in fully adjusted models (Model 3, n=66,607)

	B (95% CI)		
	Immediate recall	**Delayed recall**	**Verbal fluency**
Intercept	4.159 *** (4.099; 4.219)	2.496 *** (2.421; 2.571)	18.001 *** (17.728; 18.273)
Female	0.405 *** (0.383; 0.427)	0.527 *** (0.500; 0.554)	0.435 *** (0.340; 0.531)

	B (95% CI)		
	Immediate recall	**Delayed recall**	**Verbal fluency**
Time	-0.028 *** (-0.030; -0.025)	-0.021 *** (-0.024; -0.018)	-0.103 *** (-0.112; -0.093)
Time × Female	0.002 (-0.001; 0.006)	0.000 (-0.004; 0.004)	0.007 (-0.005; 0.020)

* p<0.05   ** p<0.01   *** p<0.001

Abbreviations: B = unstandardized beta, CI = confidence interval, n = number of participants
Models adjusted for baseline age, region, birth cohort, education, working status, marital status, depressive symptoms, instrumental activities of daily living, physical inactivity, myocardial infarction, stroke, diabetes, hypertension, dyslipidemia, body mass index

In secondary models stratified by birth cohort, females born before the World War II had faster rate of decline in immediate recall (e.g., B=-0.010, 95% CI -0.017 to -0.003 in Model 3) and delayed recall (e.g., B=-0.012, 95% CI -0.020 to -0.005 in Model 3) across all models. Females born during World War II had slower rate of cognitive decline in immediate recall than males across all models (e.g., B=0.009, 95% CI 0.003 to 0.015 in Model 3). We found slower rate of cognitive decline in immediate recall also among females in the post-World War II cohort (e.g., B=0.005, 95% CI 0.001 to 0.009 in Model 3), although the magnitude was smaller than in the World War II cohort (e.g., B=0.009, 95% CI 0.003 to 0.015 in Model 3). There were no sex differences in the rate of decline in verbal fluency. Being female was associated with higher levels of baseline cognition in all cognitive measures across birth cohorts, except for verbal fluency in the pre-World War II cohort, and the magnitude of decline in cognitive abilities was larger for older cohorts.

In models stratified by region, females in Central and Eastern Europe had slower rate of cognitive decline in delayed recall compared to males (e.g., B=0.012, 95% CI 0.003 to 0.022 in Model 3). The rate of cognitive decline in immediate recall and in verbal fluency was similar in females compared to males across all regions. Models adjusted for baseline age and sociodemographic characteristics produced similar estimates. Being female was associated with higher baseline cognition in immediate recall and delayed recall in all regions, and lower baseline cognition in verbal fluency.

4.2 Study 2: Roots in childhood socioeconomic position

Among 84,059 participants (median age at baseline 62.0 (IQR 55-71); 54.9% females), females had higher baseline scores in cognition (0.03 ± 0.85) than men (-0.04 ± 0.80; <0.001, Cohen's d= -0.092), but there was no difference in their childhood SEP (Table 8).

Table 8 Sample characteristics in Study 2

	Females (n=46 148)	Males (n=37 911)
Cognition (z-score), mean ± SD	0.03 ± 0.85	-0.04 ± 0.80
Verbal fluency, mean ± SD	19.92 ± 7.67	20.18 ± 7.45
Immediate recall, mean ± SD	5.30 ± 1.81	5.09 ± 1.73
Delayed recall, mean ± SD	3.89 ± 2.15	3.59 ± 2.01
Childhood SEP, mean ± SD	0.00 ± 0.80	0.00 ± 0.80
Age, median (IQR)	62.00 (55.00 - 71.00)	62.00 (56.00 - 70.00)
Years of education, mean ± SD	10.47 ± 4.26	11.20 ± 4.40
Depressive symptoms, n (%)	10 043 (21.84)	4 048 (10.72)
Highest decile of household net worth, n (%) [a]	4 223 (9.15)	4 181 (11.03)
Current working status, n (%)	13 312 (29.01)	13 968 (36.95)
Children: 2 and more, n (%)	33 622 (72.86)	27 848 (73.46)
Grandchildren: 2 and more, n (%)	25 145 (54.49)	18 122 (47.80)
Living with a partner, n (%)	30 467 (66.02)	30 730 (81.06)
Limitations in IADL: 1 and more, n (%)	9 263 (20.07)	4 569 (12.05)
Chronic diseases: 1 and more, n (%)	22 273 (48.27)	16 526 (43.60)
CVD, n (%)	26 340 (57.10)	22 347 (58.96)
Body mass index, mean ± SD	26.65 ± 4.99	27.17 ± 4.03
Physical inactivity, n (%)	4 682 (10.15)	2 904 (7.66)
Smoking, n (%)	16 040 (34.87)	22 860 (60.48)
Alcohol use, n (%)	4 180 (9.06)	9 146 (24.13)
Maximal grip strength, mean (±SD)	26.77 (7.16)	43.91 (10.25)

binary variable instead of continuous was used for household ratio for comprehensive interpretation of the results.

Abbreviations: SD=standard deviation; IQR=interquartile range; IADL=instrumental activities of daily living; CVD=cardiovascular disease.

Depressive symptoms are defined by 4 and more points on EURO-D scale. Alcohol use is defined as drinking more than 2 glasses of alcohol almost every day.

In models adjusted for age, higher childhood SEP was significantly associated with higher baseline cognition in both sexes, but to a larger extent in females (B=0.238, 95% CI 0.203 to 0.271 in Model 1, Table 9) compared to males (B=0.208, 95% CI 0.180 to 0.235 in Model 1, Table 9). When adjusted also for education, the model attenuated by 40.3% in females and by 39.9% in males (Model 2, Table 9). Adjusting for depressive symptoms and all sociodemographic characteristics additionally reduced the coefficients by 9.9% in females and by 8.8% in males (Model 3, Table 9). In the fully adjusted models, the coefficients were further reduced by approximately 4.6% in females and 4.4% in males (Model 4, Table 9).

Table 9 The relationship between childhood SEP and baseline cognition

	B (95% CI)	
	Females (n= 46,148)	**Males** (n= 37,911)
Childhood SEP		
Model 1	0.238 (0.203; 0.271)***	0.208 (0.180; 0.235)***
Model 2	0.142 (0.110; 0.175)***	0.125 (0.097; 0.152)***
Model 3	0.128 (0.098; 0.159)***	0.114 (0.087; 0.141)***
Model 4	0.122 (0.092; 0.151)***	0.109 (0.084; 0.135)***

* p<0.05, ** p<0.01, *** p<0.001

Abbreviations: B=beta, CI=confidence interval, SEP=socioeconomic position.

Model 1: adjusted for age and practice effect.

Model 2: + education.

Model 3: + depressive symptoms and socioeconomic characteristics (household net worth, cohabitation status, number of children, number of grandchildren and current working status).

Model 4: + health related characteristics (body mass index, depressive symptoms, limitations in instrumental activities of daily living, maximum of grip strength, physical inactivity, number of chronic diseases, smoking status, cardiovascular disease and alcohol use).

The binary variable childhood socioeconomic disadvantage was associated with higher rate

of decline in delayed recall to a greater extent in females (B=-0.023, 95% CI -0.035 to -0.011 in Model 1, Table 10) compared to males (B=-0.018, 95% CI -0.032 to -0.005 in Model 1, Table 10). Childhood socioeconomic disadvantage was not associated with a decline in immediate recall nor in verbal fluency in either sex (Table 10).

Table 10 The relationship between childhood socioeconomic disadvantage and rate of cognitive decline, stratified by sex

		B (95% CI)	
		Females (n=41,140)	Males (n=33,139)
Delayed recall	Model 1	-0.023 (-0.035; -0.011)**	-0.018 (-0.032; -0.005)***
	Model 2	-0.022 (-0.034; -0.010)***	-0.018 (-0.032; -0.005)**
	Model 3	-0.022 (-0.034; -0.010)***	-0.018 (-0.032; -0.005)**
	Model 4	-0.020 (-0.023; -0.008)**	-0.019 (-0.032; -0.005)**
Immediate recall	Model 1	-0.005 (-0.015; 0.005)	0.003 (-0.008; 0.015)
	Model 2	-0.004 (-0.014; 0.006)	0.004 (-0.008; 0.015)
	Model 3	-0.005 (-0.015; 0.005)	0.003 (-0.008; 0.015)
	Model 4	-0.004 (-0.014; 0.006)	0.003 (-0.009; 0.014)
Verbal fluency	Model 1	-0.034 (-0.074; 0.007)	-0.030 (-0.079; 0.019)
	Model 2	-0.032 (-0.073; 0.008)	-0.030 (-0.079; 0.018)
	Model 3	-0.031 (-0.072; 0.010)	-0.034 (-0.082; 0.015)
	Model 4	-0.030 (-0.071; 0.011)	-0.033 (-0.082; 0.016)

* $p<0.05$, ** $p<0.01$, *** $p<0.001$
Abbreviations: B=beta, CI=confidence interval.
Model 1: adjusted for age and practice effect.
Model 2: + education.
Model 3: + depressive symptoms and socioeconomic characteristics (household net worth, cohabitation status, number of children, number of grandchildren and current working status).
Model 4: + health related characteristics (body mass index, depressive symptoms, limitations in instrumental activities of daily living, maximum of grip strength, physical inactivity, number of chronic diseases, smoking status, cardiovascular disease and alcohol use).

