# MODIFIABLE RISK FACTORS OF ACCELERATED BRAIN AGING AND DEMENTIA

EDITED BY: Frauke Beyer, Susanne Röhr, Omar Yaxmehen Bello-Chavolla, Petronilla Battista and Francesca R. Farina

PUBLISHED IN: Frontiers in Aging Neuroscience

frontiers Research Topics

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ISSN 1664-8714
ISBN 978-2-88976-449-5
DOI 10.3389/978-2-88976-449-5

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# MODIFIABLE RISK FACTORS OF ACCELERATED BRAIN AGING AND DEMENTIA

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**Citation:** Beyer, F., Röhr, S., Bello-Chavolla, O. Y., Battista, P., Farina, F. R., eds. (2022). Modifiable Risk Factors of Accelerated Brain Aging and Dementia. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88976-449-5

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 23 June 2021
doi: 10.3389/fnagi.2021.694629

# Association Between Visceral Fat and Brain Cortical Thickness in the Elderly: A Neuroimaging Study

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**Background:** Despite emerging evidence suggesting that visceral fat may play a major role in obesity-induced neurodegeneration, little evidence exists on the association between visceral fat and brain cortical thickness in the elderly.

**Purpose:** We aimed to examine the association between abdominal fat and brain cortical thickness in a Korean elderly population.

**Methods:** This cross-sectional study included elderly individuals without dementia ($n$ = 316). Areas of visceral fat and subcutaneous fat ($cm^2$) were estimated from computed tomography scans. Regional cortical thicknesses (mm) were obtained by analyzing brain magnetic resonance images. Given the inverted U-shaped relationship between visceral fat area and global cortical thickness (examined using a generalized additive model), visceral fat area was categorized into quintiles, with the middle quintile being the reference group. A generalized linear model was built to explore brain regions associated with visceral fat. The same approach was used for subcutaneous fat.

**Results:** The mean (standard deviation) age was 67.6 (5.0) years. The highest quintile (vs. the middle quintile) group of visceral fat area had reduced cortical thicknesses in the global [β = –0.04 mm, standard error (SE) = 0.02 mm, $p$ = 0.004], parietal (β = –0.04 mm, $SE$ = 0.02 mm, $p$ = 0.01), temporal (β = –0.05 mm, $SE$ = 0.02 mm, $p$ = 0.002), cingulate (β = –0.06 mm, $SE$ = 0.02 mm, $p$ = 0.01), and insula lobes (β = –0.06 mm, $SE$ = 0.03 mm, $p$ = 0.02). None of the regional cortical thicknesses significantly differed between the highest and the middle quintile groups of subcutaneous fat area.

**Conclusion:** The findings suggest that a high level of visceral fat, but not subcutaneous fat, is associated with a reduced cortical thickness in the elderly.

**Keywords: abdominal fat, visceral fat, neuroimaging, cortical thickness, MRI**

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***Received:*** *13 April 2021*
***Accepted:*** *02 June 2021*
***Published:*** *23 June 2021*

***Citation:***
*Cho J, Seo S, Kim W-R, Kim C and Noh Y (2021) Association Between Visceral Fat and Brain Cortical Thickness in the Elderly: A Neuroimaging Study. Front. Aging Neurosci. 13:694629. doi: 10.3389/fnagi.2021.694629*

## INTRODUCTION

Obesity is a well-known risk factor for cardiovascular diseases, type 2 diabetes, and cancer (Bogers et al., 2007; Renehan et al., 2008; Bell et al., 2014). It has also been suggested that obesity is an independent risk factor for Alzheimer's disease and vascular dementia (Beydoun et al., 2008). To elucidate the effect of obesity on the brain in cognitively healthy individuals, a number of neuroimaging studies have investigated the association between obesity (including central obesity) and brain structure on magnetic resonance imaging (MRI) (Gunstad et al., 2008; Taki et al., 2008; Raji et al., 2010; Yokum et al., 2012; Kurth et al., 2013; Kim et al., 2015; Medic et al., 2016; Dekkers et al., 2019; Hamer and Batty, 2019; Morys et al., 2021). A large-scale study of the United Kingdom Biobank ($n$ = 9,652) showed that three obesity indices [body mass index (BMI), waist-to-hip ratio (WHR), and total fat mass from body impedance] were significantly associated with a reduction in global gray matter volume (Hamer and Batty, 2019). Another study of the United Kingdom Biobank ($n$ = 12,087) reported that the association between total fat mass from body impedance and global gray matter volume was significant only in men (Dekkers et al., 2019). Some of the neuroimaging studies have measured cortical thickness (Kim et al., 2015; Medic et al., 2016; Morys et al., 2021), a more sensitive indicator of gray matter changes than cortical volume (Burggren et al., 2008; Thambisetty et al., 2010). Kim et al. (2015) demonstrated inverse associations between total fat percentage from body impedance and WHR with region-of-interest (ROI)-based global and frontal thicknesses only in men. Medic et al. (2016) found several focal regions in the frontal and occipital lobes inversely associated with BMI6). Morys et al. (2021) reported that BMI, WHR, and body fat percentage were associated with thinner temporal, entorhinal, orbitofrontal, and cingulate cortices, as well as thicker frontal, parietal, and occipital cortices.

Emerging neuroimaging studies have suggested the role of visceral fat in the association between obesity and brain structures in adults (Debette et al., 2010; Isaac et al., 2011; Widya et al., 2015; Zsido et al., 2019). Debette et al. (2010) demonstrated that visceral fat on computed tomography (CT) had the strongest association with reduced total brain volumes when compared with other obesity indices (BMI, waist circumference, wait-to-hip ratio, and subcutaneous fat), and the association was independent of BMI and insulin resistance. Widya et al. (2015) reported that increased visceral fat (but not subcutaneous fat) was associated with microstructural brain tissue damage in the elderly. Zsido et al. (2019) demonstrated that increased visceral fat was associated with accelerated brain aging (based on structural brain networks derived from gray matter volume, cortical thickness, and surface area) in adults including elderly participants. Isaac et al. (2011) analyzed the data of 184 healthy elderly individuals using voxel-based morphometry, and found that visceral fat was inversely associated with cortical thicknesses in several focal regions (e.g., pre-central, post-central, superior temporal, and inferior parietal cortices). Although the ROI-based approach (compared with voxel-based morphometry) can facilitate clinical interpretation by predefining brain regions, no study has investigated the associations between visceral fat (as well as subcutaneous fat) and ROI-based cortical thicknesses.

Hence, the present study aimed to explore brain regions associated with abdominal fat in the elderly, using the ROI-based analysis of brain magnetic resonance images.

## MATERIALS AND METHODS

### Study Participants

This study recruited ≥ 60 year-old individuals (without self-reported history of dementia, movement disorders, or stroke) through local advertisements between December 2015 and September 2017 in Incheon, Republic of Korea, as part of the EPINEF study. The survey was conducted at Gachon University Gil Medical Center (Incheon, South Korea). Using a standardized survey protocol, a total of 322 participants completed questionnaires (regarding demographic characteristics, medical history, and lifestyle behaviors), anthropometric measurement (weight and height), blood sampling, abdominal fat CT scans, mini-mental state examination (MMSE), and brain 3T MRI scans. Two participants who were found to have brain tumors on brain MRI were excluded. After excluding individuals with missing values, 316 participants (129 men and 187 women) were included in the study. All individuals provided written informed consent. The study was approved by the Institutional Review Board of Gachon University Gil Medical Center (approval No. GDIRB2015-225).

### Acquisition of Abdominal Fat Areas

All subjects underwent 10-mm-slice CT scans (SOMATOM Sensation 64; Siemens Healthcare, Forchheim, Germany) at the umbilical level. The average value of pixels within the range of –200 to –20 Hounsfield units was used for the measurement of abdominal fat areas (Jackson and Thomas, 2004). The total visceral fat area and the subcutaneous fat area (unit: $cm^2$) were measured with a commercial software program (syngo Volume; Siemens Healthcare, Forchheim, Germany).

### Acquisition of Brain Imaging Markers

Brain 3D-T1-magnetization-prepared rapid gradient-echo (MP-RAGE) images were obtained with a Siemens 3T Verio MRI, using a standardized MRI protocol. The image parameters used for 3D T1-MP-RAGE were as follows: repetition time, 1,900 ms; echo time, 2.93 ms; flip angle, 8°; pixel bandwidth, 170 Hz/pixel; matrix size, 256 × 208; field of view, 256 mm; number of excitations, 1; total acquisition time, 4 min 10 s; voxel size, $1.0 \times 1.0 \times 1.0$ $mm^3$.

ROI-based analyses of the brain images were performed using the standard FreeSurfer 6.0.0 pipeline[1], which consists of subcortical segmentation (Fischl et al., 2002, 2004a); cortical surface reconstruction (Dale et al., 1999; Fischl et al., 1999); cortical thickness mapping (Fischl and Dale, 2000); surface-based inter-subject alignment (Fischl et al., 1999); and cortical parcellation (Fischl et al., 2004b; Desikan et al., 2006). Using

[1]http://surfer.nmr.mgh.harvard.edu/

these serial procedures, we obtained estimates of regional cortical thickness (frontal, temporal, parietal, occipital, cingulate, and insula) and subcortical gray matter volume (thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and nucleus accumbens). Global cortical thickness was calculated by averaging the six cortical thicknesses.

## Covariates

The questionnaire included educational years, history of disease (hypertension, diabetes mellitus, dyslipidemia, and angina or myocardial infarction), smoking status (never, former, or current smoker), and alcohol consumption (currently drinking or not). Measured weight and height were used to calculate BMI (unit: $kg/m^2$). At least 12-h fasting blood samples were tested for blood glucose and total cholesterol levels, and apolipoprotein E (APOE) genotyping.

## Statistical Analysis

To explore the non-linear relationship between abdominal fat area and cortical thickness, we used a generalized additive model (GAM), including visceral fat area as a spline variable and global cortical thickness as a dependent variable. In this analysis, we adjusted for age, sex, educational years, hypertension, diabetes, dyslipidemia, angina or myocardial infarction, smoking status, alcohol consumption, APOE status (presence/absence of ε4 allele), BMI, fasting blood glucose level, total cholesterol level, and intracranial volume (ICV). The degrees of freedom for the spline variable were automatically selected using the generalized cross validation method. A two-sided $p < 0.05$ from analysis of deviance for GAM was considered as having a significant non-linear relationship. There were significant non-linear relationships of visceral fat area with global ($p = 0.02$), frontal ($p = 0.02$), temporal ($p = 0.02$), and parietal thicknesses ($p < 0.001$), with an inverted U shape (**Figure 1**). Hence, we classified visceral fat area into quintiles (quintile 5 as the highest; quintile 3 as the reference group) and entered the quintiles into a generalized linear model (GLM). This approach was used for all the regional cortical thicknesses (though occipital and insular thicknesses did not exhibit significant non-linear relationships) with a view to presenting results in a consistent

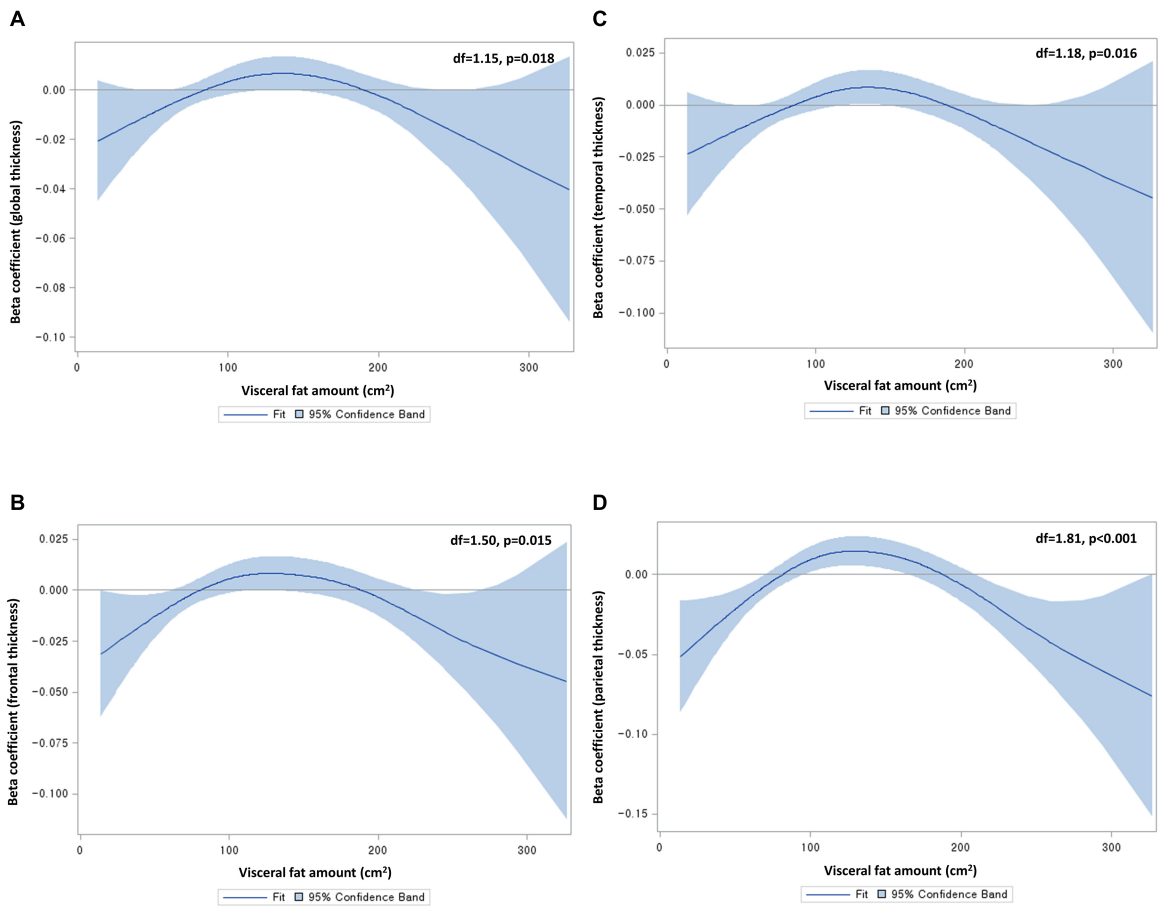


**FIGURE 1 |** Non-linear relationships of visceral fat area with **(A)** global, **(B)** frontal, **(C)** temporal, and **(D)** parietal cortical thicknesses. Df, degrees of freedom. Beta coefficients were from generalized additive models, adjusting for age, sex, educational years, hypertension, diabetes, dyslipidemia, angina or myocardial infarction, smoking status, alcohol consumption, apolipoprotein status, body mass index, fasting blood glucose level, total cholesterol level, and intracranial volume. Degrees of freedom were determined by the cross-validation method.

manner. The same method was applied to subcutaneous fat area (albeit none of the non-linear relationships were significant) in order to enable a straightforward comparison with visceral fat. Given the absence of a significant non-linear relationship in the GAM analysis of subcortical volumes, the abdominal fat variables were entered as a continuous variable into the GLM for subcortical volumes. All GLM analyses were conducted after adjusting for the same covariates as the above GAM. Given possible sex differences in abdominal fat distribution as well as brain MRI markers (e.g., cortical thickness and volume) (Ritchie et al., 2018), sex-stratified analyses were additionally conducted. Significance of sex differences was tested using the method described by Altman and Bland and expressed as p for interaction (Altman and Bland, 2003). All analyses were corrected for multiple comparisons using the false discovery rate (FDR) method (Benjamini and Hochberg, 1995).

A *post hoc* analysis was conducted to examine the associations of other obesity indices (BMI and waist circumference) with brain cortical thickness. Quintiles of either BMI or waist circumference were entered into GLMs, with adjustment for the same covariates as the main analysis.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, United States). Two-sided $p < 0.05$ were considered statistically significant.

# RESULTS

## Characteristics of Study Participants

The mean [standard deviation (SD)] age of the study participants was 67.6 (5.0) (**Table 1**). The numbers of those with hypertension and dyslipidemia were 134 (42.4%) and 104 (32.9%), respectively. The mean (SD) areas of visceral fat and subcutaneous fat were 125.3 (55.4) $cm^2$ and 167.5 (65.7) $cm^2$, respectively. The mean (SD) MMSE score was 28.3 (1.9). The mean (SD) global thickness was 2.5 (0.1) mm.

**TABLE 1 |** Characteristics of the study participants.

| | Total (*N* = 316) | Men (*N* = 129) | Women (*N* = 187) |
|---|---|---|---|
| Age, mean (SD) | 67.6 (5.0) | 68.9 (4.9) | 66.7 (5.0) |
| Educational years, mean (SD) | 9.6 (4.3) | 11.1 (4.1) | 8.6 (4.0) |
| Hypertension, N (%) | 134 (42.4) | 60 (46.5) | 74 (39.6) |
| Diabetes mellitus, N (%) | 62 (19.6) | 32 (24.8) | 30 (16.0) |
| Dyslipidemia, N (%) | 104 (32.9) | 35 (27.1) | 69 (36.9) |
| Angina or myocardial infarction, N (%) | 37 (11.7) | 19 (14.7) | 18 (9.6) |
| **Smoking status, N (%)** | | | |
| Never smoker | 214 (67.7) | 29 (22.5) | 185 (98.9) |
| Former smoker | 79 (25.0) | 77 (59.7) | 2 (1.1) |
| Current smoker | 23 (7.3) | 23 (17.8) | 0 (0.0) |
| Alcohol drinking, N (%) | 113 (35.8) | 75 (58.1) | 38 (20.3) |
| Body mass index, mean (SD) | 24.7 (3.1) | 24.8 (2.6) | 24.7 (3.4) |
| **Apolipoprotein status, N (%)** | | | |
| At least one ε4 allele | 56 (17.7) | 26 (20.2) | 30 (16.0) |
| No ε4 allele | 260 (82.3) | 103 (79.8) | 157 (84.0) |
| Fasting blood glucose, mean (SD) | 99.0 (21.7) | 100.0 (22.3) | 98.4 (21.4) |
| Total cholesterol, mean (SD) | 183.7 (37.7) | 176.1 (38.0) | 189.0 (36.7) |
| **Abdominal fat ($cm^2$), mean (SD)** | | | |
| Visceral fat | 125.3 (55.4) | 135.9 (59.9) | 118.0 (51.0) |
| Subcutaneous fat | 167.5 (65.7) | 130.1 (46.8) | 193.3 (64.5) |
| ICV ($mm^3$), mean (SD) | 1,251,894 (126,138) | 1,346,200 (101,857) | 1,186,839 (96,866) |
| **Cortical thickness (mm), mean (SD)** | | | |
| Global | 2.5 (0.1) | 2.5 (0.1) | 2.5 (0.1) |
| Frontal lobe | 2.5 (0.1) | 2.5 (0.1) | 2.6 (0.1) |
| Parietal lobe | 2.8 (0.1) | 2.7 (0.1) | 2.8 (0.1) |
| Temporal lobe | 2.3 (0.1) | 2.2 (0.1) | 2.3 (0.1) |
| Occipital lobe | 2.0 (0.1) | 2.0 (0.1) | 2.0 (0.1) |
| Cingulate | 2.6 (0.1) | 2.5 (0.1) | 2.6 (0.1) |
| Insula | 2.9 (0.1) | 2.9 (0.1) | 2.9 (0.1) |
| **Subcortical volume ($mm^3$), mean (SD)** | | | |
| Thalamus | 6474.9 (649.2) | 6691.9 (666.2) | 6325.2 (594.2) |
| Caudate | 3256.3 (477.7) | 3444.6 (476.3) | 3126.4 (434.5) |
| Putamen | 4461.1 (520.1) | 4651.5 (534.4) | 4329.7 (468.0) |
| Pallidum | 1894.8 (205.4) | 1960.8 (195.8) | 1849.3 (199.8) |
| Amygdala | 1637.6 (193.7) | 1707.5 (187.4) | 1589.4 (183.5) |
| Hippocampus | 3903.3 (379.9) | 3993.8 (363.4) | 3840.9 (379.3) |
| Nucleus accumbens | 427.4 (75.0) | 447.1 (78.8) | 413.8 (69.3) |

*SD, standard deviation, ICV, intracranial volume.*

## Association Between Abdominal Fat Area and Cortical Thickness

The quintile 3 group of visceral fat area had the greatest global cortical thickness (mean, 2.52 mm; SD, 0.07 mm), whereas the quintile 5 group had the smallest (mean, 2.48 mm; SD, 0.08 mm) (**Table 2**). In the GLM analysis of visceral fat (**Table 3**), the quintile 5 group (vs. the quintile 3 group) had significantly reduced cortical thicknesses in the global [β = –0.04 mm, standard error (SE) = 0.02 mm, $p = 0.004$], parietal (β = –0.04 mm, *SE* = 0.02 mm, $p = 0.01$), temporal (β = –0.05 mm, *SE* = 0.02 mm, $p = 0.002$), cingulate (β = –0.06 mm, *SE* = 0.02 mm, $p = 0.01$), and insula lobes (β = –0.06 mm, *SE* = 0.03 mm, $p = 0.02$). These associations remained significant after FDR correction. In men, the quintile 5 group (vs. the quintile 3 group) had significantly reduced global, temporal, and insular thicknesses, though these associations did not remain significant after FDR correction. In women, the quintiles 2, 4, and 5 groups had significantly reduced global cortical thicknesses, as compared with the quintile 3 group. The quintile 5 group (vs. the quintile 3 group) among women also had a significantly reduced parietal thickness (β = –0.04 mm, *SE* = 0.02 mm, $p = 0.04$). After FDR correction, reduced global thicknesses in the quintiles 2 and 3 groups, a reduced frontal thickness in the quintile 4 group, a reduced parietal

**TABLE 2 |** Global cortical thickness by quintiles of abdominal fat area.

| | | Abdominal fat area | | | | Global cortical thickness | |
|---|---|---|---|---|---|---|---|
| | N | Mean | *SD* | Minimum | Maximum | Mean | *SD* |
| **Visceral fat** | | | | | | | |
| **Total (*N* = 316)** | | | | | | | |
| Quintile 1 | 63 | 54.68 | 15.51 | 13.66 | 74.13 | 2.50 | 0.08 |
| Quintile 2 | 63 | 91.12 | 9.48 | 74.58 | 107.92 | 2.50 | 0.08 |
| Quintile 3 | 64 | 120.08 | 7.96 | 108.22 | 135.14 | 2.52 | 0.07 |
| Quintile 4 | 63 | 153.20 | 10.40 | 135.50 | 171.18 | 2.51 | 0.08 |
| Quintile 5 | 63 | 207.75 | 33.47 | 171.24 | 326.45 | 2.48 | 0.08 |
| **Men (*N* = 129)** | | | | | | | |
| Quintile 1 | 25 | 53.24 | 18.36 | 13.66 | 75.27 | 2.47 | 0.08 |
| Quintile 2 | 26 | 98.14 | 13.70 | 75.81 | 117.24 | 2.50 | 0.08 |
| Quintile 3 | 26 | 134.38 | 10.32 | 118.03 | 150.33 | 2.50 | 0.08 |
| Quintile 4 | 26 | 170.17 | 9.72 | 152.63 | 187.48 | 2.47 | 0.07 |
| Quintile 5 | 26 | 220.63 | 25.49 | 191.04 | 280.17 | 2.46 | 0.07 |
| **Women (*N* = 187)** | | | | | | | |
| Quintile 1 | 37 | 55.19 | 13.42 | 16.87 | 73.47 | 2.52 | 0.07 |
| Quintile 2 | 38 | 87.99 | 8.26 | 73.71 | 99.87 | 2.50 | 0.09 |
| Quintile 3 | 37 | 112.48 | 6.75 | 100.05 | 125.28 | 2.55 | 0.06 |
| Quintile 4 | 38 | 140.85 | 10.77 | 125.62 | 158.11 | 2.51 | 0.07 |
| Quintile 5 | 37 | 193.86 | 39.00 | 159.1 | 326.45 | 2.52 | 0.08 |
| **Subcutaneous fat** | | | | | | | |
| **Total (*N* = 316)** | | | | | | | |
| Quintile 1 | 63 | 90.06 | 23.79 | 15.75 | 115.14 | 2.48 | 0.07 |
| Quintile 2 | 63 | 127.14 | 7.41 | 115.51 | 140.91 | 2.49 | 0.09 |
| Quintile 3 | 64 | 157.95 | 9.71 | 142.03 | 173.87 | 2.51 | 0.07 |
| Quintile 4 | 63 | 194.44 | 13.05 | 174.85 | 220.18 | 2.50 | 0.07 |
| Quintile 5 | 63 | 268.05 | 47.02 | 221.54 | 417.81 | 2.52 | 0.08 |
| **Men (*N* = 129)** | | | | | | | |
| Quintile 1 | 25 | 69.99 | 21.65 | 15.75 | 92.57 | 2.46 | 0.07 |
| Quintile 2 | 26 | 106.58 | 7.88 | 93.16 | 116.16 | 2.48 | 0.08 |
| Quintile 3 | 26 | 125.29 | 4.80 | 116.23 | 133.09 | 2.47 | 0.10 |
| Quintile 4 | 26 | 146.75 | 7.65 | 133.71 | 160.05 | 2.49 | 0.07 |
| Quintile 5 | 26 | 199.35 | 33.93 | 163.84 | 306.01 | 2.48 | 0.06 |
| **Women (*N* = 187)** | | | | | | | |
| Quintile 1 | 37 | 114.85 | 18.21 | 40.03 | 138.36 | 2.51 | 0.07 |
| Quintile 2 | 38 | 155.22 | 9.93 | 139.16 | 170.92 | 2.52 | 0.07 |
| Quintile 3 | 37 | 184.30 | 8.88 | 171.04 | 198.74 | 2.53 | 0.07 |
| Quintile 4 | 38 | 222.01 | 12.63 | 199.73 | 242.21 | 2.51 | 0.08 |
| Quintile 5 | 37 | 290.52 | 48.13 | 243.25 | 417.81 | 2.54 | 0.08 |

*SD, standard deviation.*

thickness in the quintile 1 group, a reduced occipital thickness in the quintile 1 group, and a reduced cingulate thickness in the quintile 2 group remained significant. Regarding sex differences, the quintile 2 (vs. quintile 3) group had reduced cortical thicknesses among women but increased thicknesses among men in the global (p for interaction = 0.024), frontal (p for interaction = 0.036), parietal (p for interaction = 0.007), and cingulate lobes (p for interaction = 0.021). Otherwise sex differences were not significant.

