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No sex differences in the association between regional brain structure abnormalities and cognitive functioning in a geriatric memory clinic population

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ABSTRACT

Differences between men and women in cognitive impairment and neurodegeneration are not yet well understood. Although sex differences in brain structure abnormalities, including white matter hyperintensities (WMH) and grey matter (GM) atrophy, have been associated with cognitive decline in the ageing population, the evidence is limited and inconclusive. Therefore, we explored sex differences in brain structure abnormalities and in the association between brain structure abnormalities and cognitive functioning. We analyzed global and regional volumetric measures of WMH and GM of 475 patients visiting an academic geriatric memory clinic in the Netherlands with multiple linear regression analyses. For both global and regional WMH and GM, we found no sex differences in brain structure abnormalities. We also found no interaction of sex on the association between brain structure abnormalities and cognitive functioning. We reflect on using a binary classification of men and women based on sex in this study, which might overlook individual differences and does not elucidate gender-related factors that influence health and risk

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of pathology. Future studies should focus on exploring the relationship between sex and gender on brain structure and cognitive functioning beyond this binary model, by including more data on social context, more diverse populations and using intersectional approaches.

1. Introduction

Within clinical research, there is increasing attention for sex differences in the onset and progression of cognitive impairment and neurodegeneration [5,6] (*Explanatory Box*). When comparing men and women as groups, differences have been demonstrated in terms of prevalence, severity and progression rates of cognitive decline [7,8]. Researchers often relate these to sex, for example by relating them to (age-related reduction of) sex hormones, risk of comorbidities, and brain anatomy changes [9]. Brain anatomy changes during ageing and related to cardiovascular pathology include white matter hyperintensities (WMH) and grey matter (GM) atrophy [10], which are both independently associated with cognitive impairment [11,12,13,14]. We refer to these changes as 'brain structure abnormalities' in this paper.

Some studies show sex-related differences in cognitive functioning, brain structure abnormalities, and in the association between them. In terms of cognitive functioning, women show faster age-related cognitive decline after onset of cognitive impairment compared to men [8,15,16]. Furthermore, for brain structure abnormalities, ageing women appear to have more WMH volume compared to men, but men show a faster decrease in GM volume compared to women [17,18,19]. Lastly, sex differences have been found in the association between brain structure abnormalities and cognitive functioning. Some studies show that higher WMH volume disproportionally affects cognitive functioning in men compared to women, while lower GM volumes are more strongly related to cognitive decline in women compared to men [20,21].

However, the number of studies focusing on sex differences is limited, as many studies that evaluate brain structure abnormalities only adjust (and not stratify) for sex [18]. Also, when studying sex differences, researchers find conflicting results, and some studies do not find sex differences in brain structure and cognitive function [22,23].

Within existing literature, we identified two important research gaps which we aim to address in the current study. First, studies investigating sex differences are often not adequately representative for clinical reality as most studies include relatively young patients, or participants without cognitive impairment [17,18,19,20,23]. Geriatric memory clinic populations, which are comprised of people with a large range in cognitive functioning, are less often assessed [24]. In these populations, measurements of brain structure abnormalities and cognitive functioning are typically used in the process of diagnosis and treatment of dementia [25,26]. Although a geriatric memory clinic population might be limited by a participation bias, such as the underrepresentation of certain groups [27], we believe that investigating a clinically relevant population is valuable. Therefore, we focus on this population in the current study.

Second, most sex difference studies only use global measures of brain structure abnormalities, such as visual rating scales or total volumes. Regional quantification might provide a more sensitive measure for identifying sex differences, enabling the identification of specific patterns of WMH locations and regional GM atrophy [26,28]. For instance, when focusing on hippocampal atrophy, this is more strongly indicative of cognitive decline for women compared to men [20,21,29]. Sex differences in the relationship between regional WMH and cognition are still unclear despite some suggestion of stronger association of cognition with WMH in the occipital region for men [23]. Therefore, we use regional quantification to investigate sex differences in this study.

Therefore, this study focuses on investigating: (1) if there are sex differences in brain structure abnormalities among memory clinic patients, and (2) whether there is an influence of sex on the association between these brain structure abnormalities and cognitive functioning. We will investigate this in memory clinic patients, in which we will evaluate both global and regional measures of WMH and GM volume with a regional quantification method [30]). We hypothesize that: (i) women have more WMH volume, while men have less GM volume [18]; (ii) the association between cognitive functioning and WMH volume is stronger for men, with a stronger association in the occipital region compared to women [20,23]; (iii) the association between cognitive functioning and GM volume is stronger for women, with a more expressed association in the temporal region compared to men [20,21,29].

Explanatory Box: Sex differences

When looking at differences between men and women, it is important to distinguish between sex and gender, while recognizing that they coexist and interact. We define sex as a cluster of biological differences between men, women and intersex individuals which are the results of genes, gonads and genitals (3G's) [1,2]. Gender refers to a sociocultural construct with culture-bound roles, conventions and behaviors. Sex and gender are not always easily distinguishable in quantitative research, and these concepts are often ill-defined and conflated in biomedical research [3,4]. A binary distribution of men and women that focusses on sex but inherently also includes elements of gender, is used in this study.

2. Methods

2.1. Participants

We used cross-sectional data of 475 patients from the Amsterdam Ageing Cohort [31]. The Amsterdam Ageing Cohort recruits patients visiting the geriatric outpatient memory clinic of the Amsterdam UMC, a large academic hospital in the Netherlands. Referral to the clinic was typically based on complaints reported to their general practitioner. Patients were included if they underwent a brain MRI and visited the clinic between February 2016 and June 2022. This study was approved by the local Medical Ethics Committee and patients gave written informed consent for their data to be used.

Each patient received a standardized extensive evaluation as part of routine care, including detailed medical history, physical and neurological examination, and brain MRI. The presence of cardiovascular disease and other comorbidities were assessed in this diagnostic assessment. Cardiovascular disease is classified as reported cardiovascular event, which includes a reported event of at least one of the following: stroke, myocardial infarction, angina pectoris, heart failure or atrial fibrillation. Furthermore, current medication use, height, weight, smoking, alcohol use, and living situation were assessed for each patient in the diagnostic assessment. Gait speed was measured in meter/second, calculated from the time needed to complete a distance of 4 m at the patients' usual pace. Educational level was assessed with the qualitative Verhage score, ranging from 1 (less than 6 years of primary education) to 7 (university degree) [32]. The presence of depressive symptoms was evaluated with the Geriatric Depression Scale (GDS) [33]. The Mini Mental State Examination (MMSE) was used to assess general cognitive functioning [34]. Most patients also underwent neuropsychological testing to assess cognitive functioning on different domains (see below for details). After the diagnostic assessment, a multidisciplinary consensus meeting was held to assess the presence of subjective cognitive decline (SCD), mild cognitive impairment (MCI) or clinical dementia (with differentiation of possible or probable etiologies such as Alzheimer's disease or vascular dementia) [35,36,37].

2.2. Materials

2.2.1. MRI acquisition, processing and brain structure parameters

Structural MRI scans were acquired on a range of 1.5 T and 3 T scanners [38]. The MRI scan protocol included T1- and T2-weighted, and fluid-attenuated inversion recovery (FLAIR) sequences. Using the method described by Sudre et al. [30], the regional WMH and GM volumes were automatically segmented with a previously developed algorithm from the MRI scans for each patient. The algorithm applies an iterative model selection framework based on the combination of T1-weighted and T2-FLAIR MRI pulse sequences that models normal and outlier observations as a multivariate Gaussian mixture, informed by anatomical atlases. Once the data model is fitted, lesion segmentation is performed through voxelwise comparison to normal-appearing white matter.

