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The associations of socioeconomic position with structural brain damage and connectivity and cognitive functioning: The Maastricht Study

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ABSTRACT

Background: Socioeconomic inequalities in cognitive impairment may partly act through structural brain damage and reduced connectivity. This study investigated the extent to which the association of early-life socioeconomic position (SEP) with later-life cognitive functioning is mediated by later-life SEP, and whether the associations of SEP with later-life cognitive functioning can be explained by structural brain damage and connectivity.
Methods: We used cross-sectional data from the Dutch population-based Maastricht Study (n = 4,839; mean age 59.2 ± 8.7 years, 49.8% women). Early-life SEP was assessed by self-reported poverty during childhood and parental education. Later-life SEP included education, occupation, and current household income. Participants underwent cognitive testing and 3-T magnetic resonance imaging to measure volumes of white matter hyperintensities, grey matter, white matter, cerebrospinal fluid, and structural connectivity. Multiple linear regression analyses tested the associations between SEP, markers of structural brain damage and connectivity, and cognitive functioning. Mediation was tested using structural equation modeling.
Results: Although there were direct associations between both indicators of SEP and later-life cognitive functioning, a large part of the association between early-life SEP and later-life cognitive functioning was explained by later-life SEP (72.2%). The extent to which structural brain damage or connectivity acted as mediators between SEP and cognitive functioning was small (up to 5.9%).
Conclusions: We observed substantial SEP differences in later-life cognitive functioning. Associations of structural brain damage and connectivity with cognitive functioning were relatively small, and only marginally explained the SEP gradients in cognitive functioning.

1. Introduction

Low socioeconomic position (SEP) has been related to an increased risk for cognitive impairment and dementia (A.-Y. Wang et al., 2023). SEP is a complex multidimensional construct that can be defined as a measure of one's combined economic and social status, including education, occupation, and income. A recent meta-analysis showed that low educational attainment and low income are related to an increased

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combined risk for cognitive impairment and dementia (A.-Y. Wang et al., 2023). This is in line with the cognitive reserve hypothesis that states that older adults with higher cognitive ability and associated factors (e.g., intelligence, education and occupation) have a lower risk of dementia compared to individuals with lower cognitive ability despite similar levels of brain pathology (Whalley et al., 2004). The influence of SEP on cognitive ageing may already start early in life, although the effect of early-life SEP on later-life cognitive performance has been suggested to be mediated by later-life SEP (Beck et al., 2018; McElroy et al., 2021). Education is a major indicator of SEP, but the importance of education for cognitive functioning causes an important conceptual problem when investigating SEP-cognition relationships. Innate cognitive reserve, or intelligence, contributes to higher educational attainment levels and subsequently reaching a higher SEP (Lee, 2003). This risk for reversed causation needs to be considered in the research design.

Whether biological pathways can explain the association between SEP and cognitive impairment is not yet clear (Whalley et al., 2006). Multiple developmental changes in the brain that may contribute to structural brain damage occur during midlife, including a reduction in grey matter volume (regions of the brain that mainly contain neuronal cell bodies), particularly in regions associated with cognitive functioning, changes in the white matter (the nerve fibers that facilitate communication between brain regions), reduced blood flow regulation, atherosclerosis, hypertension, neuroinflammation (chronic low-grade inflammation in the brain), and oxidative stress (physiological imbalance between reactive oxygen species production and antioxidant defense mechanisms) (Mattson and Arumugam, 2018; Raz and Rodrigue, 2006; Sweeney et al., 2018; Wardlaw et al., 2013). Structural brain damage, including brain atrophy (Pini et al., 2016) and cerebrovascular damage (Rensma et al., 2018), are important underlying mechanisms involved in the etiology of cognitive impairment and dementia. Indicators of both early-life (Murray et al., 2014) and later-life (Chan et al., 2018; Dougherty et al., 2020; Waldstein et al., 2017) SEP have been shown to be related to structural brain damage. Early-life SEP may affect the brain via environmental, behavioral, and physiological pathways (Cohen et al., 2010), while different mechanisms may underlie the association between later-life SEP and structural brain damage, including chronic low-grade inflammation (Muscatell et al., 2020) and partly a less favorable lifestyle (Geraets and Leist, 2023). However, the extent to which structural brain damage explains the relation of early-life and later-life SEP with cognitive functioning is unknown.

Another potential pathway between SEP and cognitive impairment is via the brain connectome. The brain connectome refers to the complex network of neural connections (white matter) within the brain that enable efficient information exchange between brain regions (Sporns, 2011). Alterations in one region may affect the functioning of other regions via the white matter connections. Advancements in neuroimaging techniques have made it possible to study and map the brain connectome using graph theory analyses (Bullmore and Sporns, 2009). Here the brain connectome is represented as a graph, which is a network of grey matter regions (nodes) connected by white matter connections (edges). A simple representation of such a connectome is presented in Fig. 1. To our knowledge, no studies have linked indicators of early-life and later-life SEP to the brain connectome. Individual differences in the brain connectome are suggested to be a neurological marker for the expression of cognitive reserve (Serra et al., 2017; Stern, 2017). In addition, the number of connections in the brain may represent a more dynamic and earlier marker of brain damage (Sporns, 2018). A recent study showed that the number of white matter connections moderates the association between structural brain damage and cognitive impairment (De Jong et al., 2022), which support the cognitive reserve hypothesis by linking higher brain connectivity to higher cognitive resilience. However, whether the number of brain connections mediates the SEP-cognition relationships has not yet been investigated.

This study aimed to investigate the contributions of early-life and later-life SEP to later-life structural brain damage and connectivity, and cognitive functioning. A summary of our conceptual model and assumptions is provided in the Directed Acyclic Graph in Fig. 2. We hypothesized that 1) lower SEP is associated with lower later-life cognitive functioning; 2) the association of early-life SEP with later-life cognitive functioning is partly explained by later-life SEP; and 3) the associations of SEP with later-life cognitive functioning are partly explained by markers of structural brain damage and connectivity. As previous research suggested that the contribution of SEP to cognitive ageing may be larger in women compared to men (Jin et al., 2023), we tested whether the associations of SEP on structural brain damage and connectivity and cognitive functioning differ by sex/gender.