In the secondary analysis, the mediation model demonstrated a satisfactory fit to the data for both males and females (males: $\chi^2(24) = 4457.627$, root mean square error of approximation = 0.070 [90% CI 0.068 - 0.072], comparative fit index = 0.956, Tucker–Lewis index = 0.918; females: $\chi^2(24) = 3327.370$, root mean square error of approximation = 0.055 [90% CI 0.053 - 0.056], comparative fit index = 0.979, Tucker–Lewis index = 0.961). The model explained 40.1% of the variance in baseline total cognition among females and 34.6% among males. Education mediated 29.5% of the total effect between childhood SEP and baseline cognition in males, and 30.7% in females. This mediation effect was significantly stronger in females, although the effect size was small (d = 0.051, p < 0.001). Additionally, "physical state" mediated 14.6% of the total effect in males and 14.9% in females. Although the association was significantly stronger in females, the effect size was very small (d = 0.018, p < 0.01). In both males and females, the mediating effects of depressive symptoms between childhood SEP and baseline cognition were similarly small and negative, showing no sex difference (-0.002 in both sexes). Although childhood SEP had a proportionally stronger direct effect on the level of baseline cognition in males (48.3%) compared to females (46.8%), the absolute effect was slightly larger in females (0.2) than in males (0.1, d = 0.044, p < 0.001).

4.3   Study 3: Midlife reproductive history

4.3.1   *Study 3a: Number of children and dementia*

Among a total of 4,743 participants (mean age 74.0 ± 6.3 years, 58.6% females), there were 1,042 (22.0%) participants with no children, 484 (10.2%) participants with one child, 1,240 (26.1%) with two children, 968 (20.4%) participants with three children, and 1,009 (21.3%) participants with four or more children. Participants were followed-up for a median of 8 years (IQR 4-12 years). During the study, a total of 1,270 (26.8%) participants developed dementia and 1,568 (33.1%) participants died without dementia.

The proportion of those who achieved higher educational level was greater in both females and males without children (52.1% and 65.3%, respectively) compared to parents, although the difference was more notable among females. Regarding childhood socioeconomic variables, the proportions were similar across strata of number of children in females, whereas fathers of four or more children had the lowest maternal and paternal education and more

frequently reported absence of basic needs and luxuries during childhood. Participants' characteristics are presented in (Table 11).

Table 11 Sample characteristics in Study 3a

	Females (N= 2,778)	Males (N=1,965)
Baseline age, mean (SD)	74.5 (6.5)	73.4 (5.9)
College or more, n (%)	1241 (44.7)	1216 (61.9)
Marital status, n (%)		
Married / living as married	1183 (42.6)	1467 (74.7)
Separated / divorced	487 (17.5)	198 (10.1)
Widowed	921 (33.2)	161 (8.2)
Never married / other	187 (6.7)	139 (7.1)
Needs and luxuries, n (%)		
Basic needs only	675 (24.3)	441 (22.4)
Both	1783 (64.2)	1306 (66.5)
Neither	320 (11.5)	218 (11.1)
Paternal education, mean (SD)	10.9 (4.4)	11 (4.5)
Maternal education, mean (SD)	10.9 (3.7)	11.1 (3.6)
Depression, n (%)	290 (10.4)	153 (7.8)
Systolic BP, mean (SD)	141 (21.4)	138 (19.3)
antiHP medication, n (%)	1239 (44.6)	865 (44.0)
BMI, mean (SD)	27.3 (5.4)	27.6 (4.2)
Smoking, n (%)		
Never	1559 (56.1)	751 (38.2)
Past	1068 (38.5)	1135 (57.7)
Current	151 (5.4)	79 (4)
Diabetes, n (%)	272 (9.8)	242 (12.3)
Heart disease, n (%)	133 (4.8)	225 (11.5)
Stroke, n (%)	70 (2.5)	64 (3.3)

Abbreviations: SD = standard deviation, n = number of participants, antiHP = antihpyretensive medication, BMI = body mass index

In models adjusted for potential confounders, fathers of four or more children had higher rates of dementia compared to fathers of two children (HR 1.32, 95% CI 1.01 to 1.71 in Model 1). The HR was smaller for males without children (HR 1.26, 95% CI 0.95 to 1.66 in Model 1). Fathers of one child (HR 1.06, 95% CI 0. 0.73 to 1.55 in Model 1) and fathers of three children (HR 1.01, 95% CI 0.76 to 1.33 in Model 1) experienced the same rate of dementia as those with two children. We found no notable differences in rates of dementia in females in any model (Table 12). The model adjusted for potential confounders / mediators produced similar results for all groups of number of children.

Table 12 Relationship between number of children and incident dementia, stratified by sex

	HR (95% CI)			
	Female (N=2,778)		Male (N=1,965)	
	Model 1	Model 2	Model 1	Model 2
0 children	0.91 (0.73;1.13)	0.94 (0.76;1.17)	1.26 (0.95;1.66)	1.22 (0.92;1.61)
1 child	1.08 (0.84;1.39)	1.08 (0.84;1.39)	1.06 (0.73;1.55)	1.09 (0.75;1.60)
2 children	Ref.	Ref.	Ref.	Ref.
3 children	1.02 (0.83;1.25)	1.04 (0.85;1.28)	1.01 (0.76;1.33)	1.01 (0.77;1.34)
4 ≥ children	1.01 (0.83;1.23)	1.01 (0.83;1.23)	1.32 (1.01;1.71)	1.33 (1.03;1.73)

Abbreviations. HR=hazard ratio; CI=confidence interval.
Note. Analysis conducted on the imputed sample.
Model 1: adjusted for maternal education, paternal education, ability to afford basic needs and luxuries, education, marital status.
Model 2: + depressive symptoms, systolic blood pressure, antihypertensive medication, body mass index, smoking, diabetes, heart disease, stroke.

4.3.2   *Study 3b: Offspring sex and cognitive decline*

The analytic sample included 13,222 participants with at least one child (median age, 65; IQR, 59-73; 61.6% females). Among 10,872 (82.3%) participants who had at least one son, a total of 4,862 (44.7%) participants had one son, a total of 3,523 (32.4%) participants had two sons, and 2,487 (22.9%) participants had three or more sons. Participants in the final analytical sample had a total of 86,901 cognitive assessments over a median follow-up period of 14 years

(IQR, 8-16 years). A total of 5,809 (43.9%) participants died during follow up. We did not find differences in the sociodemographic and health-related characteristics between participants with at least one son and with no sons (Table 13).

Table 13 Sample characteristics in Study 3b

	At least one son	No son	Overall
Female, n (%)	6 697 (61.6%)	1 447 (61.6%)	8 144 (61.6%)
Cognition, mean (SD)	15.6 (4.51)	15.5 (4.58)	15.6 (4.52)
Age, mean (SD)	66.5 (9.18)	66.6 (10.0)	66.5 (9.34)
Number of children, n (%)			
one child	909 (8.4%)	891 (37.9%)	1 800 (13.6%)
two children	3 150 (29.0%)	905 (38.5%)	4 055 (30.7%)
three children	2 740 (25.2%)	347 (14.8%)	3 087 (23.3%)
four children	1 808 (16.6%)	139 (5.9%)	1 947 (14.7%)
five or more children	2 265 (20.8%)	68.0 (2.9%)	2 333 (17.6%)
Age at first birth < 20, n (%)	2 269 (20.9%)	349 (14.9%)	2 618 (19.8%)
Birth cohort, n (%)			
1899-1920	1 194 (11.0%)	342 (14.6%)	1 536 (11.6%)
1921-1928	2 134 (19.6%)	447 (19.0%)	2 581 (19.5%)
1929-1939	4 585 (42.2%)	828 (35.2%)	5 413 (40.9%)
1940-1950	2 959 (27.2%)	733 (31.2%)	3 692 (27.9%)
Race and ethnicity, n (%)			
Non-Hispanic White	8 385 (77.1%)	1 859 (79.1%)	10 244 (77.5%)
Hispanic	1 428 (13.1%)	313 (13.3%)	1 741 (13.2%)
Non-Hispanic Black	861 (7.9%)	142 (6.0%)	1 003 (7.6%)
Others	198 (1.8%)	36.0 (1.5%)	234 (1.8%)
Place of birth, n (%)			
Southern states, n (%)	3 699 (34.0%)	833 (35.4%)	4 532 (34.3%)
Other US states, n (%)	6 163 (56.7%)	1 334 (56.8%)	7 497 (56.7%)
Abroad, n (%)	1 010 (9.3%)	183 (7.8%)	1 193 (9.0%)

	At least one son	No son	Overall
Education, n (%)			
Less than high school or GED	3 165 (29.1%)	616 (26.2%)	3 781 (28.6%)
High school or some college	5 739 (52.8%)	1 280 (54.5%)	7 019 (53.1%)
College and above	1 968 (18.1%)	454 (19.3%)	2 422 (18.3%)
Father's education, mean (SD)[a]	8.88 (3.58)	8.97 (3.52)	8.90 (3.57)
Mother's education, mean (SD)[b]	9.18 (3.33)	9.35 (3.20)	9.21 (3.31)
Married/partnered, n (%)	7 473 (68.7%)	1 542 (65.6%)	9 015 (68.2%)
Diabetes, n (%)	1 516 (13.9%)	308 (13.1%)	1 824 (13.8%)
Heart disease, n (%)	2 101 (19.3%)	432 (18.4%)	2 533 (19.2%)
Stroke, n (%)	610 (5.6%)	145 (6.2%)	755 (5.7%)
Ever smoked, n (%)	6 247 (57.5%)	1 385 (58.9%)	7 632 (57.7%)
BMI, mean (SD)[c]	27.4 (5.23)	27.2 (5.36)	27.4 (5.25)
Depressive symptoms, mean (SD)[d]	1.50 (1.88)	1.49 (1.90)	1.50 (1.89)
Died, n (%)	4 767 (43.8%)	1 042 (44.3%)	5 809 (43.9%)

Abbreviations: SD=standard deviation; BMI=body mass index; GED=General Educational Development program.