To characterize the location of WMH, a subject-specific coordinate system was created. Regional WMH and GM volumes were automatically segmented, with the GM was divided into frontal, parietal, temporal and occipital lobes for each hemisphere. WMH volumes were assigned to each of these lobes based on distance maps. An additional region comprising basal ganglia, thalami and infratentorial region (BGIT) was also defined. These lobes and BGIT region were further divided into 4 equidistant layers spanning the space between ventricular surface and cortical grey matter, with layer 1 being the most periventricular and layer 4 the most juxta-cortical. This resulted in 36 regions to define the location of WMH and 9 regions for GM volume. An overview of the quantification of

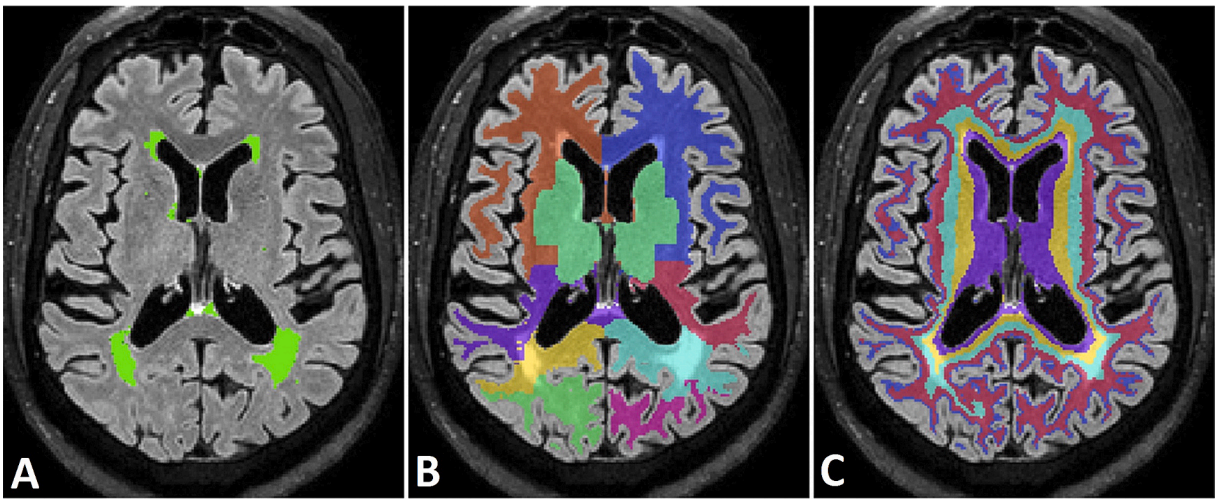

Fig. 1. Quantification of WMH volume in different brain regions and layers. Fig. 1. Representation by Sudre et al. [30] showing the quantification of WMH volume and the distribution of the regions (in the distinctive hemispheres) and layers. (A) Reflects the WMH volume segmentation. (B) Represents the separation in different brain regions (frontal, parietal, temporal, occipital lobes and BGIT). (C) Shows the layer separation from the ventricles (layer 1) to the cortical sheet (layer 4).

WMH volume in the different brain regions and layers is provided in Fig. 1. The regional volumes were also combined to compute global WMH (combining the 4 layers in the 9 lobar zones) and GM volume (combining the 9 lobar zones).

Due to their skewed distribution, all WMH volumes were log transformed. Both the regional and global WMH and GM volumes were adjusted for intracranial volume (ICV), age and scanner type using a linear regression analysis including these variables. This linear regression model was used to calculate a predicted WMH and GM volume for each patient. Then, a corresponding W-score was calculated with the following formula: *W-score* = (*observed* – *predicted*) / *standard deviation* of the volumes [39]. The W-scores of both global and regional WMH and GM volume were used for further analysis.

2.2.2. Neuropsychological testing

Cognitive functioning was assessed by trained neuropsychologists. In this study, cognitive functioning was evaluated across four domains: memory, language, processing speed and executive function. Memory was tested using a Dutch version of the Rey Auditory Verbal Learning Test [40,41]and the Visual Association Test (VAT) [42]. Language was examined with the Category Fluency Animals Test [43]and the VAT-A-naming test, a component of the VAT. Processing speed was evaluated with the Stroop Color-Word Test (SCWT) with the average score of card I (word reading) and card II (color naming) [44,45]and the Trail Making Test-A (TMT-A) [46]. Finally, executive function was assessed with the TMT B/A index and the SCWT interference score of card III (color-word interference), corrected for the average of card I and II. All test results were converted to Z-scores based on this study sample. Scores of TMT and SCWT were inversed to align all tests with a higher test score reflecting a better cognitive performance. Test Z-scores were averaged to create Z-scores for each domain.

2.3. Statistical analysis

2.3.1. Characteristics of the sample

All statistical analyses were executed in RStudio version 4.2.1 [47]. Patient demographics and clinical information were compared between men and women with Mann-Whitney *U* tests for non-parametric data and chi-squared analyses for proportions, with post-hoc comparisons if indicated.

2.3.2. Multiple imputation

There can be missing values in geriatric memory clinic populations due to numerous reasons [48]. To overcome omitting patients with worse cognitive functioning (e.g. due to termination of neuropsychological testing when this becomes too hard), it is rather beneficial to impute missing values. Multiple imputation is particularly suited for this when the missing data is missing at random (MAR), as it allows for more accurate estimates by considering the relationships between observed data. Therefore, we performed multiple imputation using predictive mean matching with the Mice procedure [49]. In this sample, there were missing values for the Education Verhage score (17 %), MMSE score (0.4 %), gait speed (7 %), memory (17 %), language (17 %), processing speed (21 %) and executive function (28 %). In total, 32 % of the sample had 1 or more missing values for these variables, and of which 71 % had a dementia diagnosis, which is larger compared to the whole sample (56 %). We therefore considered these variables to be sufficiently missing at random, meaning that the chance of missing values is dependent on observed values [49]. This is crucial because it allows for unbiased and accurate estimation of missing values using the observed data [50]. For example, general cognitive functioning (measured with MMSE score) can be used to predict missing values of executive functioning in the imputation model. Test scores were imputed before calculating domain scores of memory, language, processing speed and executive function. Global cognitive function was imputed passively by calculating the average of the Z-scores across all four domains. A total of 15 variables were included in the imputation model, with 14 main variables used for further analysis and gait speed included as an auxiliary variable. Further analyses that include the variables Education Verhage score, MMSE score, memory, language, processing speed, executive function and global cognitive function represent the pooled analysis results of 10 imputed datasets with 20 iterations per imputation, which resulted in convergence of the model. Also, we evaluated the differences in density between observed and imputed data, for reviewing the quality of the imputation model [49](*Sup. 6*).

2.3.3. Sex differences in brain structure abnormalities

First, we compared the global WMH and GM volume between men and women with Mann-Whitney *U* tests. Also, we used multiple linear regression analyses to test the association between global WMH and GM volume and sex. The variables sex (1), age (2), Education Verhage score (3), reported cardiovascular event (4) and MMSE score (5) were incrementally added to the model as covariates.

Second, we used multiple linear regression analyses to explore the association between sex and the WMH volume in different regions and layers, and GM volume in different regions. These associations were evaluated with incrementally adding the 1 – 5 covariates in the model (model 5 is shown).

The beta coefficients of sex were plotted in a radial plot to visualize these associations for the frontal, parietal, temporal, occipital and basal ganglia infratentorial region in the left and right hemisphere. We adjusted the p-values of all regional volume analyses for multiple comparisons with the False Discovery Rate (FDR) correction (Benjamini-Hochberg procedure) at a significance threshold of $q < 0.05$. This was done separately for the associations with the regional measures of WMH, which included 36 analyses in one radial plot, and regional volumes of GM, which included 9 analyses in one radial plot.

2.3.4. Association between brain structure abnormalities and cognitive function

Third, we executed multiple linear regression analyses to identify the association between both global and regional WMH and GM volume and the four cognitive domains and global cognitive function, stratified by sex. We added the covariates 1 – 4 incrementally to the models, leaving out covariate 5 (MMSE score) as this variable is too closely related to cognitive function (model 4 is shown). The beta coefficients of the regional volumes were plotted in a radial plot to visualize the associations. We adjusted the p-values for multiple testing for regional analyses with the FDR procedure.