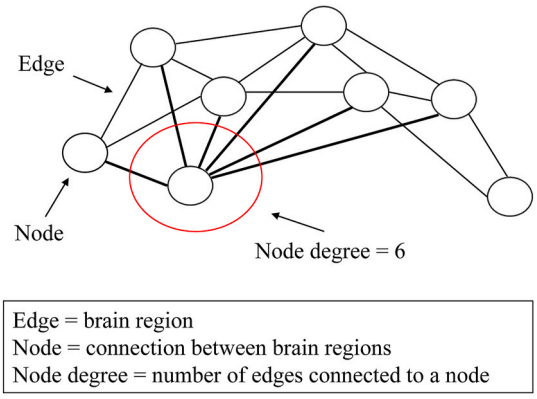

Fig. 1. Simplified representation of the human brain connectome.

2. Materials and methods

2.1. Study population and design

We used cross-sectional data from The Maastricht Study, an ongoing observational prospective population-based cohort study. Rationale and methodology have been described previously (Schram et al., 2014). In brief, the study focuses on the etiology, pathophysiology, complications, and comorbidities of type 2 diabetes mellitus (T2DM), heart disease, and other chronic conditions, and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status, with an oversampling of individuals with T2DM for reasons of efficiency. We included available baseline data collected between November 2010 and December 2017. Fig. 3 shows the flowchart of the study population. From the initial 7,689 participants, data on early-life and later-life SEP were available in n = 7,593 participants, of whom n = 7,138 had available data on the cognitive tests. Magnetic resonance imaging (MRI) measurements were implemented from December 2013 onwards and available in n = 4,839 participants. We performed complete case analyses in which n = 4,839 participants were included in the main analyses.

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Ethical approval was granted by the institutional Medical Ethical Committee (NL31329.068.10) and the Minister of Health, Welfare, and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent.

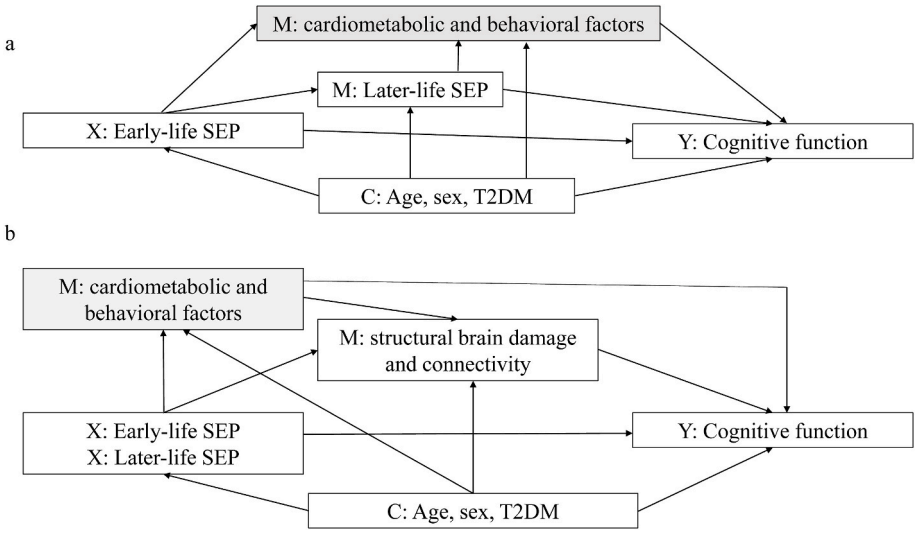

Fig. 2. Directed Acyclic Graph reflecting assumed relationships between socioeconomic position, structural brain damage and connectivity, and cognitive functioning. *Note:* X indicates exposure; C, baseline confounder; M, mediator; Y, outcome; SEP, socioeconomic position; T2DM, type 2 diabetes mellitus.

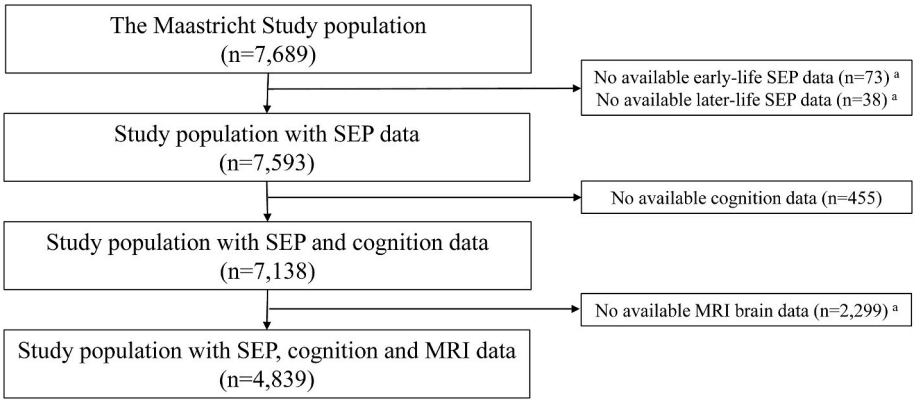

Fig. 3. Flowchart of study population. *Notes*: SEP indicates socioeconomic position; MRI, magnetic resonance imaging. [a]Numbers are not mutually exclusive.

3. Measurements

3.1. Socioeconomic position

Early-life SEP was measured with poverty during childhood and parental educational attainment as previously defined (Derks et al., 2017). Poverty during childhood was measured with the question: "Was the financial situation at your childhood's home sometimes such that there wasn't enough money to buy food or to replace outworn clothes or shoes?". The four answering categories: 1) no, never, 2) yes, sometimes, 3) yes, often, 4) yes, always, were inversed in line with earlier literature so that a higher score means lower poverty. Inversed scores were grouped into high (1–2), medium (3), and low (4) childhood poverty. Parental educational attainment included nine nationally relevant categories, ranging from no education to university education (for details see supplemental). Educational attainment was grouped into low (categories 1–4), middle (5–7), and high (8–9). A composite early-life SEP score was created by averaging the available standardized raw scores for childhood poverty (n = 4,592), educational attainment of the mother (n = 4,369), and educational attainment of the father (n = 4,307), and subsequently dividing this composite score into tertiles (low, medium, high).