Note: Percentage and mean and SD presented.

[a] Does not include 14.1% of participants who did not provide information on father's education.

[b] Does not include 10.0% of participants who did not provide information on mother's education.

[c] Does not include 1.3% of participants who did not provide information on BMI.

[d] Does not include 0.04% of participants who did not provide information on depressive symptoms.

In the model adjusted for baseline age, sex and race and ethnicity, we found a faster rate of cognitive decline in parents of at least one son (B= -0.015, 95% CI -0.029 to -0.002 in Model 1; Figure 11) compared to those without any sons. Models adjusted for additional sociodemographic and health-related variables produced similar results (Figure 11).
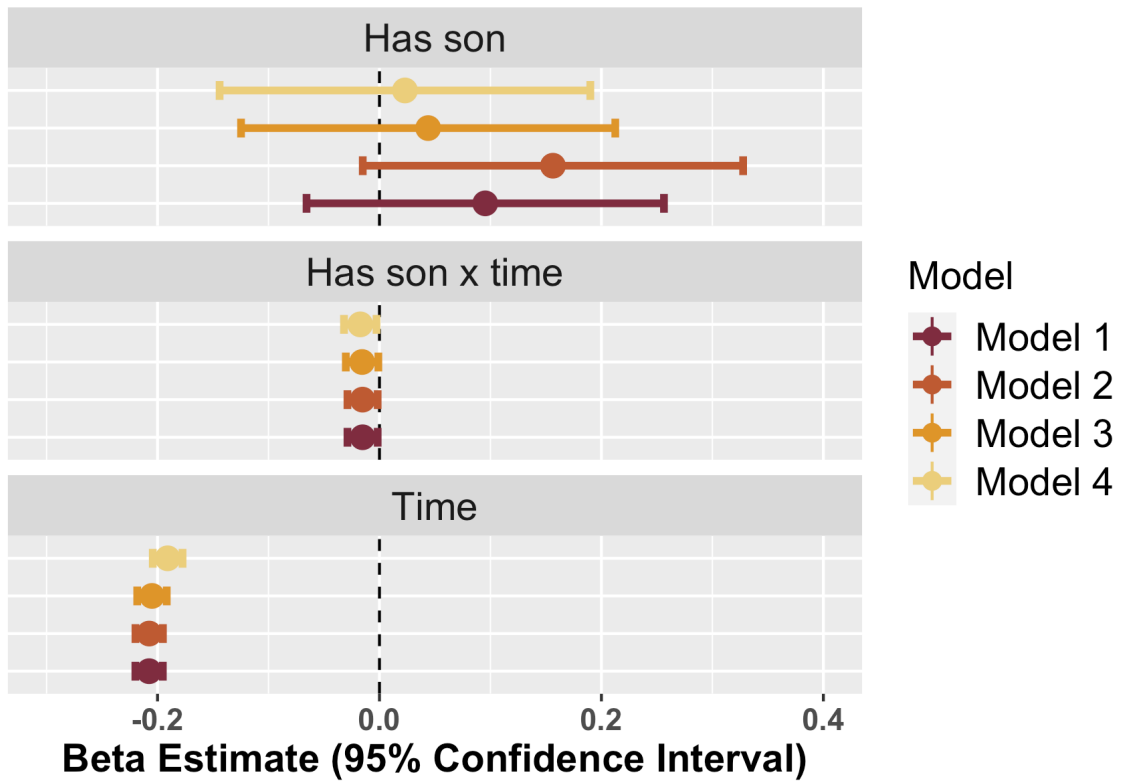
Figure 11 Relationship between having at least one son and cognition

Model 1: baseline age (in years, centered at median), sex and race and ethnicity
Model 2: + number of children
Model 3: + birth cohort, education, father's education, mother's education, age at the first birth, place of birth
Model 4: + marital status, smoking status, body mass index, depressive symptoms, diabetes, heart disease, stroke

When stratified by parental sex, the estimates of the association of having at least one son with the rate of cognitive decline were similar in both males (B= -0.016, 95% CI -0.036 to 0.005 in Model 1) and females (B= -0.014, 95% CI -0.032 to 0.004 in Model 1). Further adjustment for potential confounders did not change the results and the rate of cognitive decline in parents of at least one son was similar in both females and males (Figure 12).
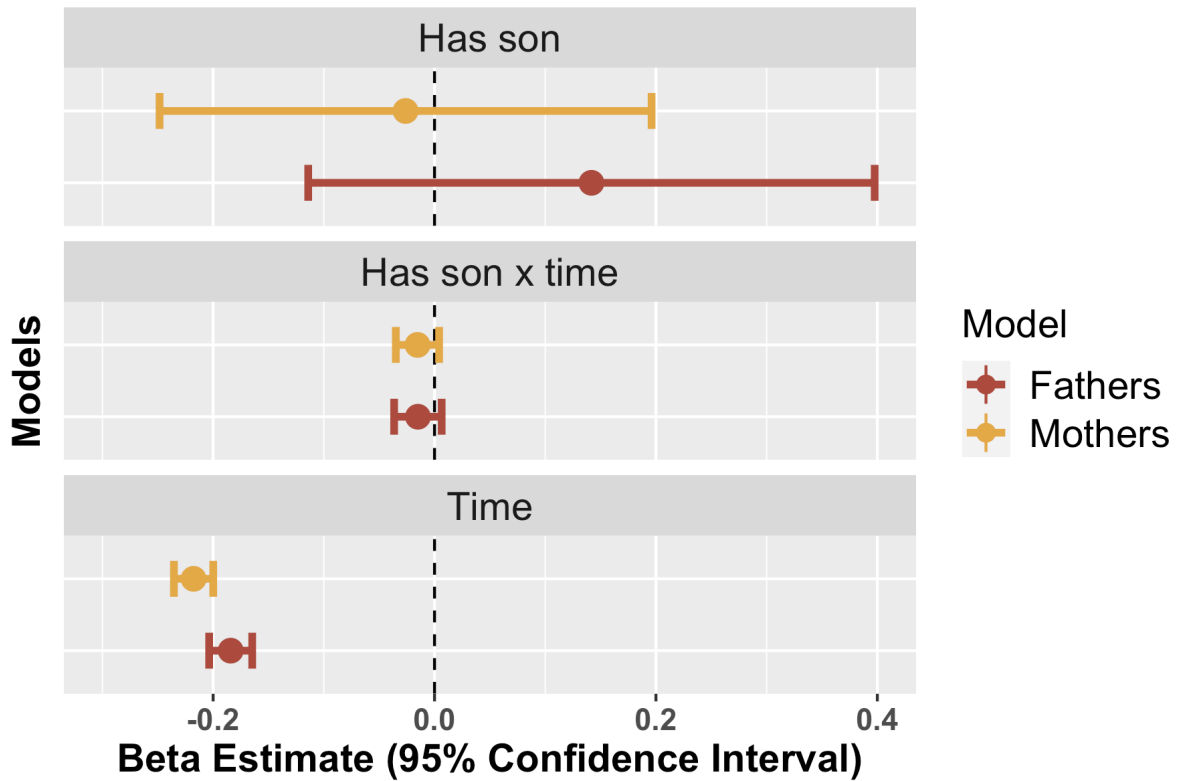
Figure 12 Relationship between having at least one son and cognition

Note: Estimates from linear mixed-effects models. Models are adjusted for baseline age, race and ethnicity, number of children, birth cohort, education, father's education, mother's education, age at the first birth, place of birth.

In the secondary analysis using an alternative primary exposure, having more sons was associated with a faster rate of cognitive decline, with a consistent association in parents of three or more sons across all models (e.g., B=-0.025, 95% CI -0.044 to -0.006 in the model adjusted for potential confounders). Having more sons was not associated with the level of baseline cognition.

In the secondary analysis using alternative outcomes, parents of at least one son had a faster rate of cognitive decline in delayed recall (e.g., B=-0.008, 95% CI -0.014 to -0.001 in the model adjusted for potential confounders), and in immediate recall (e.g., B=-0.005, 95% CI -0.011 to 0.000 in the model adjusted for potential confounders). We did not find any differences in the rate of cognitive decline in serial 7s (e.g., B=-0.003, 95% CI -0.008 to 0.002 in the model adjusted for potential confounders) and backwards counting (e.g., B=0.000; 95% CI -0.001 to 0.002; model adjusted for potential confounders).

4.4   Study 4: Mild behavioral impairment in later life

Among a total of 8,181 individuals (median age 63 years, 73% females), 11% of females and 14% of males had MBI syndrome (a score of more than 8 points on MBI-C, p for difference = 0.014). Participants had the median (IQR) of 1 (0 - 4) MBI symptoms. Females and males had different baseline distributions of individual MBI symptoms in 4 out of 5 domains: females showed more often symptoms of emotional dysregulation (45% vs. 36% in males; p<0.001), whereas less often symptoms of decreased motivation (25% vs. 30%; p<0.001), impulse dyscontrol (40% vs. 44%; p=0.001) and social inappropriateness (12% vs. 15%; p<0.001). The distribution of psychotic symptoms was similar among females compared to males. At baseline, females had lower cognitive scores than males in digit span (7.41 vs. 7.54; p=0.001), paired association learning (4.54 vs. 4.50; p=0.03) and self-ordered search (7.54 vs. 7.88; p<0.001), but higher in verbal reasoning (32.69 vs. 31.87; p<0.001, d=0.093). Males were on average older at baseline, more educated, were more frequently married, less commonly employed and had higher prevalence of hypertension, heart disease, diabetes, and hypercholesterolemia (Table 14).