2.3.5. Interaction of sex and brain structure abnormalities in the association with cognitive function

Fourth, we used multiple linear regressions to evaluate the interaction of sex on both global and regional WMH and GM volume in the association with the cognitive domains and global cognitive function. The interaction term of sex * volume was used for these associations, and we evaluated them with incrementally adding the 1 – 4 covariates in the model (model 4 is shown). The beta coefficients of the interaction were plotted in a radial plot to visualize the associations. We adjusted the p-values for multiple testing for regional analyses with the FDR procedure.

3. Results

3.1. Demographics

The demographics and clinical characteristics of the sample are presented in Table 1. From the total of 475 participants (age 79.1 [75.8, 83.2] years), 48 % were women. 56 % of the sample had a dementia diagnosis, which includes Alzheimer's disease, vascular dementia and other forms. Men had a higher educational level, higher BMI and higher gait speed compared to women. Furthermore, a greater proportion of men had a diagnosis of diabetes, a cardiovascular event reported in their medical history, and men more often smoked and used alcohol. Finally, a larger proportion of men received no care at home compared to women. There were no sex differences in MMSE, GDS or cognitive diagnosis.

3.2. Sex differences in brain structure abnormalities

3.2.1. Sex differences in global measures of WMH and GM volume

As visualized in Fig. 2, we found no sex differences in global WMH ($W = 25621$; $p = 0.09$; Fig. 2*A*) or GM volume ($W = 26570$; $p =$

Table 1
Demographic and clinical information of study participants.

	All (*n = 475*)	Men (*n = 247*)	Women (*n = 228*)	p-value
Age, *in years*	79.1 [75.8, 83.2]	78.6 [75.7, 82.9]	79.2 [76.0, 83.3]	0.28
Education Verhage score	5 [4, 6]	6 [4, 6]	5 [4, 6]	**0.014**
BMI	25.2 [22.5, 28.2]	25.5 [23.3, 28.2]	24.9 [21.8, 28.1]	**0.017**
MMSE	25 [21, 27]	24 [21, 27]	25 [21, 27]	0.82
GDS	3 [1, 5]	3 [1, 5]	3 [2, 5]	0.07
Gait speed, *in m/s*	1.0 [0.8, 1.1]	1.0 [0.8, 1.1]	0.9 [0.7, 1.1]	**0.003**
Cognitive diagnosis				0.26
SCD	68 (14 %)	30 (12 %)	38 (17 %)	
MCI	130 (28 %)	72 (29 %)	58 (26 %)	
Alzheimer's disease	177 (38 %)	86 (35 %)	91 (40 %)	
Vascular dementia	44 (9 %)	29 (12 %)	15 (7 %)	
Other [a]	52 (11 %)	29 (12 %)	23 (10 %)	
Diabetes	87 (18 %)	54 (22 %)	33 (15 %)	**0.049**
Hypertension	251 (53 %)	124 (50 %)	127 (56 %)	0.27
Hypercholesterolemia	143 (30 %)	76 (31 %)	67 (29 %)	0.82
Cardiovascular event reported [b]	224 (47 %)	142 (58 %)	82 (36 %)	**< 0.001**
- Stroke	104 (22 %)	66 (27 %)	38 (17 %)	**0.011**
- Myocardial infarction	61 (13 %)	47 (19 %)	14 (6 %)	**< 0.001**
- Angina pectoris	52 (11 %)	35 (14 %)	17 (8 %)	**0.028**
- Heart failure	29 (6 %)	15 (6 %)	14 (6 %)	1
- Atrial fibrillation	73 (15 %)	47 (19 %)	26 (11 %)	**0.030**
Number of medications	5 [3, 8]	5 [3, 8]	5 [2.8, 7.0]	0.44
(History of) smoking	277 (58 %)	166 (67 %)	111 (49 %)	**< 0.001**
Alcohol use	2 [0, 10]	3 [0, 10]	1 [0, 7]	**0.004**
Living independent	447 (94 %)	234 (95 %)	213 (93 %)	0.46
No care at home	108 (23 %)	70 (29 %)	38 (17 %)	**0.002**

Table 1. Demographic and clinical information of study participants. Values are represented as median [25th percentile, 75th percentile] or as the amount of the population and percentage, n(%), of the sample with that trait. * represents $p < 0.05$ when comparing men and women. [a] Other dementias, neurologic and psychiatric diseases. [b] Cardiovascular event reported is the total amount of participants that had either one or more cardiovascular events reported, such as stroke, myocardial infarction, angina pectoris, heart failure and atrial fibrillation. Abbreviations: BMI, body mass index (calculated as weight/height^2); MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; SCD, subjective cognitive decline; MCI, mild cognitive impairment.

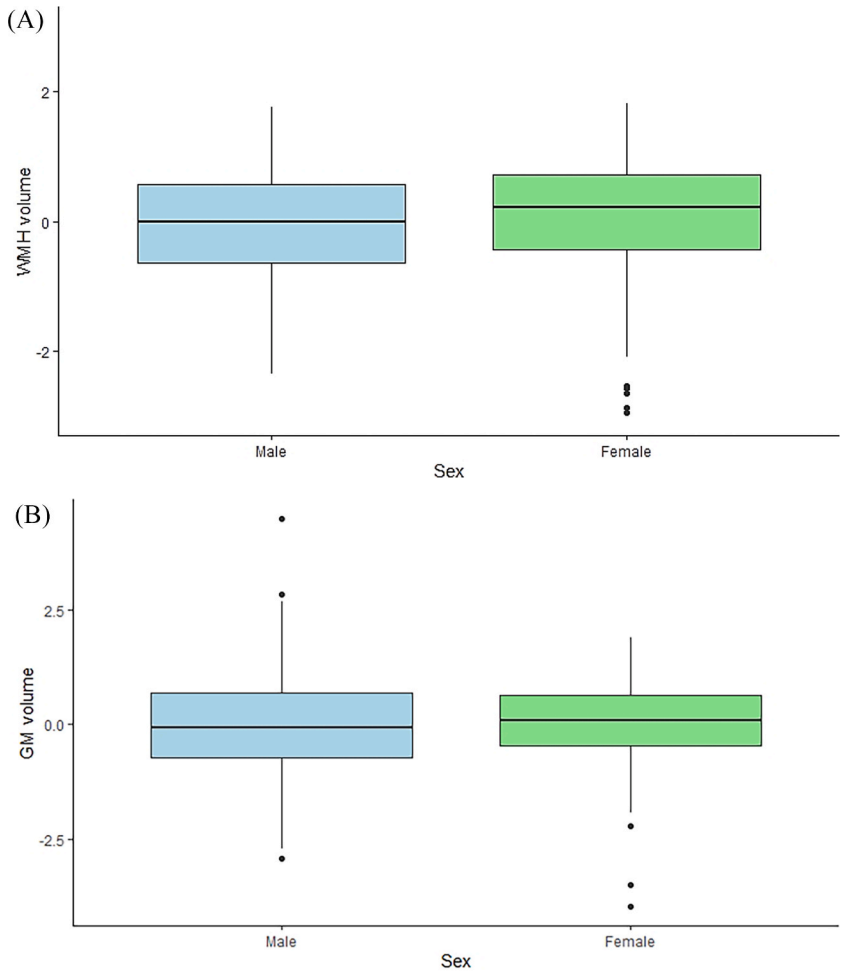

Fig. 2. Boxplot of sex differences in global WMH and GM volume. 2A. Sex differences in global WMH volume. 2B. Sex differences in global GM volume. Fig. 2. *Boxplot figures with W-scores of global WMH and GM volume, compared between men and women. (A) No difference for WMH volume between men and women. (B) Also, no difference for GM volume between men and women.*

0.29; Fig. 2*B*). Furthermore, we found no association between global WMH (β = 0.11, CI = [-0.08, 0.29]) and GM volume (β = -0.01, CI = [-0.18, 0.17]) and sex, while including covariates 2 – 5 (age, Education Verhage score, reported cardiovascular event and MMSE score) in the model.