In the GLM analysis of subcutaneous fat (**Supplementary Table 1**), there were no significant differences in global cortical thickness across the quintile groups. The quintile 4 group had significantly reduced frontal (β = –0.03 mm, *SE* = 0.02 mm, $p = 0.03$), temporal (β = –0.03 mm, *SE* = 0.02 mm, $p = 0.04$), and occipital thicknesses (β = –0.03 mm, *SE* = 0.02 mm, $p = 0.03$), as compared with the quintile 3 group. These associations did not remain significant after FDR correction. After stratification by sex, none of the associations remained significant.

## Association Between Abdominal Fat Area and Subcortical Volume

In the GLM analysis of visceral fat area (**Table 4**), an increase in visceral fat area was significantly associated with reduced volumes of the pallium (β = –0.66 $mm^3$, *SE* = 0.25 $mm^3$, $p = 0.01$) and putamen (β = –1.36 $mm^3$, *SE* = 0.63 $mm^3$, $p = 0.03$). In men, the association between visceral fat area and the reduced volume of the pallidum was significant (β = –0.55 $mm^3$, *SE* = 0.25 $mm^3$, $p = 0.03$). In women, the association between visceral fat area and the reduced volume of the putamen was significant (β = –1.78 $mm^3$, *SE* = 0.90 $mm^3$, $p = 0.05$). None of the associations between subcutaneous fat area and subcortical

**TABLE 3 |** Association between visceral fat area and cortical thickness.

| | | Total (*N* = 316) | | | Men (*N* = 129) | | | Women (*N* = 187) | | | *p* for interaction† |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Beta** | ***SE*** | ***p*** | **Beta** | ***SE*** | ***p*** | **Beta** | ***SE*** | ***p*** | |
| Global | Quintile 1 vs. 3 | –0.008 | 0.015 | 0.61 | –0.022 | 0.024 | 0.35 | –0.022 | 0.02 | 0.27 | 1.00 |
| | Quintile 2 vs. 3 | –0.01 | 0.014 | 0.45 | 0.017 | 0.023 | 0.45 | **–0.049** | **0.018** | **0.009*** | 0.024 |
| | Quintile 4 vs. 3 | –0.011 | 0.014 | 0.42 | –0.035 | 0.023 | 0.13 | **–0.05** | **0.018** | **0.007*** | 0.61 |
| | Quintile 5 vs. 3 | **–0.043** | **0.015** | **0.004*** | **–0.05** | **0.024** | **0.042** | **–0.04** | **0.019** | **0.038** | 0.74 |
| Frontal | Quintile 1 vs. 3 | –0.019 | 0.017 | 0.27 | –0.014 | 0.025 | 0.58 | –0.035 | 0.022 | 0.12 | 0.53 |
| | Quintile 2 vs. 3 | –0.007 | 0.015 | 0.63 | 0.027 | 0.024 | 0.28 | –0.04 | 0.021 | 0.055 | 0.036 |
| | Quintile 4 vs. 3 | –0.013 | 0.015 | 0.40 | –0.019 | 0.024 | 0.44 | **–0.059** | **0.021** | **0.004*** | 0.21 |
| | Quintile 5 vs. 3 | –0.028 | 0.016 | 0.082 | –0.014 | 0.026 | 0.58 | –0.035 | 0.021 | 0.11 | 0.53 |
| Parietal | Quintile 1 vs. 3 | –0.031 | 0.017 | 0.069 | –0.03 | 0.029 | 0.29 | **–0.053** | **0.021** | **0.011*** | 0.52 |
| | Quintile 2 vs. 3 | –0.009 | 0.016 | 0.58 | 0.045 | 0.028 | 0.11 | **–0.047** | **0.019** | **0.017** | 0.007 |
| | Quintile 4 vs. 3 | –0.012 | 0.015 | 0.43 | 0.006 | 0.028 | 0.82 | **–0.045** | **0.019** | **0.021** | 0.13 |
| | Quintile 5 vs. 3 | **–0.041** | **0.016** | **0.013*** | –0.038 | 0.03 | 0.20 | **–0.042** | **0.02** | **0.039** | 0.91 |
| Temporal | Quintile 1 vs. 3 | –0.019 | 0.018 | 0.28 | –0.041 | 0.026 | 0.13 | –0.014 | 0.023 | 0.55 | 0.44 |
| | Quintile 2 vs. 3 | –0.024 | 0.016 | 0.14 | –0.008 | 0.025 | 0.74 | **–0.049** | **0.022** | **0.026** | 0.22 |
| | Quintile 4 vs. 3 | –0.02 | 0.016 | 0.22 | –0.06 | 0.025 | 0.019 | **–0.043** | **0.022** | **0.046** | 0.61 |
| | Quintile 5 vs. 3 | **–0.054** | **0.017** | **0.002*** | **–0.062** | **0.027** | **0.026** | –0.043 | 0.022 | 0.056 | 0.59 |
| Occipital | Quintile 1 vs. 3 | **–0.037** | **0.017** | **0.03*** | –0.02 | 0.028 | 0.47 | **–0.065** | **0.021** | **0.003*** | 0.20 |
| | Quintile 2 vs. 3 | –0.016 | 0.016 | 0.31 | 0.021 | 0.027 | 0.43 | –0.034 | 0.02 | 0.094 | 0.10 |
| | Quintile 4 vs. 3 | –0.014 | 0.015 | 0.35 | –0.004 | 0.027 | 0.87 | –0.027 | 0.02 | 0.17 | 0.49 |
| | Quintile 5 vs. 3 | –0.016 | 0.016 | 0.32 | –0.018 | 0.028 | 0.54 | –0.016 | 0.02 | 0.44 | 0.95 |
| Cingulate | Quintile 1 vs. 3 | 0.02 | 0.023 | 0.37 | –0.007 | 0.035 | 0.83 | 0.013 | 0.028 | 0.65 | 0.66 |
| | Quintile 2 vs. 3 | –0.02 | 0.02 | 0.32 | 0.022 | 0.034 | 0.52 | **–0.078** | **0.027** | **0.004*** | 0.021 |
| | Quintile 4 vs. 3 | –0.004 | 0.02 | 0.85 | –0.034 | 0.034 | 0.31 | **–0.056** | **0.026** | **0.034** | 0.61 |
| | Quintile 5 vs. 3 | **–0.06** | **0.022** | **0.006*** | –0.056 | 0.036 | 0.12 | –0.05 | 0.027 | 0.068 | 0.89 |
| Insula | Quintile 1 vs. 3 | 0.039 | 0.026 | 0.14 | –0.021 | 0.039 | 0.60 | 0.024 | 0.034 | 0.48 | 0.38 |
| | Quintile 2 vs. 3 | 0.013 | 0.024 | 0.59 | –0.003 | 0.037 | 0.94 | –0.044 | 0.032 | 0.17 | 0.40 |
| | Quintile 4 vs. 3 | –0.004 | 0.024 | 0.85 | –0.095 | 0.037 | 0.012 | **–0.069** | **0.032** | **0.031** | 0.60 |
| | Quintile 5 vs. 3 | **–0.059** | **0.025** | **0.019*** | **–0.112** | **0.04** | **0.006** | –0.052 | 0.033 | 0.11 | 0.25 |

*SE, standard error.*

*Beta coefficients were from generalized linear models, adjusting for age, sex, educational years, hypertension, diabetes, dyslipidemia, angina or myocardial infarction, smoking status, alcohol consumption, apolipoprotein status, body mass index, fasting blood glucose level, total cholesterol level, and intracranial volume. The quintile 3 group was set as the reference group. Significant findings are highlighted in bold. *Significant ($p < 0.05$) after correction for multiple comparisons, using the false discovery rate method.*

†*Significance of sex differences.*

volumes were significant. After FDR correction, none of the associations remained significant.

## *Post hoc* Analyses

The quintile 1 group of BMI had significantly reduced global (β = –0.03 mm, *SE* = 0.01 mm, $p = 0.027$), parietal (β = –0.06 mm, *SE* = 0.02 mm, $p < 0.001$), temporal (β = –0.05 mm, *SE* = 0.02 mm, $p = 0.004$), and occipital thicknesses (β = –0.04 mm, *SE* = 0.02 mm, $p = 0.007$), as compared with the quintile 3 group. Other findings are presented in **Supplementary Table 2**. In the analyses of waist circumference, none of the associations were significant except a reduced parietal thickness in the quintile 1 group (β = –0.04 mm, *SE* = 0.02 mm, $p = 0.015$). Other findings are presented in **Supplementary Table 3**.

# DISCUSSION

The present study is the first to investigate the associations of visceral and subcutaneous fat area with ROI-based cortical thicknesses and subcortical volumes in elderly individuals without dementia. This neuroimaging study involved a relatively large sample size ($n = 316$) and adjusted for a range of covariates including well-known metabolic risk factors, as well as the apolipoprotein ε4 allele—the major genetic risk factor for Alzheimer's disease. The main finding was that individuals with the highest level of visceral fat area had significantly reduced cortical thicknesses in the global, parietal, temporal, cingulate, and insular lobes, as compared with those with the middle level of visceral fat area. These associations did not significantly differ by sex. By contrast, none of the regional cortical thicknesses significantly differed between individuals with the highest level and those with the middle level of subcutaneous fat area.

In recent decades, there has been debate surrounding the effect of high BMI on dementia risk. The largest cohort study on this topic (of two million individuals) demonstrated a protective effect of higher BMI (Qizilbash et al., 2015), while a meta-analysis of four studies showed a harmful effect of obesity (Pedditzi et al., 2016). Another cohort study of 1.3 million individuals suggested a harmful effect of higher BMI on dementia risk over > 20 years of follow-up, as well as a protective effect of higher BMI over ≤ 20 years of follow-up,

**TABLE 4 |** Association between abdominal fat area and subcortical volume.

| | Total (*N* = 316) | | | Men (*N* = 129) | | | Women (*N* = 187) | | | *p* for interaction† |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Beta** | ***SE*** | ***p*** | **Beta** | ***SE*** | ***p*** | **Beta** | ***SE*** | ***p*** | |
| **Visceral fat** | | | | | | | | | | |
| Thalamus | –0.383 | 0.643 | 0.55 | 0.2 | 0.988 | 0.84 | –0.935 | 0.913 | 0.31 | 0.40 |
| Caudate | –0.928 | 0.609 | 0.13 | –0.742 | 0.951 | 0.44 | –1.144 | 0.877 | 0.19 | 0.76 |
| Pallidum | **–0.664** | **0.25** | **0.008** | **–0.79** | **0.348** | **0.025** | –0.584 | 0.385 | 0.13 | 0.69 |
| Putamen | **–1.355** | **0.627** | **0.031** | –1.247 | 0.983 | 0.21 | **–1.781** | **0.895** | **0.048** | 0.69 |
| Amygdala | 0.203 | 0.224 | 0.37 | 0.226 | 0.346 | 0.52 | 0.164 | 0.33 | 0.62 | 0.90 |
| Hippocampus | –0.286 | 0.428 | 0.50 | –0.129 | 0.626 | 0.84 | –0.597 | 0.641 | 0.35 | 0.60 |
| Nucleus accumbens | –0.132 | 0.093 | 0.16 | –0.1 | 0.135 | 0.46 | –0.186 | 0.136 | 0.17 | 0.65 |
| **Subcutaneous fat** | | | | | | | | | | |
| Thalamus | –0.217 | 0.624 | 0.73 | –1.258 | 1.258 | 0.32 | 0.351 | 0.72 | 0.63 | 0.27 |
| Caudate | –0.602 | 0.592 | 0.31 | –1.645 | 1.209 | 0.18 | –0.445 | 0.692 | 0.52 | 0.39 |
| Pallidum | –0.008 | 0.246 | 0.97 | –0.026 | 0.455 | 0.95 | 0.051 | 0.305 | 0.87 | 0.89 |
| Putamen | 0.307 | 0.612 | 0.62 | 0.877 | 1.263 | 0.49 | 0.134 | 0.712 | 0.85 | 0.61 |
| Amygdala | 0.047 | 0.218 | 0.83 | 0.278 | 0.442 | 0.53 | –0.077 | 0.26 | 0.77 | 0.49 |
| Hippocampus | –0.148 | 0.416 | 0.72 | 0.722 | 0.797 | 0.37 | –0.395 | 0.504 | 0.44 | 0.24 |
| Nucleus accumbens | –0.157 | 0.09 | 0.082 | –0.091 | 0.173 | 0.60 | –0.165 | 0.107 | 0.13 | 0.72 |

*SE, standard error.*

*Beta coefficients were from generalized linear models, adjusting for age, sex, educational years, hypertension, diabetes, dyslipidemia, angina or myocardial infarction, smoking status, alcohol consumption, apolipoprotein status, body mass index, fasting blood glucose level, total cholesterol level, and intracranial volume. Significant findings are highlighted in bold. None of the associations remained significant after correction for multiple comparisons using the false discovery rate method.*

†*Significance of sex differences.*

possibly due to reverse causation (Kivimaki et al., 2018). Another meta-analysis of 10 prospective cohort studies demonstrated a significant U-shaped association between BMI and dementia risk, indicating that both underweight individuals and overweight individuals are at risk of dementia (Beydoun et al., 2008). This controversial relationship between BMI and dementia and its underlying mechanisms can be, at least in part, scrutinized by using more intricate biomarkers in imaging studies. An MRI analysis of 1,777 cognitively healthy individuals found a significant inverted U-shaped relationship between central obesity (WHR as a proxy) and global cortical thickness (Kim et al., 2015). In line with this, we found a significant inverted U-shaped relationship between visceral fat area on CT and global cortical thickness. It is noteworthy that, when compared with the middle quintile group of visceral fat area, global cortical thinning was significant in the highest quintile group, but not in the lowest quintile group. This highlights a harmful effect of high visceral fat on brain gray matter, as the previous neuroimaging studies have suggested (Debette et al., 2010; Isaac et al., 2011; Widya et al., 2015; Zsido et al., 2019). Taken together, it is possible that high visceral fat leads to cortical thinning and, hence, contribute to the increased risk of dementia in overweight or obese individuals. Further, in concordance with the previous study using voxel-based morphometry (Isaac et al., 2011), the present study demonstrated that the highest level of visceral fat was significantly associated with reduced thicknesses in association cortices (critical for integrating sensory inputs) such as the temporal and parietal lobes. A similar pattern was observed in the cingulate cortex in the present study. These affected brain cortices correspond to the sites that show atrophy in the early stage of mild cognitive impairment (McDonald et al., 2009). Hence, it is reasonable to suggest that individuals with high visceral fat may initially develop preclinical cortical thinning in the temporal, parietal, and cingulate lobes, followed by clinical outcomes such as mild cognitive impairment.

Given possible correlations between visceral fat area and other obesity indices (e.g., BMI and waist circumference), it is possible that the association between visceral fat and cortical thickness was driven by the impact of other obesity indices. In the present study, there was a significant correlation between BMI and visceral fat area (**Supplementary Figure 1**), and cortical thinning associated with the highest visceral fat group was found significant in the temporal, parietal, cingulate, and insular lobes, after adjusting for a range of covariates including BMI. Notably, a significant decline in cortical thickness was mainly observed in the highest quintile groups of visceral fat area, whereas cortical thinning was significant only in the lowest quintile groups of BMI or waist circumference (**Supplementary Tables 2, 3**). This suggests that visceral fat area, compared with BMI and waist circumference, might be a better indicator of obesity-induced cortical thinning. In line with this, an analysis of the Framingham Offspring cohort demonstrated that visceral fat was more strongly associated with decreased cerebral volumes compared with BMI, waist circumference, or subcutaneous fat (Debette et al., 2010). Furthermore, the relationship between visceral fat and cortical thinning is supported by animal studies, demonstrating plausible biological mechanisms such as microglial activation, upregulated pro-inflammatory cytokines in the brain, and increased blood-brain barrier permeability via visceral fat inflammation (Shin et al., 2015; Guo et al., 2020). Epidemiological evidence also suggests that visceral fat deposition may induce systemic inflammation and, in turn, cerebral small-vessel disease (e.g., white matter hyperintensities), which is related to reduced cortical thickness (Lampe et al., 2019; Morys et al., 2021).

There are several limitations to be noted. First, we cannot establish temporality between a high level of visceral fat and cortical thinning due to the cross-sectional nature of the study. Longitudinal investigations are warranted to clarify the temporal relationship between high visceral fat area and cortical thinning. Second, our findings might not be generalizable to other ethnic populations. In particular, the inverted U-shaped relationship between visceral fat area and cortical thickness in our samples might not be present in Western populations, though a meta-analysis including 10 prospective studies demonstrated a U-shaped relationship between BMI and risk of dementia (Beydoun et al., 2008). Last, we included dementia-free individuals based on self-reported information, and this approach might not have captured variation in cognitive health (including subthreshold cognitive impairment). Besides, the MMSE may not be sensitive to mild cognitive impairment (Mitchell, 2009; Yim et al., 2021). Future studies are warranted to assess cognitive health with sufficient granularity to elucidate fat-related cortical thinning.

In conclusion, a high level of visceral fat was significantly associated with a reduced global cortical thickness in the brains of elderly individuals without dementia, movement disorders, or stroke. Cortical thinning associated with the highest level of visceral fat area was significant in the parietal, temporal, cingulate, and insular lobes, whereas cortical thinning associated with the highest level of subcutaneous fat area was not significant in any of the studied lobes. These findings support the role of visceral fat in obesity-induced neurodegeneration.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

The study was approved by the Institutional Review Board of Gachon University Gil Medical Center (approval No. GDIRB2015-225). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

JC, CK, and YN designed the study. JC and YN contributed to the data collection and drafted the manuscript. JC analyzed the data. SS, W-RK, and CK provided significant intellectual input and a critical review of the manuscript. All authors approved the final version of the manuscript.

## FUNDING

This research was supported by grants from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, South Korea (Grant Nos. HI18C1629 and HI14C1135); Brain Research Program of the National Research Foundation (NRF) funded by the Korean Government (MSIT) (Grant No. 2018M3C7A1056889); and Research Program funded by the Korea Centers for Disease Control and Prevention (2020-ER6706-00).

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.694629/full#supplementary-material

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 29 June 2021
doi: 10.3389/fnagi.2021.691691

# Network Modeling Sex Differences in Brain Integrity and Metabolic Health

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Hypothesis-driven studies have demonstrated that sex moderates many of the relationships between brain health and cardiometabolic disease, which impacts risk for later-life cognitive decline. In the present study, we sought to further our understanding of the associations between multiple markers of brain integrity and cardiovascular risk in a midlife sample of 266 individuals by using network analysis, a technique specifically designed to examine complex associations among multiple systems at once. Separate network models were constructed for male and female participants to investigate sex differences in the biomarkers of interest, selected based on evidence linking them with risk for late-life cognitive decline: all components of metabolic syndrome (obesity, hypertension, dyslipidemia, and hyperglycemia); neuroimaging-derived brain-predicted age minus chronological age; ratio of white matter hyperintensities to whole brain volume; seed-based resting state functional connectivity in the Default Mode Network, and ratios of N-acetyl aspartate, glutamate and myo-inositol to creatine, measured through proton magnetic resonance spectroscopy. Males had a sparse network (87.2% edges = 0) relative to females (69.2% edges = 0), indicating fewer relationships between measures of cardiometabolic risk and brain integrity. The edges in the female network provide meaningful information about potential mechanisms between brain integrity and cardiometabolic health. Additionally, Apolipoprotein ϵ4 (ApoE ϵ4) status and waist circumference emerged as central nodes in the female model. Our study demonstrates that network analysis is a promising technique for examining relationships between risk factors for cognitive decline in a midlife population and that investigating sex differences may help optimize risk prediction and tailor individualized treatments in the future.

**Keywords: sex differences, metabolic syndrome, network model, white matter hyper intensities, brain-predicted age, functional connectivity, APOE, magnetic resonance spectroscopy**

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***Edited by:***
*Frauke Beyer, Max Planck Institute for Human Cognitive and Brain Sciences, Germany*

***Reviewed by:***
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*Laura A. Pritschet, University of California, Santa Barbara, United States*

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***Received:*** *06 April 2021*
***Accepted:*** *27 May 2021*
***Published:*** *29 June 2021*

***Citation:***
*Foret JT, Dekhtyar M, Cole JH, Gourley DD, Caillaud M, Tanaka H and Haley AP (2021) Network Modeling Sex Differences in Brain Integrity and Metabolic Health. Front. Aging Neurosci. 13:691691. doi: 10.3389/fnagi.2021.691691*

## INTRODUCTION

Sex has emerged as a moderator in many associations between brain health and cardiometabolic dysfunction. More specifically, sex appears to moderate associations between cognition and aortic stiffness (Sabra et al., 2020), between risk of dementia and plasma lipid and lipropoteins (Ancelin et al., 2013; Gilsanz et al., 2017), and between white matter hyperintensities and adiposity

(Alqarni et al., 2021). Additionally, there are pronounced sex differences in cardiovascular aging, particularly in the structures and function of the vasculature (Merz and Cheng, 2016). For example, type 2 diabetes and elevated systolic blood pressure may result in slightly higher risk for cardiovascular disease for women (Wei et al., 2017) and greater cardiovascular burden for aging women than men (Huebschmann et al., 2019). There are also sex differences in important brain biomarkers, such as connectivity (Gong et al., 2011; Zhang et al., 2018) and age-related atrophy (Xu et al., 2000). In later life, women demonstrate higher rates of Alzheimer's Disease (AD), even when controlling for survivorship effects (Zhao et al., 2016; Andrew and Tierney, 2018; Beam et al., 2018; Buckley et al., 2019). Since cardioprotective effects of estrogen that provide advantage to women (Stanhewicz et al., 2018; Peters et al., 2019; Rodgers et al., 2019) end at menopause and later life cognitive declines may originate at midlife or earlier (Rodrigue et al., 2013; Irwin et al., 2018), age 40–60 is an opportune period for investigating relationships between brain and metabolic variables for males and females separately.

Growing evidence for the causal influence of multiple variables on biological systems has increased the need for new statistical techniques that can provide greater insight into complex relationships at once. Network analysis has been primarily applied to psychiatric comorbidity (Borsboom and Cramer, 2013), and the use in biological models is relatively novel. This technique provides a visual depiction of the complex associations among symptoms, which can be understood as partial correlations. Network analysis also allows identification of "central" symptoms, defined by strong correlations with a large number of other symptoms. The theory is that, similar to a domino effect, the presence of a central symptom is likely to have greater influence over the entire network of symptoms due to its high degree of interconnectedness (van Borkulo et al., 2015; Beard et al., 2016). In respect to networks with biological variables, centrality of a node in a network may convey that a variable has an impact on other variables or may drive relationships between variables. For the purposes of research in risk for cognitive decline, centrality can help untangle which metabolic risk factors have the greatest influence on brain integrity for males vs. females.

Through two separate exploratory network analyses for males and females, we sought to understand sex differences in the relationships between brain integrity and metabolic risk. Our variables of interest, markers of brain integrity, age, genetic status and the components of metabolic syndrome, were selected based on evidence linking them to late-life cognitive decline. We hypothesized that there would be sex differences in these networks, but we did not form specific hypotheses about relationships between variables, other than anticipating that higher levels of metabolic risk factors would be more likely to relate to poorer brain integrity for both males and females.

# MATERIALS AND METHODS

## Variables of Interest

### Metabolic Syndrome Components

Metabolic Syndrome (MetS) and its five key components have been established as a cluster of risk factors for cardiovascular disease, which include: abdominal obesity, high triglyceride concentrations, low high-density lipoprotein (HDL) cholesterol, above normal blood pressure (prehypertension), and above normal blood sugar (prediabetes) (Eckel et al., 2005). MetS diagnosis is indicated by meeting criteria for 3 or more components based on the Alberti et al. (2009) consensus criteria to determine cut offs for each MetS category: fasting glucose $\geq$100 mg/dL or treatment for hyperglycemia, triglycerides $\geq$150 mg/dL, HDL-cholesterol $\leq$40 mg/dL in males and $\leq$50 mg/dL in females or treatment for dyslipidemia, systolic blood pressure $\geq$130 mmHg or diastolic $\geq$85 mmHg or antihypertensive medication, and waist circumference $\geq$102 cm for men and $\geq$88 cm for women. MetS category variables were coded as yes or no to indicate whether or not an individual met criteria for each variable of interest. MetS diagnosis and key components have been associated with negative cognitive consequences (Skoog et al., 1996; Waldstein et al., 2004; Yaffe et al., 2004; Kivipelto et al., 2005; Whitmer et al., 2005; Segura et al., 2009; Arvanitakis et al., 2010; Falkowski et al., 2014; Foret et al., 2020b). Sex differences have been observed in MetS, such as differences in prevalence and age at incidence (Regitz-Zagrosek et al., 2007; Yang and Kozloski, 2011) and clustering of risk factors (Kuk and Ardern, 2010).

### Brain-Predicted Age Difference (Brain-PAD)

Machine-learning methods that measure biological aging can aid in early detection of brain vulnerability (Cole et al., 2019) and serve as important predictors of mortality (Horvath, 2013; Putin et al., 2016; Cole et al., 2018). One such method, neuroimaging-derived 'brain age', estimates an individual's biological age based on gray and white matter volumes (Cole, 2017; Cole and Franke, 2017). By subtracting chronological age from brain age (brain-PAD), it is possible to estimate which individuals might have poorer brain health in terms of volumetric loss, which may relate to risk for neurocognitive decline. For example, in a sample of individuals with Down's Syndrome, elevated brain-PAD has been linked to amyloid deposition and cognitive decline (Cole et al., 2019). We calculated the brain-PAD of individuals in our dataset to determine which individuals might have "older" brains than their chronological age, such that a higher, positive brain-PAD would reflect higher levels of atrophy.

### White Matter Hyperintensities (WMH)

WMH are areas of hyperintense signal on MRI indicative of lesions in the deep white matter, produced through chronic hypoperfusion and disruption of the blood-brain barrier (van Swieten et al., 1991; Pantoni and Garcia, 1997; Debette and Markus, 2010; Topakian et al., 2010). WMH are commonly observed in aging populations but have been associated with vascular and metabolic risk even after correcting for age (Launer, 2003; Yoshita et al., 2006; Birdsill et al., 2014). Specific components of MetS have been associated with WMH and research has suggested white matter lesions as the mechanism behind cognitive decline in populations with MetS (Alfaro et al., 2016). Relationships between WMH and cardiometabolic risk at midlife have been observed in both cross-sectional (Pasha et al., 2017) and longitudinal follow-up studies (Aljondi et al., 2020). Additionally, relationships between WMH, cardiovascular

risk factors, and later life cognitive decline are marked by sex differences (Pasha et al., 2018b; Burke et al., 2019; Alqarni et al., 2021).