Later-life SEP included educational attainment, occupational attainment, and household income. Educational attainment was measured using the same categories as educational attainment of the parents and divided into similar groups of low (1–4), middle (5–7), and high (8–9) educational attainment. Current or previous occupational attainment was assessed using the International Standard Classification of Occupations (2008) (ISCO-08), a hierarchical classification system based on education and skills required in a job (ILO, 2012). The resulting codes were converted according to the International Socio-Economic Index of Occupational Status (ISEI-08) (Ganzeboom and Treinman, 2019). ISEI-08 is a continuous score and a more comprehensive measure of socioeconomic resources, as people's jobs in ISCO-08 (categorical/ordinal) format were matched to their education and earnings in an external dataset. Based on that, an ISEI-08 score was assigned that optimizes the associations between education, occupation, and income. As such, the ISEI-08 is a more valid and useful measure of socioeconomic status. ISEI-08 classifications were classified as low, medium, and high based on tertiles. Household income was measured by self-reported monthly net household income, including 19 categories, ranging from 0 to >5000 euros per month. To estimate the equivalized household income, household size was considered by dividing the net household income (midpoints of categories) by the square root of numbers of household members (Development, 2012). By using tertiles, the equivalent income (mean = 2044.83 EUR per month; standard deviation = 825.51) was categorized into low, medium, and high. To compute a composite later-life SEP score, available raw scores for educational attainment (n = 4,795), occupational attainment (n = 1,829), and household income (n = 3,806) were standardized, averaged, and divided into tertiles (low, medium, and high).

3.2. Cognitive function

Cognitive functioning was assessed by a concise 30-min neuropsychological test battery (Schram et al., 2014). Individual test scores were standardized and divided into three cognitive domains. Memory was assessed with the average of the Verbal Learning Test immediate and delayed recall standardized scores (Van Der Elst et al., 2005). An average information processing speed score was derived from standardized scores of the Stroop Color-Word Test Part I and II (Van der Elst et al., 2006c), Concept Shifting Test Part A and B (Van der Elst et al., 2006a), and Letter-Digit Substitution Test (Van der Elst et al., 2006b). Executive functioning and attention were evaluated with the average of the Stroop Color-Word Test Part III and Concept Shifting Test Part C standardized scores. If necessary, individual test scores were log-transformed to reduce the skewness of distributions and/or inverted so that higher scores indicated better cognitive performance. Domain scores were z-standardized by the respective study population mean and standard deviation, and, for statistical efficiency, a standardized composite cognitive score was calculated as the average of the standardized cognitive domains scores (memory, information processing speed, and executive functioning and attention).

3.3. Brain magnetic resonance imaging

Brain MRI data were acquired by use of a 3T clinical magnetic resonance scanner (MAGNETOM Prismafit, Siemens Healthineers GmbH, Munich, Germany) using a head/neck coil with 64 elements for parallel imaging. The MRI protocol included a three-dimensional T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence, a T2-weighted fluid-attenuated inversion recovery (FLAIR), and a diffusion MRI (dMRI) sequence from which volumes of white matter hyperintensity (WMH), grey matter, white matter, and cerebrospinal fluid (CSF) in mL were obtained by means of an ISO-13485:2012 certified, automated method which included additional visual inspection (De Boer et al., 2009; Vrooman et al., 2007). WMH volume was log transformed; intracranial volume was calculated as the sum of grey matter, white matter, and CSF. All volumetric brain measurements were standardized into z-scores. Contraindications for MRI assessment were non-compatible implants or devices, epilepsy, claustrophobia, and pregnancy. Details about the MRI protocol and image pre-processing are provided in the supplemental material.

3.4. Brain connections

The automatic anatomical labeling (AAL2) atlas (Rolls et al., 2015) was used to segment 94 regions. White matter tractography was calculated from the dMRI sequence using the diffusion MR Toolbox ExploreDTI, version 4.8.6 (PROVIDI lab, Image Sciences Institute, Utrecht, The Netherlands). Connectivity analysis was performed using the Brain Connectivity Toolbox (version 2017-15-01) (Rubinov and Sporns, 2010) in MATLAB Release 2016a (The Mathworks Inc., Natick, Massachusetts, USA) to identify connections between brain regions. The group-averaged connectome was proportionally thresholded to a default sparsity of 0.80, meaning that only the connections that were present in at least 80% of the participants were considered in the individual structural connectivity analyses. To minimize the effect of spurious connections, only regions connected by more than two tracts were considered. The tract volume of each connection, normalized by total intracranial volume, gave the edge weights of the connectome. From this connectome, the average number of connections per region (node degree) was calculated.

3.5. Covariates

Based on previous research, multiple covariates were included (Baumgart et al., 2015). Age and sex/gender were self-reported. Cardiometabolic and behavioral factors are considered as mediators, as a lower SEP has been related to an increased cardiometabolic risk profile (including a higher waist circumference, high blood pressure, high cholesterol level, high blood sugar level, and depression) and poorer lifestyle (including smoking, more alcohol consumption, lower physical activity, and a less healthy diet) (Schultz et al., 2018; T. Wang et al., 2024). Therefore, cardiometabolic and behavioral factors were included as covariates in sensitivity analyses. Waist circumference, office blood pressure, and plasma lipid profile were measured as described previously (Schram et al., 2014). Presence of T2DM was determined by an oral glucose tolerance test after overnight fasting (Schram et al., 2014). Medication use was assessed in a medication interview where the generic name, dose, and frequency were registered. Current episodes of major depressive disorder (MDD) were assessed by the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). History of cardiovascular diseases, smoking status (never, current, former), leisure-time physical activity (hours per week), alcohol consumption (g/day), and adherence to the Dutch Healthy Diet 2015 guidelines were assessed by questionnaires (Schram et al., 2014).

3.6. Statistical analyses

All statistical analyses were performed by use of Stata (version 17; StataCorp LLC, College Station, TX, USA). To assess the associations of SEP with cognitive functioning and MRI brain markers, we used multiple linear regression analyses reporting the unstandardized regression coefficient B and the 95% confidence interval (CI). Because MRI assessment did not always take place at the same time as the baseline assessment for logistic reasons, all analyses that included MRI measures were adjusted for MRI lag time, i.e., the time in years between baseline assessment and MRI assessment (median, interquartile range = 0.76 [0.33–1.46]). Analyses were adjusted for potential confounders in different models. Model 1 was adjusted for MRI time lag (only for MRI measures), intracranial volume (only for MRI measures), age, and sex/gender. Model 2 was additionally adjusted for T2DM (because of oversampling) and was considered as the main model. To assess the direct associations of early-life and later-life SEP with cognitive functioning, we analyzed them simultaneously in model 3, and expressed these in terms of years of cognitive aging to indicate the level of clinical relevance. Preliminary analyses showed that, in the study population with available cognition data and after adjusting for sex/gender and T2DM, each additional year of age was associated with a 0.054 standard deviation (SD) lower cognitive score. Interactions of SEP with sex/gender and T2DM (because of oversampling of our study by individuals with T2DM) on MRI-derived brain measures and cognitive functioning were tested in model 2.