3.2.2. Sex differences in regional measures of WMH and GM volume

Also when assessing regional measures of WMH and GM volume, we found no association with sex, as shown in Fig. 3. Yet, we did observe a trend in which women have lower WMH volumes than men in layer 1 and 2 of the left- and right-hemispheric frontal lobes, and layer 3 of the right-hemispheric occipital lobes (beta coefficients and significance ranges between [*FL1 – OR3*]: β = [-0.20 – −0.26]; *p* = [0.0380 – 0.0060]; Fig. 3*A*). Also, women appeared to have lower GM volume in the occipital right cortex compared to men (β = -0.24, CI = [-0.43, −0.06]; Fig. 3*B*). This trend did not remain significant after correction for multiple testing.

3.3. Association between brain structure abnormalities and cognitive function

3.3.1. Association between global measures of WMH and GM volume and cognitive domains

For both men and women, lower GM volume was associated with a lower score for global cognitive function, memory, language and processing speed (Table 2). Although lower GM volume was associated with lower scores of executive function in men, this was not the case for women. For all associations with global measures of WMH and GM volume, there seemed to be a trend of a stronger relation with the cognitive domains for women than for men. However, there were no associations between global WMH volume and the cognitive domains for men or women.

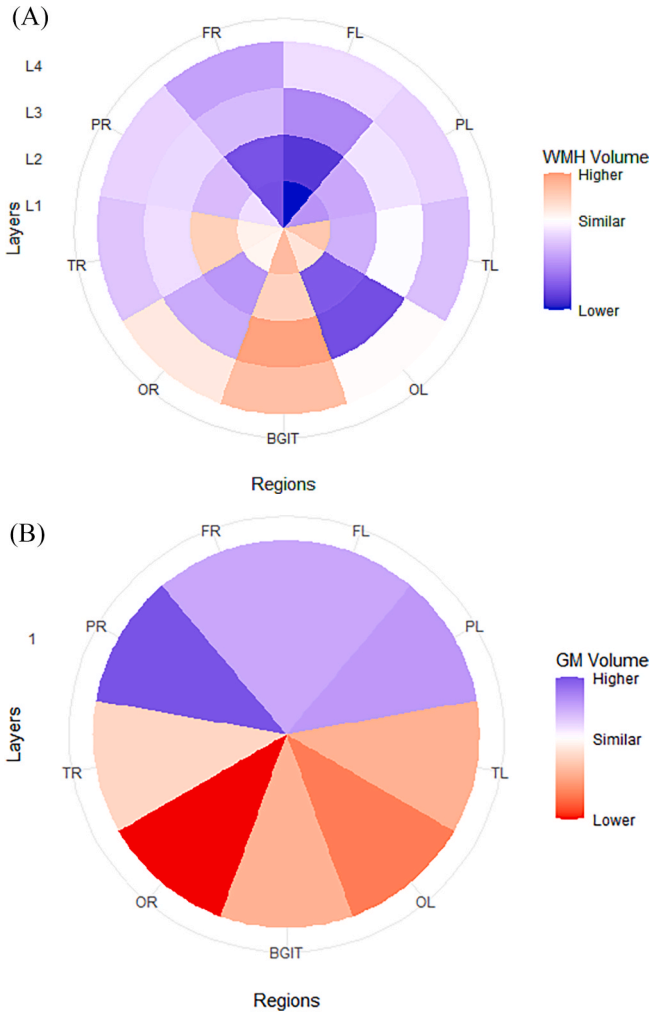

Fig. 3. Radial plot of the association of sex with regional WMH and GM volumes. 3A. Association of sex with regional WMH volumes 3B. Association of sex with regional GM volumes. Fig. 3. *The beta coefficients of sex from model 5 including covariates 1–5 for regional WMH (A) and GM (B) volumes. No association between sex and regional WMH or GM volume. Regions in left and right hemisphere are frontal (FL, FR), parietal (PL, PR), temporal (TL, TR), occipital (OL, OR) and basal ganglia infratentorial region (BGIT). In* Fig. 3A*, the inner layers (1 and 2) represent the region closest to the ventricles, as the outer layers (3 and 4) represent the layers closest to the cortex. Red indicates that being female is associated with higher WMH volume (A), or lower GM volume (B).*

Table 2
Association between cognitive domains and brain structure abnormalities, stratified by sex.

Model		Global cognitive function	Memory	Language	Processing speed	Executive function
WMH volume	Men	β = -0.11	β = -0.01	β = -0.01	β = -0.02	β = -0.08
		[-0.40, 0.17]	[-0.12, 0.11]	[-0.13, 0.11]	[-0.16, 0.12]	[-0.22, 0.06]
	Women	β = -0.31	β = -0.04	β = -0.12	β = -0.09	β = -0.15
		[-0.63, 0.01]	[-0.18, 0.09]	[-0.26, 0.01]	[-0.28, 0.10]	[-0.32, 0.03]
GM volume	Men	β = 0.67 *	β = 0.26 *	β = 0.21 *	β = 0.23 *	β = 0.13 *
		[0.43, 0.91]	[0.16, 0.36]	[0.10, 0.32]	[0.10, 0.36]	[0.01, 0.25]
	Women	β = 0.90 *	β = 0.35 *	β = 0.32 *	β = 0.34 *	β = 0.14
		[0.57, 1.24]	[0.19, 0.50]	[0.17, 0.47]	[0.16, 0.51]	[-0.04, 0.32]

Table 2. Beta coefficients from model 4 with covariates 1–4 of the associations are shown with 95 % confidence intervals, * represents $p < 0.05$.

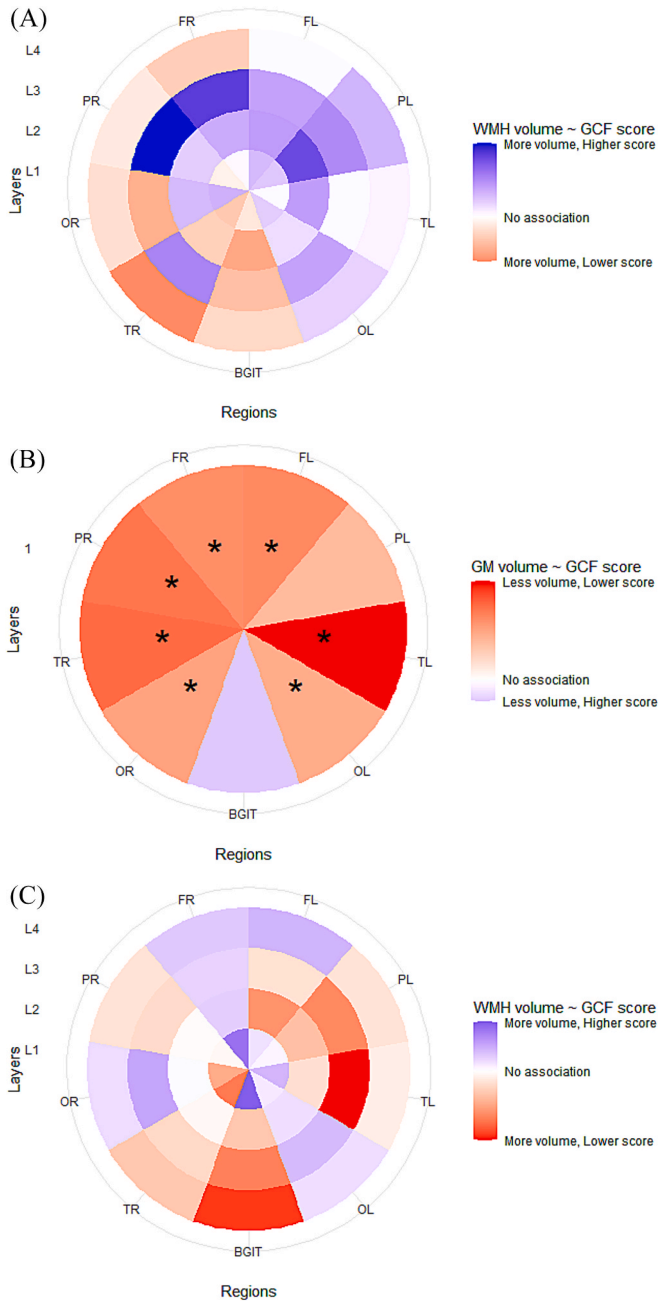

Fig. 4. Radial plot of the association between regional WMH and GM volume and global cognitive function, stratified by sex. 4A. Association between regional WMH volume and global cognitive function for men. 4B. Association between regional GM volume and global cognitive function for men. 4C. Association between regional WMH volume and global cognitive function for women. 4D. Association between regional GM volume and global cognitive function for women. Fig. 4. *The beta coefficients from model 4 including covariates 1–4 of regional WMH and GM volume for global cognitive function (GCF score) for men and women separately. No associations between regional WMH volume and global cognitive function for men (A) and women (C). Less GM is associated with lower global cognitive function score for frontal, parietal, temporal and occipital cortex left and right hemisphere for men (B) and women (D). Red indicates that more WMH and less GM volume are associated with lower cognitive functioning scores.*