### Rs-fcMRI

Resting state functional connectivity MRI (rs-fcMRI) identifies temporal correlation of brain regions through low frequency background fluctuations in neuronal activity measured by the blood oxygen level dependent (BOLD) signal during a period of rest (Biswal et al., 1995; Fox and Greicius, 2010). *rs*-fcMRI is one way to examine early brain vulnerability, particularly through examining one of the most widely-studied networks in this context, the Default Mode Network (DMN). The primary nodes of the DMN are the dorsal and ventral medial prefrontal cortices (dMPFC and vMPFC) and the posterior cingulate cortex (PCC) (Greicius et al., 2003). Both the MPFC and PCC have relationships to age-related brain pathologies (Zhou et al., 2008, 2016; Zhang et al., 2010). Dyssynchrony in the DMN is thought to occur before clinical manifestation of the disease and changes in structure (Habib et al., 2017) and may be one of the earliest markers for late-life cognitive decline. Additionally, differential relationships between DMN connectivity and executive function have been examined in middle-aged adults with varying numbers of MetS components (Foret et al., 2020a). While sex differences have been observed in task-based functional connectivity at midlife (Jacobs et al., 2017), relationships between sex and DMN dyssychrony requires further investigation.

### Magnetic Resonance Spectroscopy ($^1$H MRS)

Proton Magnetic Resonance Spectroscopy allows for detection of cerebral metabolites. $^1$H MRS may have greater sensitivity to tissue vulnerability than MRI and thus is appropriate for early, pre-clinical changes in midlife brain metabolism (Barker et al., 1994). Three metabolites were selected for their significance in neurobiological models of aging: N-acetyl aspartate (NAA), a metabolite that is highly concentrated in neurons and considered a marker of neuronal health (Danielsen and Ross, 1999; Haley et al., 2010b; Gonzales et al., 2013); glutamate, an excitatory neurotransmitter implicated in synaptic plasticity (Danielsen and Ross, 1999) and metabolic health (Haley et al., 2010a, 2012; Magi et al., 2019); and *myo*-inositol (mI), an organic osmolyte and substrate for the synthesis of the secondary messenger, inositol triphosphate, which has been elevated in beta amyloid positive individuals and associated with decreased DMN connectivity independent of amyloid accumulation (Voevodskaya et al., 2016, 2019). Significant sex differences have been observed in cerebral metabolites, particularly in concentrations of NAA and mI, as early as childhood and adolescence (Cichocka et al., 2018).

### Apolipoprotein E (ApoE)

The allele frequency of ApoE ϵ4 (ϵ4) in the ApoE genotype has been consistently associated with increased risk for AD (Roses and Saunders, 1994; Green et al., 2009) and other forms of neurocognitive decline (Rohn, 2014; Mukerji et al., 2016). Disruptions in neuronal metabolism due to ApoE's role in cholesterol transport are cited as the mechanism behind this association (Lahoz et al., 2001; Eichner et al., 2002). Young healthy ϵ4 carriers have distinct patterns of activity in the DMN (Filippini et al., 2009). Additionally, research has shown that the effect of ϵ4 status on Alzheimer's risk may be stronger for female than male carriers (Sampedro et al., 2015; Riedel et al., 2016).

### Age

Many of the above risk factors and markers of neuropathology have the strongest relationships with cognitive decline as individuals age (Hädel et al., 2013; Vidal-Piñeiro et al., 2014; Makkar et al., 2020). However, the impact of age at midlife on the relationships between metabolic health and brain integrity is not fully understood. Including this variable in the model could provide further information about the importance of age in these relationships.

## Participants

Four hundred nine adults between the ages of 40 and 61 were recruited for the study through local newspaper advertisements and flyers. Among them, 274 individuals were enrolled, and metabolic, demographic and imaging data were available on 266 participants. Exclusion criteria were history of neurological disease, major psychiatric illness, history of substance abuse, or MRI contraindication.

When grouping by sex, there were no significant differences between groups in age [$t_{(264)} = -0.19$, $p = 0.850$], education [$t_{(258)} = 1.41$, $p = 0.160$], or ApoE status ($\chi^2(1, N = 244) < 0.001$, $p = 1$). Males had significantly higher levels of mI [$t_{(201)} = 2.85$, $p < 0.01$], waist circumference [$t_{(259)} = 3.38$, $p < 0.001$], triglycerides [$t_{(239)} = 2.25$, $p = 0.025$] and glucose [$t_{(260)} = 3.13$, $p < 0.01$] while females had significantly higher functional connectivity [$t_{(204)} = -2.38$, $p = 0.018$] and HDL-cholesterol [$t_{(254)} = -7.08$, $p < 0.001$]. Only 12 female participants were actively taking hormone replacement therapies (HRT), which was not a sufficient sample size to include HRT as a covariate in our analyses. Participant characteristics are provided in **Table 1**.

## Procedures

The Institutional Review Board at the University of Texas at Austin approved all study procedures. Written informed consent before enrolling in the study was provided by participants. Medical history was collected through self-report questionnaires and participants underwent a neuropsychological evaluation, brain imaging and a general health assessment. Assessments and imaging were completed in separate visits and most participants completed the study in 1 month.

## Neuropsychological Assessment

Participants completed a neuropsychological battery consisting of tests of memory, verbal fluency and executive function. Raw scores from a neuropsychological battery were converted to sample-based z scores. Scores from the Mini-Mental Status Exam (MMSE; Kurlowicz and Wallace, 1999); the California Verbal Learning Test-2nd Edition, short delay free recall, long delay free recall and recognition discriminability conditions (CVLT-II; Delis et al., 2000); Digit Span forward and backward conditions total score from the Weschler Adult Intelligence Scale—Fourth Edition (WAIS-IV) (Lichtenberger and Kaufman,

**TABLE 1 |** Selected participant characteristics ($n = 266$).

| Participant characteristics | Male | | Female | | | |
|---|---|---|---|---|---|---|
| | *N* | *Mean ± SD* | *N* | *Mean ± SD* | *t* | *p* |
| Age, y | 121 | 49 ± 6 | 145 | 49 ± 6 | −0.19 | 0.850 |
| Education, y | 118 | 16 ± 3 | 142 | 16 ± 2 | 1.41 | 0.160 |
| MMSE | 116 | 29 ± 2 | 133 | 29 ± 2 | −0.16 | 0.874 |
| ApoE ϵ4, (yes/no) | 118 | 103/15 | 126 | 109/17 | $\chi^2 < 0.001$ | 1 |
| **Neuroimaging Measures** | | | | | | |
| WMH/TIV | 78 | 0.002 ± 0.002 | 82 | 0.002 ± 0.003 | 0.71 | 0.476 |
| brain–PAD, years | 92 | −4.8 ± 6.7 | 110 | −6.3 ± 6.8 | 1.49 | 0.137 |
| NAA/Cre | 90 | 1.34 ± 0.24 | 117 | 1.35 ± 0.22 | −0.08 | 0.936 |
| Glutamate/Cre | 88 | 1.25 ± 0.15 | 115 | 1.23 ± 0.11 | 1.45 | 0.149 |
| mI/Cre | 88 | 0.77 ± 0.09 | 115 | 0.73 ± 0.08 | 2.85 | 0.005 |
| DMPFCxPCC | 88 | 0.18 ± 0.30 | 118 | 0.28 ± 0.28 | −2.38 | 0.018 |
| **Metabolic Measures** | | | | | | |
| Systolic blood pressure, mmHg | 118 | 138 ± 22 | 144 | 136 ± 22 | 0.66 | 0.508 |
| Waist circumference, cm | 118 | 101 ± 15 | 143 | 94 ± 16 | −3.51 | <0.001 |
| HDL–cholesterol, mg/dL | 117 | 42 ± 15 | 139 | 56 ± 16 | 2.97 | 0.003 |
| Triglyceride, mg/dL | 109 | 128 ± 68 | 133 | 109 ± 63 | 2.25 | 0.025 |
| Blood glucose, mg/dL | 118 | 104 ± 32 | 142 | 94 ± 22 | 3.50 | <0.001 |
| Physical activity, hours/week | 117 | 1.66 ± 2.15 | 140 | 1.42 ± 1.60 | 1.02 | 0.311 |
| **Mets Criteria** | | | | | | |
| Systolic blood pressure, (yes/no) | 118 | 16%/84% | 144 | 13%/87% | | |
| Waist circumference, (yes/no) | 118 | 47%/53% | 143 | 69%/31% | | |
| HDL-cholesterol, (yes/no) | 117 | 50%/50% | 139 | 32%/68% | | |
| Triglyceride, (yes/no) | 109 | 47%/53% | 133 | 27%/73% | | |
| Blood glucose, (yes/no) | 118 | 43%/57% | 142 | 23%/77% | | |

*Brain-PAD, Brain predicted age difference; DMNPFCxPCC, Resting State Functional Connectivity in the Default Mode Network; NAA, N-Acetylaspartate; mI, Myo-inositol; Cre, Creatine; WMH/TIV, White Matter Hyperintensities adjusted for total intracranial volume; Physical Activity sum of hours moderate.*

2012); Controlled Oral Word Fluency total score (Ruff et al., 1996); Stroop Color and Word Test, third condition (Jensen and Rohwer, 1966); and inverted scores from the Trail Making Test (Bowie and Harvey, 2006), conditions A and B were combined into an average overall current cognitive test performance score, to limit the number of comparisons.

## Health Assessment

Blood samples were collected after 8 h of fasting using venipuncture of the antecubital vein and resting blood pressure was measured with a semiautomated device following 15 min of rest (VP-1000, Omron Healthcare, Bannockburn, IL). A non-elastic tape measure was used for waist and hip circumference. Blood concentrations of glucose, triglycerides, total cholesterol and HDL-cholesterol were measured using a standard enzymatic technique. Participants were asked to report hours per week of low, moderate (e.g., fast walking, tennis, easy bicycling, easy swimming) or vigorous (e.g., running, jogging, hockey, vigorous swimming) physical activity which exceeded 15 min intervals, based on the classifications used by the Godin leisure-time physical activity questionnaire (Godin and Shephard, 1985). Hours of moderate and vigorous physical activity were summed to derive a total measure of weekly physical activity (Pasha et al., 2018a).

Saliva samples were collected using the Oragene Discover (OGR-500) kit and stored at room temperature prior to analysis. The prepIT·L2P kit from DNAgenotek was used for DNA extraction using 500 μL of saliva. Samples were stored at −40°C prior to genotyping. ApoE-Fwd4 and ApoE-snapR primers were used for polymerase chain reaction amplification, which was performed with 10 ng of DNA and 10 pMol primer. Amplification protocol was as follows: 95°C for 15 min, 35 cycles of (95°C 30 s, 65°C 30 s, 72°C 30 s) and hold at 4°C.

ApoE genotyping was conducted using PCR amplification and Sanger sequencing (Sanger et al., 1977) with Variant Reporter Software from Life Technologies (Thermo Fisher Scientific). Sequence data was obtained with KB basecaller and chromatograms were analyzed via visual inspection for the rs429358C>T and rs7412C>T SNPs. Participants were categorized according to allele type. Due to sample size, ApoE ϵ4 hetero- and homozygous individuals were combined together ($n_{male} = 15$; $n_{female} = 17$), and compared with all ApoE ϵ4 non-carriers ($n_{male} = 103$; $n_{female} = 109$).

# MRI Data

## Structural MRI

Structural images were collected, registered, and normalized to MNI space. The entire brain was included in structural images and were collected in the sagittal plane using a high-resolution magnetization prepared rapid gradient echo (MPRAGE) sequence (256 × 256 matrix, flip angle = 7°, FOV = 24 × 24 $cm^2$, 1 mm slice thickness, 0 gap).

Brain-predicted age was estimated using the machine-learning framework (Gaussian Process) devised by Cole (2017) and Cole et al. (2017) and trained on data available via public repositories from 2001 healthy individuals ages 18–90. brain-PAD was calculated by subtracting chronological age from brain-predicted age.

WMH volume was quantified by Lesion Segmentation Tool version 1.2.3 (http://www.applied-statistics.de/lst.html), which is an automated algorithm implemented in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). As previously described by Pasha et al. (2017), voxels were assigned to tissue probability maps and given a probability of being a white matter lesion based on spatial and intensity probabilities from T1 images and hyperintensity outliers on T2 FLAIR images. An initial threshold of 0.30 was applied to a conservative lesion belief map to create lesion seeds. A growth algorithm then grew these seeds toward a liberal lesion belief map and a final threshold of 0.99 was applied to the resulting lesion belief map to remove any voxels with a lower probability of being a lesion. Total volume of WMH was divided by intracranial volume, obtained through Freesurfer (https://surfer.nmr.mgh.harvard.edu/) which was then multiplied by 100 to provide a percent.

## Resting State fMRI

Participants were instructed to fixate on a crosshair for 6 min of continuous rs-fMRI collection while keeping their eyes open. A whole brain echo-planar imaging (EPI) sequence with the following parameters was used: TR = 3,000 ms, TE = 30 ms, FOV = 24 × 24 $cm^2$, 64 × 64 matrix, 42 axial slices, 3 mm slice thickness, 0.3 mm gap. MRI data were processed using default preprocessing pipeline of the Conn toolbox for MatLab (Whitfield-Gabrieli and Nieto-Castanon, 2012) implemented with SPM12 for ROI-to-ROI analysis, using the methods described by Foret et al. (2020a). Artifact Detection Tools was used for outlier detection (ART; https://www.nitrc.org/projects/artifact_detect) with default thresholds (z = 9 for global signal; 2 mm motion) and first level within-subject analysis utilized the general linear model consisting of realignment and scrubbing with a band-pass filter was set to [0.008 0.09] Hz. Denoising was performed and linear and quadratic effects of white matter and CSF BOLD time series, all first-level covariates, and rest were included as covariates. Connectivity matrices constructed between the source Posterior Cingulate Cortex (PCC) and region of interest, in this case Medial Prefrontal Cortex (MPFC), for each subject. Multivariate analysis was performed to determine the difference between PCC and DMN connectivity across subjects.

## Magnetic-Resonance Spectroscopy

Point-RESolved Spectroscopy (PRESS) sequence (svs_se_30) to obtain cerebral metabolite ratios for $^1$H-MRS data. The following parameters were used: TE/TR = 30/3,000 ms, 80 excitations, 2,000 Hx spectral width, volume ∼6 $cm^3$ in the occipitoparietal gray matter including the posterior cingulate gyrus (Kaur et al., 2017). Metabolic changes in the posterior cingulate gyrus have been implicated in early stages of dementia (Herholz et al., 2002). A digital archive was saved and reviewed to maintain consistency of voxel placement. Concentrations of glutamate, mI and NAA were reported as ratios relative to creatine (Cre), a marker of energy metabolism, the most stable metabolite for use as an internal reference (Kantarci et al., 2000; Ross and Sachdev, 2004). The commercially available software, LCModel, was used to separate the metabolite resonance from the macromolecule background.

# Statistical Analyses

## Network Analyses

Network analyses were estimated in JASP (JASP Team, 2020), which is based on the bootnet package in R (R Core Team; version 3.2.3) package qgraph (Version 1.3.3; Epskamp et al., 2012). In network analysis terminology, observed variables are referred to as nodes and relationships between observed variables as edges. Our analysis used a regularized estimation method, Extended Bayesian Information Criterion Graphical Least Absolute Shrinkage and Selection Operator (EBICglasso), which estimates partial correlations between variables and shrinks absolute weights to zero (Foygel and Drton, 2010). This method is appropriate for estimating networks when binary variables are included (van Borkulo et al., 2014). Tuning parameters were set to 0.5 and missing values were excluded pairwise from analyses to preserve as much of the sample as possible. A power analysis was performed using the netPower package in R (https://github.com/mihaiconstantin/netpaw) and revealed that, for the smallest number of individuals in a single correlation ($n$ = 78 males with WMH volume), sensitivity is estimated at ∼91.6% and specificity at 81.8% with <20% probability of a type I error and <10% probability of a type II error. This method estimates 100 different network models with varying degrees of sparsity. The starting value of the hyperparameter y was set to 0.5 (Foygel and Drton, 2010). We used normalized estimation of centrality measures to calculate which nodes are most central to the network (Opsahl et al., 2010). Measures of centrality for each node included betweenness (which nodes serve as bridges between other nodes in the network), closeness (relative closeness of a node to all other nodes in a network) and strength (how many direct connections a node has with other nodes).

Network graphs, also produced in JASP, are based on the R package (R Core Team; version 3.2.3) qgraph (Version 1.3.3; Epskamp et al., 2012). Positioning of the nodes was done using the Fruchterman-Reingold algorithm, which uses pseudo-random numbers to organize the network based on the strength of connections between nodes (Friedman et al., 2008, 2014; Epskamp et al., 2012, 2018).

### Follow-Up Linear Regression Analyses

A central aim of this paper was to examine how network analysis might enhance our understanding of vulnerability to later-life cognitive decline. Thus, we conducted follow-up analyses examining the ability of the strongest nodes in the network, selected based on the methods described above where "strong" nodes were those with strength centrality measures more than 1 SD above the mean, to account for variance in current cognitive performance. Four separate linear analyses were conducted in JASP (JASP Team, 2020).

## RESULTS

Descriptive statistical analyses (**Table 1**) revealed a cognitively normal middle-aged sample. As discussed in the previous section, males and females significantly differed in levels of mI as well as measures of waist circumference, HDL-cholesterol, triglycerides, blood glucose levels and functional connectivity. Sex differences in MetS variables are expected as the Alberti et al. (2009) criteria utilizes different cutoffs for HDL-cholesterol, blood pressure, and waist circumference. We have included frequencies of male and female participants meeting MetS criteria for each component in addition to the average blood pressure, blood glucose, waist circumference, triglyceride and HDL-cholesterol levels in the sample. Approximately 69% of females met criteria for elevated waist circumference vs. 47% of males, 27% met criteria for elevated triglycerides vs. 47% of males and frequencies of hypertension were similar between male and female participants. **Figure 1** represents the network for males and **Figure 2** represents the network for females.

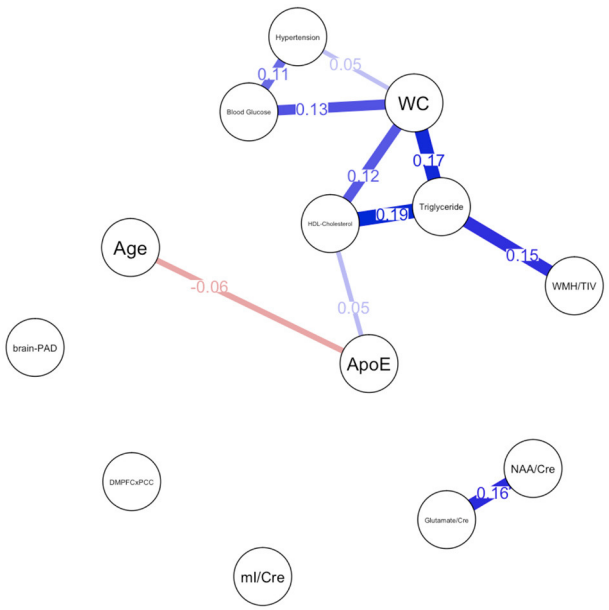


**FIGURE 1 |** Network plot for males. Brain-PAD, Brain predicted age difference, DMNPFCxPCC, Resting State Functional Connectivity in the Default Mode Network; WC, Waist Circumference; NAA/Cre, Ratio of N-Acetylaspartate to Creatine; mI/Cre, Ratio of Myo-inositol to Creatine; WMH/TIV, White Matter Hyperintensities adjusted for total intracranial volume. Red bars indicate negative correlations and blue bars indicate positive correlations. Thicker, shorter bars indicate stronger relationships. Minimum edge strength set to 0.5 was ignored in network plots because it was larger than the absolute value of the strongest edge.

## MALE NETWORK

For males, ∼87.2% of edges were set to zero. Centrality measures are provided in **Table 2** and **Figure 3**. Visual examination of the graph revealed that the strongest edges were between the MetS components, particularly between plasma triglyceride levels and HDL-cholesterol as well as triglycerides and waist circumference. There was also a strong edge between levels of NAA and glutamate. According to the graph, there is a negative association between age and ApoE status for males, indicating that male ϵ4 carriers in our sample are younger overall. Nodes with measures of strength more than 1 SD above the mean for males were triglyceride levels and waist circumference, indicating that these variables might hold more information for connecting with the wider network. Measures of closeness revealed that nodes for males were not close to any other nodes in the network, which is typical of a sparsely connected network. For males, HDL-cholesterol and waist circumference had the highest measures of betweenness.

### Female Network

For females, ∼69.2% of edges were set to zero. Centrality measures are provided in **Table 2** and **Figure 3**. Visual examination of the graph revealed several edges for females. The strongest edges were between MetS components, particularly HDL-cholesterol and triglyceride, glucose and blood pressure, as well as NAA and glutamate. ApoE status had positive and negative associations with several other variables, but in particular was positively associated with white matter hyperintensities. This indicates that ϵ4+ females in our sample may have greater white matter burden at midlife. Other edges of interest included: the positive association between ϵ4 status and waist circumference and systolic blood pressure, the negative association between NAA and waist circumference and NAA and brain-PAD, suggesting that individuals with older brains than their chronological age and higher waist circumferences have lower levels of NAA. Nodes with measures of strength more than 1 SD above the mean for females were functional connectivity in the DMN and mI, indicating that these variables might hold more information for connecting with the wider network. Measures of closeness revealed that several nodes for females were close to other nodes in the network, but functional connectivity in the DMN, hypertension, waist circumference and ApoE were all above the mean and mI was more than 1 SD above the mean closeness for the other variables. For females, variables or nodes with the highest degrees of betweenness included ApoE and hypertension.

### Follow-Up Linear Regression Analyses

The strongest male network nodes, triglycerides levels and waist circumference, analyzed as continuous variables for the purpose

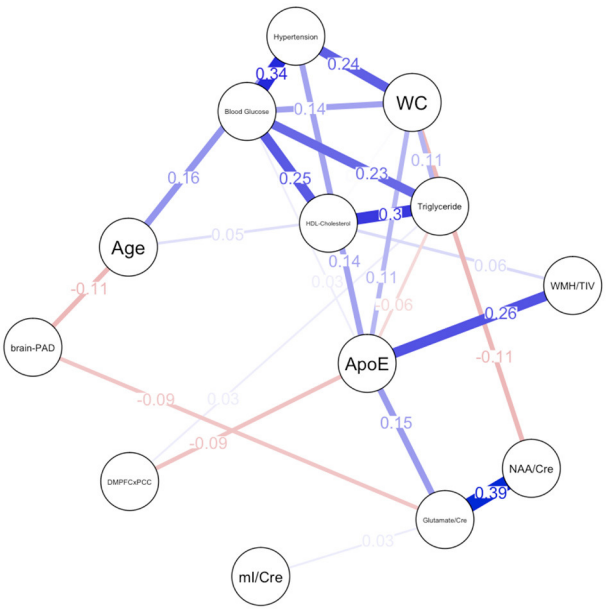


**FIGURE 2 |** Network plot for females. Brain-PAD, Brain predicted age difference; DMNPFCxPCC, Resting State Functional Connectivity in the Default Mode Network; WC, Waist Circumference; NAA/Cre, Ratio of N-Acetylaspartate to Creatine; mI/Cre, Ratio of Myo-inositol to Creatine; WMH/TIV, White Matter Hyperintensities adjusted for total intracranial volume. Red bars indicate negative correlations and blue bars indicate positive correlations. Thicker, shorter bars indicate stronger relationships. Minimum edge strength set to 0.5 was ignored in network plots because it was larger than the absolute value of the strongest edge.

of the regression analysis, significantly predicted cognitive performance for male [$F_{(2,\ 73)} = 3.47$, $p = 0.036$] but not female [$F_{(1,\ 101)} = 0.34$, $p = 0.711$], participants. The strongest female network nodes, mI and DMN connectivity, predicted cognitive performance for female [$F_{(2,\ 99)} = 4.65$, $p = 0.012$] but not male [$F_{(2,\ 73)} = 2.93$, $p = 0.060$] participants. Thus, midlife cognitive performance appears sensitive to markers of metabolic dysfunction in men, while cognition appears more sensitive to brain integrity markers in women, particularly markers that are associated with risk for AD pathologies such as mI and DMN Connectivity (Voevodskaya et al., 2016, 2019).

## DISCUSSION

In this study, we investigated relationships between cardiometabolic risk factors and brain integrity through network analysis. Network metrics suggested meaningful differences between males and females at midlife. Although the networks revealed many metrics about the relationships between brain, demographic and metabolic variables for males and females, measures of density and betweenness centrality are of the greatest interest for understanding how many links exist between variables in a network, which can be an indicator of higher risk, and which variables might bridge the relationship between other variables of interest.

### Potential Mechanisms

Overall, the findings of the present study suggest that the network for males was sparse relative to the network for females. Consistent with prior research (Pasha et al., 2018b), the network for males revealed greater interconnectedness between metabolic risk factors and white matter hyperintensities. Additionally, though one study found women to have higher levels of WMH than men overall, higher BMI was associated with higher WMH only in men (Alqarni et al., 2021), providing further support for sex differences in the relationship between metabolic risk factors and WMH. HDL cholesterol and waist circumference appear to be of particular importance for males as this node had the highest level of betweenness. Low HDL-cholesterol and elevated triglyceride levels, which also had a high degree of strength centrality in the network, have been associated with increased risk for dementia only in men in another study (Ancelin et al., 2013). Waist circumference has emerged as an important predictor of cardiovascular disease markers, such as elevated C-reactive protein, over the other MetS components for both sexes (Nakamura et al., 2008; Cheong et al., 2015), though our findings suggest that this effect may be more robust for males.