Of note, as the reported associations cannot be interpreted as causal, the statistical terms of 'direct' and 'indirect effects' will be maintained in the following to increase clarity of the statistical approach. To test whether later-life SEP acts as a mediator between early-life SEP and later-life cognitive functioning, structural equation modeling was used to decompose total associations between the continuous composite score for early-life SEP and cognitive functioning into direct and indirect effects via later-life SEP (continuous composite score) using bootstrapping (200 replications) to calculate bias-corrected 95% confidence intervals (StataCorp, 2023). Although structural equation modeling does not provide information on causal mechanisms in cross-sectional observational data, it allows for estimating the relationship between multiple independent variables and multiple dependent variables at the same time to test mediation. It provides effect estimates for direct, indirect, and total effects in the same model. Mediation by structural brain damage and connectivity in the SEP-cognition relationships was also assessed using structural equation modeling. Here, the total effects of respectively early-life and later-life SEP on cognitive functioning were decomposed into direct and indirect effects via markers of structural brain damage and connectivity. A two-sided p-value<0.05 was

considered statistically significant.

3.7. Sensitivity analyses

Several sensitivity analyses were performed. Because the association between SEP and cognitive functioning can depend on the chosen indicator of SEP (Ford et al., 2022), we investigated the associations of the individual SEP indicators with cognitive functioning. Educational attainment may overestimate the SEP-cognition relationship (Lövdén et al., 2020). To focus on economic inequalities in cognitive performance and eliminate the influence of innate cognitive reserve (Lee, 2003), the associations of childhood poverty and household income with cognitive functioning were additionally adjusted for educational attainment. Furthermore, we tested the interaction of high educational attainment with respectively childhood poverty and household income on cognitive functioning, as education has been suggested to be key to cognitive reserve (Roe et al., 2011). To test whether socioeconomic differences can be seen as a gradient, aside of the categorical differences between high/medium versus low, we analyzed the composite scores and individual indicators as continuous scores. To take into account genetic influences of verbal intelligence on cognition (Harris and Deary, 2011), associations between SEP and cognitive functioning were additionally adjusted for verbal intelligence using the Groninger Intelligence Test (Barelds, 2004). In the models testing the contribution of SEP to cognitive functioning, only in additional analyses we included cardiovascular (waist circumference, total cholesterol to high-density lipoprotein ratio, lipid-modifying medication use, systolic blood pressure, antihypertension medication use) and behavioral risk factors (smoking, alcohol use, depression, physical activity, and healthy diet), because these variables are assumed to be on the causal pathway. Similar sensitivity analyses were performed for the association between SEP and markers of structural brain damage and connectivity. To minimalize the confounding contribution of ageing, we excluded participants that had their MRI assessment more than one year after the cognitive assessment (MRI lag time >1 year) from the analyses. As preserved brain connections may overestimate the effect of the node degree, we additionally adjusted analyses including node degree for structural brain damage. Lastly, we ran models using domain and individual test level as outcomes, as earlier research found that respectively 33% and 28% of the contribution of age to cognitive functioning were explained by these levels (Tucker and Stern, 2011).

4. Results

4.1. Characteristics of the study population

Table 1 shows the general characteristics of the study population (n = 4,839). Participants had a mean age of 59.2 ± 8.7 years and 49.8% were women. Most participants did not experience childhood poverty (78.1%), while around half of the parents had a low educational attainment. A minority of the study sample had a low educational attainment (15%). Participants excluded from the analyses due to missing data (n = 2,850) were older, had lower early-life and later-life SEP, lower cognitive functioning, and a worse cardiometabolic risk profile compared to participants included in the analyses (data not shown).

4.2. SEP and cognitive functioning

Table 2 shows the associations of indicators of SEP with cognitive functioning. Compared to participants with a low early-life SEP, participants with a medium and high early-life SEP had higher overall cognitive scores (B [95% confidence interval] = 0.17[0.12; 0.23] and B = 0.26[0.20; 0.32], respectively) after adjustment for age, sex/gender, and T2DM. Medium and high later-life SEP were associated with higher cognitive scores (B = 0.46[0.41; 0.52] and B = 0.72[0.67; 0.78], respectively) compared to low later-life SEP. Using the study population-wide standard of cognitive decline per year (−0.054), the direct statistical effects of low versus high early-life and later-life SEP were equivalent to, respectively, 1.30(−0.07/-0.054) and 12.96(−0.70/-0.054) years of accelerated cognitive ageing (Table 2). However, mediation analyses showed that 72.2% of the association between early-life SEP and later-life cognitive functioning (total effect = B = 0.18[0.15; 0.21]) was mediated by later-life SEP (indirect effect = B = 0.13[0.12; 0.14]), while the direct effect of early-life SEP on later-life cognitive functioning of 27.8% remained statistically significant (B = 0.05[0.02; 0.08]; Fig. 4). No consistent interactions with sex/gender or T2DM were found (eTable 1-2).

Table 1
Characteristics of study population.

Characteristic	Statistic
Demographics	
Age (years)	59.2 ± 8.7
Sex, n (% female)	2,408 (49.8)
Early-life SEP	
Early-life poverty (often or always/sometimes/never), n (%)	203/803/3,586 (4.4/17.5/78.1)
Educational attainment mother (low/medium/high), n (%)	2,898/1,293/178 (66.3/29.6/4.1)
Educational attainment father (low/medium/high), n (%)	2,081/1,608/618 (48.3/37.3/14.4)
Composite score early-life SEP	1,549/1,795/1,495 (32.0/37.1/30.9)
Later-life SEP	
Educational attainment (low/medium/high), n (%)	720/2,126/1,949 (15.0/44.3/40.7)
Occupational attainment (low/medium/high), n (%)	588/609/632 (32.2/33.3/34.6)
Household income (low/medium/high), n (%)	1,273/1,310/1,223 (33.5/34.4/32.1)
Composite score later-life SEP	1,422/1,714/1,703 (29.4/35.4/35.1)
MRI-derived brain measures	
WMH volume (ml)	0.21 [0.07–0.68]
Grey matter volume (ml)	611.96 ± 60.91
White matter volume (ml)	476.07 ± 58.76
CSF volume (ml)	252.30 ± 47.78
Average node degree	17.76 ± 0.35
MRI lag time (years)	0.75 [0.33–1.46]
Cognition	
Memory score	0.09 ± 0.93
Information processing speed score	0.06 ± 0.79
Executive functioning & attention score	0.06 ± 0.76
Overall cognitive score	0.07 ± 0.65
Cardiovascular risk factors	
Type 2 diabetes mellitus, n (%)	946 (19.6)
History of cardiovascular disease, n (%)	592 (12.4)
Waist circumference (cm)	93.9 ± 12.9
Total cholesterol-to-HDL ratio	3.60 ± 1.17
Systolic blood pressure (mm Hg)	132.9 ± 17.2
Diastolic blood pressure (mm Hg)	75.5 ± 9.7
Hypertension, n (%)	2,413 (49.9)
Behavioural risk factors	
Alcohol consumption (g/day)	12.3 ± 14.0
Smoking (never/former/current), n (%)	1,902/2,335/578 (39.5/48.5/12.0)
Current major depressive episode, n (%)	153 (3.2)
Leisure-time physical activity (h/week)	14.1 ± 8.0
Moderate-vigorous physical activity (h/week)	5.6 ± 4.4
Dutch Healthy Diet adherence score[a]	77.0 ± 14.4
Medication use	
Lipid-modifying medication, n (%)	1,307 (27.0)
Antihypertensive medication, n (%)	1,582 (32.7)
Antidepressant medication, n (%)	327 (6.8)