3.3.2. Association between regional measures of WMH and GM volume and cognitive domains

For both men and women, there were associations with regional GM volumes and global cognitive function (Fig. 4*B; 4D*). Less regional GM volume was associated with a lower global cognitive function score in the frontal, parietal, temporal and occipital cortex in both hemispheres for men (beta coefficients and significance ranges between [*OL – TL*]: $\beta = [0.29 – 0.64]$; $p = [0.0270 – < 0.0001]$;

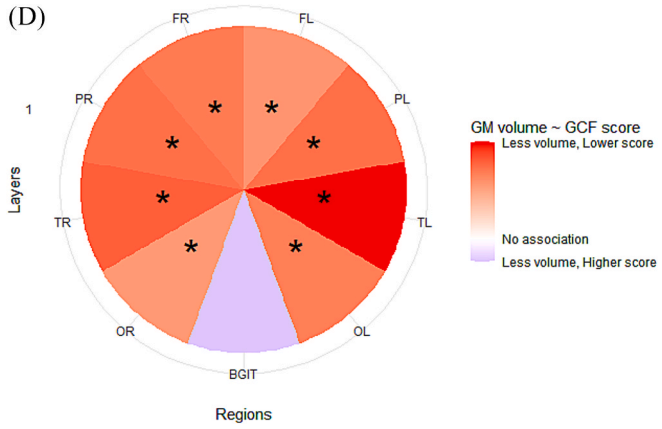

Fig. 4. (*continued*).

Fig. 4*B*) and women ([*OR – TL*]: β = [0.37 – 0.67]; *p* = [0.0389 – 0.0006]; Fig. 4*D*). Exact beta coefficients, confidence intervals and p-values can be found in *Sup. 1*. In contrast, there were no associations of regional WMH volumes with global cognitive function for either men or women.

For both men and women, there were associations between less GM volume and a lower score on the cognitive domains separately (*Sup. 2*). For men, less GM volume in the frontal left, parietal, temporal and occipital cortex was associated with lower score for memory, language and processing speed. For women, less GM volume in the parietal right, temporal and occipital cortex was

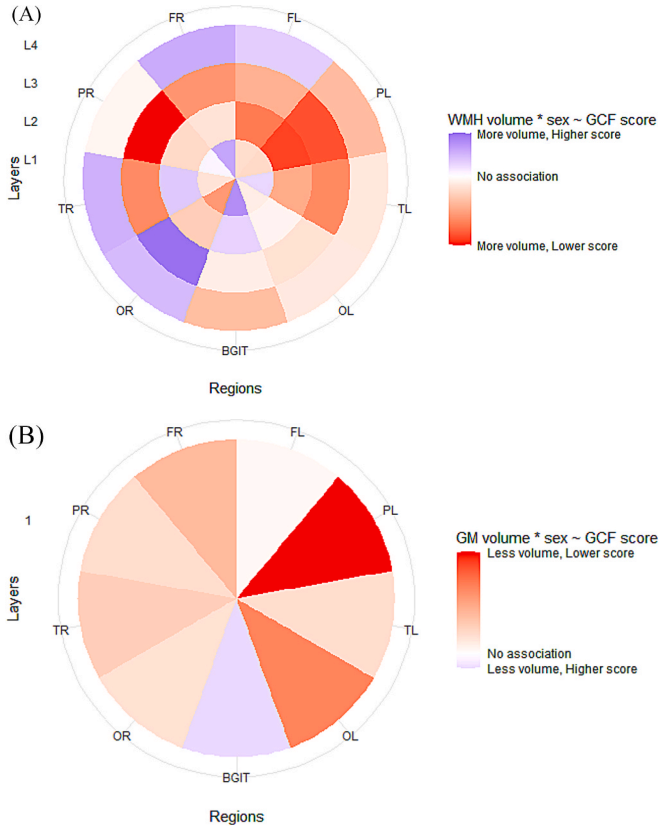

Fig. 5. Radial plot of the interaction of sex with regional WMH and GM volume for global cognitive function. 5A. Interaction of sex with regional WMH volume for global cognitive function. 5B. Interaction of sex with regional GM volume for global cognitive function. Fig. 5. *The beta coefficients from model 4 including covariates 1–4 of the interaction of sex with the regional WMH and GM volume for global cognitive function (GCF score). No interaction of sex with the regional WMH volumes (A) and GM volumes (B) for global cognitive function. Red indicates that the interaction of sex with WMH and GM volume are associated with lower cognitive functioning scores.*

associated with lower score for memory, language and processing speed. Contrastingly, there was only one association for regional WMH volume for men, in which more WMH volume was associated with higher processing speed in layer 3 of the right-hemispheric parietal lobes (β = 0.24, CI = [0.10, 0.39]; *Sup. 3*).

3.4. Interaction of sex on the global and regional measures of WMH and GM volume for the cognitive domains

However, we found no interaction of sex on the association between global WMH and GM volume and the cognitive domains (*Sup. 4*). Finally, there was also no interaction of sex with the regional WMH and GM volumes for global cognitive function (Fig. 5) or any of the other cognitive domains (*Sup. 5*). Although not significant after correction for multiple testing, we did observe a trend in which more WMH volume was associated with lower global cognitive function score in the parietal lobes for women, in layer 2 of the left-hemisphere and layer 3 of the right hemisphere (*PL2:* β = -0.43, CI = [-0.84, −0.03]; *PR3:* β = -0.49, CI = [-0.89, −0.09]; Fig. 5*A*).

4. Discussion

4.1. Summary and interpretation of results

In this geriatric memory clinic population, we found (1) no sex differences in brain structure abnormalities, both for global and regional measures, and (2) no interaction of sex in the association between brain structure abnormalities and cognitive function. We did observe the expected association between less global and regional GM volume and lower scores on the cognitive domains, but there were no sex-specific associations. This result diverged from research that did find sex differences in cognitive functioning and brain structure abnormalities, that was done in younger samples with more homogeneous aetiologies compared to our study [17,18,19]. Investigating a memory clinic population that is relatively older and with more comorbidities might have obscured differences in brain structure abnormalities and cognitive functioning between women and men.

Although we expected that the regional quantification method used in this study could provide new insights in sex differences compared to often used global quantification methods, we did not find conclusive sex differences with our method. We did see a trend in some regional results, with more WMH volume in frontal left and right and occipital right cortex for men, which is partly in accordance with previous research that shows slightly more WMH in the occipital cortex for men [23]. Moreover, there was a trend for lower GM volume in the occipital right cortex for women, which was in contrast with previous studies showing more pronounced temporal atrophy in women [20,21,29]. We also observed a trend in which more WMH volume was associated with a lower global cognitive function score in the parietal cortex for women, which contrasted our expectation that men are more affected by WMH volume [20]. However, all these trends in regional results did not remain significant after correction for multiple testing. We will provide several explanations for this below, and discuss implications.