Table 14 Sample characteristics in Study 4

	Females (n=5,970)	**Males (n= 2,211)**
Age, median (IQR)	61.8 (56.9–66.8)	64.8 (59.5–69.5)
White ethnic origin, n (%)	5 569 (93.3)	2 089 (94.5)
Married/co-habiting, n (%)	4 603 (77.1)	1 979 (89.6)
Education level, n (%)		
Low	755 (12.65)	286 (12.9)
Middle	3 963 (66.4)	1 354 (61.3)
High	1 252 (21.0)	570 (25.8)
Employed, n (%)	2 506 (42.0)	799 (36.2)
Cognition		
Digit span, mean ± SD	7.41 ± 1.48	7.54 ± 1.45
Paired associate learning, mean ± SD	4.54 ± 0.76	4.50 ± 0.74
Verbal reasoning, mean ± SD	32.70 ± 8.98	31.87 ± 8.70
Spatial working memory, mean ± SD	7.55 ± 2.04	7.88 ± 2.26
MBI		
MBI syndrome (< 8 points), n (%)	656 (10.99)	300 (13.57)
Decreased motivation, n (%)	1 508 (25.26)	669 (30.26)

	Females (n=5,970)	Males (n= 2,211)
Emotional dysregulation, n (%)	2 701 (44.8)	797 (35.6)
Impulse dyscontrol, n (%)	2 350 (39.36)	962 (43.51)
Social inappropriateness, n (%)	704 (11.79)	336 (15.20)
Psychotic symptoms, n (%)	405 (6.78)	127 (5.74)
BMI, median (IQR)	24.2 (22.1–27.3)	25.3 (23.2–27.8)
Hypertension, n (%)	1 420 (23.85)	741 (33.71)
Heart disease, n (%)	160 (2.7)	184 (8.4)
Diabetes, n (%)	135 (2.3)	117 (5.3)
Hypercholesterolemia, n (%)	211 (3.5)	122 (5.6)

Abbreviations. IQR = interquartile range, SD = standard deviation, MBI = mild behavioral impairment, BMI = body mass index.

The MBI syndrome was associated with a lower level of paired associate learning score only in males (B -0.158, 95% CI -0.245 to -0.072 in Model 1, Table 15). The estimates obtained from the model adjusted for sociodemographic characteristics and from the fully adjusted model were similar (Table 15). Impulse dyscontrol was associated with a lower level of digit span score only in males (B=-0.229, 95% CI -0.351 to -0.108 in Model 1, Table 15) and with paired associate learning score only in males (B=-0.093, 95% CI -0.153 to -0.033 in Model 1, Table 15). Estimates obtained from models adjusted for sociodemographic characteristics and for health-related characteristics were mildly attenuated (Table 15).

Table 15 Relationship between mild behavioral impairment and the level of cognitive performance, stratified by sex

	B (95% CI)			
	Digit span		Paired associate learning	
	Females	Males	Females	Males
MBI syndrome				
Model 1	-	-	-0.036 (-0.096; 0.024)	-0.158 (-0.245; -0.072)***
Model 2	-	-	-0.029 (-0.089; 0.032)	-0.153 (-0.240; -0.066)***
Model 3	-	-	-0.023 (-0.084; 0.038)	-0.154 (-0.241; -0.067)***

	B (95% CI)			
	Digit span		**Paired associate learning**	
	Females	**Males**	**Females**	**Males**
Impulse dyscontrol				
Model 1	-0.074 (-0.150; 0.003)	-0.229 (-0.351; -0.108)***	-0.019 (-0.058; 0.020)	-0.093 (-0.153; -0.033)**
Model 2	-0.066 (-0.143; 0.011)	-0.200 (-0.321; -0.078)**	-0.016 (-0.055; 0.023)	-0.080 (-0.141; -0.020)**
Model 3	-0.061 (-0.138; 0.016)	-0.200 (-0.321; -0.080)**	-0.014 (-0.053; 0.024)	-0.080 (-0.140; -0.019) **

*** p<0.001 ** p<0.01 * p<0.05

Note. CI, confidence interval; MBI, mild behavioral impairment

Model 1: baseline age

Model 2: + employment status, ethnic origin, co-habitation status, education level)

Model 3: + body mass index, hypertension, history of heart disease, diabetes, hypercholesterolemia

In analysis stratified by sex, the MBI syndrome, decreased motivation and impulse dyscontrol were associated with a higher rate of decline in verbal reasoning in both sexes, but to a greater extent in males than females (Table 16). Emotional dysregulation was associated with the rate of decline in verbal reasoning only in females (B=-0.175, 95% CI -0.297 to -0.052 in Model 1, Table 16), whereas social inappropriateness (B=-0.298, 95% CI -0.564 to -0.031 in Model 1, Table 16) and psychotic symptoms (B=-0.554; 95% CI -0.977 to -0.132 in Model 1, Table 16) were associated with a higher rate of decline in verbal reasoning only in males. The estimates were similar in model adjusted for sociodemographic characteristics and in the fully adjusted model (Table 16). We did not find any sex differences in cognitive decline in other measures.

Table 16 Relationship between mild behavioral impairment and the rate of decline in verbal reasoning, stratified by sex

	B (95% CI)	
	Females	**Males**
MBI syndrome		
Model 1	-0.282 (-0.479; -0.084)**	-0.324 (-0.604; -0.045)*
Model 2	-0.282 (-0.479; -0.084)**	-0.325 (-0.604; -0.046)*
Model 3	-0.273 (-0.472; -0.074) **	-0.323 (-0.602; -0.043)*
Emotional dysregulation		
Model 1	-0.175 (-0.297; -0.052)**	-0.178 (-0.376; 0.021)

	Females	**Males**
Model 2	-0.175 (-0.297; -0.052)**	-0.176 (-0.375; 0.022)
Model 3	-0.172 (-0.295; -0.049)**	-0.177 (-0.376; 0.022)
Decreased motivation		
Model 1	-0.229 (-0.371; -0.088)**	-0.334 (-0.541; -0.127)**
Model 2	-0.231 (-0.372; -0.090)**	-0.334 (-0.541; -0.128)**
Model 3	-0.223 (-0.364; -0.081)**	-0.335 (-0.542; -0.128)**
Impulse dyscontrol		
Model 1	-0.135 (-0.260; -0.010)*	-0.216 (-0.407; -0.024)*
Model 2	-0.135 (-0.260; -0.011)*	-0.216 (-0.407; -0.024)*
Model 3	-0.133 (-0.259; -0.008)*	-0.211 (-0.403; -0.019)*
Social inappropriateness		
Model 1	-0.188 (-0.378; 0.003)	-0.298 (-0.564; -0.031)*
Model 2	-0.190 (-0.380; 0.001)	-0.297 (-0.563; -0.031)*
Model 3	-0.186 (-0.378; 0.005)	-0.283 (-0.550; -0.016)*
Psychotic symptoms		
Model 1	-0.160 (-0.408; 0.087)	-0.554 (-0.977; -0.132)*
Model 2	-0.159 (-0.406; 0.088)	-0.557 (-0.978; -0.135)**
Model 3	-0.143 (-0.392; 0.106)	-0.553 (-0.976; -0.131)*

The header **B (95% CI)** spans both the Females and Males columns.

*** $p < 0.001$ ** $p < 0.01$ * $p < 0.05$

Note. B, beta; CI, confidence interval; MBI, mild behavioral impairment

Model 1: baseline age, sex

Model 2: + employment status, ethnic origin, co-habitation status, education level

Model 3: + body mass index, hypertension, history of heart disease, diabetes, hypercholesterolemia

5   Discussion

5.1   Summary

Findings from the presented studies reveal several insights into sex differences and cognitive aging. Study 1 suggests limited overall sex differences in cognitive decline, but the variations observed among birth cohorts and regions emphasize the influence of contextual and historical factors on cognitive aging trajectories. Study 2 highlights that low childhood SEP has a greater negative impact on cognition in females, with education playing a significant mediating role. These findings underscore the importance of early-life experiences and social determinants in shaping cognitive outcomes in later life.

Study 3 provides insights into the potential influence of parenthood on cognitive health. Although in Study 3a fathers with four or more children had an increased risk of dementia, the lack of a similar association in females raises intriguing questions about the underlying mechanisms and the need for further exploration. Study 3b expands on the parental influence by indicating a slightly faster cognitive decline in parents with at least one son, regardless of parental sex. These findings suggest a potential role of sociocultural factors related to parenting experiences in cognitive aging.

Lastly, Study 4 sheds light on the relationship between MBI and cognitive aging, highlighting sex differences in symptom prevalence and their impact on cognition. Males exhibit a higher frequency of MBI symptoms and their association with cognitive decline, while emotional dysregulation appears to be particularly relevant to females. These findings suggest that considering behavioral and emotional factors alongside cognitive measures may provide a more comprehensive understanding of age-related cognitive changes.

Overall, these findings emphasize the importance of considering sex-specific effects when studying cognitive aging and associated risk factors. Individual studies are further discussed in detail.

5.2   Study 1: Sex differences in cognitive decline among older Europeans

In this population-based study capitalizing on 66,607 participants from 19 European countries, we observed no evidence of sex differences in cognitive decline within the overall sample. However, when examining potential variations among different birth cohorts, we found that

females in the oldest birth cohort exhibited a faster decline in memory compared to males, while females in younger cohorts had slower decline in memory relative to males. Furthermore, except for Central and Eastern Europe, where females experienced slower cognitive decline than males, we did not observe significant variations in sex differences in cognitive aging across European regions. These findings remained consistent even after accounting for various sociodemographic and health-related factors. It is worth noting that in line with previous studies, females exhibited higher baseline performance than males across all measures, both in the overall sample and when stratified by birth cohort and region.