For females, the network had a higher measure of density and indicated many relationships between metabolic risk factors, brain integrity and genetic status at midlife. Though strong edges were visible between MetS components in females as in males, relationships between WMH and metabolic syndrome components were weak. This finding is consistent with the findings discussed previously on sex differences in white matter burden (Pasha et al., 2018b; Alqarni et al., 2021). Most notable was the centrality of ApoE and age in the graphical model of the female network. Most notable was the centrality of ApoE and age in the graphical model of the female network. The prevalence of $\epsilon$4+ individuals in our sample is ∼15%, which is consistent with the general population (Heffernan et al., 2016). This, unfortunately, results in an unbalanced sample for the network analysis. It would be interesting to re-examine the female network in sample with a more balanced ratio of $\epsilon$4+ and $\epsilon$4- individuals, to see if it remains stable. Though our findings are somewhat limited by the small sample of $\epsilon$4+ individuals, our results suggest that age and genetics may play an important role in driving brain-metabolic health relationships in midlife, which is consistent with prior literature (Plassman et al., 2010). ApoE $\epsilon$4 status has been shown to have larger impact on memory performance and hippocampal atrophy in women than in men (Azad et al., 2007), and this network suggests that midlife cardiovascular mechanisms might be responsible for this relationship. This finding is unsurprising, as ApoE $\epsilon$4 status conveys greater risk of neurocognitive and cardiovascular disease for females (Mortensen and Høgh, 2001; Riedel et al., 2016), and sex has been found to moderate associations between amyloid burden, $\epsilon$4 status and functional connectivity in the DMN (Damoiseaux et al., 2012; Caldwell et al., 2019). Biological changes occurring during the menopausal transition may lead to additional vulnerabilities in cardiovascular and metabolic

**TABLE 2 |** Centrality measures for each node including betweenness (which nodes serve as bridges between other nodes in the network), closeness (relative closeness of a node to all other nodes in a network), and degree/strength (how many direct connections a node has with other nodes).

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| **Variable** | **Betweenness** | **Closeness** | **Strength** | **Betweenness** | **Closeness** | **Strength** |
| brain-PAD | −0.722 | 0.000 | −1.079 | −0.766 | −0.664 | −1.087 |
| DMPFCxPCC | −0.722 | 0.000 | −1.079 | −0.766 | −0.993 | −1.333 |
| Glutamate/Cre | −0.722 | 0.000 | −0.154 | 0.975 | 0.370 | 0.388 |
| Blood Glucose | 0.760 | 0.000 | 0.312 | 0.684 | 0.654 | 1.430 |
| HDL-Cholesterol | 1.747 | 0.000 | 1.041 | −0.766 | −0.149 | 0.264 |
| Hypertension | −0.722 | 0.000 | −0.158 | 1.748 | 1.255 | 1.109 |
| Triglyceride | 0.760 | 0.000 | 1.937 | −0.766 | −0.143 | 0.766 |
| WC | 1.747 | 0.000 | 1.683 | −0.089 | 0.788 | 0.605 |
| NAA/Cre | −0.722 | 0.000 | −0.154 | −0.379 | 0.254 | −0.118 |
| WMH/TIV | −0.722 | 0.000 | −0.181 | −0.766 | 0.116 | −0.687 |
| Age | −0.722 | 0.000 | −0.694 | −0.283 | −0.117 | −0.699 |
| ApoE | 0.760 | 0.000 | −0.394 | 1.942 | 1.150 | 0.989 |
| mI/Cre | −0.722 | 0.000 | −1.079 | −0.766 | −2.521 | −1.625 |

*Brain-PAD, Brain predicted age difference; DMNPFCxPCC, Resting State Functional Connectivity in the Default Mode Network; WC, Waist Circumference; NAA, N-Acetylaspartate; mI, Myo-inositol; Cre, Creatine; WMH/TIV, White Matter Hyperintensities adjusted for total intracranial volume.*

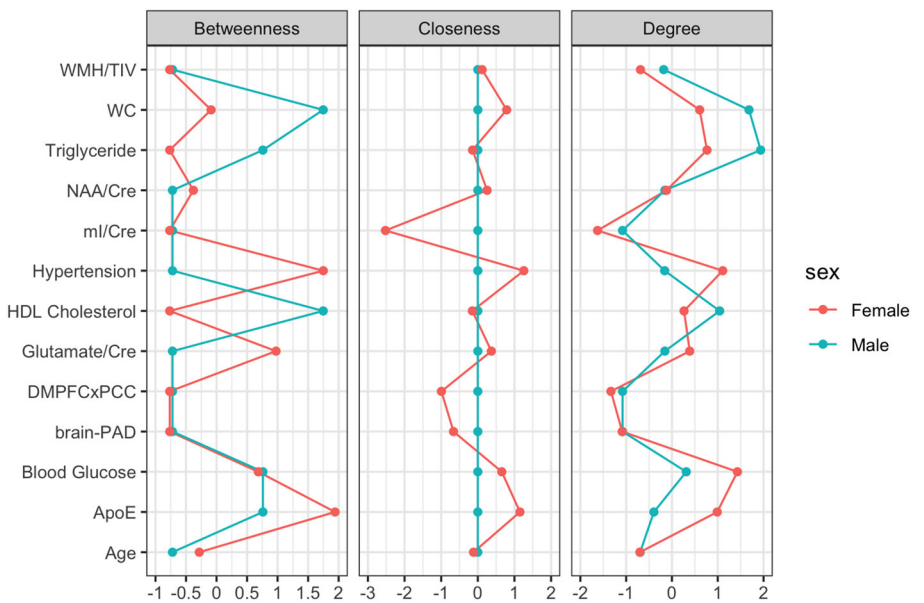


**FIGURE 3 |** Centrality Plot for each node including betweenness (which nodes serve as bridges between other nodes in the network), closeness (relative closeness of a node to all other nodes in a network), and degree/strength (how many direct connections a node has with other nodes).

health (Gordon et al., 1978; El Khoudary et al., 2020). Since the average age at natural menopause in the United States is around 52.6 years (Reynolds and Obermeyer, 2005), the age range in our sample could be capturing women with variable hormonal profiles that encompass premenopausal, perimenopausal, and postmenopausal women. Recent literature has suggested that perimenopause, in particular, could drive changes in brain integrity and metabolic processes (Brinton et al., 2015; Palla et al., 2020). Reproducibility of self-reported menopausal status varies (Paganini-Hill and Ross, 1982; Horwitz and Yu, 1985; Colditz et al., 1987; den Tonkelaar, 1997; Rödström et al., 2005). However, it is important for these issues to continue to be explored further by measuring the endogenous levels of relevant sex hormones (Wildman et al., 2008) and documenting the use of HRT, as many sex differences in cardiovascular disease are attributed to protective effects of estrogen (Stanhewicz et al., 2018; Peters et al., 2019; Rodgers et al., 2019). Due to the small number of participants on HRT, we were unable to

examine any potential effects of medication. Future studies with a larger number of participants on HRT could examine the role of either testosterone or estrogen therapies on relationships between brain integrity and metabolic function using a similar statistical technique to our analysis as research studies on HRT to protect against neurocognitive decline have shown mixed findings (LeBlanc et al., 2001; Wu et al., 2020).

Somewhat challenging to interpret is the high level of betweenness of systolic blood pressure for females. Hypertension in midlife has been associated with increased risk for dementia among women but not men (Gilsanz et al., 2017). Another study has shown that midlife hypercholesterolemia and hypertension convey risk for dementia in both men and women (Azad et al., 2007). Even though our networks demonstrate that there are sex differences in the degree of impact of these risk factors on brain health, it is unclear if hypertension acts as the driving force for other MetS risk factors. Unlike ApoE, the betweenness of hypertension appears to be driven more by its relationship with other MetS risk factors rather than a position between brain integrity and MetS. Females in our sample who meet MetS criteria for elevated systolic blood pressure appear to be older and more likely to be $\epsilon$4 carriers (**Figure 2**), which re-emphasizes the significance of $\epsilon$4 status in the network.

In both males and females, glutamate and NAA were positively related to one another. Concentrations of these neural metabolites have been correlated in other research, with some hypothesizing that NAA can be converted to glutamate when supplies are low (Clark et al., 2006). Ultimately, these $^{1}$ H MRS findings are difficult to untangle and only suggest that our sample is relatively healthy without notable levels of pathology. However, an edge between NAA and waist circumference was visible only in females, such that females meeting MetS criteria for elevated waist circumference had lower levels of NAA. Relationships between female neuronal viability and waist circumference are not widely studied, but previous research has found that elevated BMI and subclinical atherosclerosis is associated with lower levels of NAA in the anterior (Gazdzinski et al., 2010) and posterior cingulate cortex (Haley et al., 2010b). Additionally, NAA was associated with brain-PAD in females, such that women with greater brain-age gaps might have poorer neuronal viability. Though application of brain-aging algorithms in a midlife population is still relatively novel, previous literature using a similar technique to analyze brain-PAD (brainageR, https://github.com/james-cole/brainageR) has shown that accelerated brain aging may be observable in midlife women in relation to lifestyle factors which impact hormone levels, in this case number of childbirths. Further, their findings are consistent with observed patterns of parity and risk of AD, where increased number of childbirths conveys lower risk of neurocognitive decline (de Lange et al., 2019). This provides additional evidence that brain-PAD at midlife could relate to later life outcomes and that female populations experience hormonal changes throughout their life that convey unique risk factors for neurocognitive decline. Myo-inositol provided the least information of any node in the network, which is surprising as myo-inositol and the other brain variables selected are considered preclinical markers of AD, and elevations have been found in asymptomatic individuals with cardiometabolic risk (Kantarci et al., 2000; Haley et al., 2010a; Voevodskaya et al., 2016, 2019).

The application of network modeling in this study is novel and significant in that graph-theory techniques can contribute unique information to cognitive risk assessment about the interconnectedness and organization of relationships among risk factors, over and above the measured levels of physiological variables of neurobiological significance. Research applying network modeling to psychopathology suggests that a more tightly connected network is riskier because "activation" of one symptom can spread to others (Borsboom and Cramer, 2013). This seems even more likely with biological systems as there are mechanistic relationships between nodes in our network. Relationships in the male body-brain network suggest that males have greater vulnerability than females to cerebrovascular lesions under conditions of metabolic syndrome. The female picture appears to be more complicated. Our network analyses suggest direct relationships between $\epsilon$4 status and metabolic risk factors in women, such as waist circumference and systolic blood pressure, supporting previous research on the role of ApoE in females with cardiovascular disease (Sampedro et al., 2015; Riedel et al., 2016). As mentioned, women have higher incidence of AD (Zhao et al., 2016; Andrew and Tierney, 2018; Beam et al., 2018; Buckley et al., 2019) and cardiovascular risk factors have been suggested as a mechanism for this disparity (Volgman et al., 2019). Our follow-up linear regression analyses demonstrate the ability of the strongest nodes in the sex-specific body-brain network models to better account for variance in current cognitive performance of their respective sex, even in midlife when cognitive function is relatively preserved. These findings further support the utility of the network analysis method to identify variables which convey unique vulnerability for neurocognitive decline in male and female populations. In midlife, the constructed sex-specific networks also provide valuable information about mechanisms of brain vulnerability in at-risk populations, before cognitive function is significantly impaired, by simultaneously examining the effects of multiple physiological variables on each other as well as on brain and cognitive function.

Our study assessed sex, not gender identity, so our findings may or may not generalize to transgender men and women. As our work stands, it is unclear whether observed sex differences are a result of biological mechanisms based on genotype, hormone levels or sociocultural experiences of sex and gender. However, these observed differences between midlife males and females suggest a personalized medical approach which takes sex into consideration as key to early identification and management of modifiable risk factors for cognitive aging.

## CONCLUSIONS

Our findings support prior research on sex differences in relationships between cardiometabolic risk, genetics and brain integrity and provide further support for a personalized medicine approach which takes sex into consideration. Network analysis has the additional benefit of untangling complex mechanisms by

allowing researchers and clinicians to consider multiple variables at once. The network for females suggests an important influence of genetic status on metabolic risk and brain integrity and may warrant additional attention when presenting clinically with any of these risk factors, which may be modifiable with appropriate pharmaceutical or behavioral intervention.

## DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Data and code available on request. Requests to access these datasets should be directed to haley@austin.utexas.edu.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board University of Texas at Austin. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

JF and AH: conception and study design. AH and HT: resources, project administration, and funding acquisition. JF, MD, and JC: statistical analysis. JF, MD, MC, and AH: interpretation of results. JF, MD, DG, MC, HT, and AH: drafting the manuscript work or revising it critically for important intellectual content. All authors: approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work.

## FUNDING

This work was supported by the National Institutes of Health grants R21AG050898 and R01NS075565.

## ACKNOWLEDGMENTS

We would like to thank our participants and research assistants without whom this work would not be possible.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

BRIEF RESEARCH REPORT
published: 09 July 2021
doi: 10.3389/fnagi.2021.697528

# Influence of Physical Activity Levels and Functional Capacity on Brain β-Amyloid Deposition in Older Women

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**Edited by:**
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**Received:** *19 April 2021*
**Accepted:** *26 May 2021*
**Published:** *09 July 2021*

**Citation:**
*Pedrero-Chamizo R, Szoeke C, Dennerstein L and Campbell S (2021) Influence of Physical Activity Levels and Functional Capacity on Brain β-Amyloid Deposition in Older Women. Front. Aging Neurosci. 13:697528. doi: 10.3389/fnagi.2021.697528*

Physical activity (PA) and Alzheimer's disease are associated. However, how PA influences the cerebral β-amyloid (Aβ) burden remains unclear. The aim of this study was to determine if PA levels and/or functional capacity (FC) are associated with Aβ plaque deposition, and whether these associations differed according to APOE-ε4 genotype. A total of 117 women (69.7 ± 2.6 years; 33.3% APOE-ε4-carriers) from the Women's Healthy Ageing Project cohort (WHAP) were analyzed. PA was measured using the International Physical Activity Questionnaire and, FC was evaluated using the Timed Up and Go test (TUGt). Positron emission tomography with F-18 Florbetaben was carried out to assess cerebral Aβ burden, and quantified using standardized uptake value rations. The sample was split into PA and TUGt tertiles (T1, T2 and T3), and compared according to APOE-ε4 genotype (positive/negative). There were no significant differences in Aβ accumulation according to PA tertiles and APOE-ε4 genotype. Regarding FC, APOE-ε4+ participants in the first TUGt tertile (high performance) obtained significant lower Aβ accumulations compared with the other two tertiles ($p < 0.05$). Comparing between genotypes, greater Aβ depositions were found between T2 and T3 in APOE-ε4+ compared with those who were APOE-ε4– ($p < 0.05$). Values of TUGt ≥ 6.5 s (APOE-ε4+) and 8.5 s (APOE-ε4–) were associated with an increased risk of having higher Aβ retention. In conclusion, low performance in TUGt is associated with a negative effect on brain pathology with increasing cerebral Aβ depositions in older women who are APOE-ε4+. In physically active older women (> 600 METs·min/week), higher PA levels are not associated with reduction in Aβ depositions.

**Keywords: function, cognition, Alzheimer's disease, physical activity, women, PET, APOE ε4, healthy ageing**

# INTRODUCTION

The accumulation of amyloid beta (Aβ) peptides in the brain is recognized as the earliest detectable pathophysiological abnormality in Alzheimer's disease (AD) (Gandy, 2005). Previous studies have observed how cognitively healthy people, with a predisposition to accumulate Aβ brain, can begin to experience progressive increases in the retention of this peptide even 20 years before reaching the thresholds for amyloidosis (Rowe et al., 2010; Perani et al., 2014).

Among principal non-modifiable AD risk factors, age is the most well-known factor, showing an almost exponential increase with advancing age, especially in female sex, following by family history and genetics (e.g., APOE-ε4 carriers) (Livingston et al., 2020). However, in the absence of disease-modifying therapies for AD, there is a necessity to identify modifiable risk factors that may delay and even prevent disease.

Increasing regular exercise is considered a protective component against cognitive decline and AD (Rabin et al., 2019; Livingston et al., 2020), and is now recommended in the WHO report (WHO, 2019) on preventing dementia, since it improves cerebral perfusion, reduces neuronal loss, improves brain plasticity and preserves brain volume (Valenzuela et al., 2020), besides being an independent factor of cardiovascular health (Rabin et al., 2019). Nevertheless, there are limitations in assessing physical activity (PA) using objective methods, which often do not reflect personal physical performance. In this sense, evaluation of functional capacity (FC) has been identified as an objective measure which is a reflection of individual fitness, positively associated with many indices of health, and as early predictive factor of brain deterioration (Erickson et al., 2014; Rabin et al., 2019). However, information on the associations between PA and FC with biomarkers of AD has not been consistently replicated, particularly regarding Aβ brain deposition. The objective of this study was to determine if PA levels and/or FC are associated with Aβ plaque deposition in older women, and whether these associations differed according to APOE-ε4 genotype.

# METHODS

## Sample

All data for the present study were collected from theWHAP cohort. The complete methodology of the WHAP has been described elsewhere (Szoeke et al., 2016). In brief, WHAP started in 1992, when 438 Australian women (aged between 45 and 55 years) were selected by random population sampling and enrolled into a prospective longitudinal follow up study. In the present study, participants who completed brain MRI scan plus Positron Emission Tomography (PET), completed a PA questionnaire and carried out a FC test in 2012 data collection were eligible for inclusion in the analysis (see **Supplementary Figure 1**). To make maximum use of the data, all valid data on PA and FC were included in this report. Consequently, sample sizes vary for the PA analysis ($n = 117$) and FC analysis ($n = 98$).

The study protocol for the WHAP project was approved by the University of Melbourne Human Research Ethics Committee and fully compliant with the guidelines of the National Health and Medical Research Council ethical standards (HREC 931149X, 1034765, 110525, 1339373, 010411, 1647448 & 1750632) and was carried out in accordance with the Declaration of Helsinki. All subjects provided written informed consent before participation.

## Cerebral Imaging

Data from PET scan were conducted with participants receiving 250 MBq of F-18 Florbetaben intravenously, with a 20 min acquisition commencing 90 min post injection. Standardized Uptake Values (SUV) were calculated for all brain regions examined and SUV ratios (SUVRs) generated by normalizing regional SUV using the cerebellar cortex. Neocortical SUVRs, a global measure of Aβ burden, is expressed as the average SUVRs of the area-weighted mean of frontal, superior parietal, lateral temporal, lateral occipital and anterior and posterior cingulate regions (Szoeke et al., 2016). A SUVRs threshold of 1.2 or greater was used to discriminate participants with an intermediate brain Aβ load (+SUVRs). Similar threshold value was identified in previous studies (Ciarmiello et al., 2019; Kim et al., 2020).

## Physical Activity and Functional Capacity

Data on PA were collected using the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003). The reported minutes per week in four activity domains (work-related PA, transportation PA, domestic PA, and recreational PA) were multiplied by the metabolic equivalent (MET) score (METs·min/week), based on the intensity of the activity being undertaken.

Data on FC were evaluated using the Timed Up and Go test (TUGt) (Podsiadlo and Richardson, 1991). The TUGt measures the time (in seconds) taken to rise from a seated position, walk 3 meters from the chair, walk back to the chair and sit down again. A shorter time to complete this test reflects better physical performance.

In the current study, participants were separated into tertiles (T1, T2 and T3) dependent upon IPAQ and TUGt based on the calculated scores.

## Confounders

Potential confounders were selected from the literature and included age, body mass index (BMI; kg/m$^2$), educational level (> 12 years), physical activity, cognitive status (assessed using Mini-Mental State Examination [MMSE]) (Folstein et al., 1975), cardiovascular disease risk (assessed using Framingham score for cardiovascular risk) (Kannel et al., 1976), and APOE-ε4 genotype (positive [APOE-ε4+] or negative [APOE-ε4–]). All analyses presented are adjusted for these covariates.

## Statistical Analysis

All statistical analyses were conducted using statistical package for the social sciences (SPSS) version 24.0 (SPSS Inc., Chicago, IL, USA). The normal distribution of the variables was examined with the Kolmogorov-Smirnov test. Since SUVRs variable was not normally distributed, non-parametric statistic was

**TABLE 1 |** Participant characteristics.

| | **Overall ($n$ = 117)** |
|---|---|
| Age at testing (years) | 69.7 ± 2.6 |
| APOE ε4 carrier n (%) | 39 (33.3%) |
| Body mass index (kg/m$^2$) | 28.3 ± 5.5 |
| Energy expenditure (METs·min/week)‡ | 4070 (2129 – 7332) |
| TUG test (seconds)† | 7.6 ± 1.7 |
| MMSE (score) | 28.5 ± 1.4 |
| Past smokers n (%) | 45 (38.5) |
| Current smoker n (%) | 10 (8.5%) |
| Alcohol intake (≤2 drinks/week) | 46 (39.3%) |
| Education (≤12 years) n (%) | 65 (55.6%) |

*APOE, apolipoprotein E; METs, metabolic equivalent score; MMSE, Mini Mental State Exam; TUG, Timed up and go.*
*Values are expressed as mean ± standard deviation unless otherwise indicated.*
*‡Value is expressed as median (interquartile range).*
*†TUG values on a sample of 98 subjects.*

utilized. Spearman correlation coefficient was used to examine associations among IPAQ, TUGt, APOE-ε4 genotype, and SUVRs. Differences in the mean SUVRs across IPAQ tertiles and TUGt tertiles were analyzed using Kruskal-Wallis test and Mann-Whitney U-test. A receiver operating characteristic (ROC) curve was generated and the Youden index was used to identify optimal cut-off points which were related with an increased risk of suffering +SUVR (SUVRs ≥ 1.2). Due to the fact that APOE-ε4 genotype shows an interaction with Aβ levels, this analysis was carried out separately obtaining two differences cut-off points according to APOE-ε4 genotype. Binary logistic regression analyses were performed to examine associations between TUGt cut-off and different thresholds for amyloid positivity, according to previous studies (Villemagne et al., 2011; Duara et al., 2019). Odds ratios with 95% confidence intervals (CI) are reported for the studying models. Model I included the independent variable. Model II incorporated all confounders. Statistical significance was set at $p < 0.05$.

# RESULTS

## Sample Characteristics

The study participants had a mean age of 69.7 ± 2.6 years and the 33.3% of the sample was APOE-ε4+. Participant characteristics are displayed in **Table 1**. SUVRs correlated significantly with APOE-ε4 genotype (*Spearman's rho* = 0.234, $p < 0.05$) and TUGt values (*Spearman's rho = 0.255*, $p < 0.05$).

## Association Between PA and Aβ Brain Concentrations

The sample was split into tertiles according to IPAQ scores. The first tertile (T1) was composed of subjects who reported the lowest activity (IPAQ < 2769 METs·min/week) while subjects reporting the highest activity were allocated to T3 (IPAQ > 6492 METs·min/week). All subjects, except for one person, met the current PA guidelines (≥ 600 METs·min/week) as per the IPAQ and WHO (Craig et al., 2003; Bull et al., 2020). There were no statistical differences according to age, MMSE and BMI, neither among tertiles nor between APOE-ε4 genotype ($p > 0.05$).

Analyzing SUVRs between tertiles, we can observe similar values between them ($p > 0.05$). When the sample was compared taking into account the APOE-ε4 genotype, again no significant differences were observed in Aβ brain concentrations. In the same way, comparing SUVRs between APOE-ε4 genotypes (positive vs. negative) in each tertile, no statistically significant differences were found except for APOE-ε4+ participants placed in T1 who showed a tendency to accumulate greater cerebral Aβ deposits compared to APOE-ε4– allocated in the same tertile ($p < 0.1$) (**Supplementary Figure 2**).

## Association Between FC and Aβ Brain Concentrations

The sample was split into tertiles according to TUGt values. Individuals placed in T1 performed TUGt in lesser time than subjects allocated to T3, showing a better performance of T1 with respect to T3 (T1: TUGt < 7.0 s; T3: TUGt > 7.99 s). The 23.5% of the sample obtained values for the TUGt higher than the mean of the reference values published for healthy women over 60 years old (TUGt > 8.87 s) (Long et al., 2019), denoting that the majority of the cohort (76.5%) maintains an optimal functional mobility, especially participants allocated in the first tertile.

Statistically significant differences were observed in brain Aβ deposits among tertiles ($p = 0.016$, see **Figure 1**). When the cohort was split according to TUGt tertiles and APOE-ε4 genotypes (**Figure 2**), APOE-ε4– participants obtained similar brain concentrations of Aβ among tertiles, except for subjects in T3 who showed a trend to accumulate greater cerebral Aβ deposits compared to T1 ($p = 0.97$) (data not shown). Regarding to APOE-ε4+, participants placed in T1 accumulated significantly lower Aβ levels compared with the other two tertiles ($p < 0.05$ in both cases). When SUVRs were compared between APOE-ε4 genotypes and according to TUGt tertiles, APOE-ε4+ subjects placed in T2 and T3 obtained significantly higher Aβ brain concentrations compared with APOE-ε4–subjects ($p < 0.05$), as shows in **Figure 2**.

ROC curve analysis demonstrates an area under the curve (AUC) of 0.621 and 0.644 (APOE-ε4+ and APOE-ε4–, respectively). The Youden index identified optimal cut-off values; a threshold of 6.5 s (APOE-ε4+) and 8.5 s (APOE-ε4–) maximizes sensitivity and specificity of the TUGt performance as a tool for discriminating participants with an intermediate brain Aβ load (+SUVRs ≥ 1.2). A binary logistic regression examining the association between TUGt cut-off points and +SUVR was carried out. Participants whose TUGt performance was slower than cut-off points were associated with 6.0-fold higher odds (95%$CI$ = 1.962–18.644) for having +SUVRs compared with those performing TUGt faster than cut-off points (**Table 2**). The adjustment for confounders (Model II) did not significantly change this result. In addition, a new binary logistic regression was run to analysis the association between TUGt cut-off points proposed and amyloidosis cut-off points reported by other authors (Villemagne et al., 2011; Duara et al., 2019) obtaining similar results (see **Table 2**).