4.2. Strengths and limitations

There are some strengths and limitations in this study that have impact for the implications and generalizability of our findings. First of all, a strength of this study is that we used a real world sample derived from a geriatric memory clinic population, aiming to resemble clinical reality [25,26]. This population is more directly affected by research on brain structure abnormalities, which plays a crucial role in establishing clinical diagnoses and initiating treatment and support. The inclusion of memory clinic patients with a large range of cognitive diagnoses and varying levels of cognitive functioning is important, because a homogenous sample in terms of diagnosis and cognitive function can give rise to a false observation of a negative association between studied determinants and outcomes, when in reality, these are unrelated or even positively related [51]. Also, studying various forms of dementia (e.g. Alzheimer's disease, vascular dementia) separately limits the translatability to the large spectrum of neurodegenerative diseases, which often overlap and are simultaneously present in the ageing population [24]. Furthermore, the regional quantification of brain structure abnormalities in this study provided a more sensitive measure for identifying sex differences in comparison to global measures. Lastly, using multiple imputation for dealing with missing data is a strength of this study. When comparing the entire sample to those with missing data, the latter group had a higher proportion of people diagnosed with dementia (diagnosis of 56 % in the whole sample, and of 71 % in those with missing data). To avoid omitting patients with worse cognitive functioning, it was beneficial to impute missing values. However, the relatively large proportion of missing values of processing speed (21 %) and executive functioning (28 %) might have influenced our results. As a larger burden of WMH is associated with less processing speed and executive functioning [14], it is possible that this relation was underestimated in our sample. Furthermore, a limitation of this study is its sample size. It is possible that the power was insufficient to substantiate the number of analyses needed for the regional quantification of brain structure abnormalities, which a larger sample size might resolve [28]. Additionally, the sample size limited the number of variables we could include as covariates, resulting in the exclusion of important factors such as smoking and diabetes from the analyses. A larger sample would have enabled us to look more extensively at other covariates, the influence of using different scanner strengths, or look at stratified analyses in terms of age groups.

Another limitation of this study is that the sample lacked diversity in socioeconomic and ethnic backgrounds, due to geographic and cultural homogeneity in the sample. Geriatric memory clinic populations can be challenged with participation bias, due to differences in referral rates between men and women, and differences in health literacy and socioeconomic status [27]. What exemplifies this, is the proportion of women in our sample (48 %). This is not concurrent with incidence rates of dementia in The Netherlands, which is suggested to be slightly higher for women compared to men [52]. Therefore, our sample might have been more homogeneous than

expected, which influenced our findings. This limits the generalizability of this study to a more diverse population. Moreover, it is known that a lower socioeconomic status is associated with faster cognitive decline, which can cause health disadvantages [53]. It is therefore important to strive for the inclusion of more diverse populations in research. Furthermore, our operationalisation of sex as a binary construct has implications on our findings and conclusions, and we reflect on some of these implications below [54].

4.3. Reflecting on sex differences

We used a binary classification of sex, focusing on differences between men and women as groups. By operationalising sex in a binary fashion, we not only exclude the reality of intersex individuals, but also risk overlooking within group differences – such as ethnicity, socioeconomic status and geographical location [53]. In reality, patients belong to multiple social groups, and health-related behaviour and healthcare experiences are influenced by the relations and overlaps between these social groups and identities [55]). This complexity might be captured using the framework of intersectionality [56,57]. Due to the absence of available data on other social variables – including ethnicity and socioeconomic status – as well as a relatively limited number of patients, we were not able to apply an intersectional framework. However, earlier studies show that sex differences may vary between ethnic groups; therefore our findings should be generalized with caution [58].

Furthermore, focusing on sex differences falls within a common pattern in biomedical sciences in which researchers have focused on a sexually dimorphic view of the brain (e.g. 'female brain' vs. 'male brain'), overlooking evidence that there is extensive overlap between men and women in brain structure as well as brain function [54]. First, there is a large bias towards publication of findings which suggest differences between men and women in terms of brain structure and cognition, resulting in an excessive attribution of brain structure and function to sex-linked biology [59,60]. Therefore, we stress the importance of publication of 'negative' findings such as the present study – which might strengthen our understanding of the relations between sex, brain structure and cognition. For future studies, a better approach for studying the relation between sex and the brain might be starting from the assumption there is greater heterogeneity within than between groups of men and women [54]. Although there might be sex differences in frequencies of certain brain structures on a group-level, most individual brains are a uniquely composed mix of these more typically 'male' or 'female' components. Also, possible group-level differences between men and women in brain structure do not necessarily translate into functional differences due to compensatory mechanisms, which reduce instead of create differences.

Lastly, gender bias in referral rates and in cognitive assessment, and gender-related socio-structural factors which shape risk of cognitive impairment and dementia, are relevant in the interpretation of our findings [61,62,63,64]. For example, research has shown that gender-related differences in the formation and function of social networks among older men and women are linked to cognitive function [65,66,67], highlighting the importance of studying gender to better understand their impact on cognitive health in aging populations. Due to limitations of our dataset, we could not assess these variables, and by dichotomizing our data based on sex, we could not differentiate between the influences of sex and gender on brain structure abnormalities and cognitive functioning. Thus, while it is evident that both sex and gender-related factors play a significant role in disease progression, our database lacked in gender-specific data, a limitation that is not unique to our study [68,69]. Not considering or not having the data to consider these gender-related factors might overlook opportunities to reduce current sex- and gender-based healthcare disparities in the prevention, diagnosis and treatment of cognitive impairment and dementia.

4.4. Aims for future research

In future studies investigating brain structure abnormalities and cognitive functioning, gender-specific data and data relating to intersecting social positions and behavioural contexts should be included [54]. Also, it should be made explicit whether sex or gender is being investigated, or both, and researchers should critically reflect on the potential impact and interrelatedness of sex and gender in their data and interpretation of results [70]. This can aid in a more nuanced understanding of sex and gender-related differences in brain structure and function, and in the scientific and clinical implications of clinical research in this field.

5. Conclusions

In this study, in which we looked at sex differences in a memory clinic population, we found no differences in brain structure abnormalities or in the association between brain structure abnormalities and cognitive function between men and women. We reflect on our methodological approach of dichotomous analysis based on sex, which might overlook differences within groups of men and women, and does not elucidate the influence of gender-related factors. Future studies should focus on elucidating within group differences, by including more diverse patients in terms of social background and using intersectional approaches. This way, we might move towards better understanding the influence of sex and gender on brain pathology and function, with the ultimate goal of improving healthcare for all sexes and genders.

CRediT authorship contribution statement

A. Lamé: Writing – original draft. **E.G. Thomas:** Writing – review & editing. **S.A.J. van de Schraaf:** Writing – review & editing. **C. Groot:** Writing – review & editing. **C.H. Sudre:** Writing – review & editing. **F. Barkhof:** Data curation. **M. Muller:** Writing – review & editing. **R. Ossenkoppele:** Writing – review & editing. **H.F.M. Rhodius-Meester:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