Our findings based on the analysis of the overall sample align with a systematic review conducted between 2001 and 2011, which indicated no sex differences in cognitive decline among older adults aged 60 to 80 years (Ferreira, Ferreira Santos-Galduróz et al. 2014). However, subsequent longitudinal studies published after the review yield mixed findings. A study conducted in the US, combining data from five cohorts with up to 21 years of follow-up, observed faster decline in global cognition and executive function among females, while rates of memory decline, a domain particularly affected by AD, were similar (Levine, Gross et al. 2021). Another US-based study, with up to 9 years of follow-up, found that males exhibited a faster rate of decline in mental status, perceptuomotor speed and integration, and visuospatial ability, but rates of decline in memory were comparable to females (McCarrey, An et al. 2016). In Europe, a Dutch study based on two large aging cohorts identified a faster memory decline in females (Nooyens, Wijnhoven et al. 2022). On the other hand, females in an English study exhibited a slower decline in memory compared to males (Zaninotto, Batty et al. 2018). Additionally, another study from the UK combined data from two cohorts and reported a slower decline in memory in females only among participants born between 1946 and 1955, but analysis of older birth cohorts did not show any sex differences (Bloomberg, Dugravot et al. 2021). These inconsistent findings may be attributed to secular trends over time.

Our findings indicate variability in sex differences in the rate of cognitive decline among different birth cohorts. One possible explanation of this variation might be the competing risk of death. While females traditionally have had higher life expectancy than males, the disparity in mortality between the sexes has been narrowing (Sundberg, Agahi et al. 2018). Consequently, it might appear that fewer males in older birth cohorts experience cognitive problems due to increased mortality rates in this group. Another contributing factor might be selective survival. One group of participants who are more likely to live longer, in our case males in older cohorts, may possess other characteristics that protect them from dementia.

Previous literature has emphasized the significance of competing risk of death and selective survival in sex differences in dementia incidence, while acknowledging that additional mechanisms may contribute to this inequality (Shaw, Hayes-Larson et al. 2021).

Our results don't allow us to draw conclusions about specific reasons for the observed slower cognitive decline among females in younger birth cohorts and faster decline in females in older birth cohorts. One plausible explanation is that societal advancements in the 20th century, such as increasingly better childhood living standards, could have contributed to a decline in dementia incidence and improved cognitive health (Rocca 2017), with potentially varying effects on cognitive outcomes between females and males. Research indicates that early-life socioeconomic conditions influence later-life health outcomes more strongly in females compared to males (Janicki-Deverts, Cohen et al. 2012), suggesting that females may benefit more from improvements in early-life factors. Another possible explanation might relate to the closing sex gap in educational inequalities over the 20th century in Europe (Permanyer and Boertien 2019). The attainment of higher education among females has led to improved earning potential and access to a wider range of careers. Further, high educational attainment and occupational complexity play a vital role in the development and maintenance of cognitive abilities throughout life (Stern 2009). Adjusting for years of education and current employment status did not affect our estimates. However, we cannot rule out residual confounding as other aspects of education and employment, such as the quality of education, resource access, social connections, and job opportunities across the lifespan, may contribute to the observed sex difference.

Sex differences in dementia incidence differ based on the studied region (Andrew and Tierney 2018). In our study, females in Central and Eastern Europe exhibited slower cognitive decline, which may be attributed to differences in social structures and the interplay between social factors and general health. Experiences related to one's sex in this region are distinct compared to other European countries. For example, the labor force participation under the totalitarian state social system was almost the same for males and females as all eligible adults were mandated to work by law (Pérez-Izquierdo and Pronkina 2023). Although the influence of occupation on cognitive decline is not fully clear (Marquie, Duarte et al. 2010, Fisher, Stachowski et al. 2014, Then, Luck et al. 2015, Pool, Weuve et al. 2016) (Singh-Manoux, Marmot et al. 2011, Hyun, Katz et al. 2021), it is possible that females might have been benefited from high rates of participation in labor force. We might have partially addressed this

issue by controlling for baseline employment, however, it is likely that there is residual confounding caused by an effect of length and types of occupation during the life course.

Next, the delay in cardiovascular risk reduction, with distinct patterns between males and females, is evident in Central and Eastern Europe compared to Western Europe (Hartley, Marshall et al. 2016, Cífková, Bruthans et al. 2020). For instance, a study from the Czech Republic revealed a decrease in hypertension prevalence among females, while Lithuania reported an increase among males during the same period (Tamosiunas, Klumbiene et al. 2016, Cífková, Bruthans et al. 2020). Conversely, Sweden experienced an overall increase in hypertension prevalence except among males aged 45-55 (Törmä, Carlberg et al. 2015). Although adjustment for hypertension and other cardiovascular and metabolic factors had minimal impact on our results, we did not have information on comorbid conditions during midlife, which might have greater effect on cognition. Despite the consistent observations of higher prevalence of dementia in females, the underlying reasons for this sex disparity are still not clear. Our study did not find substantial sex differences in cognitive decline in memory; however, the observed variation across birth cohorts and regions indicates the potential influence of sociocultural factors in shaping sex differences in cognitive aging. Our findings highlight the importance of conducting additional research to uncover the pathways and develop policies aimed at addressing sex disparities in cognitive aging.

5.3   Study 2: Roots in childhood socioeconomic position

Studying a large population-based cohort of over 80,000 individuals from 20 European countries and Israel, we found that the impact of low SEP during childhood on worse cognitive performance is more pronounced in females compared to males. Further, this difference could not be accounted for by other socioeconomic and health-related risk factors. However, the effects of childhood socioeconomic disadvantage on the rate of cognitive decline show less clarity, as we observed the association only in delayed recall. Our study reveals that education plays a significant role as a mediator between childhood SEP and baseline cognition, with a stronger association observed in females.

Our results are in line with previous studies that show that females, compared to males, are more likely to experience negative long-term effects of childhood socioeconomic disadvantage on their health (Ryff, Krueger et al. 2018, Suglia, Koenen et al. 2018). Taking cardiovascular health as an example, the relationship between childhood socioeconomic status and obesity,

hypertension and risk of myocardial infarction was found to be more pronounced in females compared to males (Hamil-Luker and O'Rand 2007, González, Nazmi et al. 2009, Janicki-Deverts, Cohen et al. 2012, Pudrovska, Reither et al. 2014). Only a few previous studies have examined whether the relationship between childhood SEP and cognition in later life varies by sex (Hurst, Stafford et al. 2013, Lyu 2015, Suglia, Koenen et al. 2018). A study based on a birth cohort from the UK identified a slightly stronger association between childhood socioeconomic status and reaction time in males compared to females (Hurst, Stafford et al. 2013). Another study from the UK found that socioeconomic hardship during childhood was associated with decreased rates of decline in memory, executive functions and global cognition in females compared to males (Zaninotto, Batty et al. 2018). A study from the US reported no sex difference in the association between a composite childhood SEP and the rate of decline in memory, but they found that being well-off during childhood was associated with a faster rate of decline in memory in males but not in females (Lyu 2015).

Contrary to the findings of these previous studies (Hurst, Stafford et al. 2013, Lyu 2015), our results indicate that the relationship between SEP and cognition is stronger in females. While we found consistent sex differences in the association with the level of cognitive performance across three measures, the sex difference in the association with the rate of cognitive decline held only for memory measured by delayed recall. Our findings are supported by a study from the US that identified an association between childhood hunger, an indicator of severe socioeconomic hardship, and worse cognition only in females (Barnes, Peterson et al. 2020). The underlying biological mechanisms might operate through sex-specific stress response pathways. Adverse experiences stemming from low childhood socioeconomic status can lead to dysregulation of the hypothalamic-pituitary-adrenal axis (Winchester, Sullivan et al. 2016). Early-life exposure to increased levels of corticotropin-releasing hormone has been linked to thinning of specific cortical regions associated with cognition, and this relationship appears to be more pronounced in females (Ivy, Rex et al. 2010, Curran, Sandman et al. 2017, Sandman, Curran et al. 2018). As a result, females who experience socioeconomic hardship in childhood may have lower cognitive reserve compared to males, thereby might have lower ability to tolerate neuropathologic changes in later life.

Among the examined mediators, education had the largest mediating effect on the association between childhood SEP and baseline cognitive level. While the strong link between family's socioeconomic resources and children's education is well-established, sex differences in this relationship are less clear (Lawlor, Batty et al. 2005). Our findings suggest that education plays

a significant role in improving cognitive outcomes associated with early life conditions to a greater degree in females compared to males. Although the difference was statistically significant, it might have been attributed to the large sample size.

Prior research suggests that females derive greater advantages from education compared to males in mitigating the negative impact of adverse childhood SEP, as previously reported in the context of depression (Schaan and Medicine 2014, Csajbók, Kagstrom et al. 2021). Ross and Mirowsky's theory of resource substitution offers an explanation for this sex disparity (Ross, Mirowsky et al. 2006). The theory suggests that having access to various resources mitigates the negative consequences of lacking any specific resource. Given that females have lower levels of power, authority, independence, and earnings compared to males, education serves them as a substitute for these resources (Ross, Mirowsky et al. 2006). As a result, education may compensate for the deficit of alternative resources in females with low childhood SEP, while males may rely more on these alternative resources.