Notes: n = 4,839. Data are presented as means ± standard deviation, number (%) or median [interquartile range]. SEP indicates socioeconomic position; MRI, magnetic resonance imaging; WMH, white matter hyperintensities; CSF, cerebrospinal fluid; HDL, high-density lipoprotein. [a]Score range 0–122.34 because of exclusion of coffee and alcohol consumption.

Table 2
Associations of socioeconomic position and markers of structural brain damage and connectivity with composite cognitive score.

	Model 1 B (95% CI)	*p*-value	Model 2 B (95% CI)	*p*-value	Model 3 B (95% CI)	*p*-value	Cognitive aging (years)[a]
Early-life SEP							
Composite score early-life SEP							
= Low	Reference		Reference		Reference		Reference
= Medium	**0.19(0.13;0.24)**	**<0.001**	**0.17(0.12;0.23)**	**<0.001**	**0.05(0.00;0.11)**	**0.044**	**−0.93**
= High	**0.27(0.21;0.33)**	**<0.001**	**0.26(0.20;0.32)**	**<0.001**	**0.07(0.01;0.12)**	**0.020**	**−1.30**
Later-life SEP							
Composite score later-life SEP							
= Low	Reference		Reference		Reference		Reference
= Medium	**0.48(0.42;0.53)**	**<0.001**	**0.46(0.41;0.52)**	**<0.001**	**0.45(0.40;0.51)**	**<0.001**	**−8.33**
= High	**0.74(0.69;0.80)**	**<0.001**	**0.72(0.67;0.78)**	**<0.001**	**0.70(0.65;0.76)**	**<0.001**	**−12.96**
Markers of structural brain damage							
WMH volume[b] (per 1 SD)	**−0.11(-0.14; -0.08)**	**<0.001**	**−0.10(-0.13; -0.07)**	**<0.001**	–	–	**1.85**
Grey matter volume (per 1 SD)	**0.10(0.05;0.15)**	**<0.001**	**0.09(0.04;0.14)**	**0.001**	–	–	**−1.67**
White matter volume (per 1 SD)	**0.10(0.05;0.15)**	**<0.001**	**0.09(0.04;0.14)**	**<0.001**	–	–	**−1.67**
CSF matter volume (per 1 SD)	**−0.12(-0.16; -0.08)**	**<0.001**	**−0.10(-0.14; -0.07)**	**<0.001**	–	–	**1.85**
Markers of structural brain connectivity							
Node degree (per 1 SD)	**0.09(0.07;0.12)**	**<0.001**	**0.08(0.06;0.11)**	**<0.001**	–	–	**−1.48**

Notes: n = 4,839. B indicates unstandardized regression coefficient; CI, confidence interval; SEP, socioeconomic position, WMH, white matter hyperintensities; SD, standard deviation; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.
[a] Associations in Model 3 (SEP) and Model 2 (MRI-derived brain measures) were additionally expressed in years of cognitive aging (−0.054 per year).
[b] White matter hyperintensity volumes were log transformed. Model 1: adjusted for MRI time lag (MRI only) and intracranial volume (brain volumes only), age, and sex. Model 2: additionally adjusted for type 2 diabetes mellitus (because of oversampling). Model 3: model 2 including both early-life and later-life SEP.

4.3. Associations of MRI brain markers with cognitive function

Higher volumes of WMH and CSF were associated with lower cognitive functioning (B = −0.10[−0.13;-0.07] and B = −0.10[−0.14;-0.07], respectively), while higher volumes of grey matter and white matter were associated with higher cognitive functioning (B = 0.09 [0.04; 0.14] and B = 0.09[0.04; 0.14], respectively), after adjustment for MRI time lag, intracranial volume, age, sex/gender, and T2DM. Furthermore, a higher node degree was associated with higher cognitive functioning (B = 0.08[0.06; 0.11]; Table 2). The associations of MRI-derived brain measures with cognitive functioning were equal to <2 years of cognitive ageing (Table 2).

4.4. SEP and markers of structural brain damage and connectivity

The associations of SEP with markers of structural brain damage and connectivity are shown in Table 3. Participants with a high early-life SEP had lower white matter (B = −0.05[−0.09;-0.02] and higher CSF volumes (B = 0.07[0.03; 0.12]), and a higher node degree (B = 0.07[0.01; 0.14]) compared to participants with a low early-life SEP. High later-life SEP was related to higher grey matter (B = 0.05[0.02; 0.08]) and lower white matter volumes (B = −0.04[−0.07;-0.01]), and higher node degrees (B = 0.11[0.04; 0.18]) compared to participants with a low later-life SEP. There was an interaction of later-life SEP with T2DM on WMH volume (Table S5). In stratified analyses, medium and higher later-life SEP were associated with lower WMH volume in participants without T2DM (B = −0.08[−0.15;-0.01] and B = −0.09[−0.16;-0.02]), but not in participants with T2DM (B = 0.11[−0.02; 0.24] and B = 0.09[−0.05; 0.23], respectively). No other consistent interactions of SEP with sex/gender or T2DM on the MRI-derived measures were found (eTable 3-6).

4.5. Mediation of the SEP-cognition relationships by structural brain damage and connectivity

All markers of structural brain damage and connectivity were associated with cognitive functioning; however, SEP was only associated with volumes of grey matter (later-life SEP), white matter (early-life and later-life SEP), CSF (early-life SEP), and node degree (early-life and later-life SEP). Therefore, mediation analyses were restricted to these brain markers. Table 4 shows the decomposed association of SEP with cognitive functioning by markers of structural brain damage and connectivity. The indirect effects of SEP on cognitive functioning via volumes of grey matter, white matter volume, CSF, and node degree were small but statistically significant (range 0.0–5.9%). Direct effects of SEP on cognitive functioning were almost equal to the total effects.