[1] Fausto-Sterling A. *Sex/gender: Biology in a Social World*. Routledge 2012. https://books.google.nl/books?id=amsxkgAACAAJ.
[2] Krieger N. Genders, sexes, and health: what are the connections–and why does it matter? *Int J Epidemiol* 2003;32(4):652–7. https://doi.org/10.1093/ije/dyg156.
[3] Hankivsky O, Grace D, Hunting G, Giesbrecht M, Fridkin A, Rudrum S, et al. An intersectionality-based policy analysis framework: critical reflections on a methodology for advancing equity. *Int J Equity Health* 2014;13(1):119. https://doi.org/10.1186/s12939-014-0119-x.
[4] King BM. Point: a call for proper usage of "gender" and "sex" in biomedical publications. *American J Physiol-Regulatory, Integrative Compar Physiol* 2010;298(6):R1700–1. https://doi.org/10.1152/ajpregu.00694.2009.
[5] Laws KR, Irvine K, Gale TM. Sex differences in cognitive impairment in Alzheimer's disease. *World J Psychiatry* 2016;6(1):54–65. https://doi.org/10.5498/wjp.v6.i1.54.
[6] Nebel RA, Aggarwal NT, Barnes LL, Gallagher A, Goldstein JM, Kantarci K, et al. Understanding the impact of sex and gender in Alzheimer's disease: A call to action. *Alzheimers Dement* 2018;14(9):1171–83. https://doi.org/10.1016/j.jalz.2018.04.008.
[7] Cao Q, Tan C-C, Xu W, Hu H, Cao X-P, Dong Q, et al. The Prevalence of Dementia: A Systematic Review and Meta-Analysis. *J Alzheimers Dis* 2020;73:1157–66. https://doi.org/10.3233/JAD-191092.
[8] Nooyens ACJ, Wijnhoven HAH, Schaap LS, Sialino LD, Kok AAL, Visser M, et al. Sex Differences in Cognitive Functioning with Aging in the Netherlands. *Gerontology* 2022;68(9):999–1009. https://doi.org/10.1159/000520318.
[9] Li R, Singh M. Sex differences in cognitive impairment and Alzheimer's disease. *Front Neuroendocrinol* 2014;35(3):385–403. https://doi.org/10.1016/j.yfrne.2014.01.002.
[10] Makovac E, Serra L, Spanò B, Giulietti G, Torso M, Cercignani M, et al. Different Patterns of Correlation between Grey and White Matter Integrity Account for Behavioral and Psychological Symptoms in Alzheimer's Disease. *J Alzheimers Dis* 2016;50:591–604. https://doi.org/10.3233/JAD-150612.
[11] Li M, Meng Y, Wang M, Yang S, Wu H, Zhao B, et al. Cerebral gray matter volume reduction in subcortical vascular mild cognitive impairment patients and subcortical vascular dementia patients, and its relation with cognitive deficits. *Brain and Behavior* 2017;7(8):e00745. https://doi.org/10.1002/brb3.745.
[12] Ramanoël S, Hoyau E, Kauffmann L, Renard F, Pichat C, Boudiaf N, et al. Gray Matter Volume and Cognitive Performance During Normal Aging. A Voxel-Based Morphometry Study [Original Research]. *Front Aging Neurosci* 2018;10. https://doi.org/10.3389/fnagi.2018.00235.
[13] Sanderson-Cimino M, Panizzon MS, Elman JA, Tu X, Gustavson DE, Puckett O, et al. Periventricular and deep abnormal white matter differ in associations with cognitive performance at midlife. *Neuropsychology* 2021;35(3):252–64. https://doi.org/10.1037/neu0000718.
[14] van den Berg E, Geerlings MI, Biessels GJ, Nederkoorn PJ, Kloppenborg RP. White Matter Hyperintensities and Cognition in Mild Cognitive Impairment and Alzheimer's Disease: A Domain-Specific Meta-Analysis. *J Alzheimers Dis* 2018;63(2):515–27. https://doi.org/10.3233/jad-170573.
[15] Ferretti MT, Iulita MF, Cavedo E, Chiesa PA, Schumacher Dimech A, Santuccione Chadha A, et al. Sex differences in Alzheimer disease — the gateway to precision medicine. *Nat Rev Neurol* 2018;14(8):457–69. https://doi.org/10.1038/s41582-018-0032-9.
[16] van Zutphen EM, Rijnhart JJM, Rhebergen D, Muller M, Huisman M, Beekman A, et al. Do Cardiovascular Risk Factors and Cardiovascular Disease Explain Sex Differences in Cognitive Functioning in Old Age? *J Alzheimers Dis* 2021;80:1643–55. https://doi.org/10.3233/JAD-201173.
[17] DeCarli C, Massaro J, Harvey D, Hald J, Tullberg M, Au R, et al. Measures of brain morphology and infarction in the framingham heart study: establishing what is normal. *Neurobiol Aging* 2005;26(4):491–510. https://doi.org/10.1016/j.neurobiolaging.2004.05.004.
[18] Exalto LG, Boomsma JMF, Babapour Mofrad R, Barkhof F, Groeneveld ON, Heinen R, et al. Sex differences in memory clinic patients with possible vascular cognitive impairment. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring* 2020;12(1):e12090. https://doi.org/10.1002/dad2.12090.
[19] Vinke EJ, de Groot M, Venkatraghavan V, Klein S, Niessen WJ, Ikram MA, et al. Trajectories of imaging markers in brain aging: the Rotterdam Study. *Neurobiol Aging* 2018;71:32–40. https://doi.org/10.1016/j.neurobiolaging.2018.07.001.
[20] Burke SL, Hu T, Fava NM, Li T, Rodriguez MJ, Schuldiner KL et al. Sex differences in the development of mild cognitive impairment and probable Alzheimer's disease as predicted by hippocampal volume or white matter hyperintensities. *J Women Aging* 2019;*31*(2):140–64. doi: 10.1080/08952841.2018.1419476.
[21] Koran MEI, Wagener M, Hohman TJ. Sex differences in the association between AD biomarkers and cognitive decline. *Brain Imaging Behav* 2017;11(1):205–13. https://doi.org/10.1007/s11682-016-9523-8.
[22] Fjell AM, Grydeland H, Krogsrud SK, Amlien I, Rohani DA, Ferschmann L, et al. Development and aging of cortical thickness correspond to genetic organization patterns. *Proc Natl Acad Sci* 2015;112(50):15462–7. https://doi.org/10.1073/pnas.1508831112.
[23] Morrison C, Dadar M, Collins DL. Sex differences in risk factors, burden, and outcomes of cerebrovascular disease in Alzheimer's disease populations. *Alzheimers Dement* 2024;20(1):34–46. https://doi.org/10.1002/alz.13452.
[24] Banerjee G, Jang H, Kim HJ, Kim ST, Kim JS, Lee JH, et al. Total MRI Small Vessel Disease Burden Correlates with Cognitive Performance, Cortical Atrophy, and Network Measures in a Memory Clinic Population. *J Alzheimers Dis* 2018;63(4):1485–97. https://doi.org/10.3233/jad-170943.
[25] Jahn H. Memory loss in Alzheimer's disease. *Dialogues Clin Neurosci* 2013;15(4):445–54. https://doi.org/10.31887/DCNS.2013.15.4/hjahn.
[26] Masdeu JC. Future Directions in Imaging Neurodegeneration. *Curr Neurol Neurosci Rep* 2017;17(1):9. https://doi.org/10.1007/s11910-017-0718-1.
[27] Brodaty H, Mothakunnel A, de Vel-Palumbo M, Ames D, Ellis KA, Reppermund S et al. Influence of population versus convenience sampling on sample characteristics in studies of cognitive aging. *Ann Epidemiol* 2014;*24*(1):63–71. doi: 10.1016/j.annepidem.2013.10.005.

[28] Biesbroek JM, Coenen M, DeCarli C, Fletcher EM, Maillard PM, Initiative A, et al. Amyloid pathology and vascular risk are associated with distinct patterns of cerebral white matter hyperintensities: A multicenter study in 3132 memory clinic patients. *Alzheimers Dement* 2024;20(4):2980–9. https://doi.org/10.1002/alz.13765.

[29] Ardekani BA, Convit A, Bachman AH. Analysis of the MIRIAD Data Shows Sex Differences in Hippocampal Atrophy Progression. *J Alzheimers Dis* 2016;50:847–57. https://doi.org/10.3233/JAD-150780.

[30] Sudre CH, Gomez Anson B, Davagnanam I, Schmitt A, Mendelson AF, Prados F, et al. Bullseye's representation of cerebral white matter hyperintensities. *J Neuroradiol* 2018;45(2):114–22. https://doi.org/10.1016/j.neurad.2017.10.001.

[31] Rhodius-Meester HFM, van de Schraaf SAJ, Peters MJL, Kleipool EEF, Trappenburg MC, Muller M. Mortality Risk and Its Association with Geriatric Domain Deficits in Older Outpatients: The Amsterdam Ageing Cohort. *Gerontology* 2021;67(2):194–201. https://doi.org/10.1159/000512048.

[32] Verhage F. Intelligence and age: study with Dutch people aged 12–77. Assen: Van Gorcum; 1964.

[33] Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. In *Clinical gerontology*. Routledge; 2014. p. 165–73.

[34] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journalof psychiatric research* 1975;12(3):189–98.

[35] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7(3):263–9. https://doi.org/10.1016/j.jalz.2011.03.005.

[36] Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004;256(3):183–94. https://doi.org/10.1111/j.1365-2796.2004.01388.x.