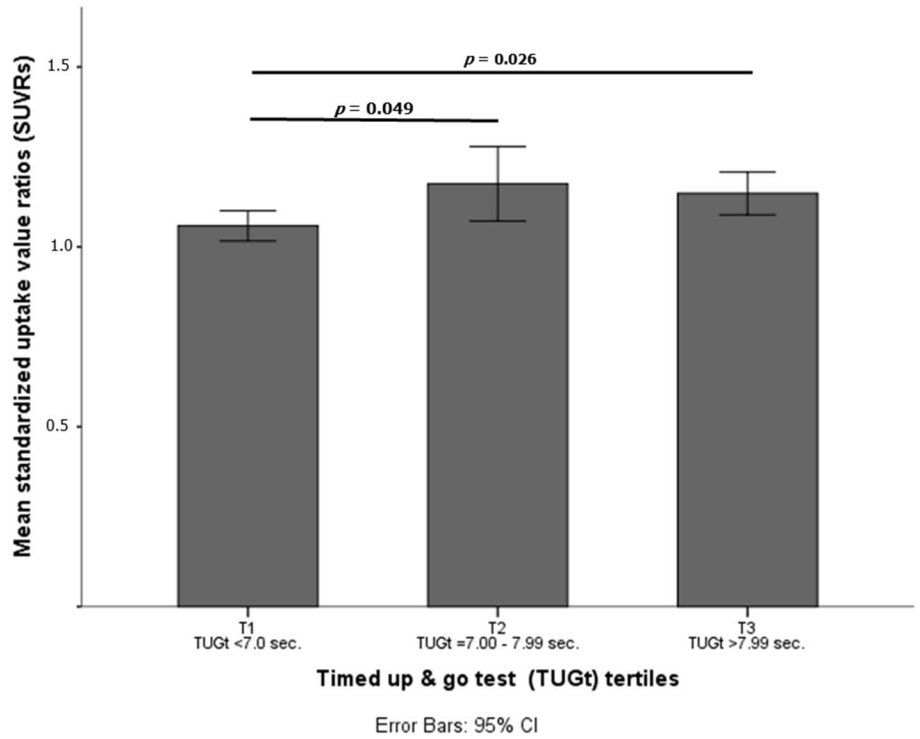


**FIGURE 1 |** Mean standardized uptake value ratios (SUVRs) according to timed up and go test (TUGt) tertiles.

## DISCUSSION

This study evaluated associations between PA (measured by IPAQ) and FC (measured by TUGt) and cerebral Aβ deposition (assessed using F-18 florbetaben) in older women from the WHAP cohort. The main findings of the present study are: (1) in physically active older women (> 600 METs·min/week), higher PA levels are not associated with reduction in cerebral Aβ deposition; (2) better performance in the TUGt is associated with lower Aβ brain deposition in APOE-ε4+; (3) a high PA level and faster TUGt results appear to lead to less cerebral Aβ retention in APOE-ε4+; (4) TUGt results slower than 6.5 (APOE-ε4+) and 8.5 s (APOE-ε4–) are associated with an increased risk of amyloid accumulation at levels above the accepted normal range.

Physical inactivity has been identified as a risk factor on various chronic diseases and has been associated with a higher risk of mortality (Kyu et al., 2016; Ekelund et al., 2020), while an active lifestyle has been associated with numerous benefits. Regarding AD-biomarkers, few studies have evaluated the potential benefits of habitual PA on Aβ brain concentrations not finding a significant association between cerebral Aβ concentrations and PA in the majority of studies (Landau et al., 2012; Okonkwo et al., 2014; Wirth et al., 2014; Schultz et al., 2015; Frederiksen et al., 2019). Nevertheless, some factors such as APOE-ε4 genotype can influence this association and not all studies took this into account. Brown et al. (2013) evaluated the association between PA and amyloid brain depositions in a cohort of 116 older people and did not find significant associations when the cohort was analysis on the whole; however, when the sample was stratified by genotypes, APOE-ε4+ participants with more active lifestyle showed significant lower cerebral Aβ concentrations than their counterparts. Conversely, our findings did not find associations between PA levels and cerebral Aβ accumulations, not even when the sample was split into APOE-ε4 genotypes, corroborating results presented in other observational studies (Vemuri et al., 2012; de Souto Barreto et al., 2015).

Another important factor to take into account is the PA level from which the individual starts. Previous studies (Kyu et al., 2016; Ekelund et al., 2020) have observed that the greatest health benefits are obtained by people whose activity level is greater than the 600 METs·min/week recommended by the WHO (Bull et al., 2020). In relation to cerebral Aβ concentrations, similar results were reported. Liang et al. (2010) evaluated the association of exercise on AD-biomarkers concluding that individuals who satisfied the American Heart Association's physical exercise recommendation for older adults (≥ 7.5 METs-h/week) (Nelson et al., 2007) accumulated lower cerebral Aβ concentrations compared with physically inactive elderly. Similar results were found in other studies (Head et al., 2012; Okonkwo et al., 2014) among which we can highlight the study by Head et al. (2012), in which a greater effect of exercise was observed on brain concentrations of Aβ in APOE-ε4+ physically inactive participants. When analyzing our results, we observed that the

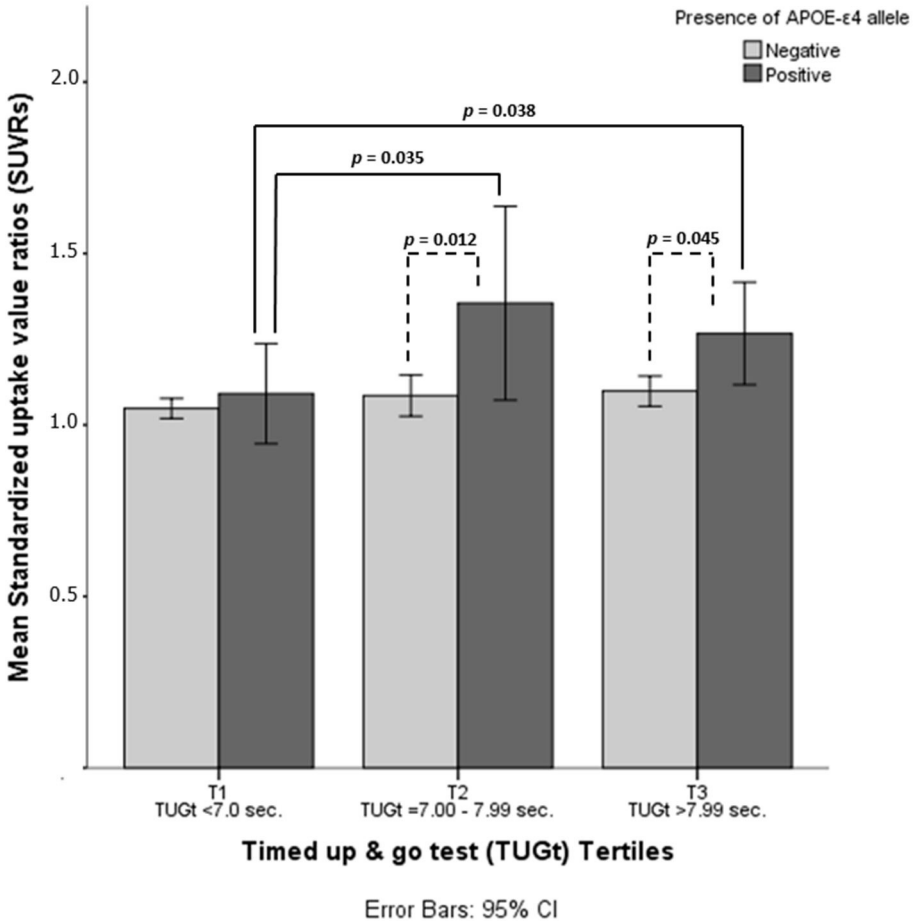


**FIGURE 2 |** Mean standardized uptake value ratios (SUVRs) according to timed up and go test (TUGt) tertiles and APOE-ε4 genotypes.

entire sample was physically active. This fact could explain the lack of statistical significance between the variables, since the main differences in relation to Aβ retention have been observed comparing people who meet the PA recommendations vs. people who do not meet them. Moreover, previous studies have established that the most health gains occur at relatively lower levels of activity (> 600 METs·min/week) up to 3000 METs·min/week, approximately (Kyu et al., 2016; Ekelund et al., 2020). In our case, participants performed a habitual PA equal to or even higher than these thresholds, with the exception of one woman, elucidating that it is a cohort with a very active lifestyle and, though these PA cut-off points are not specific for brain amyloidosis risk, it may be influenced in the same way.

Although PA and FC are related, they are separate physiological and behavioral measures that can explain different aspects and predict various health outcomes. Physical activity has been defined as any bodily movement that results in energy expenditure (Caspersen et al., 1985) while FC reflects the ability to perform activities of daily living (Lawton and Brody, 1969). In this sense, FC requires integrated efforts of the cardiopulmonary and skeletal muscle systems, providing important diagnostic and prognostic information in clinical and research settings (Arena et al., 2007), especially when it is assessment by physical tests as objective measure of physical capacity instead of questionnaires.

The most common test to assess FC in relation to brain Aβ load is gait speed. Slow walking speed has been considered a predictor of cognitive decline, dementia, disability, neuropathologies, and even death (Abellan van Kan et al., 2009; Wennberg et al., 2017). Few human studies have examined the association between cerebral Aβ load and gait speed and functional mobility, finding in most studies a stronger association between greater cerebral Aβ and lower extremity motor decline and poorer performance on multiple gait parameters among people without dementia (Nadkarni et al., 2017; Tian et al., 2017; Wennberg et al., 2017).

In this study FC was evaluated through the TUGt. It has a high correlation with other validated tests that measure pure gait speed (Bohannon, 2006), and it is appropriated for evaluating functional mobility and dynamic balance. According to our results, the TUGt evaluation showed very interesting findings with slower TUGt performance associated with greater cerebral Aβ depositions in APOE-ε4+. In addition, a positive trend was

**TABLE 2 |** Binary logistic regression examining the association between TUGt cut-off points and different thresholds for amyloid positivity.

| Amyloid positive thresholds | | Risk values of TUGtδ OR (95% CI) | *p* value |
|---|---|---|---|
| Cut-off ≥ 1.20 SUVRs | Model I | 6.05 (1.96 – 18.64) | 0.002 |
| | Model II | 8.12 (2.26 – 29.19) | 0.001 |
| Cut-off ≥ 1.31 SUVRs† | Model I | 4.12 (1.17 – 14.53) | 0.027 |
| | Model II | 4.97 (1.22 – 20.22) | 0.025 |
| Cut-off ≥ 1.40 SUVRs‡ | Model I | 7.35 (1.47 – 36.80) | 0.015 |
| | Model II | 17.21 (2.12 – 139.86) | 0.008 |
| Cut-off ≥ 1.42 SUVRs† | Model I | 6.23 (1.22 – 31.82) | 0.028 |
| | Model II | 17.21 (2.12 – 139.86) | 0.008 |

*CI, confident interval; OR, odds ratio; SUVRs, standardized uptake values ratios; TUGt, timed up and go test.*

*†Amyloid positivity threshold by Duara et al., 2019; ‡Amyloid positivity threshold by Villemagne et al., 2011. δTUGt cut-off points: ≥ 6.5 s (APOE-ε4+) and ≥ 8.5 s (APOE-ε4–).*

*Model I, included the independent TUGt cut-off variable; Model II, adjusted by age, BMI, physical activity (IPAQ score), education (>12 years), cognitive status (MMSE score), and cardiovascular disease risk (Framingham score).*

observed when comparing T1 and T3 in APOE-ε4–; however, this association did not reach statistical significance. In extension of these findings, the results of our study further affirm that cognitively healthy women who preserve a good reserve of functional mobility are associated with optimal levels of brain Aβ, especially for those with an APOE-ε4 risk genotype. Nevertheless, our findings are not supported by all authors. Dao et al. (2019) found that Aβ deposition was not associated with the TUGt. However, this study assessed a relatively small sample, in addition to not stratifying by sex and APOE genotype, both APOE-ε4+ and women being strongly associated with cerebral Aβ retention and functional mobility (Wennberg et al., 2017; Szoeke et al., 2019).

An interesting observation from our results is that women obtaining higher performance in TUGt (T1) maintain lower cerebral Aβ concentrations, regardless of APOE-ε4 genotype. In contrast, slower results in TUGt were associated with greater cerebral Aβ depositions in APOE-ε4+ participants, who had a significantly greater amyloid accrual compared to APOE-ε4– women placed in the same tertile (T2 and T3). Previous studies in this area have observed that those with the APOE-ε4+ genotype tend to accumulate higher amyloid loads than APOE-ε4–, at all ages and at all cognitive impairment levels (Duara et al., 2019). Our data suggest higher performance on functional mobility and high PA levels attenuate the negative effect of APOE-ε4+ on amyloid concentrations, slowing down brain Aβ accumulations in accordance with previous studies (Head et al., 2012).

A novel aspect of our research is that we describe cut-off points for TUGt which are related with an increase in the risk of presenting an intermediate brain Aβ load (+SUVRs ≥ 1.2). We decided to use a lower cut-off point than current thresholds for amyloid positivity with the purposes of early diagnosis and thus to afford opportunity for successful therapeutic interventions aimed at delaying disease onset and limiting further neuronal damage. To our knowledge, this is the first time that cut-off points have been established for TUGt in relation to the risk of suffering from amyloidosis. Our results indicate that slower values at the established cut-off points are associated with a greater risk of having high brain concentrations of amyloid.

Given the strong relationship between functional mobility and cognition seen in this study also relates to measures of brain pathology, other measures of FC and physical fitness known to relate to later life frailty may be useful clinical tools to help identify those at risk dementia. In this sense, TUGt is an accessible and easy measurement that may be used in clinical assessment. Further research could examine the specificity of these measures for the later life development of dementia. It will be necessary to have longitudinal studies to establish the precise association between FC and Aβ brain concentrations and the interaction with APOE-ε4 genotypes. Given we now know that amyloid accumulates over 30 years, it will be essential to examine PA over the prodrome of disease to understand if there are particular therapeutic windows or at risk periods which are relevant to proposed intervention.

We acknowledge this study had limitations. Whilst the optimal questionnaires to evaluate PA was utilized, objective measurement, such as accelerometer, could provide actual measures of activity, although the duration of this would be limited and there is evidence that when wearing the device, participants change their behavior. The relatively modest number of subjects included in the study is critical to the interpretation and generalizability of the findings. Our significant findings in a sample size around a hundred healthy women indicate that the strength of the effect is large.

Finally, as we have only one measure of amyloid accumulation we cannot address causality of these associations. Further longitudinal studies are needed to determine whether FC level predicts Aβ brain depositions, and human intervention studies are required to observe if increasing exercise influences Aβ.

In conclusion, this study provides valuable information on the association between PA and FC on AD risk. Our findings suggest that PA levels higher than global recommendations and a better performance on TUGt could be associated with slowing down cerebral Aβ retention in APOE-ε4 carriers and with a protective effect against brain Aβ depositions. Finally, TUGt performance slower than cut-off points proposed increases the risk of presenting an intermediate brain Aβ load (SUVRs ≥ 1.2).

## DATA AVAILABILITY STATEMENT

The datasets presented in this article are not publicly available because of patient confidentiality and participant privacy reasons. Requests to access the datasets can be found in online repository. The name of the repository is Women's Healthy Ageing Project University of Melbourne VIC and applications for data access can be made through the following URL: https://www.biogrid.org.au/data-directory.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Melbourne Human Research Ethics Committee and fully compliant with the guidelines of the

National Health and Medical Research Council ethical standards (HREC 931149X, 1034765, 110525, 1339373, 010411, 1647448, and 1750632) and was carried out in accordance with the Declaration of Helsinki. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

CS contributed to the conception and design of the study and protocol. CS, LD and SC participated in the assessment and clinical classifications. RP-C, CS and LD provided scientific input into the paper. RP-C and CS performed the statistical analysis plan and statistical analysis, interpreted the results, and wrote and edited the manuscript. All authors have read and approved the final version of the manuscript and agreed with the order of presentation of the authors.

## FUNDING

Funding for the Healthy Aging Program (HAP) has been provided by the National Health and Medical Research Council [NHMRC grants 547600, 1032350, and 1062133], Ramaciotti Foundation, Australian Healthy Aging Organisation, the Brain Foundation, the Alzheimer's Association [NIA320312], and Australian Menopausal Society, Bayer Healthcare, Shepherd Foundation, Scobie and Claire Mackinnon Foundation, Collier Trust Fund, J.O. & J.R. Wicking Trust, Mason Foundation, the Alzheimer's Association of Australia and Royal Australian College of Physicians. Inaugural funding was provided by VicHealth and the NHMRC. The Principal Investigator of HAP (CS) is supported by the National Health and Medical Research Council. RP-C was supported by Spanish Ministry of Education under Programa Estatal de Promoción del Talento y su Empleabilidad en I+D+i, Subprograma Estatal de Movilidad, del Plan Estatal de Investigación Científica y Técnica y de Innovación 2013–2016 [CAS18/00457]. The content of this paper is the responsibility of the authors. The funders did not take any part in this work.

## ACKNOWLEDGMENTS

We would like to acknowledge the contribution of the participants and their supporters for their time and commitment for over 25 years to the University. We thank BioGrid for providing data linkage, Melbourne Health Pathology services for providing blood biomarker storage and analyses. We thank the research assistants who assisted in data collection. A full list of all researchers contributing to the project and the membership of our Scientific Advisory Board is available online. In addition, this research work was awarded in the National Sports Medicine Research Awards-Liberbank, year 2019, Faculty of Sports Medicine, University of Oviedo.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.697528/full#supplementary-material

**Supplementary Figure 1 |** Flow chart of participants in the study.

**Supplementary Figure 2 |** Mean standardized uptake value ratios (SUVRs) according to physical activity (PA) tertiles and APOE-ε4 genotypes.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 05 October 2021
doi: 10.3389/fnagi.2021.694982

# Optimal Blood Pressure Keeps Our Brains Younger

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**Background**: Elevated blood pressure (BP) is a major health risk factor and the leading global cause of premature death. Hypertension is also a risk factor for cognitive decline and dementia. However, when elevated blood pressure starts impacting cerebral health is less clear. We addressed this gap by estimating how a validated measure of brain health relates to changes in BP over a period of 12 years.

**Methods**: Middle-age (44–46 years at baseline, *n* = 335, 52% female) and older-age (60–64 years, *n* = 351, 46% female) cognitively intact individuals underwent up to four brain scans. Brain health was assessed using a machine learning approach to produce an estimate of "observed" age (BrainAGE), which can be contrasted with chronological age. Longitudinal associations between blood pressures and BrainAGE were assessed with linear mixed-effects models.

**Results**: A progressive increase in BP was observed over the follow up (MAP = 0.8 mmHg/year, SD = 0.92; SBP = 1.41 mmHg/year, SD = 1.49; DBP = 0.61 mmHg/year, SD = 0.78). In fully adjusted models, every additional 10 mmHg increase in blood pressure (above 90 for mean, 114 for systolic, and 74 for diastolic blood pressure) was associated with a higher BrainAGE by 65.7 days for mean, and 51.1 days for systolic/diastolic blood pressure. These effects occurred across the blood pressure range and were not exclusively driven by hypertension.

**Conclusion**: Increasing blood pressure is associated with poorer brain health. Compared to a person becoming hypertensive, somebody with an ideal BP is predicted to have a brain that appears more than 6 months younger at midlife.

**Keywords: MAP—mean arterial pressure, systolic, diastolic, hypertension, machine learning, MRI**

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***Edited by:***
*Omar Yaxmehen Bello-Chavolla, Instituto Nacional de Geriatría, Mexico*

***Reviewed by:***
*Ricki Colman, University of Wisconsin-Madison, United States*
*Edo Richard, University of Amsterdam, Netherlands*

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***Received:*** *14 April 2021*
***Accepted:*** *23 July 2021*
***Published:*** *05 October 2021*

***Citation:***
*Cherbuin N, Walsh EI, Shaw M, Luders E, Anstey KJ, Sachdev PS, Abhayaratna WP and Gaser C (2021) Optimal Blood Pressure Keeps Our Brains Younger. Front. Aging Neurosci. 13:694982. doi: 10.3389/fnagi.2021.694982*

## INTRODUCTION

Elevated blood pressure (BP) is a major health risk factor and a leading global cause for premature death (Egan and Stevens-Fabry, 2015; Rahimi et al., 2015). In addition, hypertension is a demonstrated risk factor for dementia, and recent findings indicate a non-linear dose-response between systolic and diastolic blood pressure levels and incident dementia (Wang et al., 2018).

This complex dose-response is known to be modulated by age, and by the progression of the underlying pathology, which develops over decades (e.g., amyloid plaques, neurofibrillary tangles, cerebrovascular disease). The point at which elevated blood pressure starts to impact cerebral health, and the extent of that impact, is less clear. In this study, we address this gap by estimating how a well-validated measure of brain age (BrainAGE; Franke et al., 2013; Gaser et al., 2013; Luders et al., 2016; Cole et al., 2019; Elliott et al., 2019), which reflects global brain health, relates to differences and changes in BP in community-living individuals over a follow-up of 12 years. Thus, we seek to answer the question "Does the brain of individuals with optimal blood pressure stay younger for longer?"

Worldwide, approximately 31% of all adults suffer from hypertension and a further 25–50% suffer from pre-hypertension, also referred to as phase 1 hypertension in the latest American Heart Association guidelines (Egan and Stevens-Fabry, 2015; Rahimi et al., 2015). Both hypertension and pre-hypertension are associated with an increased risk of coronary heart disease, stroke and cardiovascular disease (Huang et al., 2013; Son et al., 2018; Satoh et al., 2019). The risk increases exponentially across the diastolic and systolic blood pressure ranges above the minimum risk levels, which have been estimated at 60–74 mmHg for diastolic and 90–114 mmHg for systolic blood pressure (Rapsomaniki et al., 2014). Moreover, those suffering from pre-hypertension have a two-fold increased risk of developing hypertension (Leitschuh et al., 1991). Although hypertension is more prevalent at older ages, it is becoming increasingly common at younger ages. In the US, 7.5% of 18–39 year-olds and 33.2% of 40–59 year-olds suffer from hypertension, and substantially higher rates have been reported in some Asian countries (Son et al., 2018).

A clear link has already been established between hypertension and the development of cerebrovascular disease (Meissner, 2016). In addition to hemorrhagic strokes, elevated blood pressure is associated with cerebral micro-bleeds and with more diffuse brain changes that can be detected using Magnetic Resonance Imaging (MRI; e.g., as white matter hyperintensities, cortical thinning, enlarged Virchow-Robin spaces, brain atrophy; Alateeq et al., 2021). These changes are known to reflect pathologic microscopic processes in the underlying tissue. However, their diffuse nature makes it difficult to precisely quantify their presence and co-occurrence and therefore hampers the detection of early effects of increasing BP on brain structure.

Assumption-free machine learning approaches that consider all the information present in a brain scan without the need for *a priori* definition of regions of interest have been effectively implemented to assess the impact of several conditions on cerebral health. One such approach is the use of relevance vector machines to estimate the "brain age" of individuals based on their MRI scans. The estimated brain age can then be compared to the chronological age to determine whether specific exposures are associated with "younger-looking" or "older-looking" brains in a specific population. For example, older brain age has been detected in individuals with mild cognitive impairment (Gaser et al., 2013), with type 2 diabetes (Franke et al., 2013), exposed to maternal nutrient restriction during early gestation (Franke et al., 2018), with poor personal health markers (Franke et al., 2014), and *APOE ε4* carriers (Löwe et al., 2016), while younger brain age has been demonstrated in people who meditate (Luders et al., 2016), or make music (Franke and Gaser, 2019). Apart from not requiring an *a priori* determination of which brain regions should be selected for investigation in relation to a particular research question of risk factors, a major benefit of this type of approach is that it does not rely exclusively on a single index of brain integrity such as brain volume. Instead, it integrates information across key explanatory regions, which might reflect relative atrophy, vascular lesions, white matter hyperintensities, as well as other contributors which can influence MRI signals such as iron deposition, inflammation, myelination.

Using the same approach, the aim of the present study is to estimate the brain age in a large sample of people aged in their 40s to 70s for whom longitudinal MRI scans and rich epidemiological data are available and to investigate how the full range of blood pressure relates to cerebral health over time. We predicted that individuals with higher blood pressure and those suffering from hypertension would present with a higher BrainAGE. Importantly, in this research, we conceptualize BrainAGE as a marker of brain health with higher BrainAGE suggesting poorer brain health. This is because extensive research is available indicating that BrainAGE (and similar approaches)—in addition to being methodologically robust and reliable (Franke and Gaser, 2012, 2019; Baecker et al., 2021)—is associated with cognitive decline, the transition from MCI to Alzheimer's disease, and markers of the underlying pathology and its main genetic risk factor, APOE genotype (Gaser et al., 2013; Löwe et al., 2016; Wang et al., 2019). Moreover, BrainAGE is significantly increased in several chronic conditions including type 2 diabetes (Franke et al., 2013), stroke (Egorova et al., 2019), Parkinson's disease (Beheshti et al., 2020), Multiple Sclerosis (Cole et al., 2020), and known health and lifestyle risk factors for cardiovascular health, neurodegeneration, brain ageing, and dementia (Bittner et al., 2021).

