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Autoreferát disertační práce

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

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Abstrakt

Úvod: Nerovnoměrné rozdělení sociálních a zdravotních rizikových faktorů v průběhu života může vést k rozdílům mezi muži a ženami v riziku demence a kognitivním stárnutí. Cílem této práce je přispět k lepšímu porozumění toho, co způsobuje nerovnosti v kognitivním stárnutí mezi muži a ženami. Konkrétně jsme se zaměřili na zkoumání rozdílů mezi pohlavími v míře poklesu kognitivních funkcí u starších dospělých Evropanů (Studie 1), souvislostí mezi socioekonomickou pozicí v dětství a kognicí (Studie 2), počtem dětí a rizikem demence (Studie 3a), pohlavím potomků a kognicí (Studie 3b) a mírnou poruchou chování a kognicí (Studie 4).

Metody: Provedli jsme celkem pět studií za použití čtyř kohort dospělých středního a staršího věku žijících ve 21 zemích napříč Evropou, v Izraeli a ve Spojených státech amerických. Data jsme čerpali ze Survey of Health, Ageing and Retirement in Europe (Studie 1 a 2), z amerických Health and Retirement Study (Studie 3a) a Adult Changes in Thought (Studie 3b) a z britské Platform for Research Online to Investigate Genetics and Cognition in Aging (Studie 4). Kognice byla měřena testy pro okamžité vybavení, oddálené vybavení a verbální fluenci (Studie 1, 2), testy pro okamžité a oddálené vybavení, sedmičkovým testem a odečítacím testem (Studie 3b) a pomocí testů na řadu čísel, párové asociativní učení, prostorovou pracovní paměť a verbální uvažování (Studie 4). Ve Studii 3a byla demence diagnostikována na základě konsenzu panelu expertů dle DSM IV kritérií. V analýzách jsme použili lineární regresní modely, lineární modely se smíšenými efekty a Coxovy modely.

Výsledky: Ve Studii 1 byla rychlost kognitivního poklesu kognice měřené testy okamžitého vybavení (interakce pohlaví × čas: B=0,002; 95% CI -0,001; 0,006), oddáleného vybavení (interakce pohlaví × čas: B=0,000; 95% CI -0,004; 0,004) nebo verbální fluence (interakce pohlaví × čas: B=0,007; 95% CI -0,005; 0,020) podobná pro muže a ženy. Při zohlednění rozdílů mezi kohortami dle roku narození a regionálních rozdílů se rychlost poklesu kognitivních funkcí mezi pohlavími lišila. Ve Studii 2 jsme našli vztah mezi vyšší socioekonomickou pozicí v dětství a vyšší kognicí měřenou na začátku studie u obou pohlaví, vztah byl ale silnější u žen (B=0,238; 95% CI 0,203; 0,271) než u můžu (B=0,208; 95% CI 0,180; 0,235). Socioekonomické znevýhodnění v dětství souviselo s rychlejším poklesem oddáleného vybavení ve větší míře u žen (B=-0,023; 95% CI -0,035; -0,011) ve srovnání s muži (B=-0.018; 95% CI -0.032; -0.005). Ve Studii 3a měli otcové čtyř a více dětí vyšší riziko demence ve srovnání s otci dvou dětí (HR=1,317; 95% CI 1,014; 1,710), u žen jsme nenašli žádné rozdíly v riziku demence. Ve Studii 3b jsme našli rychlejší kognitivní pokles u rodičů alespoň jednoho syna (B=-0,015; 95% CI -0,029; -0,002) ve srovnání s těmi, kteří neměli žádné syny, bez výraznějších rozdílů mezi matkami a otci. Ve Studii 4 byl syndrom mírné poruchy chování spojen s nižší úrovní skóre párového asociativního učení pouze u mužů (B=-0,158; 95% CI -0,245; -0,072).

Diskuze: Naše výsledky naznačují, že existují menší variace v kognitivním stárnutí napříč různými populacemi a kohortami, s potenciálními rozdíly mezi muži a ženami. Výsledky ukazují, že rizikové faktory během raného, středního a pozdějšího života mají rozdílný vliv na muže a ženy. Budoucí studie by měly brát v úvahu význam rozdílů mezi muži a ženami ve vztahu mezi rizikovými faktory a kognitivním stárnutím.

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

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.

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).

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 Alzheimer's disease (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). 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).

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). Other studies 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). Similarly, cognitive health in older adulthood might be shaped by early childhood experiences with varying effects in females and males.

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). However, studies that would explore sex differences in the relationship between number of children and dementia are lacking.

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). An opposite relationship was found between male microchimerism of foetal origin and maternal health outcomes. 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). It is not known for how long after delivery this effect persists and whether the effect of parenting boys versus daughters rather than biological effect of pregnancy is the same in both males and females.

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. 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.

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 SEP

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 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 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.

3.2 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.

3.3 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).

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

Data on participants comes from four European regions 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.

Our exposure was participant's self-reported sex (as described above) and our outcome was 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.

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 (in years), 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, limitations in activities of daily living, physical inactivity, heart disease, stroke, diabetes, hypertension, dyslipidemia, body mass index).