The study suggests that addressing childhood socioeconomic adversity may help alleviate the disproportionate burden of cognitive disorders later in life to a higher degree in females than males. Considering the higher prevalence of cognitive disorders among females, our findings suggest that enhancing educational opportunities can potentially have a more substantial effect on cognitive health of females. However, it is important to note that while education plays a role as a mediator, its effect is relatively limited for both females and even more limited for males.

5.4 Study 3: Midlife reproductive history

5.4.1 *Study 3a: Number of children and dementia*
In the present study, which utilized data from a sample of older US adults who were followed up for a median of 8 years, we found weak evidence of an association between higher number of children and increased risk of dementia. Fathers who had four or more children had an increased dementia rate relative to fathers of two children. The increased risk of dementia was not explained by social factors such as early-life socioeconomic conditions and marital status, nor by baseline cardiovascular risk factors and depressive symptoms. The risk of dementia did not differ across strata of children in females.

Our findings indicate that the number of children may predominantly influence brain health outcomes by means of pathways involving health behaviors and life course social factors. We did not observe any association among females, challenging previous studies, which propose that the connection between number of children and brain health is attributable to hormonal and cardiometabolic changes during pregnancy (Bae, Lipnicki et al. 2020, Bae, Lipnicki et al. 2020, Harville, Guralnik et al. 2020, Jung, Lee et al. 2020). Assuming there is a biological mechanism that connects the number of children born to the risk of dementia through pregnancy-related effects, it is conceivable that this effect is overshadowed by social and behavioral factors. While the number of children in females could potentially serve as an indicator of endogenous estrogen exposure, which has been suggested as a risk factor for dementia (Prince, Acosta et al. 2012), it is important to acknowledge that the number of children is interconnected with various other aspects of life, and the relationship might be influenced by these factors. For example, it is worth noting that females in our study had a higher average level of education compared to the general population.

Although both parents share experiences related to raising a child, the impact of becoming a parent on health and behavior can differ in strength and direction depending on the individual's sex and gender role. For instance, prior research indicates that the addition of each child is associated with weight gain in both mothers and fathers (Laroche, Wallace et al. 2013), but other behavioral changes might be more sex-specific. For example, the transition to parenthood has been shown to be linked to smoking cessation exclusively in mothers (Bricard, Legleye et al. 2017). Although we adjusted for current smoking status in our analysis, it is possible that more granular data would help to elucidate the link between higher number of children and increased dementia risk in fathers.

Moreover, many previous studies have shown that females' socioeconomic status in the US is inversely associated with the number of children they have, whereas this correlation has not been observed in males (Fieder, Huber et al. 2005, Huber, Bookstein et al. 2010). Postponing having children in order to pursue higher education and increase income is more common among females than males, which results in a sex gap in reproductive output across strata of socioeconomic groups (Nitsche and Hayford 2020). In other words, higher socioeconomic status is more strongly linked to lower number of children in females than in males. Lower SEP has been shown to correspond with worse access to healthcare and poor health behaviors, which subsequently increases the risk of dementia in later life and may lead to sex disparities in dementia risk (Marden, Tchetgen Tchetgen et al. 2017). Although in our study, early life

socioeconomic indicators were distributed similarly across different categories of the number of children in females, levels of maternal and paternal education were notably lower among fathers with four or more children. This group also reported lacking basic needs and luxuries during childhood more often than males with less children. Despite accounting for multiple indicators of SEP, it is possible that our study suffers from residual confounding.

The results of our study, indicating a higher prevalence of dementia among males with a larger number of children, emphasize the importance of considering both biological and social pathways in future investigations. Exploring potential mechanisms, such as health behaviors, can provide insight into the relationship between the number of children and dementia. Furthermore, conducting further research that incorporates additional early-life factors associated with parity could shed more light on these findings.

5.4.2 *Study 3b: Offspring sex and cognitive decline*
In the present study, which includes a representative sample of middle-aged and older adults in the US, we observed that parents with at least one son experienced a slightly faster rate of cognitive decline. Although this difference was relatively small in comparison to the overall decline in cognition over time, it remained significant even after accounting for various sociodemographic and health-related characteristics. We observed similar patterns between having sons and cognitive decline in both mothers and fathers, although the strength of this relationship was somewhat weaker in comparison to the overall sample. Furthermore, our findings indicated that cognitive decline was accelerated among parents who had multiple sons compared to those who only had daughters. We did not find any difference in baseline cognitive levels between parents without sons and parents with at least one son.

Our study presents a novel perspective challenging previous research that has suggested a connection between having male offspring and improved maternal health. Some studies have proposed that pregnancies with boys may offer a protective effect on maternal health outcomes through the effects of male microchimerism, presence of fetal DNA and cells in maternal tissues that persist years after delivery (Kamper-Jørgensen, Hjalgrim et al. 2014, Hallum, Gerds et al. 2020). However, these studies are limited by the omission of crucial social variables related to parenting boys, including factors like lower rates of divorce or higher socioeconomic status among parents of boys. In case these variables were considered, the effect of having sons would likely be observed in both fathers and mothers or would attenuate after adjusting for

sociodemographic factors. Although we did not directly measure male microchimerism, we controlled for various sociodemographic and health-related variables in a sample encompassing both males and females. Our findings demonstrated that cognitive decline occurred at a faster rate in both mothers and fathers who had sons compared to those who did not, suggesting that shared aspects of parenting sons may have negative effects on parental cognition.

However, our results align with evidence from studies conducted on non-human subjects, which have indicated that bearing male offspring is associated with accelerated maternal aging (Douhard, Festa-Bianchet et al. 2020, Froy and Gamelon 2020). These findings have been attributed to the increased resource demands during pregnancy with male fetuses, as well as higher maternal energy investment following birth (Douhard, Festa-Bianchet et al. 2020). Similar mechanisms have been suggested in humans, as male newborns tend to have higher average birth weight (Loos, Derom et al. 2001) and the birth of a male offspring is often followed by a longer interval until next conception (Mace and Sear 1997). Moreover, some previous studies have reported higher long-term mortality rate in mothers of sons, although not all studies have found this association (Jasienska, Nenko et al. 2006, Cesarini, Lindqvist et al. 2007, Næss, Mortensen et al. 2017). To address potential differences in mortality among parents of sons, we accounted for selective attrition through joint modeling, which yielded results consistent with those obtained from linear mixed-effects models.

Research investigating the association between the number of offspring and parental cognition highlights the significance of considering the social aspects of parenting in human studies. Previous studies have shown that mothers and fathers of two children have better health outcomes compared to other groups (Ning, Zhao et al. 2020). However, while in more traditional societies having sons may be expected to enhance the family's socioeconomic resources, this may not hold true in the contemporary US (Hurt, Ronsmans et al. 2006). On the contrary, having daughters might be more beneficial as they tend to provide more social support and are more likely to become caregivers (Friedman, Shih et al. 2015, Cascella Carbó and García-Orellán 2020). Additionally, having daughters or sons might have differential effects on parental health behaviors. For instance, mothers of daughters tend to have lower body weight long after delivery compared to mothers of sons (Pham-Kanter 2010). Further, parents of daughters are less inclined to engage in smoking, alcohol consumption, or drug use (Powdthavee, Wu et al. 2009). Our findings indicate that having sons is associated with a faster

rate of cognitive decline rather than the baseline level of cognition, suggesting the potential influence of later-life factors.

Our findings provide evidence in favor of the hypothesis that having sons is linked to enduring negative consequences for parents. While the exact mechanisms underlying this relationship require further investigation, our results indicate that the pathways involved are predominantly social in nature, as we observed similar patterns in both mothers and fathers.

5.5   Study 4: Mild behavioral impairment in later life

In this study, we investigated the role of sex in the relationship between MBI and cognitive aging. Males were affected by symptoms of MBI in individual domains more often compared to females. Specifically, they experienced decreased motivation, impulse dyscontrol, and social inappropriateness more frequently. The syndrome of MBI (total MBI-C score) and specific domains were found to be linked to the baseline cognitive level and the rate of decline across the entire sample. When we considered sex differences, the relationship was present only in males or was more pronounced in males in most of the domains, whereas emotional dysregulation was associated with worse cognition only in females.

Our findings extend existing literature on sex differences in MBI as previous studies have mostly focused on differences in the prevalence of MBI symptoms. For example, one population-based study reported that older males had symptoms of decreased motivation and impulse dyscontrol more frequently than older females (Mortby, Ismail et al. 2018). Other studies of older adults found that apathy, agitation and irritability was more common in males than females (Hölttä, Laakkonen et al. 2012, Geda, Roberts et al. 2014). Our results show that males and females differ not only in the prevalence of non-cognitive symptoms of dementia during the early stages of the diseases but also in the relationship between individual non-cognitive and cognitive symptoms. These differences could potentially be attributed to the complex nature of cognitive disorders, including differences in structural and functional correlates, neurochemical variations, as well as the fact that cognitive disorders arise from various distinct underlying brain pathologies that may affect females and males in an unequal manner.

Neuropathological changes in the entorhinal cortex present one of the potential correlates that could help elucidate our findings. Previous research has established a connection between

neuropathological changes in the entorhinal cortex and impulse dyscontrol, a symptom that encompasses agitation, disinhibition, gambling, obsessiveness, behavioral perseveration, or stimulus binding and is one of the recognized characteristics of neurodegenerative diseases. (Ismail, Agüera-Ortiz et al. 2017, Matuskova, Ismail et al. 2021). Further, volumetric loss in the entorhinal cortex and hippocampus have been found to be associated MBI (Matuskova, Ismail et al. 2021), and tau-PET signal in the entorhinal cortex and hippocampus is higher among individual who score higher on the MBI-C scale (Johansson, Stomrud et al. 2021). Further, another study reported that impulse dyscontrol is related to brain changes in fornix, superior fronto-occipital fasciculus, cingulum, uncinate fasciculus and lower cortical thickness in the parahippocampal gyrus (Gill, Wang et al. 2021). Moreover, a US-based study revealed that males with amyloid pathology, indicative of AD, exhibit a faster volumetric decline in the entorhinal and parahippocampal regions compared to females, indicating greater resilience against volumetric loss in these specific regions among females (Armstrong, Huang et al. 2019).