# MATERIALS AND METHODS

## Study Population

Participants included in the present study were selected from the larger PATH Through Life (PATH) project which has been described elsewhere (Anstey et al., 2012). Briefly, PATH randomly sampled individuals from the electoral roll of the city of Canberra and the adjoining town of Queanbeyan across three age groups. The focus of this investigation is on the middle-age (MA; $n = 431$) and older-age (OA; $n = 478$) participants who undertook a brain scan and were aged 44–46 years and 60–64 years respectively at first MRI assessment. Participants were followed up for up to four waves of assessment over a 12 year period and were included on the basis of having two or more brain scans (MA: $n = 354$, OA: $n = 402$). Participants were excluded if they had neurological conditions (stroke, MMSE $< 25$, either Parkinson's or Dementia diagnosis at any part of the study (MA: $n = 0$, OA $n = 29$) assessed based on a detailed neuropsychological assessment and consensus diagnosis using established criteria

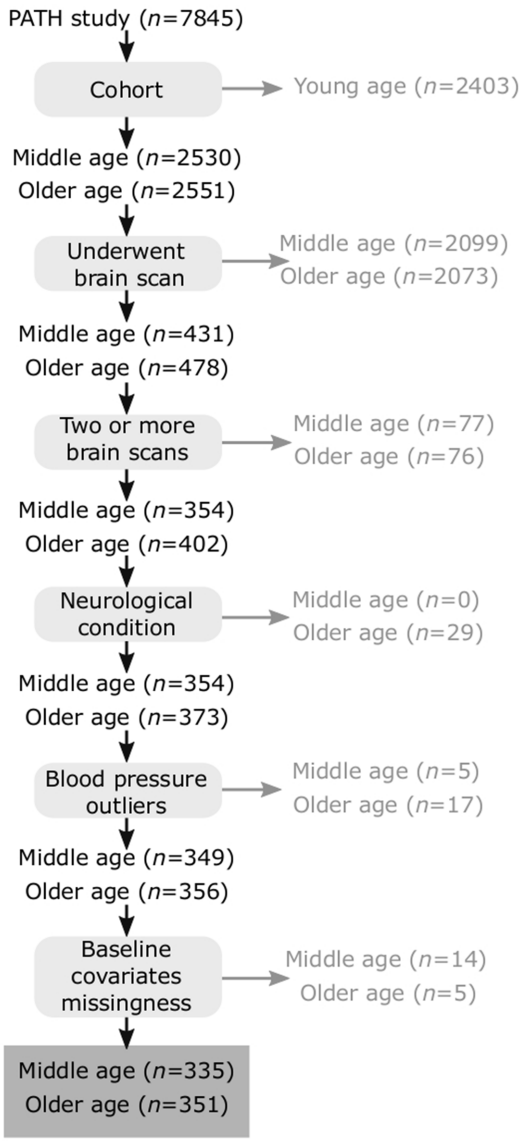


**FIGURE 1** | Flowchart of participants included and excluded from analyses.

as well as self-report of a diagnosis established by a clinician (Cherbuin et al., 2019). Other inclusion criteria included blood pressure exceeding three standard deviations from the mean (MA: $n$ = 5, OA: $n$ = 17), or missing key covariates at baseline (**Figure 1**). This resulted in a final sample of 686 participants (MA: $n$ = 335, 52% female; OA $n$ = 351, 46% female) with 180 (26%) having two, 287 (42%) having three, and 219 (32%) having four brain scans over the follow-up. Compared with the broader PATH sample at baseline (MA; $n$ = 2,530; OA: $n$ = 2,551), selected participants had a slightly higher education (14.12 excluded vs. 14.39 years included, $t$ = 2.45, $p$ = 0.01) but were not significantly older (53.06 years excluded vs. 53.39 years included, $t$ = 0.81, $p$ = 0.41) and did not differ in terms of sex ($\chi^2$ = 1.08, $p$ = 0.29) or intracranial volume (ICV = 1,585,868 mm$^3$ excluded vs. 1,554,810 mm$^3$ included, $t$ = 1.51, $p$ = 0.13).

## Blood Pressure

Sitting systolic and diastolic brachial blood pressure (SBP/DBP) were measured on the left upper arm at each assessment using an Omron M4 monitor after a rest of at least 5 min using a medium or large cuff as required and were computed over two measurements. Participants were classified as hypertensive if their mean systolic or diastolic blood pressure measures were higher than 140 and 90 mmHg respectively or if they took anti-hypertensive medication. Anti-hypertensive medication was assessed by self-report at each assessment. Mean arterial pressure (MAP) was calculated with the formula 1/3(SBP) + 2/3(DBP) and centered on 90. Participants were considered to have optimal BP if their DBP was <75 mmHg and their SBP was <115 mmHg (Rapsomaniki et al., 2014), which corresponds to an optimal MAP of 90 mmHg or below. These thresholds were selected based on findings from large studies indicating that SBP of 90–114 mm Hg and DBP of 60–74 mmHg were associated with the least adverse cardiovascular outcomes (Rapsomaniki et al., 2014; Li et al., 2021).

## Socio-demographic and Health Measures

Chronological age across up to three follow-up assessments was computed as baseline age in years and months plus the precise interval (years, months and days) between each assessment. Total years of education, diabetes mellitus, depression symptomatology (Goldberg depression; Goldberg et al., 1988), and smoking (ever) were assessed by self-report. Body mass index (BMI) was computed with the formula weight (kg)/height × height (m$^2$) based on a self-report of weight and height. *APOE ε4* genotype was determined based on buccal swabs using QIAGEN DNA Blood kits (#51162; QIAGEN, Hilden, Germany). Participants were classified as *APOE ε4* carriers if they possessed one or two ε4 alleles. To preserve sample size across waves, the 7% or less missingness across these covariates was dealt with *via* 5,000 iterations Missing Value Analysis in SPSS.

## MRI Scan Acquisition and Image Analysis

Detailed imaging protocols are provided in the Supplementary Material (**Supplementary Table 1**) and are extensively published (Shaw et al., 2016a,b; Fraser et al., 2018). Briefly, at each wave, all participants were imaged with a T1 3D fast-field echo sequence on a 1.5T scanner of the same type. Some scanner/protocol changes occurred between assessments and to control for variance owing to these changes the volumetric data were orthogonalized with respect to a scanner covariate, as described elsewhere (Shaw et al., 2016a,b; Fraser et al., 2018).

## BrainAGE

As described previously (Franke et al., 2010), pre-processing of the T1-weighted images was done using the SPM8 package[1] and the VBM8 toolbox[2], running under MATLAB. All T1-weighted images were corrected for bias-field inhomogeneities, then spatially normalized and segmented into gray matter, white matter, and cerebrospinal fluid within the same generative model

[1]http://www.fil.ion.ucl.ac.uk/spm
[2]http://dbm.neuro.uni-jena.de

(Ashburner and Friston, 2005). The gray matter images were spatially normalized using an affine registration and smoothed with a 4-mm full-width-at-half-maximum kernel and resampled to a spatial resolution of 4 mm.

The BrainAGE framework, which has been extensively described and validated elsewhere, and used to investigate other clinical conditions (Franke et al., 2010; Luders et al., 2016; Cole et al., 2019; Franke and Gaser, 2019), was applied to the processed gray matter images. Briefly, this approach comprises three analytical steps, including data reduction, training of the algorithm, and estimation of BrainAGE. Data reduction is achieved through principal component analysis (PCA) as many MRI scan voxels are highly correlated and provide redundant information, and because using PCA has been shown to produce more sensitive measures of brain health than approaches which do not apply a data reduction step (Franke et al., 2010). The purpose of the training step, which is based on a machine learning pattern recognition method, specifically relevance vector regression (RVR; Tipping, 2001), is to identify the most accurate predictive statistical model. The BrainAGE algorithm was trained using 2,601 images from the PATH study spanning the ages of 44–76 years, since participants were randomly selected from the population in this study this sample provides the best reference for this investigation. Finally, individual BrainAGE scores are estimated by using a leave-one-out approach cross-validation. The individual BrainAGE estimate produced represents a deviation in years from chronological age. A BrainAGE of 0 means that a person's brain appears to be the same age as their chronological age. In contrast, a negative BrainAGE indicates that a brain appears younger, and a positive BrainAGE indicates that a brain appears older than the person's chronological age. "The Spider" package[3], a freely available toolbox running under MATLAB, was used to train the BrainAGE estimation model as well as to predict individual brain ages. Finally, the shared variance between chronological age and the estimated brain age measure was removed using a regression approach to ensure the final BrainAge measure was not correlated with chronological age.

## Statistical Analysis

Statistical analyses were computed using the R statistical package (version 3.2). Group differences (gender and age group) were tested using Chi-square tests for categorical data and *t*-tests for continuous variables. Mixed-effects analyses were conducted to test the association between BP (MAP, DBP and SBP) and BrainAGE while controlling for age and sex (base model) as well as for education, diabetes mellitus, BMI, smoking, depression, physical activity, alcohol intake, and *APOE ε4* genotype (fully adjusted model). Anti-hypertensive medication effects were tested based on treatment status at each assessment. To clarify the effects of time and the effects of the cohort, age was decomposed into two variables: time in study (years from baseline) and cohort (the 40s or 60s).

[3]https://people.kyb.tuebingen.mpg.de/spider

# RESULTS

Participants' demographic measures are presented in **Table 1**. MA had, on average, a higher education level than OA, but had a lower DBP, SBP and also was less likely to be hypertensive, be on hypertension medications, or to have diabetes. Across the whole cohort, men had a higher education level, SBP and DBP, undertook more physical activity, and were more likely to be hypertensive than women.

## BrainAGE Characteristics

Group- and wave-specific BrainAGE are reported in **Supplementary Table 2**. The Pearson correlation between BrainAGE and chronological age was −0.037 ($p$ = 0.09), and the mean absolute deviation of measurement between these measures was 1.26 years. Together this indicates that BrainAGE indexed brain features unrelated to chronological age. On average, BrainAGE did not differ between OA (range −13.19–16.24 years) and MA (range −11.50–16.23 years), where a lower value indicates a "younger" and a higher value an "older" appearing brain compared to chronological age. However, on average, women had a lower BrainAGE than males by almost 10 months (female mean = −0.55 years, male = 0.26 years, $p < 0.01$).

## Blood Pressure Characteristics

The mean, systolic and diastolic blood pressures (**Table 1**) were significantly higher in OA compared to MA (5%, 9%, 2% respectively), and in men compared to women (5.9% for all measures). While more than 28% of MA and more than 61% of OA were hypertensive, only 9% of MA and 30% of OA reported taking anti-hypertensive medication. There were 64 MA and 19 OA participants who presented with optimal BP (DBP < 75 and SBP < 115), of whom seven were on anti-hypertensive medication (MA: 2; OA: 5). A progressive increase in BP was observed over the follow-up (MAP = 0.8 mmHg/year, SD = 0.92; SBP = 1.41 mmHg/year, SD = 1.49; DBP = 0.61 mmHg/year, SD = 0.78). MA experienced a 5% greater increase in MAP and a 28% greater increase in DBP than OA, while OA experienced a 24% greater increase in SBP.

## Associations Between Blood Pressure and BrainAGE

Associations between BrainAGE and mean, diastolic and systolic BP are presented in **Figure 2**. None of the analyses revealed an interaction between BP and Time-in-Study or a random effect of blood pressure on BrainAGE indicating that a change in BrainAGE over time was not predicted by baseline BP or by a change of BP over time (**Supplementary Table 2**). Therefore, only fixed effects are reported below.

## MAP, SBP, and DBP

In fully adjusted models, fixed effects indicated that every 1 mmHg higher MAP over 90 was significantly associated with just under a week (6.57 days) greater BrainAGE (**Figure 2A**, **Table 2**, **Supplementary Table 3**) indicative of older-appearing brains.

**TABLE 1** | Participants' demographic characteristics.

| Measures | Whole sample ($n$ = 686) | 40s ($n$ = 335) | 60s ($n$ = 351) | $t/\chi^2$ test ($p$ value) | Males ($n$ = 352) | Females ($n$ = 334) | $t/\chi^2$ test ($p$ value) |
|---|---|---|---|---|---|---|---|
| Age, years (SD) | 55.28 (8.04) | 47.18 (1.36) | 63.01 (1.42) | −149.07 (<0.001)* | 55.65 (8.06) | 54.89 (8.00) | 1.24 (0.214) |
| Education, years (SD) | 14.49 (2.49) | 14.89 (2.24) | 14.11 (2.65) | 4.19 (<0.001)* | 14.85 (2.37) | 14.11 (2.55) | 3.93 (<0.001)* |
| Total years in study (SD) | 11.51 (1.68) | 11.53 (1.66) | 11.50 (1.70) | 0.03 (0.97) | 11.34 (1.74) | 11.59 (1.60) | −1.94 (0.05) |
| SBP, mmHg (SD) | 131.80 (18.24) | 125.41 (16.83) | 137.90 (17.45) | −9.54 (<0.001)* | 135.72 (16.58) | 127.68 (19.02) | 5.89 (<0.001)* |
| DBP, mmHg (SD) | 81.70 (10.02) | 80.83 (9.89) | 82.53 (10.09) | −2.23 (0.026)* | 84.15 (9.92) | 79.13 (9.47) | 6.78 (<0.001)* |
| MAP, mmHg (SD) | 98.40 (11.83) | 95.69 (11.57) | 100.99 (11.51) | −6.01 (<0.001)* | 101.34 (11.13) | 95.31 (11.77) | 6.89 (<0.001)* |
| BMI, kg/m$^2$ (SD) | 26.91 (4.43) | 27.22 (4.61) | 26.61 (4.23) | 1.79 (0.074) | 27.10 (3.82) | 26.70 (4.98) | 1.18 (0.240) |
| Physical activity, METs/day | 39.15 (34.95) | 37.79 (31.78) | 40.44 (37.72) | −1.00 (0.319) | 44.92 (37.78) | 33.07 (30.58) | 4.53 (<0.001)* |
| Smoker, $n$ (%) | 305 (44.46%) | 154 (45.97%) | 151 (43.02%) | 0.49 (0.484) | 138 (41.32%) | 167 (47.44%) | 2.36 (0.124) |
| Hypertension, $n$ (%) | 306 (44.61%) | 93 (27.76%) | 213 (60.68%) | 73.86 (<0.001)* | 117 (50.02%) | 113 (33.83%) | 24.92 (<0.001)* |
| BP Med, $n$ (%) | 133 (19.39%) | 29 (8.66%) | 104 (29.63%) | 46.91 (<0.001)* | 61 (18.26%) | 72 (20.45%) | 0.40 (0.529) |
| Diabetes, $n$ (%) | 86 (12.54%) | 21 (6.27%) | 65 (18.52%) | 22.35 (<0.001)* | 40 (11.98%) | 46 (13.07%) | 0.10 (0.752) |
| *APOE ε4*, $n$ (%) | 204 (29.74%) | 101 (30.15%) | 103 (29.34%) | 0.02 (0.883) | 94 (28.14%) | 110 (31.25%) | 0.65 (0.420) |

*Note.* * *indicates significance at* $p < 0.05$.

In fully adjusted models, fixed effects indicated that every 1 mmHg higher SBP over 114 was significantly associated with 5.11 days older brains (**Figure 2B**, **Table 2**, **Supplementary Table 4**).

In fully adjusted models, fixed effects indicated that every 1 mmHg higher SBP over 74 was significantly associated with 5.11 days older brains (**Figure 2C**, **Table 2**, **Supplementary Table 5**).

## Optimal BP

Individuals with an optimal BP (MBP < 90, SBP < 115, DBP < 75) had a significantly lower BrainAGE than those who did not have an optimal BP (mean −0.45 vs. 0.3 years at baseline, and in mixed-effects models $b = -0.48$ 95% CI [−0.843, −0.119], $p < 0.001$). However, no significant difference in BrainAGE was detected when analyses were stratified by age groups (i.e., MA and OA analyzed separately).

## Hypertension

After controlling for age and sex, the association between BP and BrainAGE did not significantly differ between those who were or were not hypertensive (MAP × hypertension status interaction $b = 0.013$ 95% CI [−0.010, 0.037]). Limiting the sample to those with hypertension only, there were no significant differences in BrainAGE between those who were and were not on antihypertensive medication (mean −0.08 vs. 0.22 years, $b = -0.042$, 95% CI [−0.420, 0.336]) when considering treatment at each wave.

## Sensitivity Analyses

There were no significant interactions between MAP and sex, hypertension, or *APOE ε4* carrier status (**Figure 2**, **Supplementary Tables 3–5**). The significant relationship between MAP and BrainAGE remained significant in most subgroup analyses (MA only vs. OA only, women only vs. men only, *APOE ε4* carriers only vs. non-carriers only). In subgroup analysis based on hypertension status (not hypertensive, medicated hypertension, un-medicated hypertension) MAP continued to be positively associated with BrainAGE, but only reached significance in individuals with un-medicated hypertension. This pattern was broadly similar for DBP and SPB as predictors of BrainAGE (**Figure 2**, **Supplementary Tables 3–5**).

# DISCUSSION

The main findings of this study were that all BP measures were associated with older BrainAGE, that these associations were stronger in men than women, and were not only detected in hypertensive individuals but across the whole BP range, with individuals with optimal blood pressure presenting with the lowest BrainAGE.

It is notable that associations were very similar between all BP measures and BrainAGE, with every 1-mmHg increase above optimal thresholds being associated with a 5–7 day increase in BrainAge. On first appearance, these effect sizes may seem trivial. However, when considered for typically observed differences in

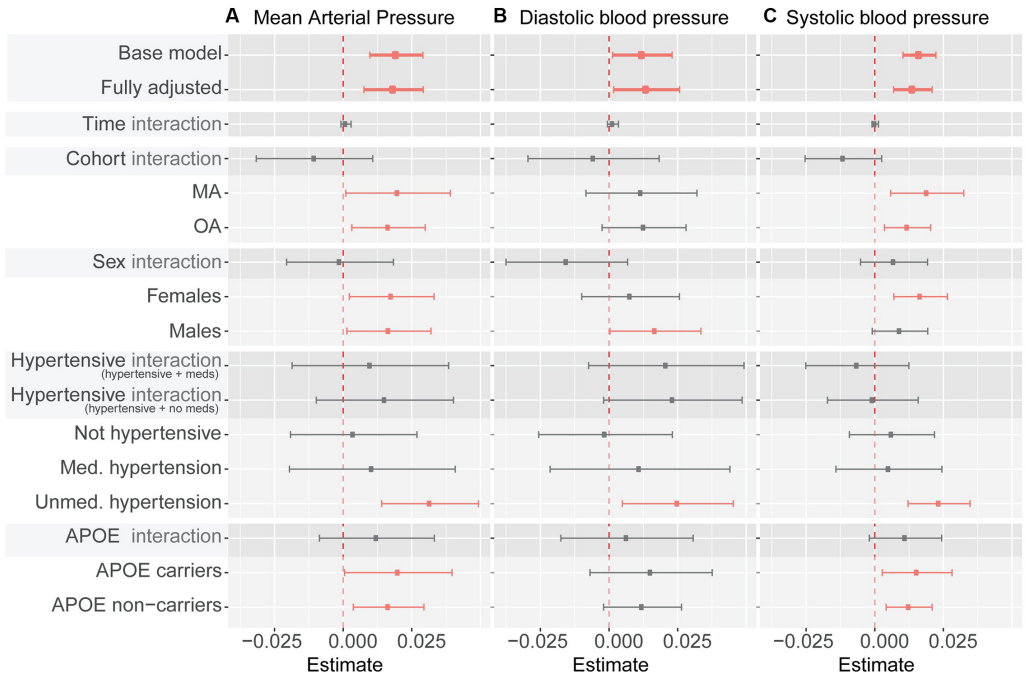


**FIGURE 2 |** Summary of blood pressure measures as predictor of BrainAGE. Note. Whiskers indicate 95% confidence intervals. Dashed line indicates zero. "Interaction" indicates interaction term between listed predictor (cohort, sex, hypertensive category, and APOE ε4 carrier status) and blood pressure measures (mean arterial pressure in panel **A**, diastolic blood pressure in panel **B**, systolic blood pressure in panel **C**). Statistically significant coefficients are depicted in pink. All coefficients except for the base model (which controls for age and sex only) control for sex, cohort, time in study, smoking, education, physical activity, BMI, diabetes, depression, APOE ε4 carrier status, alcohol intake, hypertension, and hypertensive medication (except when subgroup analyses use a specific variable as a grouping criterion). Model coefficients can be found in **Table 1**, and **Supplementary Tables 2–4**.

BP between individuals in good cardiovascular health compared to those who are pre-hypertensive or above, their magnitude stands out. Indeed, compared to an individual with optimal blood pressure (e.g., 110/70), an individual with pre-hypertension (e.g., 135/85) would be predicted to have a brain more than 6 months older. Although, larger age deviations (up to 6.7 years) have been detected in Alzheimer's disease (Franke and Gaser, 2012), an average difference of 6 months has high relevance as it can serve as an additional risk marker, which if combined with other risk factors, may be predictive of premature conversion to dementia. However, more longitudinal and mechanistic evidence is required to determine the extent to which BrainAGE is a risk factor for future cognitive decline.

Importantly, these effects were not uniquely driven by some extreme cases with poorly or un-controlled hypertension because sensitivity analyses showed similar associations between BP and BrainAGE in those who were normotensive, treated hypertensive, or untreated hypertensive indicating that a consistent effect was detected across the whole BP range.

As previously reported in the literature (Luders et al., 2016), women in this cohort had a lower BrainAGE than men indicating that their brains appeared on average almost 10 months younger than those of men. The underlying reasons for this effect are not completely clear. However, it is likely that differences in cardiovascular health between men and women, which are frequently reported in the literature (Cherbuin et al., 2015), contributed substantially to this difference. Indeed, 48% more men were hypertensive compared to women in this study. Moreover, the interaction between sex and blood pressure was not significant in regression analyses, suggesting that blood pressure was the likely underlying reason for the initial sex difference.

A particularly important finding is that the association between BP (all measures) and BrainAGE was not substantially different between middle-aged and older individuals. This indicates that the negative impact of elevated blood pressure on the brain do not emerge in old age but rather progressively across the lifespan. Although the present study did not investigate young adults, the fact that associations between BP and brain are already detectable in early middle-age suggests that these effects start developing in the 30s or younger. Emerging evidence suggests that this is indeed the case. For example, Shaare and Colleagues (Schaare et al., 2019) have recently shown that moderately elevated BP (≥120/80) in 19–40 year-olds was associated with smaller gray matter volume. It is therefore imperative that greater preventative efforts be directed at this population.

## Benefits of the BrainAGE Methodology

Given the relative complexity of the BrainAGE method, one might reasonably ask whether its use is justified since other more typical methods such as regional brain volumes could perhaps

**TABLE 2** | Mixed-effects model results.

| | Mean arterial pressure | | Systolic blood pressure | | Diastolic blood pressure | |
|---|---|---|---|---|---|---|
| | **Base model** | **Controlled model** | **Base model** | **Controlled model** | **Base model** | **Controlled model** |
| Mean arterial pressure | 0.019*** | 0.018*** | 0.015*** | 0.014*** | 0.016** | 0.014* |
| | (0.009, 0.028) | (0.008, 0.029) | (0.008, 0.021) | (0.007, 0.021) | (0.005, 0.027) | (0.002, 0.026) |
| Time in study (years) | 0.035*** | 0.037*** | 0.026** | 0.029** | 0.041*** | 0.041*** |
| | (0.017, 0.054) | (0.017, 0.057) | (0.008, 0.044) | (0.009, 0.049) | (0.023, 0.059) | (0.020, 0.062) |
| Cohort (OA relative to MA) | −0.402 | −0.565 | −0.536 | −0.667* | −0.322 | −0.521 |
| | (−0.968, 0.164) | (−1.157, 0.026) | (−1.107, 0.035) | (−1.261, −0.072) | (−0.888, 0.244) | (−1.114, 0.072) |
| Sex (Female relative to Male) | −0.837** | −0.775** | −0.840** | −0.788** | −0.858** | −0.800** |
| | (−1.402, −0.272) | (−1.357, −0.193) | (−1.405, −0.274) | (−1.370, −0.205) | (−1.423, −0.292) | (−1.381, −0.220) |
| *APOE ε4* carriers (relative to non-carriers) | | −0.079 | | −0.085 | | −0.072 |
| | | (−0.693, 0.535) | | (−0.701, 0.530) | | (−0.686, 0.543) |
| Unmedicated hypertension only | | −0.01 | | 0.004 | | 0.017 |
| | | (−0.283, 0.263) | | (−0.266, 0.275) | | (−0.254, 0.289) |
| Non-hypertensive only | | −0.04 | | 0.012 | | −0.106 |
| | | (−0.378, 0.299) | | (−0.329, 0.354) | | (−0.437, 0.224) |
| Constant | 0.073 | −0.51 | 0.15 | −0.45 | 0.163 | −0.308 |
| | (−0.451, 0.598) | (− 2.722, 1.702) | (−0.368, 0.669) | (− 2.661, 1.761) | (−0.358, 0.683) | (− 2.490, 1.874) |
| Random effects intercept | 3.633 | 3.615 | 3.641 | 3.622 | 3.636 | 3.616 |
| | (3.427, 3.839) | (3.394, 3.803) | (3.435, 3.847) | (3.401, 3.811) | (3.430, 3.842) | (3.397, 3.867) |
| Random effects residual | 1.590 | 1.593 | 1.584 | 1.589 | 1.592 | 1.595 |
| | (1.531, 1.650) | (1.529, 1.647) | (1.526, 1.643) | (1.526, 1.644) | (1.534, 1.652) | (1.532, 1.649) |
| Observations | 2,070 | 2,070 | 2,085 | 2,070 | 2,085 | 2,080 |
| Log Likelihood | −4,860.409 | −4,870.309 | −4,887.345 | −4,868.801 | −4,893.34 | −4,892.469 |
| Akaike Inf. Crit. | 9,734.818 | 9,784.618 | 9,788.691 | 9,781.602 | 9,800.679 | 9,826.939 |
| Bayesian Inf. Crit. | 9,774.265 | 9,908.595 | 9,828.189 | 9,905.579 | 9,840.177 | 9,945.381 |

*Note. *indicates significance at $p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Rounded brackets include 95% confidence intervals. Controlled models include education, diabetes mellitus, BMI, smoking, depression, physical activity, alcohol intake, and APOE ε4 genotype (coefficients not reported).*

be more easily used and/or explained instead. The conceptual benefits of the BrainAGE methodology—including its lack of assumption of which brain regions might be most affected and its capacity to integrate a variety of mechanisms reflecting brain integrity and not just atrophy—have already been highlighted in the introduction. In addition, the BrainAGE methodology might be particularly useful in detecting subtle, diffuse effects in young to middle-age population in which relatively low levels of atrophy and therefore low variability between individuals is observed. But perhaps as important is that BrainAGE might be easier to communicate to scientifically less informed individuals. How meaningful is it to communicate to a patient that if lifestyle modifications are not embraced now to keep their BP in a healthy range their hippocampus might shrink by an additional 1%? In contrast, being able to explain that without adequate action their brain is likely to age faster such that they may acquire a dementia diagnosis 6 months earlier than they otherwise would, might send a clearer and more potent message. This issue may be even more important in communicating with younger generations who appear to be more health-conscious but might be more responsive to more proximal health messages.

## Policy and Population Health Implication

These findings support the view that maintaining blood pressure in an optimal range (SBP $< 115$, DBP $< 75$) across the lifespan starting before mid-life (i.e., in early adulthood and before) is essential to maintain good cerebral health. The premature brain ageing associated with pre-hypertension compared to optimal blood pressure ($\sim$6 months) is likely to be associated with a very large additional burden of disease and economic costs as it is expected to directly lead to a corresponding early dementia onset, all other factors being equal.