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.

3.5 Study 2: Roots in childhood SEP

In the present study, we used data from SHARE encompassing participants from up to 19 European countries. Our 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.

Our exposures were childhood SEP and childhood socioeconomic hardship. 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 [101-200 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.

Our outcome was 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).

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 (household net worth, current working status, cohabitation status, umber of children, number of grandchildren); and Model 4 additionally for health-related characteristics (number of limitations in activities of daily living, cardiovascular disease, number of chronic diseases, physical inactivity, body mass index, smoking, alcohol use, maximal grip strength).

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.

3.6 Study 3: Midlife reproductive history

Study 3a: Number of children and dementia

We used data from the ACT Study. Participants were recruited in the Greater Seattle area in the US state of Washington. Final analytic sample included 4,743 participants.

Our exposure was number of children and our outcome was the diagnosis of dementia (dementia, no dementia). 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). 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.

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, body mass index).

Study 3b: Offspring sex and cognitive decline

We utilized data from the HRS in the US. 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.

In the primary analysis, the exposure was offspring sex created as a binary indicator defined as no son vs. at least one son. In the secondary analysis, the exposure was offspring sex represented by a categorical variable number of sons (no sons, one son, two sons, three or more sons). 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.

Our outcome was 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.

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.

3.7 Study 4: Mild behavioral impairment in later life

We utilized data from the British PROTECT study. Our final analytical sample comprised 8,181 individuals with a median follow-up of 3.07 years (interquartile range [IQR] 2.02-3.22). Only participants with complete data on MBI-C and cognition were included in the analyses.

Our exposure was MBI. 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 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).

Our outcome was 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.

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 (ethnic origin, education level, employment status, co-habitation status), and Model 3 additionally for health-related characteristics (hypertension, heart disease, diabetes, hypercholesterolemia, body mass index).

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). Thus, we stratified the analysis by sex. We added additional covariates as fixed effects: sociodemographic characteristics in Model 2, and health-related characteristics in Model 3. 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. 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.

The rate of cognitive decline in immediate recall (B=0.002, 95% CI -0.001 to 0.006 in Model 3), delayed recall (B=0.000, 95% CI -0.004 to 0.004 in Model 3), or verbal fluency (B=0.007, 95% CI -0.005 to 0.020 in Model 3) 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.

In secondary models stratified by birth cohort, females born before the World War II had faster rate of decline in immediate recall (B=-0.010, 95% CI -0.017 to -0.003 in Model 3) and delayed recall (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 (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 (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 (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 (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 SEP

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.

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) compared to males (B=0.208, 95% CI 0.180 to 0.235 in Model 1). When adjusted also for education, the model attenuated by 40.3% in females and by 39.9% in males (Model 2). 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). In the fully adjusted models, the coefficients were further reduced by approximately 4.6% in females and 4.4% in males (Model 4).

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) compared to males (B=-0.018, 95% CI -0.032 to -0.005 in Model 1). Childhood socioeconomic disadvantage was not associated with a decline in immediate recall nor in verbal fluency in either sex.

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 to 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 to 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

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.

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 71 in Model 1). Fathers of one child (HR 1.06, 95% CI 0. 0.73 to 1.55 71 in Model 1) and fathers of three children (HR 1.01, 95% CI 0.76 to 1.33 71 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. The model adjusted for potential confounders / mediators produced similar results for all groups of number of children.

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.

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) compared to those without any sons. Models adjusted for additional sociodemographic and health-related variables produced similar results.

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, 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.

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 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 (B=-0.008, 95% CI -0.014 to -0.001 in the model adjusted for potential confounders), and in immediate recall (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 (B=-0.003, 95% CI -0.008 to 0.002 in the model adjusted for potential confounders) and backwards counting (B=0.000, 95% CI -0.001 to 0.002 in the 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). 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).

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). The estimates obtained from the model adjusted for sociodemographic characteristics and from the fully adjusted model were similar. 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). In stratified models, 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) and with paired associate learning score only in males (B=-0.093, 95% CI -0.153 to -0.033 in Model 1). Estimates obtained from models adjusted for sociodemographic characteristics and for health-related characteristics were mildly attenuated.

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. 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), whereas social inappropriateness (B=-0.298, 95% CI -0.564 to -0.031 in Model 1) and psychotic symptoms (B=-0.554, 95% CI -0.977 to -0.132 in Model 1) 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. We did not find any sex differences in cognitive decline in other measures.

5 Discussion

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. 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. Some previous studies show faster decline in certain cognitive domains among females, while others find no significant differences or even slower decline (Ferreira, Ferreira Santos-Galduróz et al. 2014, Zaninotto, Batty et al. 2018, Levine, Gross et al. 2021). These inconsistencies may be due to factors such as changes in mortality rates and selective survival. Our results suggest that societal advancements

and improvements in early-life factors could contribute to the observed differences in cognitive decline between females and males.

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. 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).

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. Our results challenge 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).

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. 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). 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.

Lastly, Study 4 sheds light on the relationship between MBI and cognitive aging, highlighting sex differences in symptom prevalence and their impact on cognition. 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. Males in our study 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.

6 Conclusion

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.

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