4.6. Sensitivity analyses

Several sensitivity analyses were performed (Supplemental eTables 7-14). Associations of the individual SEP indicators with cognitive functioning were stronger for parental and self-attained education compared to childhood poverty, occupational attainment, and household income (eTable 7), and results patterns were similar when we used continuous scores for SEP (eTable 8). Associations of individual SEP

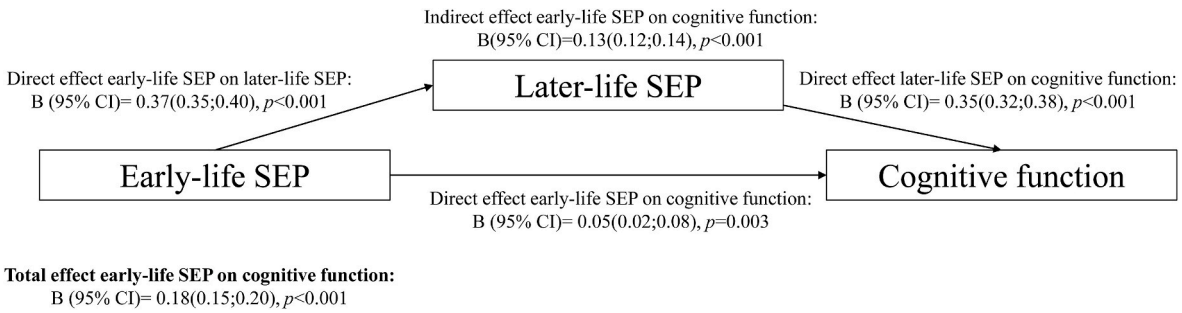

Fig. 4. Decomposed associations of socioeconomic position with composite cognitive score. *Notes*: n = 4,839. SEP indicates socioeconomic position; B, unstandardized coefficient; CI, confidence interval.

Table 3
Associations of socioeconomic position with markers of structural brain damage and connectivity.

	WMH volume[a] (per 1SD) B (95% CI)	*p*-value	Grey matter volume (per 1 SD) B (95% CI)	*p*-value	White matter volume (per 1 SD) B (95% CI)	*p*-value	CSF volume (per 1 SD) B (95% CI)	*p*-value	Node degree (per 1 SD) B (95% CI)	*p*-value
Early-life SEP										
Model 1										
SEP										
= Low	Reference		Reference		Reference		Reference		Reference	
= Medium	−0.05(-0.10; 0.01)	0.128	**0.03(0.00; 0.06)**	**0.045**	−0.02(-0.06; 0.01)	0.131	−0.01(-0.05; 0.04)	0.765	**0.08(0.02;0.15)**	**0.012**
= High	−0.04(-0.10; 0.02)	0.217	0.00(-0.03; 0.03)	0.937	**−0.05(-0.08; -0.02)**	**0.004**	**0.06(0.01;0.11)**	**0.010**	**0.09(0.02;0.15)**	**0.012**
Model 2										
SEP										
= Low	Reference		Reference		Reference		Reference		Reference	
= Medium	−0.03(-0.09; 0.02)	0.240	0.03(-0.00; 0.06)	0.093	−0.03(-0.06; 0.00)	0.082	0.00(-0.04; 0.05)	0.852	**0.07(0.01;0.13)**	**0.033**
= High	−0.03(-0.09; 0.03)	0.366	−0.00(-0.04; 0.03)	0.812	**−0.05(-0.09; -0.02)**	**0.002**	**0.07(0.03;0.12)**	**0.002**	**0.07(0.01;0.14)**	**0.035**
Later-life SEP										
Model 1										
SES										
= Low	Reference		Reference		Reference		Reference		Reference	
= Medium	−0.05(-0.11; 0.01)	0.126	0.02(-0.01; 0.05)	0.189	−0.02(-0.06; 0.01)	0.168	0.01(-0.04; 0.05)	0.734	**0.10(0.03;0.17)**	**0.004**
= High	**−0.07(-0.14; -0.01)**	**0.019**	**0.06(0.03;0.10)**	**<0.001**	−0.03(-0.06; 0.00)	0.066	−0.03(-0.08; 0.01)	0.133	**0.14(0.07;0.21)**	**<0.001**
Model 2										
SES										
= Low	Reference		Reference		Reference		Reference		Reference	
= Medium	−0.03(-0.10; 0.03)	0.278	0.01(-0.02; 0.05)	0.364	−0.03(-0.06; 0.00)	0.093	0.02(-0.02; 0.07)	0.336	**0.08(0.02;0.15)**	**0.015**
= High	−0.05(-0.11; 0.01)	0.115	**0.05(0.02;0.08)**	**0.002**	**−0.04(-0.07; -0.01)**	**0.019**	−0.01(-0.06; 0.04)	0.663	**0.11(0.04;0.18)**	**0.001**

Notes: n = 4,839. WMH indicates white matter hyperintensities; SD, standard deviation; B, unstandardized regression coefficient; CI, confidence interval; CSF, cerebrospinal fluid; SEP, socioeconomic position; MRI, magnetic resonance imaging.

[a] White matter hyperintensity volumes were log transformed. Model 1: adjusted for MRI time lag and intracranial volume (brain volumes only), age, and sex. Model 2: additionally adjusted for type 2 diabetes mellitus (because of oversampling).

Table 4
Decomposed associations of socioeconomic position with composite cognitive score by markers of structural brain damage and connectivity.