## Limitations

This study had a number of strengths and limitations. It investigated a large longitudinal neuroimaging sample of individuals randomly drawn from the population whose age covered a period of more than three decades. BP was objectively measured, and analyses contrasted different components (SBP, DBP, MAP) while also considering the impact of clinical hypertension, anti-hypertensive medication, and variation across the whole BP range. Importantly, this study applied a state-of-the-art method to assess cerebral health without limiting *a priori* what MRI information should or could contribute to this evaluation. However, limitations included the lack of data for early adulthood, the known sub-optimal precision of brachial measurements, the possible impact of other factors not measured and accounted for in the present analyses, and the punctual nature of the assessments. In addition, while the investigation of middle-age and older-age participants was a strength, some cohort differences may have explained, at least in part, differences in findings between these groups. For example, education was significantly different between age groups. However, this difference was small in the context of a well-educated population (average $>14$ years of education) and fully adjusted models including education and many other covariates did not produce substantially different findings. Similarly, while the proportion of participants with higher BMI and diabetes was higher in older participants, fully controlled analyses were adjusted for these factors. Furthermore, sensitivity analyses conducted separately in middle-aged and older participants demonstrated consistent associations between BP and BrainAGE in the two age groups. Thus, it is unlikely that these differences explain the present results. Finally, BMI was computed on a self-report of weight and height and may not have been completely accurate. However, a previous study including 608 older adults has investigated the accuracy of self-reports for these measures and found that while self-report overestimated height (1.24 cm) and underestimated weight (0.55 kg) and BMI (0.56 kg/m$^2$), there were strong correlations (>0.95) between measured and reported data and excellent agreement between BMI categories was observed (Ng et al., 2011).

In conclusion, the present findings show that elevated BP is associated with a relatively consistent decrease in BrainAGE across middle-age and into old age which may be indicative of worsening brain health. While much is known about the risk factors leading to elevated blood pressure and ensuing hypertension, future research is required to investigate how best to prevent exposure to these factors in early to mid-adulthood. It is also critical that such findings inform policy more effectively and are communicated widely to the population.

# DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because data sharing is constrained by study governance and participants' consent, however it will be made available on request for the purpose of reviewing the methodology used. Data may be made available for other purposes but this is subject to formal study data sharing processes available through the authors. Requests to access the datasets should be directed to nicolas.cherbuin@anu.edu.au.

# ETHICS STATEMENT

The study was reviewed and approved by the Australian National University Ethics Committee and the ACT Health Human Research Ethics Committee. The participants provided their written informed consent to participate in this study.

# AUTHOR CONTRIBUTIONS

NC contributed to the design of the study and to statistical analyses, and managed all aspects of manuscript preparation and submission. EW and CG provided theoretical expertise, contributed to data preparation and statistical analyses, and contributed to writing and editing the manuscript. MS provided theoretical expertise, conducted part of the neuroimaging analyses, and contributed to writing and editing the manuscript. EL, KA, PS, and WA provided theoretical expertise and contributed to writing and editing the manuscript. All authors contributed to the article and approved the submitted version.

## FUNDING

The study was supported by NHMRC grants 973302, 179805, 157125, 1063907, 568969; ARC grant 120100227; and the ACT Private Practice Fund.

## ACKNOWLEDGMENTS

The authors are grateful to Anthony Jorm, Helen Christensen, Simon Easteal, Keith Dear, Bryan Rogers, Peter Butterworth, Andrew McKinnon, and the PATH Team. This research was partly undertaken on the National Computational Infrastructure (NCI) facility in Canberra, Australia, which is supported by the Australian Commonwealth Government.

## SUPPLEMENTARY MATERIALS

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.694982/full#supplementary-material.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 06 October 2021
doi: 10.3389/fnagi.2021.720990

# Physically Active Lifestyle Is Associated With Attenuation of Hippocampal Dysfunction in Cognitively Intact Older Adults

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Alterations in hippocampal function have been shown in older adults, which are expressed as changes in hippocampal activity and connectivity. While hippocampal activation during memory demands has been demonstrated to decrease with age, some older individuals present increased activity, or hyperactivity, of the hippocampus which is associated with increased neuropathology and poor memory function. In addition, lower functional coherence between the hippocampus and core hubs of the default mode network (DMN), namely, the posteromedial and medial prefrontal cortices, as well as increased local intrahippocampal connectivity, were also demonstrated in cognitively intact older adults. Aerobic exercise has been shown to elicit neuroprotective effects on hippocampal structure and vasculature in aging, and improvements in cardiorespiratory fitness have been suggested to mediate these exercise-related effects. However, how these lifestyle factors relate to hippocampal function is not clear. Fifty-two cognitively intact older adults (aged 65–80 years) have been recruited and divided into physically active ($n = 29$) or non-active ($n = 23$) groups based on their aerobic activity lifestyle habits. Participants underwent resting-state and task-based fMRI experiments which included an associative memory encoding paradigm followed by a post-scan memory recognition test. In addition, 44 participants also performed cardiopulmonary exercise tests to evaluate cardiorespiratory fitness by measuring peak oxygen consumption ($Vo_2$peak). While both groups demonstrated increased anterior hippocampal activation during memory encoding, a physically active lifestyle was associated with significantly lower activity level and higher memory performance in the recognition task. In addition, the physically active group also demonstrated higher functional connectivity of the anterior and posterior hippocampi with the core hubs of the DMN and lower local intra-hippocampal connectivity within and between hemispheres. $Vo_2$peak was negatively associated with the hippocampal activation level and demonstrated a positive correlation with hippocampal-DMN connectivity. According to these findings, an aerobically active lifestyle may be associated with attenuation of hippocampal dysfunction in cognitively intact older adults.

**Keywords: hippocampus, aerobic exercise, neuroimaging, memory, functional connectivity**

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***Edited by:***
*Susanne Röhr,*
*University Hospital Leipzig, Germany*

***Reviewed by:***
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***Received:*** *05 June 2021*
***Accepted:*** *12 August 2021*
***Published:*** *06 October 2021*

***Citation:***
*Eisenstein T, Giladi N, Hendler T, Havakuk O and Lerner Y (2021) Physically Active Lifestyle Is Associated With Attenuation of Hippocampal Dysfunction in Cognitively Intact Older Adults. Front. Aging Neurosci. 13:720990. doi: 10.3389/fnagi.2021.720990*

## INTRODUCTION

Episodic memory, the ability to encode, consolidate, and retrieve past experiences and events, is one of the most affected cognitive abilities during aging (Nyberg et al., 2012). The hippocampus is a brain region that plays a key role in episodic memory processes (Squire and Zola-Morgan, 1991; Squire and Wixted, 2011; Insausti et al., 2013), through anatomical and functional interactions with cortical and subcortical regions across the brain (Ranganath and Ritchey, 2012; Cooper and Ritchey, 2019). The hippocampus presents distinct structural and functional connections along its longitudinal axis with its anterior part being more connected to anterior temporal and ventromedial prefrontal regions and its posterior part more linked to posterior-medial cortices and hubs of the default mode network (DMN) such as the posterior cingulate cortex (Ranganath and Ritchey, 2012). Moreover, from a cognitive perspective, the anterior hippocampus has been shown to be more associated with memory encoding while its posterior part has been more related to retrieval (Grady, 2020).

Older adults have been demonstrated to exhibit age-related alterations in hippocampal function. Hippocampal activity patterns during memory demands have been shown to generally decrease with age (Mormino et al., 2012; Ta et al., 2012; Nyberg et al., 2019). Furthermore, this age-related hypoactivity pattern was suggested to be region and process selective, affecting more pronouncedly the anterior part of the hippocampus during encoding (Ta et al., 2012; Nyberg et al., 2019). However, some older individuals demonstrate abnormally increased hippocampal activation during memory encoding and retrieval compared with both old and younger counterparts, also referred to as hippocampal hyperactivity. In addition, although this phenomenon has been observed in both healthy aging and prodromal stages of Alzheimer's disease (AD), such as mild cognitive impairment (MCI), it is not clear whether this activity pattern represents a compensatory effect or a dysfunctional pathological consequence.

While increased hippocampal activity or hyperactivity has been generally demonstrated to be associated with poorer neurobiological and cognitive outcomes in cognitively healthy older adults, it has been both negatively and positively linked with cognitive and clinical outcomes in patients with MCI (Kircher et al., 2007; Clement and Belleville, 2010; Bakker et al., 2012; Huijbers et al., 2015; Eisenstein et al., 2020). For example, increased left hippocampal activation during memory encoding in MCI was correlated with better memory performance and cognitive-clinical status in some studies (Kircher et al., 2007; Clement and Belleville, 2010), while others found it to be associated with poorer memory performance and increased Aβ burden (Bakker et al., 2012; Huijbers et al., 2015).

In addition to altered activation levels, changes in the resting-state functional connectivity of the hippocampus have also been documented to take place during aging. The hippocampus constitutes a part of the medial temporal subsystem of the DMN and is functionally and anatomically connected with regions comprising this network (Andrews-Hanna et al., 2010). However, the study suggests that with increasing age, the hippocampal activity becomes less coherent with the activity of distant brain regions such as major hubs of the DMN including the posteromedial and medial prefrontal cortices (or decreased hippocampal-DMN resting-state functional connectivity) and more locally connected within itself (or increased intra-hippocampal resting-state functional connectivity) (Salami et al., 2014; Damoiseaux et al., 2016; Harrison et al., 2019). Furthermore, this increased local connectivity was found to be associated with increased AD pathology burden in distinct memory networks and poorer episodic memory performance.

While neurobiological alterations have been well documented in the hippocampus during aging, several lifestyle factors have been proposed to attenuate this age-related deterioration, one of which is physical activity. The physically active lifestyle has been associated with the prevention of cognitive decline and the risk of AD and dementia (Rovio et al., 2005; Larson et al., 2006; Andel et al., 2008). Aerobic exercise has been associated with hippocampal neuroprotective effects in both animal models (van Praag et al., 1999, 2005; Vaynman et al., 2004; Bednarczyk et al., 2009; Van der Borght et al., 2009) and healthy human subjects (Erickson et al., 2011; Maass et al., 2015; Kleemeyer et al., 2016). However, studies examining the effect of physical exercise on the hippocampus in older adults had largely focused on structural characteristics, and to our knowledge, no previous work had focused specifically on the relationship between the aerobically active lifestyle and hippocampal function in human aging.

Several factors have been suggested to potentially mediate the effects of aerobic exercise on the brain. Peak oxygen consumption ($Vo_2$peak) is perhaps the most studied physiological correlate of aerobic/cardiorespiratory fitness in this context, and it reflects the peak metabolic rate of the body in generating adenosine triphosphate molecules through aerobic metabolism (Wilmore et al., 2008). Previous studies that demonstrated neuroprotective effects of aerobic exercise intervention in older adults also found favorable structural and cerebrovascular hippocampal changes to correlate with improved $Vo_2$peak (Erickson et al., 2011; Maass et al., 2015; Kleemeyer et al., 2016). However, to our knowledge, no study to date specifically examined the relationship between $Vo_2$peak and age-related hippocampal dysfunction patterns.

This study aimed to address this gap by investigating the relationship between aerobic exercise and hippocampal function of lifestyle during both resting-state and active memory demands in cognitively intact older adults. In addition, we aimed to examine whether the extent of these trends may be associated with the level of $Vo_2$peak. We first aimed to examine the activity levels of the anterior hippocampus during the associative memory encoding task, since this hippocampal subpart has been shown to be more involved in memory encoding processing (Grady, 2020). The associative memory paradigm was chosen as this form of episodic memory has been shown to be highly sensitive to aging compared with item memory and relies greatly on hippocampal function (Old and Naveh-Benjamin, 2008). Then, we aimed to investigate both remote and local resting-state functional connectivity patterns of both anterior and posterior hippocampal subparts. Distant hippocampal resting-state functional connectivity was examined with the two core hubs of the DMN, i.e., the posteromedial and medial prefrontal

cortices (hippocampal-DMN), and intra-hippocampal resting-state functional connectivity patterns were examined between bilateral anterior and posterior hippocampi. We then examined whether physically active individuals may demonstrate distinct patterns of hippocampal activity and functional connectivity compared with sedentary individuals, and whether it may explain differences in memory performance between the two groups. Finally, we investigated the correlations between $Vo_2$peak and all hippocampal and memory measures. According to the previous findings in the literature, we hypothesized that physically active older adults will demonstrate lower anterior hippocampal activity during memory encoding, higher memory performance, higher distant functional connectivity with the cortical DMN hubs, and lower within hippocampal functional correlation. In accordance, we hypothesized that $Vo_2$peak, as a potential mediator of aerobic exercise, will demonstrate dose-response correlations with hippocampal function and memory measures in the same directions as physically active lifestyle.

# MATERIALS AND METHODS

## Participants

Fifty-two older adults aged 65–80 years were recruited for this study (22 women/30 men). All participants were recruited from the community via an online advert on the Israeli Ministry of Health research website, social media, and by "word-of-mouth." Participants were fluent Hebrew speakers and reported no current or previous neuropsychiatric disorders (e.g., Parkinson's disease, brain tumor, head injury, transient memory loss, stroke, subjective cognitive/memory decline, psychosis, bipolar disorder, and depressive symptoms) or any other current significant uncontrolled and unbalanced medical illness (e.g., cardiac or vascular disease, hypertension, type II diabetes, cancer, and autoimmune syndromes). Nine participants reported being diagnosed with hypertension; however, they were included in this study since their blood pressure was controlled and balanced. This study was approved by the Human Studies Committee of Tel Aviv Sourasky Medical Center (TASMC), and all participants provided written informed consent to participate in this study.

## Assessment of Aerobic Activity Lifestyle Habits

The current aerobically active lifestyle of participants was assessed using a background interview that examined background characteristics and the physical exercise habits of the participants during the last year. The interview was administered face-to-face on the first assessment day. Specifically, participants were asked regarding the amount of weekly exercise-oriented activity sessions of some types of aerobic exercises (i.e., walking, running, cycling, swimming, elliptical/cross-training gym machines, etc.) or *"How often during the week did you participate in leisure time aerobic activity for the purpose of sporting or exercise that lasts at least 20 min in the passing year?"* Then, based on their reported activity patterns, the participants were divided into two groups, namely, active ($n = 29$) and non-active ($n = 23$). Frequency of twice-a-week or higher was set as the cutoff for active lifestyle based on previous methodologies (Rovio et al., 2005, 2010), findings (Liu-Ambrose et al., 2012), and recommendations (Voelcker-Rehage et al., 2010; Petersen et al., 2018). In addition, since we used a subjective measure of physical activity, using a cutoff of several times per week may help to decrease potential information bias from the reports of participants on their true activity levels. Also, regarding the potential of self-selection bias of volunteering in this study, it is important to note that the fraction of the active group out of the whole sample (56%) was similar to a recent report on the aerobically active lifestyle habits among older adults in the areal county from which participants were recruited (53.5% who reported being active) (Central Bureau of Statistics of Israel, 2021).

## $Vo_2$Peak Measurement

Out of 52 participants, 44 participants (16 women/28 men) also underwent a graded maximal cardiopulmonary exercise test performed on a cycle ergometer (Ergoselect 100, Ergoline, GmBH, Germany) to evaluate $Vo_2$peak. Assessments were conducted at the Non-Invasive Cardiology Outpatient Clinic at TASMC. Tests were performed using a metabolic cart (ZAN, nSpire Health Inc., Longmont, Colorado) while continuously measuring breath-by-breath minute ventilation, carbon dioxide production ($Vco_2$), oxygen consumption ($Vo_2$), and respiratory exchange ratio (RER). In addition, a 12-lead electrocardiograph, non-invasive arterial saturation, heart rate, and blood pressure were monitored continuously. All tests were supervised by a cardiologist and an exercise physiologist. An automated computerized ramp protocol was used to increase the exercise intensity by 10 W/min for women and 15 W/min for men, while participants were asked to maintain a constant velocity of 60 revolutions per minute. All tests were performed until volitional exhaustion, and no adverse events or medical symptoms were reported. An RER value of $\geq$1.1 was used as the indication for a satisfactory effort level during test (Balady et al., 2010) and was demonstrated in all examinations. Plateau in $Vo_2$ was not evident in any participant; therefore, the highest $Vo_2$ demonstrated in each test was considered as a $Vo_2$peak. The highest average $Vo_2$ value recorded during an intensity interval (2/2.5 W increment for women and men, respectively) was considered as the $Vo_2$peak value obtained from the procedure and that was used in further analyses.

## Experimental Procedure and Stimuli

### Inside the MRI Scanner

A face-name associative memory encoding task based on the classic paradigm by Sperling et al. (2001, 2003) was used to evaluate the hippocampal function. During scanning, participants were shown novel images of non-famous faces, each face paired with a fictional name (**Figure 1A**). Participants were asked to memorize which name was coupled with each face and to subjectively decide (by pressing a button) whether the name "fits" or not to the face. This subjective decision has been shown to enhance associative encoding (Sperling et al., 2003). Participants performed one run of a block-design picture-viewing paradigm consisted of 8 blocks with 4 faces presented in

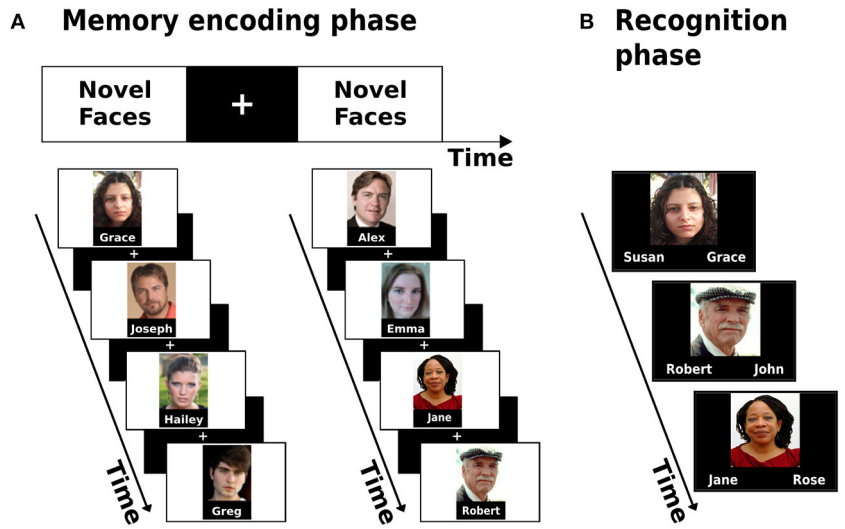


**FIGURE 1 |** Associative memory encoding paradigm conducted in the scanner **(A)** and the post-scan memory recognition task **(B)**.

each block (overall 32 faces). Between blocks and consecutive in-block images, participants were shown "resting" fixation blocks of a white cross in the middle of a black background. Before the scanning session, participants underwent a familiarization practice with the task to minimize novel task learning effects which could bias the neurocognitive outcome. Each stimuli block lasted for 21 s, while the overall run lasted 5:06 min.

### Outside the Scanner–Memory Performance Evaluation

Following the acquisition phase in the scanner, participants performed a two-alternative forced-choice recognition task. During the task, participants were shown images of all 32 faces presented during the encoding task and were asked to decide between two options which name was paired with each face (**Figure 1B**). The scores on the task were later used as the measure of memory performance.

## MRI Data Acquisition

MRI scanning was performed at TASMC on a 3 T Siemens system (MAGNETOM Prisma, Germany). High resolution, anatomical T1-weighted images (voxel size = 1 × 1 × 1 mm) were acquired with a magnetization prepared rapid acquisition gradient-echo protocol with 176 contiguous slices using the following parameters: field of view (FOV) = 256 mm; matrix size = 256 × 192; repetition time (TR) = 1,740 ms; echo time (TE) = 2.74 ms, inversion time (TI) = 976 ms, flip angle (FA) = 8°. These anatomical volumes were used for structural segmentation and co-registration with functional images. Blood oxygenation level-dependent functional MRI was acquired with T2*-weighted imaging. The memory encoding task was conducted using the following parameters: 102 TRs of 3,000 ms each; TE = 35 ms; FA = 90°; FOV = 220 mm; matrix size = 96 × 96; 44 slices, size = 2.3 × 2.3 × 3 mm, no gap (5:06 min run). The resting-state run was carried out with the same parameters with 120 TRs (6:00 min run).

To minimize head movements, the head of participants was stabilized with foam padding. MRI-compatible headphones (OPTOACTIVEtm) were used to considerably attenuate the scanner noise and communicate with the participants during the session. Designated software (Presentation®, Neurobehavioral Systems) was used for the presentation of visual stimuli.

## Functional MRI Analysis

### Hippocampal Activation

The fMRI analysis was carried out using the FEAT tool in FMRIB's Software Library 6.00 (FSL, www.fmrib.ox.ac.uk/fsl). The first five TRs of the functional data were discarded to allow steady-state magnetization. Registration of the functional data to the high-resolution structural images was carried out using boundary-based registration algorithm (Greve and Fischl, 2009). Registration of high-resolution structural to standard space (MNI152) was carried out using FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002) and then further refined using FNIRT non-linear registration. Motion correction of functional data was carried out using MCFLIRT (Jenkinson et al., 2002), brain removal using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of 5-mm FWHM, grand-mean intensity normalization of the entire 4D dataset by using a single multiplicative factor, and high-pass temporal filtering was performed with a Gaussian-weighted least-squares straight-line fitting with a cutoff period of 100 s. Time-series statistical analysis (pre-whitening) was carried out using FILM with local autocorrelation correction (Woolrich et al., 2001). A first-level task regressor of interest was defined and convolved using the block onset times with a double-gamma hemodynamic response function and a temporal derivative regressor of the task timing. In addition, 24 nuisance motion regressors were added to each first-level model and included 6 standard motion parameters

(i.e., 3 rotations and 3 translations), their temporal derivatives, and squares of all the above. Moreover, volumes with excessive head motion (predetermined as frame-wise-displacement value $> 0.9$ mm) were scrubbed by adding an additional regressor for each volume to be removed. The participants were removed and excluded from the group analysis if they had 30% or more of their volumes scrubbed out (one participant from the non-active group). $Z$ statistic images were thresholded non-parametrically using clusters determined by $Z > 3.1$ and a corrected cluster significance threshold of $p = 0.05$. Group-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 (Beckmann et al., 2003; Woolrich et al., 2004; Woolrich, 2008). Group-level $Z$ statistic images were thresholded non-parametrically using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $p = 0.05$. Another participant from the non-active group did not go through the encoding run. The mean activation patterns observed during the encoding task of the entire sample were used to identify anterior hippocampal regions which demonstrated increased activity during the task. Then, a mask was created for these regions (for each hemisphere) by masking the activation map with anatomical anterior hippocampal masks from https://neurovault.org/collections/3731/ based on the study by Ritchey et al. (2015; **Figure 2A**). Then, we used the *Featquery* tool of FSL, which enables the interrogation of FEAT results within a specific mask, to extract the parameter estimates from the bilateral anterior hippocampal regions activated during the task. The parameter estimate values were then used to examine the differences in activation levels between the groups.

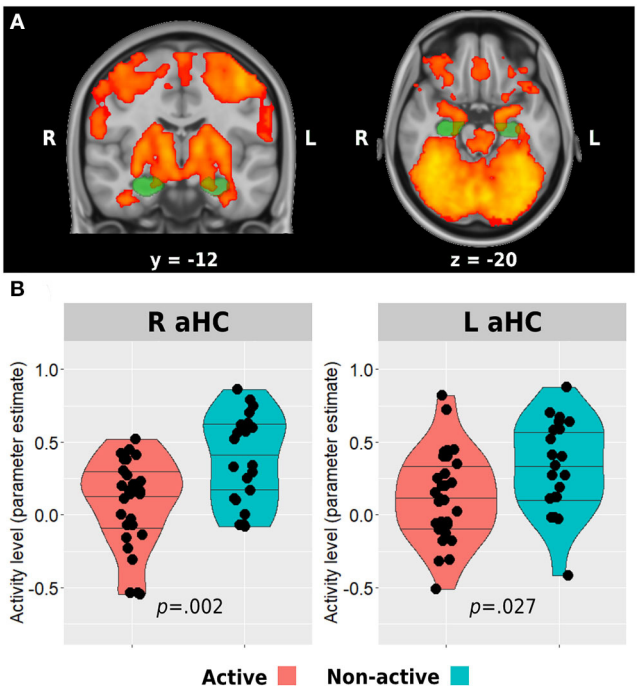


**FIGURE 2 |** Anterior hippocampus activation during memory encoding. The whole sample mean activation during the task is presented in **(A)**. Green regions represent anatomical masks of anterior hippocampi, while activated voxels within these areas were used to extract the activity level for the between-group analysis presented in **(B)**. Horizontal lines in between-group plots represent 25, 50, and 75% quantiles. aHC, anterior hippocampus; L, left; R, right.

### Hippocampal Resting-State Functional Connectivity

Resting-state functional connectivity was carried out using the functional connectivity toolbox *CONN* v.19c (nitrc.org/projects/conn). Preprocessing included discarding the first five TRs to allow steady-state magnetization. Functional images were slice-time corrected, realigned to the middle volume, motion-corrected, and normalized to the standard MNI152 space. Spatial smoothing was performed using a 5-mm FWHM Gaussian kernel. To reduce noise, functional volumes were band-pass filtered at 0.008–0.15, and the component-based method (CompCor) was used to extract noise signals (e.g., white matter, cerebrospinal fluid (CSF), and movement artifact) that were used as nuisance regressors to denoise the data. In addition, images that were regarded as movement outliers were regressed out. Movement outlier volumes were detected using the ART toolbox (nitrc.org/projects/artifact_detect/) and defined as volumes with a movement $>0.9$ mm or signal intensity changes $>5$ SD. These volumes were also used as nuisance regressors at the denoising step. No participant demonstrated more than 30% of removed volumes. One participant from the active group did not go through the resting-state run. Remote functional connectivity of the anterior and posterior hippocampi with the main hubs of the DMN was examined by creating specific masks of these regions of interest. Anterior and posterior hippocampal masks were again created from https://neurovault.org/collections/3731/ (**Figure 3A**). To create the DMN masks, we used a deactivation contrast in the memory encoding task to elicit areas demonstrating decreased activity during the task (**Supplementary Table 1**). The two main and larger clusters revealed from this analysis were anatomically corresponding to the posteromedial and medial prefrontal cortices and were used to create the masks for the hippocampal-DMN analyses. The mean $z$-transformed correlation value between each pair of these eight areas was then used to examine differences in hippocampal-DMN functional connectivity between the groups. Intra-hippocampal resting-state connectivity was examined in two ways. First, we computed the $z$-transformed correlation between the time series of bilateral anterior hippocampi and bilateral posterior hippocampi. Second, we calculated the local correlation within each hemispheric anterior or posterior region using the local correlation implemented in *CONN*. This index represents a measure of local coherence at each voxel, characterized by the strength and sign of connectivity between a given voxel and the neighboring regions in the brain (Deshpande et al., 2009). We used a 6-mm kernel for the Gaussian weighting function characterizing the size of the local neighborhoods.