[37] Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia. *Neurology* 1993;43(2):250. https://doi.org/10.1212/WNL.43.2.250.

[38] ten Kate M, Barkhof F, Visser PJ, Teunissen CE, Scheltens P, van der Flier WM, et al. Amyloid-independent atrophy patterns predict time to progression to dementia in mild cognitive impairment. *Alzheimers Res Ther* 2017;9(1):73. https://doi.org/10.1186/s13195-017-0299-x.

[39] Ossenkoppele R, Cohn-Sheehy BI, La Joie R, Vogel JW, Möller C, Lehmann M, et al. Atrophy patterns in early clinical stages across distinct phenotypes of Alzheimer's disease. *Hum Brain Mapp* 2015;36(11):4421–37. https://doi.org/10.1002/hbm.22927.

[40] Brand N, Jolles J. Learning and retrieval rate of words presented auditorily and visually. *J Gen Psychol* 1985;112(2):201–10. https://doi.org/10.1080/00221309.1985.9711004.

[41] Van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J. Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation. *J Int Neuropsychol Soc* 2005;11(3):290–302. https://doi.org/10.1017/s1355617705050344.

[42] Lindeboom J, Schmand B, Tulner L, Walstra G, Jonker C. Visual association test to detect early dementia of the Alzheimer type. J Neurol Neurosurg Psychiatry 2002;73(2):126. https://doi.org/10.1136/jnnp.73.2.126.

[43] Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. Normative data for the Animal, Profession and Letter M Naming verbal fluency tests for Dutch speaking participants and the effects of age, education, and sex. *J Int Neuropsychol Soc* 2006;12(1):80–9. https://doi.org/10.1017/s1355617706060115.

[44] Hammes J. *De stroop kleur-woord test : handleiding*. Swets & Zeitlinger; 1971.

[45] Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. The Stroop color-word test: influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment* 2006;13(1):62–79. https://doi.org/10.1177/1073191105283427.

[46] Reitan RM. The relation of the Trail Making Test to organic brain damage. *J Consult Psychol* 1955;19(5):393–4. https://doi.org/10.1037/h0044509.

[47] RStudioTeam. RStudio: Integrated Development for R. PBC, Boston: RStudio; 2020.

[48] Mehdipour Ghazi M, Nielsen M, Pai A, Cardoso MJ, Modat M, Ourselin S, et al. Training recurrent neural networks robust to incomplete data: Application to Alzheimer's disease progression modeling. *Med Image Anal* 2019;53:39–46. https://doi.org/10.1016/j.media.2019.01.004.

[49] van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *J Stat Softw* 2011;45(3):1–67. https://doi.org/10.18637/jss.v045.i03.

[50] van Ginkel JR, Linting M, Rippe RCA, van der Voort A. Rebutting Existing Misconceptions About Multiple Imputation as a Method for Handling Missing Data. *J Pers Assess* 2020;102(3):297–308. https://doi.org/10.1080/00223891.2018.1530680.

[51] Westreich D. Berkson's Bias, Selection Bias, and Missing Data. *Epidemiology* 2012;23(1). https://journals.lww.com/epidem/fulltext/2012/01000/berkson_s_bias,_selection_bias,_and_missing_data.24.aspx.

[52] van Bussel EF, Richard E, Arts DL, Nooyens AC, Coloma PM, de Waal MW, et al. Dementia incidence trend over 1992-2014 in the Netherlands: Analysis of primary care data. *PLoS Med* 2017;14(3):e1002235. https://doi.org/10.1371/journal.pmed.1002235.

[53] Avila-Rieger J, Turney IC, Vonk JMJ, Esie P, Seblova D, Weir VR, et al. Socioeconomic Status, Biological Aging, and Memory in a Diverse National Sample of Older US Men and Women. *Neurology* 2022;99(19):e2114–24. https://doi.org/10.1212/WNL.0000000000201032.

[54] Joel D, Fausto-Sterling A. Beyond sex differences: new approaches for thinking about variation in brain structure and function. *Philos Trans R Soc Lond B Biol Sci* 2016;371(1688):20150451. https://doi.org/10.1098/rstb.2015.0451.

[55] McCall L. The Complexity of Intersectionality. *Signs J Women Cult Soc* 2005;30(3):1771–800. https://doi.org/10.1086/426800.

[56] Crenshaw K. Demarginalizing the Intersection of Race and Sex: A Black Feminist Critique of Antidiscrimination Doctrine, Feminist Theory and Antiracist Politics. *The University of Chicago Legal Forum* 1989;140:139–67.

[57] Hankivsky O. Women's health, men's health, and gender and health: implications of intersectionality. *Soc Sci Med* 2012;74(11):1712–20. https://doi.org/10.1016/j.socscimed.2011.11.029.

[58] Avila JF, Vonk JMJ, Verney SP, Witkiewitz K, Arce Rentería M, Schupf N, et al. Sex/gender differences in cognitive trajectories vary as a function of race/ethnicity. *Alzheimers Dement* 2019;15(12):1516–23. https://doi.org/10.1016/j.jalz.2019.04.006.

[59] de Vries GJ, Södersten P. Sex differences in the brain: the relation between structure and function. *Horm Behav* 2009;55(5):589–96. https://doi.org/10.1016/j.yhbeh.2009.03.012.

[60] Joel D. Beyond the binary: Rethinking sex and the brain. *Neurosci Biobehav Rev* 2021;122:165–75. https://doi.org/10.1016/j.neubiorev.2020.11.018.

[61] Courtenay WH. Constructions of masculinity and their influence on men's well-being: a theory of gender and health. *Soc Sci Med* 2000;50(10):1385–401. https://doi.org/10.1016/S0277-9536(99)00390-1.

[62] Hinton L, Tran D, Peak K, Meyer OL, Quiñones AR. Mapping racial and ethnic healthcare disparities for persons living with dementia: A scoping review. *Alzheimer's & Dementia* 2024. https://doi.org/10.1002/alz.13612.

[63] Misiura MB, Butts B, Hammerschlag B, Munkombwe C, Bird A, Fyffe M, et al. Intersectionality in Alzheimer's Disease: The Role of Female Sex and Black American Race in the Development and Prevalence of Alzheimer's Disease. *Neurotherapeutics* 2023;20(4):1019–36. https://doi.org/10.1007/s13311-023-01408-x.

[64] Scheffels JF, Ballasch I, Scheichel N, Voracek M, Kalbe E, Kessler J. The Influence of Age, Gender and Education on Neuropsychological Test Scores: Updated Clinical Norms for Five Widely Used Cognitive Assessments. *J Clin Med* 2023;12(16):5170. https://www.mdpi.com/2077-0383/12/16/5170.

[65] Haines VA, Beggs JJ, Hurlbert JS. Contextualizing Health Outcomes: Do Effects of Network Structure Differ for Women and Men? *Sex Roles* 2008;59(3):164–75. https://doi.org/10.1007/s11199-008-9441-3.
[66] Lee S, Lee S, Lee E, Youm Y, Cho HS, Kim WJ. Gender differences in social network of cognitive function among community-dwelling older adults. *Geriatr Gerontol Int* 2020;20(5):467–73. https://doi.org/10.1111/ggi.13906.
[67] Takagi D, Kondo K, Kawachi I. Social participation and mental health: moderating effects of gender, social role and rurality. *BMC Public Health* 2013;13:701. https://doi.org/10.1186/1471-2458-13-701.
[68] Ballering AV, Olde Hartman TC, Rosmalen JGM. Gender scores in epidemiological research: methods, advantages and implications. *The Lancet Regional Health – Europe* 2024;43. https://doi.org/10.1016/j.lanepe.2024.100962.
[69] Bauer GR. Sex and Gender Multidimensionality in Epidemiologic Research. *Am J Epidemiol* 2023;192(1):122–32. https://doi.org/10.1093/aje/kwac173.
[70] Johnson JL, Greaves L, Repta R. Better science with sex and gender: Facilitating the use of a sex and gender-based analysis in health research. *Int J Equity Health* 2009;8(1):14. https://doi.org/10.1186/1475-9276-8-14.