Model	Model 1 B (95% CI)	*p*-value	Model 2 B (95% CI)	*p*-value
Composite score early-life SEP[a]				
White matter volume				
High early-life SEP direct on cognition	**0.25(0.19;0.31)**	**<0.001**	**0.07(0.01;0.13)**	**0.021**
High early-life SEP indirect on cognition	**−0.01(-0.01;0.00)**	**0.017**	**−0.01(-0.01;-0.00)**	**0.025**
High early-life SEP total on cognition	**0.24(0.19;0.30)**	**<0.001**	**0.06(0.01;0.12)**	**0.033**
CSF matter volume				
High early-life SEP direct on cognition	**0.25(0.20;0.31)**	**<0.001**	**0.07(0.01;0.13)**	**0.016**
High early-life SEP indirect on cognition	**−0.01(-0.01; -0.00)**	**0.006**	**−0.01(-0.01;-0.00)**	**0.004**
High early-life SEP total on cognition	**0.24(0.19;0.30)**	**<0.001**	**0.06(0.01;0.12)**	**0.033**
Node degree				
Medium early-life SEP direct on cognition	**0.17(0.11;0.22)**	**<0.001**	0.05(-0.00; 0.11)	0.065
Medium early-life SEP indirect on cognition	**0.01(0.00;0.01)**	**0.035**	0.00(-0.00; 0.01)	0.114
Medium early-life SEP total on cognition	**0.17(0.12;0.23)**	**<0.001**	**0.06(0.00;0.11)**	**0.048**
High early-life SEP direct on cognition	**0.25(0.20;0.31)**	**<0.001**	**0.06(0.01;0.12)**	**0.031**
High early-life SEP indirect on cognition	0.01(-0.00; 0.01)	0.053	0.00(-0.00; 0.01)	0.225
High early-life SEP total on cognition	**0.26(0.20;0.31)**	**<0.001**	**0.07(0.01;0.13)**	**0.023**
Composite score later-life SEP[a]				
Grey matter volume				
High later-life SEP direct on cognition	**0.71(0.65;0.76)**	**<0.001**	**0.69(0.63;0.75)**	**<0.001**
High later-life SEP indirect on cognition	**0.00(0.00;0.01)**	**0.033**	**0.00(0.00;0.01)**	**0.031**
High later-life SEP total on cognition	**0.71(0.65;0.77)**	**<0.001**	**0.69(0.63;0.75)**	**<0.001**
White matter volume				
High later-life SEP direct on cognition	**0.71(0.66;0.77)**	**<0.001**	**0.69 (0.63;0.75)**	**<0.001**
High later-life SEP indirect on cognition	**−0.00(-0.01;-0.00)**	**0.040**	−0.00(-0.01; 0.00)	0.137
High later-life SEP total on cognition	**0.71(0.65;0.77)**	**<0.001**	**0.69(0.63;0.75)**	**<0.001**
Node degree				
Medium later-life SEP direct on cognition	**0.46(0.40;0.52)**	**<0.001**	**0.45(0.39;0.51)**	**<0.001**
Medium later-life SEP indirect on cognition	**0.01(0.00;0.01)**	**0.020**	**0.00(0.00;0.01)**	**0.037**
Medium later-life SEP total on cognition	**0.46(0.40;0.52)**	**<0.001**	**0.45(0.39;0.51)**	**<0.001**
High later-life SEP direct on cognition	**0.71(0.66;0.77)**	**<0.001**	**0.69(0.63;0.75)**	**<0.001**
High later-life SEP indirect on cognition	**0.01(0.00;0.01)**	**0.004**	**0.01(0.00;0.01)**	**0.012**
High later-life SEP total on cognition	**0.72(0.66;0.78)**	**<0.001**	**0.70(0.64; 0.76)**	**<0.001**

Notes: n = 4,839. B indicates unstandardized regression coefficient; CI, confidence interval; WMH, white matter hyperintensities; SD, standard deviation; CSF, cerebrospinal fluid; SEP, socioeconomic position; MRI, magnetic resonance imaging.

[a] Compared to low socioeconomic position. Model 1: adjusted for MRI time lag, intracranial volume (brain volumes only), age, sex, and type 2 diabetes mellitus (because of oversampling). Model 2: additionally adjusted for later-life SEP (early-life SEP) or early-life SEP (later-life SEP).

indicators with markers of structural brain damage and connectivity were in the similar direction, albeit only statistically significant if using a continuous score for the SEP indicators (eTables 9 and 10). After additional adjustment for educational attainment, the association between childhood poverty and cognitive functioning attenuated and became statistically non-significant, while the association of household income with cognitive functioning was reduced by around 50%, but remained statistically significant (eTable 11). Furthermore, associations of childhood poverty and household income with MRI-derived brain markers attenuated and became non-significant after additional adjustment for educational attainment, with exception of low versus high childhood poverty with lower white matter volume and high versus low household income with higher node degree (eTable 13). No consistent interactions of childhood poverty and household income with high educational attainment on cognitive functioning or the MRI-derived brain markers were found, suggesting that the role of education was independent of that of economic situation. Additional adjustment for verbal intelligence attenuated the results. However, only the associations of SEP with node degree became statistically non-significant (eTable 11-12). Additional adjustment for cardiovascular and behavioral factors practically did not change the result patterns (eTable 13-14). Excluding participants that had their MRI assessment more than one year after the cognitive assessment neither changed the association between SEP and structural brain damage (eTable 14), nor between the markers of structural brain damage and cognitive functioning (eTable 15). The association of node degree with cognitive functioning did not change after additional adjustment for structural brain damage (eTable 16). Finally, result patterns were confirmed when using cognitive domain and test level as outcomes (results not shown).

5. Discussion

This study investigated the contribution of early-life and later-life SEP with later-life cognitive functioning and several markers of structural brain damage and connectivity. There was a rather strong association of early-life SEP with later-life cognitive functioning, and a large part of this was explained by later-life SEP. Structural brain damage and connectivity marginally explained SEP-cognition relationships. Educational attainment was stronger associated with cognitive functioning compared to economic indicators of SEP, albeit the role of household income was just slightly lower than that of educational attainment.

The finding that early-life SEP and later-life cognitive functioning relationships can largely be explained by later-life SEP is in line with results from previous population-based studies (Aartsen et al., 2019; Beck et al., 2018; Ford et al., 2022; McElroy et al., 2021; Peterson et al., 2021; Wolfova et al., 2021). We found no consistent sex/gender differences in the association between SEP and cognitive functioning. In contrast, a recent pooled multi-cohort study that included 61,019 individuals from Europe, the USA, UK, and China found stronger SEP-cognition relationships in women compared to men (Jin et al., 2023), mirrored by another study testing the role of early-life SEP (Wolfova et al., 2021). Differences in methodology, including SEP indicators and age and country of study population may explain this variation in sex/gender differences.