Nevertheless, structural and functional correlates alone may not provide a comprehensive explanation for the observed sex differences, as these symptoms could potentially relate to underlying sex differences in brain neurochemistry. While the literature on sex differences in the serotonergic system in individuals with cognitive disorders is sparse, several previous studies have examined sex disparities in serotonin neurotransmission across other psychiatric conditions (Cosgrove, Mazure et al. 2007). For instance, estrogens exert a modulatory influence on 5-HT1A receptors, which has been proposed as one of the factors contributing to the higher prevalence of depression among females (Kaufman, DeLorenzo et al. 2016). The decline in neuroprotective effects of estrogen during menopausal changes in females, including its impact on neurotransmitter synthesis, synaptic plasticity, and mitochondrial activity, could potentially contribute to the distinct manifestations of MBI symptoms (Conde, Verdade et al. 2021). Additionally, serotonin has been demonstrated to play an important role in the development of NPS. Specifically, genetic variation in the serotonin receptor gene 5-HT2A has been linked to the presence of hallucinations and delusions in patients diagnosed with AD (Tang, Wang et al. 2017, Burstein 2021).

Finally, females and males are affected disproportionately by distinct types of dementia, which are characterized by different NPS. The occurrence of psychotic symptoms is observed in approximately 50% of patients with Parkinson's disease dementia and dementia with Lewy bodies, both of which are less prevalent in females than males, whereas psychotic symptoms

occur in only around 30% of patients with AD, a type of dementia that is more common among females (Nelson, Schmitt et al. 2010, Smith and Dahodwala 2014, Gallagher, Fischer et al. 2017). Late onset of psychiatric symptoms is of special diagnostic importance in diagnosis of dementia with Lewy bodies and has been proposed as one of the three main diagnostic criteria of the prodromal phase (McKeith, Ferman et al. 2020). Furthermore, decreased motivation and the presence of psychotic symptoms have emerged as robust indicators of disease progression in frontotemporal degeneration, a condition that seems to be more prevalent among males (Ranasinghe, Rankin et al. 2016, Santacruz Escudero, Beltrán et al. 2019, de Boer, Riedl et al. 2021). Additionally, recent studies suggest that females diagnosed with the behavioral variant of frontotemporal dementia demonstrate a higher resilience to cope with neuropathological changes compared to males. Despite having a similar level of atrophy, females have fewer behavioral symptoms, such as apathy, in contrast to their male counterparts (Illán-Gala, Casaletto et al.). On the contrary, the progression of AD, where females constitute 60% of patients, has frequently been associated with the occurrence of depressive symptoms (Santacruz Escudero, Beltrán et al. 2019, Desai, Charlesworth et al. 2020)

In summary, our study presents distinctive findings indicating sex disparities in the prevalence of MBI symptoms and in their relationship with baseline level of cognition and cognitive decline in older adults. Our results demonstrate that older males who develop MBI symptoms prior to cognitive impairment are more susceptible to accelerated cognitive decline compared to females, particularly in the presence of psychotic symptoms and symptoms of decreased motivation. To fully comprehend the role of sex in the relationship between MBI symptoms and neurodegenerative pathology, additional longitudinal studies with biomarker assessment are needed.

5.6   Methodological considerations

The strength of the presented studies is the use of large samples of older adults from Europe and the US. Moreover, all the presented studies are longitudinal, allowing us to follow studied individuals over an extended period and to examine changes and trends over time. Although longitudinal studies enable us to better understand cause-and-effect associations, we cannot draw definitive causal conclusions based on observational studies. Observational studies are prone to confounding, which occurs when an unmeasured or inadequately controlled factor is

associated with both the exposure and outcome. Such confounding might lead to spurious associations or mask true relationships.

In addition, the presented studies might suffer from selection bias, which occurs when the study population is not representative of the target population or when certain groups are more likely to be included or excluded. Although SHARE and HRS are population-based studies with carefully designed enrolment strategies, we still observed that the participants had higher education than the general population. Even greater selection might be expected in PROTECT and ACT. Selection bias can affect the generalizability of our findings.

Further, observational studies rely on the quality and completeness of the data collected. Thus, our studies might suffer from information bias, which occurs when there is a difference between the information recorded and the true values of the variables of interest. We assume that the exposure and outcome would be equally misclassified among males and females and our studies would suffer mostly from non-differential misclassification.

The following sections discuss strengths, limitations, and potential biases related to the individual presented studies.

5.6.1   Study 1: Sex differences in cognitive decline among older Europeans

Strengths of this study inclusion of a wide range of European regions including previously underrepresented countries of Central and Eastern Europe. We utilized multiple cognitive assessments over up to 17 years of follow-up, and our findings remained consistent in sensitivity analyses. Moreover, we adjusted for a wide range of sociodemographic and health-related factors, including often overlooked limitations in IADL and depressive symptoms (Levine, Gross et al. 2021). On the other hand, we did not control for early life characteristics, leaving room for residual confounding. Future studies may need to consider factors such as childhood SEP, more granular data on education and occupational complexity to better understand underlying pathways that drive sex differences in cognitive decline. Another limitation is that we could not include death as a competing risk, which likely influences sex differences in dementia incidence (Shaw, Hayes-Larson et al. 2021), because the data on mortality for our cohort were not available.

5.6.2   Study 2: Roots in childhood socioeconomic position

Although previous studies show satisfactory internal and external validity of early-life histories

in SHARE (SHARELIFE) (Havari and Mazzonna 2015), retrospectively collected data might suffer from recall bias. However, our main results are further supported by results from the sensitivity analysis in which we created an alternative exposure using a different set of indicators of childhood SEP (Annex 1). Second, it is possible that healthier individuals were overrepresented in the study, which could result in an underestimation of the observed associations. Individuals who experienced socioeconomic hardship during their upbringing are at a higher risk of cardiovascular mortality in later life (Stringhini, Zaninotto et al. 2018). Third, we cannot exclude a possibility of residual confounding. We did not account for other potential important confounders such as genetic factors and innate cognitive abilities. Nevertheless, this study represents the largest longitudinal, population-based study to date, utilizing consistent data from most European countries, to examine sex differences in the relationship between childhood SEP and cognitive aging.

5.6.3 Study 3: Midlife reproductive history

5.6.3.1 Study 3a: Number of children and dementia

The strength of this study is that we used data from a prospective observational cohort comprising over 4,700 participants, with a follow-up period of up to 24 years. The ACT study employs a biennial comprehensive cognitive screening test, and dementia diagnoses are established through consensus, minimizing the likelihood of misclassification bias or underdiagnosis. Additionally, our data included important and often underreported early-life factors to mitigate confounding. Our study is limited in restriction to individuals aged 65 years and above, who were recruited from Kaiser Permanente Washington healthcare system in the broader Seattle area. This cohort exhibits higher levels of educational attainment and socioeconomic status compared to the average population in the US, with a predominantly non-Hispanic white composition. Consequently, the findings may not generalize to other populations or geographic regions. Next, although we adjusted for baseline health factors in sensitivity analysis, there is potential for residual confounding due to unmeasured conditions, for example due to heart and vascular health in midlife (McGrath, Beiser et al. 2017). Although it is unlikely that the main exposure, number of children, would be self-reported incorrectly, other data, such as health conditions, might suffer from recall bias. Lastly, it is important to note that our analysis solely focuses on biological children. The observation that a higher number of children is associated with elevated rates of dementia exclusively in males implies the involvement of social mechanisms. Consequently, the exclusion of stepchildren and

adopted children from the analysis may have introduced a bias towards null results.

5.6.3.2 Study 3b: Offspring sex and cognitive decline

The strength of this study is that our sample size was substantial and based on data from a population-based study. To address potential confounding, we accounted for race, ethnicity, and whether the participant was born in a Southern state or abroad. Extensive literature shows persisting cognitive disparities among Black individuals born in the South that may stem from the impact of historical trauma, deprivation, and segregation (Liu, Glymour et al. 2015). In sensitivity analysis, we employed a methodological approach that accounted for the competing risk of death, minimizing the potential bias that could arise from differential attrition. However, our study is subject to certain limitations that should be taken into consideration. First, we were unable to differentiate between participants' biological, adopted, or stepchildren, potentially introducing bias in the results pertaining to mothers if the biological pathways of pregnancy play a role in the association between having a son and cognition. Furthermore, despite the extensive range of data available in the HRS, certain important factors could not be controlled for, including sex differences in parenting, caregiving throughout the life course, social and emotional aspects of the parent-child relationship, and risk-taking behaviors of children (Woodley of Menie, Schwartz et al. 2016, Liao and Scholes 2017, Hallum, Gerds et al. 2020). Lastly, it is important to note that our findings may not be generalizable to other populations that differ in social, cultural, and economic characteristics from the nationally representative sample of US adults aged 50 years and older, born between 1899 and 1950.