In line with earlier findings (Waldstein et al., 2017), we found that a higher later-life SEP was associated with lower WMH volume, albeit restricted to participants without T2DM. In contrast to an earlier study, we did not find an association between high early-life SEP and lower WMH volume in participants without T2DM (Murray et al., 2014). The smaller study size, older age of participants, and use of visual rating scales to quantify WMH in the previous study (Murray et al., 2014) may have contributed to divergent results. In line with previous research, we found that higher later-life SEP was associated with higher grey matter volume (Chan et al., 2018; Dougherty et al., 2020; Waldstein et al., 2017). Against our expectations, both high early-life and later-life SEP were associated with lower white matter volume in our study. However, sensitivity analyses showed that this association was driven by the oversampling for T2DM, as SEP and white matter volume were unrelated in participants without T2DM. Although interactions of SEP with T2DM on white matter volume were not significant, we consider this finding spurious. In summary, our findings support previous smaller studies that found an association of markers of structural brain damage and connectivity with worse and better cognitive performance, respectively (Pini et al., 2016; Rensma et al., 2018). These associations were smaller than those between SEP and cognitive functioning. Consequently, structural brain damage and connectivity mediated SEP and cognitive functioning only marginally.

Innate cognitive reserve may contribute to achieving high SEP (Lee, 2003). The most widely accepted mechanism thought to underlie these relationships are those of fetal programming by nutritional stimuli or excess fetal glucocorticoid exposure, in which the fetus makes physiological adaptations in response to changes in its environment to prepare itself for postnatal life (De Boo and Harding, 2006). In accordance with previous research, we found that educational attainment was the most important SEP factor for later-life cognitive functioning (A.-Y. Wang et al., 2023; Wolfova et al., 2021). Education as indicator of SEP may overstate the SEP-cognition relationship, as innate cognitive abilities may have contributed to higher educational attainment and subsequent SEP (Lee, 2003). However, sensitivity analyses showed that household income was associated with cognitive functioning independently of educational attainment, as was childhood poverty. Therefore, reducing socioeconomic inequalities in early life may contribute towards less variation in later-life cognitive functioning. Previous research suggested that individual differences in the brain connectome are suggested to be a neurological marker for the expression of cognitive reserve (Serra et al., 2017; Stern, 2017). Although we found associations of SEP with the number of brain connections, and the number of brain connections with cognitive functioning, the number of brain connections explained less than 5.9% of the SEP-cognition relationships. Our understanding of how human brain networks change over the life course remains fragmentary. Future research is needed to investigate how early-life and later-life SEP associate with the brain connectome, and if so, how the brain connectome contributes to the SEP-cognition relationships. Investigation of multiple graph measures, cortical thickness, cortical gyrification, functional connectivity, and specific regions seems warranted for future studies to further elucidate the pathways. The Human Connectome Project in Development (HCP-D) and the Human Connectome Project in Aging (HCP-A) may provide in-depth data to study these questions (Bookheimer et al., 2019; Somerville et al., 2018). Recent research has shown that the anatomy of the brain may reflect separable genetic and environmental components of SEP, in which genetic effects are stronger in some areas (prefrontal cortex, insula), and environmental effects are likely more influential in others (cerebellum, lateral temporal) (Kweon et al., 2022). The social (contextual) environment, which includes home (e.g., crowding), neighborhood (e.g., noise, air pollution), and school/work (e.g., building conditions), may affect the brain through direct and indirect psychological (e.g., aggression, social withdrawal), behavioral (e.g., nutrition, physical activity), and physiological pathways (e.g., infection, cell damage) (Cohen et al., 2010). Although previous studies found that the associations of SEP with brain outcomes may to some extent act through a poor lifestyle and associated cardiovascular risk factors (Geraets and Leist, 2023), sensitivity analyses in this study showed that these factors did not contribute towards explaining the relationships between SEP, structural brain damage, connectivity, and cognitive functioning. Future research is needed to investigate alternative pathways, like contextual determinants of cognition, personality, and the influence of genetics and the physical environment on the associations of SEP, brain health, and cognition.

Strengths of our study include its large sample size and population-based design; the assessment of SEP by multiple indicators of early-life and late-life SEP; the extensive assessment of cognitive functioning by means of a comprehensive neuropsychological test battery; inclusion of

sex/gender stratified analyses; inclusion of a broad range of potential confounders; and the performance of several sensitivity analyses to test the robustness of findings.

This study also has some limitations. First, the data were cross-sectional. Therefore, we cannot exclude reverse causality, and findings need to be interpreted with caution. However, educational attainment is less vulnerable to reversed causation as education is typically completed in late adolescence or early adulthood (Härkönen et al., 2018). In addition, we cannot rule out omitted-variable bias, that is, life course factors that contribute to socioeconomic inequalities in later-life cognitive functioning that could not be considered due to lack of information on these factors. Therefore, future research may benefit from longitudinal data collected across the life course. Second, selection bias inherent to observational studies is a major point of concern, especially when examining socioeconomic inequalities. Participants were living in the same region, more likely had a higher SEP, and despite the oversampling of T2DM, probably healthier compared to the general population (Lorant et al., 2007). Underrepresentation and missing data of those from the most disadvantaged SEP groups might have resulted in underestimation of the associations or even type 2 errors due to limited variation in the SEP gradient. However, our study sample included quite a substantial group in the low-SES range; the variation in SEP was sufficient to test our research question. We cannot rule out selection bias, as older participants with a lower SEP and worse cognitive functioning were less likely to undergo MRI (Honningsvåg et al., 2012). Structural brain damage may contribute more to the associations between SEP and cognitive functioning among older individuals from more adverse environments. Therefore, replication of our findings in more heterogeneous samples is recommended to increase external validity of our findings. Third, measures of SEP were self-reported, possibly leading to response bias, such as social desirability. Childhood poverty may be more affected by recall bias than parental education, however, other research found self-reported childhood socioeconomic circumstances to be largely reliable to reflect larger macro-economic conditions (Havari and Mazzonna, 2015). To limit the influence of these biases, we created composite scores for SEP and performed a range of sensitivity analyses with the individual indicators.

6. Conclusion

This study observed substantial SEP differences in cognitive functioning and markers of brain damage and connectivity. Associations of structural brain damage and connectivity with cognitive functioning were relatively modest, and subsequently only marginally explained socioeconomic gradients in cognitive functioning. Eliminating socioeconomic inequalities in early-life may play an important role in reducing socioeconomic inequalities in later-life cognitive functioning. More research is needed to investigate alternative pathways that explain these socioeconomic inequalities.

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Ethics approval

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Ethical approval was granted by the institutional Medical Ethical Committee (NL31329.068.10) and the Minister of Health, Welfare, and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent.

CRediT authorship contribution statement

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Declaration of competing interest

The authors have no relevant financial or nonfinancial interests to disclose.

Data availability

Restrictions apply to the availability of these data, which were used under license. Data are however available upon reasonable request and with permission of The Maastricht Study management team.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.socscimed.2024.117111.

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