5.6.4 *Study 4: Mild behavioral impairment in later life*

The strength of our study is the use of MBI rather than relying on an algorithm to convert another neuropsychological scale. We employed a validated MBI-C tool along with a comprehensive battery of four tests that assess multiple cognitive domains. This allowed us to explore all possible connections between MBI and cognition. Although our study's follow-up period for a cognitively healthy community dwelling sample is relatively short, it represents the most extensive and detailed neuropsychological analysis of MBI conducted to date. Our study has several limitations. Because people with higher educational attainment, White people and females were overrepresented in the PROTECT study, our findings might not be generalizable to the whole British population. Second, even though participants who self-reported a diagnosis of dementia are not included in the PROTECT study, it is possible that

some participants might have been in an early stage of the disease. However, findings from the sensitivity analysis that included only participants without any indication of mild cognitive impairment produced similar results as our main analysis. Third, we acknowledge that our study conducted a substantial number of statistical tests, thereby increasing the potential for type I error. Finally, although the observed effect sizes are relatively small, they hold significance at a population level.

5.7   Summary and future directions

Our findings shed light on the identification of modifiable risk factors during a life course that can impact cognition, providing valuable insights into the disparities in the relationship between sex and cognitive health and individual risk factors. These studies collectively suggest that there are nuanced variations in cognitive aging across different populations and birth cohorts, with potential differences between males and females. Socioeconomic factors, such as childhood SEP and education, appear to play a significant role in shaping cognitive performance and decline, particularly in females. Sex appears to play a less important role in the relationship between reproductive history and cognitive health of females and males than originally thought. Finally, presence of individual NPS prior to cognitive impairment plays a different role in risk assessment for females and males. By considering these multifaceted factors, we can gain a better understanding of the complex interplay between sex and cognitive aging, contributing to future research and interventions aimed at tailoring optimal strategies for both males and females.

6   Ethical considerations

SHARE was approved by the Ethics Committee of the University of Mannheim. All participants signed written informed consent and were informed about the storage and use of data and their right to withdraw informed consent. All data were pseudo-anonymized.

The ACT study was approved by the institutional review boards of Kaiser Permanente Washington, Columbia University, and the University of Washington. All participants signed written informed consent and were informed about their rights. All data were pseudo-anonymized.

HRS was approved by the Ethics Committee of the University of Michigan and the National Institute on Aging. All participants signed written informed consent and were informed about their rights. All data were pseudo-anonymized.

PROTECT was approved by the London Bridge National Research Ethics Committee (Reference: 13/LO/1578), all participants provided informed consent via an online platform and were informed about their rights. Their data were pseudo-anonymized.

Annex 1

Sensitivity analyses in Study 1

Methods

We conducted two sets of sensitivity analyses. In the first sensitivity analysis, we used a data set with increased sample size (n=73,315) which included participants from countries that had joined SHARE in wave 7 (Western Europe (n=1,204): Ireland; Southern Europe (n=1,700): Cyprus, Malta; Central and Eastern Europe (n=3,114): Lithuania, Latvia, Romania, Bulgaria, Slovakia; Northern Europe (n=254): Finland). These new participants had two observations in two time points on immediate recall and delayed recall and they had available information on all covariates used in the main analysis. Verbal fluency was not measured. In the second sensitivity analysis, we refitted our models using imputed data set provided by SHARE team (described in detail at http://www.share-project.org/data-documentation.html) that includes participants from wave 1 to wave 7 (n=71,922). Model 1 was adjusted for baseline age; Model 2 for age, birth cohort, region, education, employment status and marital status; and Model 3 for the same covariates as Model 2 plus physical inactivity, limitations in IADL, depressive symptoms, BMI and total number of chronic diseases.

Results

In the sensitivity analysis with the increased sample size, females had slower cognitive decline in immediate recall compared to males (e.g., B=0.007, 95% CI 0.004 to 0.011 in Model 3), whereas the rate of cognitive decline in delayed recall was similar in females compared to males (e.g., B=0.003, 95% CI -0.001 to 0.007 in Model 3). The sensitivity analysis based on imputed data set produced similar results as the main analysis.

Sensitivity analyses in Study 2

Methods

To check the robustness of our findings, we conducted a sensitivity analysis with an alternative exposure variable. Childhood SEP was operationalized as the sum score of four binary variables that characterized socioeconomic conditions at the time the participant was 10 years old: (1) the main breadwinner's occupational position (low skilled vs. high skilled), (2) number of books at home (less than 10 vs. 10 or more), (3) overcrowding (more than 1 person per 1

room vs. 1 person per 1 room or less), and (4) poor housing quality (lacking all of the following features: fixed bath, cold running water supply, hot running water supply, inside toilet, and central heating vs. having at least one of the features). We constructed the same sets of multilevel linear regression models as in the main cross-sectional analysis.

Results

Using an alternative measure of childhood SEP, we found that sex was a moderator in the association between childhood SEP and the baseline level of cognitive performance (p from LR test < 0.05). Stratifying by sex and using the most advantaged group as a reference category, we found a strong socioeconomic gradient across all four entries (disadvantaged, middle, advantaged, and most advantaged) in the level of cognitive performance in the fully adjusted model in both females and males (table not included).

Sensitivity analyses in Study 3a

Methods

We conducted three sets of sensitivity analyses. First, to assess the robustness of our results, we refitted the models using a complete case data set (n=3,668). Second, we included only parents of at least one child and adjusted the models for age at first birth. We created a variable to younger age at first birth using sex-specific age cut offs for timing of births. The cut off values were selected based on previous literature (Read and Grundy 2017). Based on the distributions in our sample, younger age at first birth in females was defined as less than 20 years and less than 23 years in males.

Results

Both analyses of complete cases (HR= 1.16, 95% CI 0.97 to 1.40) and analysis of parents that adjusted also for parental age at first birth (HR= 1.11, 95% CI 0.95 to 1.30) produced similar results as the main analysis.

Sensitivity analyses in Study 3b

Methods

To ensure robustness of our results, we conducted three sets of sensitivity analyses using the whole sample. First, to investigate the impact of missing data on covariates we repeated the analysis using only complete cases who had all variables used in Model 4 (n=10,827). Second, we restricted the sample to parents of two or more children and adjusted the model for age at the first birth (< 20 years old, ≥20 years old). Third, to address potential selection bias caused by mortality, as observed in previous studies, we employed a joint model using the R package "JM" (Rouanet, Avila-Rieger et al. 2022). The joint model simultaneously integrates a linear mixed-effects model, which considers cognition as a continuous outcome, and a Cox model, which treats death as a time-to-event process, while also accounting for their common random effects.

Results

We did not find any substantial differences in results from the analysis of complete cases (B=-0.017; 95% CI -0.032 to -0.002; model adjusted for potential confounders). Models that considered only parents of two or more children produced similar results as the models in the main analysis (B=-0.021, 95% CI -0.038 to -0.003). Results from the joint model were similar to results from linear mixed-effects models (B=-0.016; 95% CI -0.031 to -0.001; model adjusted for potential confounders). Having at least one son was not associated with the level of baseline cognition in any model.

Sensitivity analyses in Study 4

Methods

We performed two sets of sensitivity analyses. First, we included a three-way interaction of MBI and sex with age group (55-65 vs. 65 and more) and then stratified the analysis by age groups and sex where the interaction was significant. Because the prevalence of NPS is lower in younger patients with AD (van Vliet, de Vugt et al. 2012, Zhao, Tan et al. 2016), the prevalence of MBI might follow the same age group pattern. Moreover, recent research suggests that the association between genetic factors and cognitive decline is stronger in older age (Creese, Arathimos et al. 2021). Second, we restricted the sample to participants without indication of cognitive impairment. We used self-reported mild cognitive impairment (n=15) at baseline and a baseline level of cognitive performance 1.5 or more standard deviations below

the average (indicating mild cognitive impairment) on 2 or more cognitive domains (n=325) as indicators of cognitive impairment.

Results

We found an interaction (p value from LR test < 0.05) between MBI and age group in cognitive performance in paired associate learning. In the analysis stratified by age group, we found similar associations as in the cross-sectional analysis only in the group of older males (65 years or older, table not presented). When we re-fitted the linear mixed effects models on a sample of cognitively healthy individuals, we obtained similar results as in the main analysis. Specifically, we the domain of psychotic symptoms was associated with faster rate of decline in verbal reasoning in all three models only in males. Decreased motivation was associated with faster rate of decline verbal reasoning to a greater extent in males across all three models (table not presented).

Annex 2

List of published studies that formed the basis of this thesis:

Study 2: Wolfova, K., Csajbok, Z., Kagstrom, A., Kåreholt, I., & Cermakova, P. (2021). *Role of sex in the association between childhood socioeconomic position and cognitive ageing in later life.* Scientific Reports, 11(1), Article 1. https://doi.org/10.1038/s41598-021-84022-1

Study 3b: Wolfova, K., Wu, D., Weiss, J., Cermakova, P., Kohler, H.-P., Skirbekk, V. F., Stern, Y., Gemmill, A., & Tom, S. E. (2022). *Sons and parental cognition in mid-life and older adulthood.* Journal of Psychiatric Research, 156, 284–290. https://doi.org/10.1016/j.jpsychires.2022.10.026

Study 4: Wolfova, K., Creese, B., Aarsland, D., Ismail, Z., Corbett, A., Ballard, C., Hampshire, A., & Cermakova, P. (2022). *Gender/Sex Differences in the Association of Mild Behavioral Impairment with Cognitive Aging.* Journal of Alzheimer's Disease, 88(1), 345–355. https://doi.org/10.3233/jad-220040

List of manuscripts in preparation that formed the basis of this thesis:

Study 1: Wolfova, K., Frycova, B., Seblova, D., Tom, S., Skirbekk, V., Cermakova, P. *Sex differences in cognitive decline among European middle-aged and older adults.*

Study 3a: Wolfova, K., Hubbard, R., Cermakova, P., Chang,V., Crane, P., LaCroix, A., Larson, E., Tom, S. *Number of children and risk of dementia.*

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