## General Cognitive Evaluation

All participants were evaluated for general cognitive functioning and were screened for objective general cognitive decline using the Montreal Cognitive Assessment (MoCA) (Oren et al., 2015).

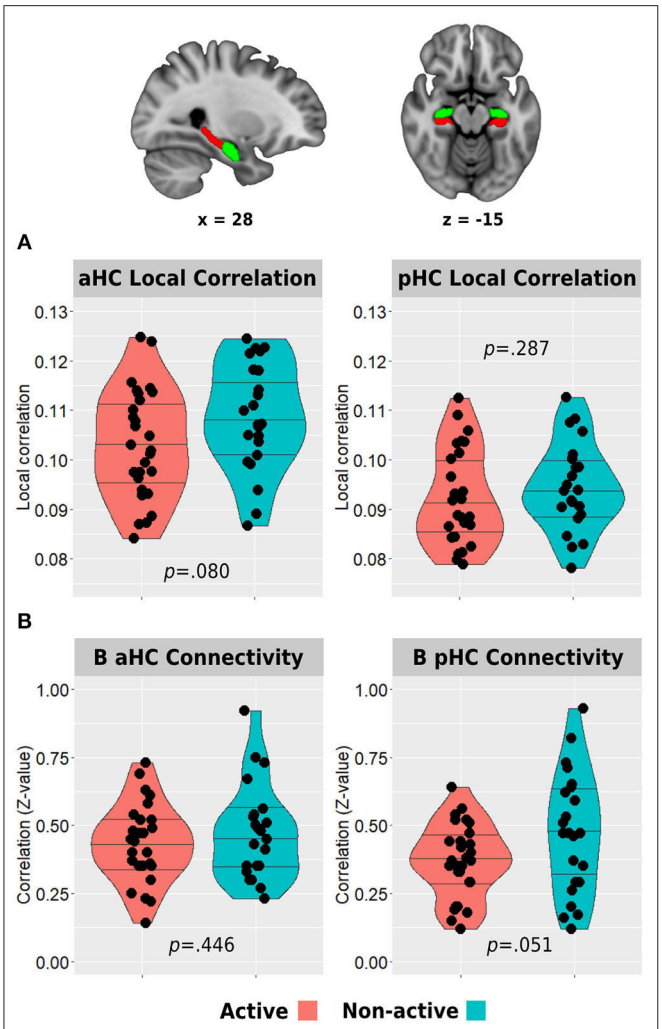


**FIGURE 3 |** Between-group differences in hippocampal resting-state local correlation **(A)** and between-hemisphere anterior and posterior hippocampal resting-state functional connectivity **(B)**. The top row demonstrates the anterior (green) and posterior (red) hippocampal masks used in the analyses. Horizontal lines in between-group plots represent 25, 50, and 75% quantiles. B, bilateral; aHC, anterior hippocampus; pHC, posterior hippocampus.

## Statistical Analysis

Statistical analyses and visualizations were performed and constructed using IBM SPSS Statistics Version 24.0 (Armonk, NY: IBM Corp.) and R Version 4.0.3 (R Core Team, Vienna, Austria; https://www.R-project.org/). Between-group differences were tested using non-parametric permutation testing. These procedures were conducted with 10,000 iterations, permuting each hippocampal or memory measure, and preserving the original group sizes. Then, the observed between-group mean difference in each measure was compared with all between-group differences obtained from the permuted null distribution. The *p*-values were determined as the probability of getting equal or greater between-group differences based on the null distribution. Correlations between $Vo_2$peak and hippocampal and memory measures were evaluated using non-parametric partial Spearman's rank correlations controlling for age, sex, and years of education. Since the implemented recognition task has no well-established norms, a linear regression was used to create standardized residuals of the memory scores controlled for age, sex, and education, which was used as the memory performance measure for further analyses. In addition, since the local correlation of bilateral anterior or posterior hippocampi was highly correlated between the homologous regions, we used the average local correlation value of the bilateral anterior/posterior hippocampal regions for further analyses. Between-group differences in continuous background characteristics (i.e., age, education, and MoCA) were evaluated using the Wilcoxon–Mann–Whitney *U*-test. Between-group differences in the proportions between males and females, marital status, smoking status, and hypertension diagnosis were assessed using the chi-squared test. As only two participants reported being currently smoking, we characterized the participants as "*current or past smokers*" and "*non-smokers.*" *p*-values of hippocampal-DMN connectivity between-group tests and correlations (8 tests each) were corrected for multiple comparisons using the false discovery rate (FDR) method (Benjamini and Hochberg, 1995).

# RESULTS

## Study Participants

The active and non-active groups were not statistically different in any background characteristics, including years of education, general cognitive functioning, smoking status, and hypertension diagnosis ($p > 0.05$; **Table 1**).

## Aerobic Exercise Habits and $Vo_2$Peak Characteristics

The report of study participants of weekly aerobic activity ranged from being completely sedentary (not engaging in exercise-oriented activities, $n = 18$) to 6 days per week ($n = 3$). Seventeen participants reported exercising 3 times per week. Exercising on a single day ($n = 5$), twice a week ($n = 3$), 4 times per week ($n = 4$), and 5 times ($n = 2$) were also reported. The active group demonstrated statistically significant higher weekly frequency of exercise sessions and $Vo_2$peak values (**Table 2**).

## Hippocampal Activation

### Between-Group Differences

Whole-brain analysis of all participants revealed bilateral anterior hippocampal activation during the associative memory encoding task (**Figure 2A**). Both groups demonstrated a positive mean activation level in both right and left anterior hippocampi during the task. However, the active group activation levels were significantly lower compared with the non-active group (right anterior hippocampus: $0.09 \pm 0.31$ vs. $0.38 \pm 0.31$, $p = 0.002$; left anterior hippocampus: $0.13 \pm 0.31$ vs. $0.33 \pm 0.32$, $p = 0.027$; **Figure 2B**).

### Association With $Vo_2$Peak

In accordance with the between-group results, higher $Vo_2$peak was negatively correlated with both right and left anterior

**TABLE 1 |** General socio-demographic and cognitive characteristics of participants (means ± SD).

| Variable | Whole sample ($n = 52$) | Aerobically active ($n = 29$) | Non-Active ($n = 23$) | Between-Group $p$-value |
|---|---|---|---|---|
| Age (years) | 70.83 ± 3.9 | 70.34 ± 4.0 | 71.43 ± 3.7 | 0.247 |
| Sex (female/male) | 22/30 | 11/18 | 11/1 | 0.473 |
| Education (years) | 15.84 ± 3.3 | 16.17 ± 3.7 | 15.41 ± 2.8 | 0.644 |
| Marital status (married/unmarried) | 45/7 | 26/3 | 19/4 | 0.460 |
| Smoking (current or past smokers/non-smokers) | 25/27 | 14/15 | 11/12 | 0.974 |
| Hypertension (diagnosed/undiagnosed) | 9/43 | 3/26 | 6/17 | 0.136 |
| MoCA (raw score) | 24.81 ± 2.5 | 25.13 ± 2.2 | 24.39 ± 2.8 | 0.349 |

*MoCA, Montreal Cognitive Assessment; SD, standard deviation.*

**TABLE 2 |** Aerobic activity and fitness characteristics of participants (means ± SD).

| Variable | Whole sample ($n = 52$) | Aerobically active ($n = 29$) | Non-Active ($n = 23$) | Between-Group $p$-value |
|---|---|---|---|---|
| Aerobic exercise (d/week) | 2.04 ± 1.8 | 3.48 ± 1.1 | 0.22 ±.4 | <0.001 |
| $Vo_2$peak (ml/kg/min) | 25.25 ± 8.3 | 30.58 ± 6.2 | 18.86 ± 3.8 | <0.001 |

*d/week, days per week; kg, kilogram; min, minute; ml, milliliter; SD, standard deviation; $Vo_2$peak, peak oxygen consumption.*

hippocampal activation levels during the memory encoding task [$r(38) = -0.439$, $p = 0.004$ and $r(38) = -0.334$, $p = 0.031$, respectively] (**Figures 4A,B**).

## Distant Hippocampal Resting-State Functional Connectivity

### Between-Group Differences

Whole-brain analysis of deactivation contrast during memory encoding revealed several clusters of areas demonstrating decreased activity which are usually attributed to the DMN (**Supplementary Table 1**). The two main and larger clusters observed corresponded to the posteromedial and medial prefrontal cortices, which were used as the regions of interest for the hippocampal-DMN resting-state functional connectivity analysis (**Figure 5**). In turn, between-group analysis revealed both the left and right posterior hippocampi to demonstrate higher functional connectivity with the posteromedial cortex in the physically active group compared with the non-active group (left posterior hippocampus: 21 ± 0.14 vs. 0.09 ± 0.16, $p = 0.009$, $p$FDR = 0.026; right posterior hippocampus: 23 ± 0.16 vs. 0.11 ± 0.17, $p = 0.007$, $p$FDR = 0.055; **Figures 5A,B**). In addition, the aerobically active group demonstrated higher functional connectivity between the right anterior hippocampus and both DMN hubs (posteromedial: 0.15 ± 0.13 vs. 0.04 ± 0.15, $p = 0.009$, $p$FDR = 0.037; medial prefrontal: 21 ± 0.17 vs. 0.10 ± 0.15, $p = 0.023$, $p$FDR = 0.046; **Figures 5C,D**). All other hippocampal-DMN regional connectivity values were not different between the groups ($p > 0.40$).

### Association With $Vo_2$Peak

Higher $Vo_2$peak was found to demonstrate a moderate positive correlation with the connectivity strength of the left posterior hippocampus and the posteromedial cortex [$r(38) = 0.415$, $p = 0.004$, $p$FDR = 0.064; **Figure 4C**] and a weak-to-moderate positive correlation with the connectivity strength of the right posterior hippocampus and the posteromedial cortex which demonstrated a trend toward statistical significance before multiple testing correction [$r(38) = 0.282$, $p = 0.078$, $p$FDR = 0.312; **Figure 4D**]. All other hippocampal-DMN connectivity values demonstrated weak to negligible correlations.

## Local Hippocampal Resting-State Functional Connectivity

### Between-Group Differences

The active group demonstrated lower resting-state local correlation in both anterior and posterior hippocampi, but only the anterior hippocampus reached a trend for statistical significance (anterior: 0.103 ± 0.011 vs. 0.108 ± 0.011, $p = 0.080$; posterior: 0.092 ± 0.010 vs. 0.094 ± 0.009, $p = 0.287$; **Figure 3A**). In addition, the resting-state connectivity of the bilateral posterior hippocampus was lower in the active group compared with the non-active group (0.37 ± 0.14 vs. 0.47 ± 0.22, $p = 0.051$). No difference was found between the bilateral anterior hippocampus connectivity across the groups (0.43 ± 0.14 vs. 0.47 ± 0.17, $p = 0.446$; **Figure 3B**).

### Association With $Vo_2$Peak

Peak oxygen consumption ($Vo_2$peak) demonstrated weak correlations with anterior and posterior intra-hippocampal local correlations [$r(38) = -0.232$, $p = 0.150$ for both regions] and with inter-hemispheric hippocampal connectivity [anterior: $r(38) = 0.089$, $p = 0.585$; posterior: $r(38) = -0.166$, $p = 0.305$].

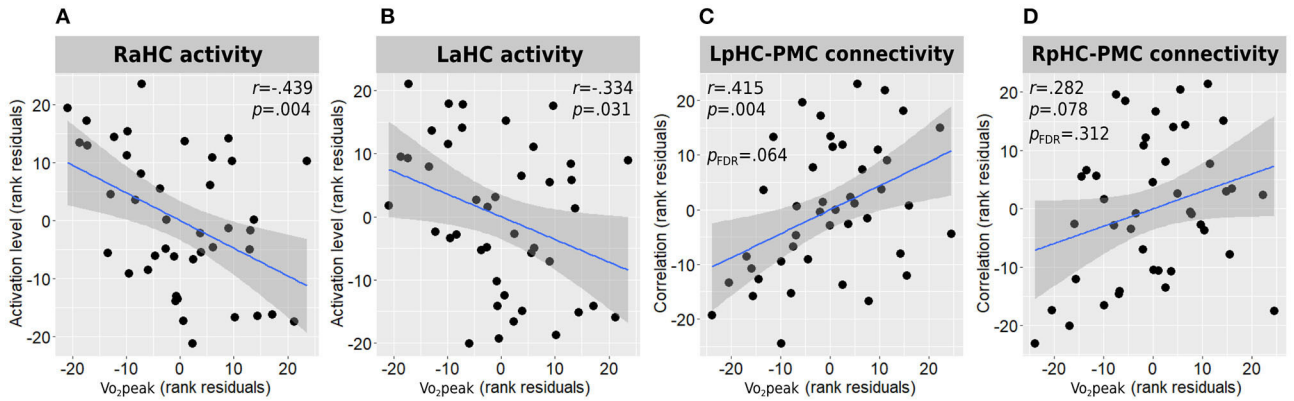


**FIGURE 4 |** Associations between $Vo_2$peak and hippocampal function. Correlations between $Vo_2$peak and right **(A)** and left **(B)** anterior hippocampal activity during memory encoding and with the connectivity strength of the left **(C)** and right **(D)** posterior hippocampi connectivity with the posteromedial cortex are presented. All correlations are adjusted for age, sex, and education. L/RaHC, left/right anterior hippocampus; L/RpHC, left/right posterior hippocampus; PMC, posteromedial cortex; $Vo_2$peak, peak oxygen consumption.

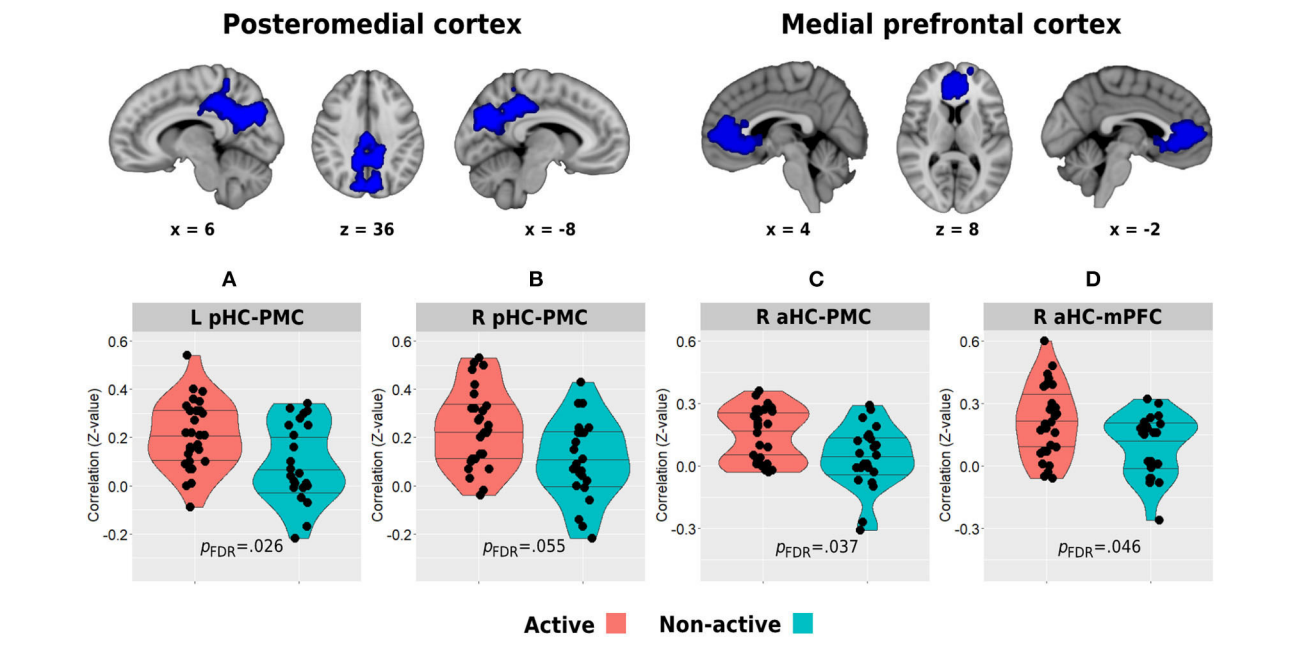


**FIGURE 5 |** Between-group differences in resting-state functional connectivity of the posterior **(A,B)** and anterior **(C,D)** hippocampi with the posteromedial and medial prefrontal cortical clusters which demonstrated decreased activity during the memory encoding paradigm. The top row demonstrates the DMN clusters of interest. Horizontal lines in between-group plots represent 25, 50, and 75% quantiles. aHC, anterior hippocampus; pHC, posterior hippocampus; mPFC, medial prefrontal cortex; PMC, posteromedial cortex; L, left; R, right.

## Memory Performance and Relationship With Hippocampal Activation During the Task

Between-group analysis revealed a statistically significant difference between the groups with the active group demonstrating higher performance on the memory recognition task compared with the non-active group (residual score $0.24 \pm 0.95$ vs. $-0.30 \pm 0.93$, $p = 0.043$; **Figure 6A**). In addition, higher $Vo_2$peak was positively associated with higher performance in the recognition task [$r(39) = 0.354$, $p = 0.023$; **Figure 6B**]. No correlation was found between anterior hippocampal activity level and memory performance on the whole sample level in both right [Spearman rho(45) $= -0.139$, $p = 0.350$] and left [Spearman rho(45) $= -0.199$, $p = 0.180$] hippocampi while controlling for age, sex, and education, or when examined separately within each group for the active [right: Spearman rho(24) $= 0.009$, $p = 0.967$, left: Spearman rho(24) $= 0.009$, $p$

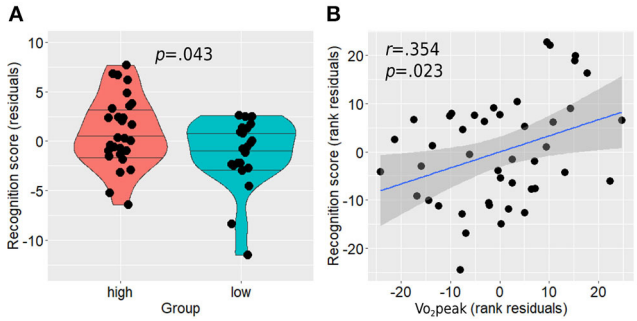


**FIGURE 6 |** Memory recognition performance differences between the groups **(A)** and its association with $Vo_2$peak while controlling for age, sex, and education **(B)**. Horizontal lines in between-group plots represent 25, 50, and 75% quantiles. $Vo_2$peak, peak oxygen consumption.

$= 0.964$] and non-active [right: Spearman rho(16) $= 0.156$, $p = 0.536$, left: Spearman rho(16) $= -0.261$, $p = 0.296$] groups.

## DISCUSSION

As aging has been demonstrated to be associated with compromised brain structure and function (Raz et al., 2005; Mormino et al., 2012; Nobis et al., 2019; Nyberg et al., 2019), a study has been conducted to investigate lifestyle factors that may attenuate this deterioration with advanced age (Akbaraly et al., 2009; Foubert-Samier et al., 2012). Physical exercise, aerobic in particular, has been associated with a reduced risk of cognitive decline and dementia (Rovio et al., 2005) and hippocampal resilience in older adults (Erickson et al., 2011; Maass et al., 2015; Sexton et al., 2016). However, studies investigating the neuroprotective relationship between physical activity and hippocampus have been mainly focusing on hippocampal structure (Sexton et al., 2016) and to a lesser extent on hippocampal cerebrovascular properties (Zimmerman et al., 2014; Maass et al., 2015). This study aimed to broaden this line of research by investigating the relationship between aerobically active lifestyle and hippocampal function in cognitively intact older adults using both resting-state and task-based fMRI experiments. In addition, we aimed to examine whether $Vo_2$peak, a potential mediator of aerobic exercise effects, may be associated with hippocampal functional characteristics in a dose-response manner.

While anterior hippocampal activity patterns during memory encoding have been generally demonstrated to exhibit age-related decline, some older individuals have been shown to exhibit increased hippocampal activity, or hyperactivity, exceeding values demonstrated in even younger counterparts. In this study, both active and non-active groups demonstrated increased bilateral anterior hippocampal activation during the associative memory task. However, the non-active group demonstrated a significantly higher activity level compared with the active group, with this difference being more pronounced in the right anterior hippocampus. In accordance with this trend, $Vo_2$peak was also negatively correlated with bilateral anterior hippocampus activation level. Mormino et al. (2012) found successful episodic memory encoding to be associated with right hippocampal hyperactivity in cognitively normal older adults with high Aβ burden compared with young adults and older adults without significant AD pathology. While not reporting on the specific relationship between the hippocampal hyperactivity and post-task memory performance, they demonstrated that the general increase in brain activity observed in the high-risk participants was associated with favorable memory performance, suggesting for a compensatory mechanism as being previously shown in patients with amnestic MCI (Dickerson et al., 2005; Eisenstein et al., 2020). However, this explanation was ruled out in the current cognitively intact sample, since the increased hippocampal activity was not associated with better memory performance in each group separately or at the whole sample level. In fact, previous studies supported the possibility that increased hippocampal activity may reflect an aberrant dysfunctional activity pattern. Nyberg et al. (2019) found older adults exhibiting right anterior hippocampal hyperactivity to demonstrate lower memory performance, higher genetic risk of AD, and higher incidence of deteriorating to dementia at follow-up. Leal et al. (2017) found increased right hippocampal activity during memory encoding to be associated with longitudinal accumulation of Aβ several years later, which in turn was associated with steeper memory decline. Importantly, this association was not demonstrated for other cortical areas demonstrating increased activity prior to follow-up. Hippocampal hyperactivity during different types of memory encoding tasks was also shown to be associated with increased tau pathology and lower memory performance in cognitively normal older adults (Berron et al., 2019; Huijbers et al., 2019). Further, the study supporting the potential link between AD pathology and hippocampal hyperactivity comes from the findings in genetic models of the disease. Aberrant hyper-excitatory activity in the hippocampus is a consistent finding in animal models of AD (Palop et al., 2007; Haberman et al., 2017), whereas young adults carrying the mutation for the familial subtype of AD have been repeatedly demonstrating right anterior hippocampal hyperactivity during memory encoding compared with non-carrier controls (Quiroz et al., 2010; Reiman et al., 2012). Furthermore, increased hippocampal activity during memory encoding has also been shown in young individuals at risk for late-onset sporadic AD, i.e., APOE ε4 carriers (Filippini et al., 2009; Dennis et al., 2010). The observed relationship between hippocampal hyperactivity and Aβ accumulation may be a reflection of a vicious neuropathological cycle in which over-excitatory neurons drive local Aβ aggregation, which, in turn, further increases neuronal excitability levels (Palop et al., 2007; Bero et al., 2011). While aerobic exercise has been repeatedly demonstrated to be associated with a lower risk of AD and dementia (Rovio et al., 2005; Larson et al., 2006; Andel et al., 2008), a mechanism that may link aerobic exercise with hippocampal hyper-excitability and dysfunction attenuation in aging may lie in Aβ metabolism. AD model mice demonstrated lower hippocampal amyloid plaque load following exercise intervention, with greater training intensity resulting in lower Aβ burden (Thomas et al., 2020). Furthermore, evidence for increased glymphatic clearance of hippocampal amyloid plaques in aged mice was also demonstrated following

a single session of aerobic exercise (He et al., 2017). A study in already diagnosed human patients with AD did not find the aerobic intervention to affect Aβ levels; however, the late clinical stage of the participants on the AD continuum, the relatively short duration of the intervention, and significantly higher Aβ levels in the exercise group at baseline may account for the lack of interventional efficacy observed in this study (Frederiksen et al., 2019). In addition, while normal hippocampal function requires a balance between excitation and inhibition, abnormal hippocampal excitation in pathological aging has also been linked to GABAergic inhibitory dysfunction (Hazra et al., 2013; Tong et al., 2014). Aerobic exercise, in turn, has been demonstrated to induce neuroprotective inhibitory modulation in the hippocampus of hyper-excitatory epileptic rats (Lim et al., 2015; Barzroodi Pour et al., 2019). This, in turn, suggests another potential neurobiological mechanism that may underlie the relationship between aerobic exercise and attenuated hippocampal hyperactivity observed in this study.

The second primary finding in this study is the differences observed in hippocampal resting-state connectivity between the groups. Namely, aerobically active lifestyle (and to a lesser extent $Vo_2$peak) was found to be associated with higher distant hippocampal functional connectivity with core hubs of the DMN, i.e., the posteromedial and medial prefrontal cortices and with lower local intra-hippocampal connectivity. The hippocampus is a part of the medial temporal subsystem of the DMN (Andrews-Hanna et al., 2010), and these regions have been shown to functionally cooperate in cortico-hippocampal memory networks (Ranganath and Ritchey, 2012; Cooper and Ritchey, 2019). Previous studies demonstrated decreased cortico-hippocampal connectivity in healthy older adults. While Damoiseaux et al. (2016) found only the posterior hippocampus to demonstrate an age-related decline in functional connectivity with the DMN, Salami et al. (2014) demonstrated this age-related effect to occur in both anterior and posterior hippocampal subparts, and that higher connectivity values were positively correlated with episodic memory performance. We found a link between the physically active lifestyle and higher connectivity of the bilateral posterior hippocampus with the posteromedial cortex while also higher connectivity of the right anterior hippocampus with both posteromedial and medial prefrontal cortices. In addition to higher distant connectivity, the active group in our study also demonstrated a trend toward lower intra-hippocampal connectivity expressed as lower local correlations within the anterior hippocampus and between the posterior hippocampi across the two hemispheres. Higher within- and between-hippocampus correlations have been previously demonstrated with increasing age, negatively correlating with memory performance, and load of AD pathology (Salami et al., 2014; Harrison et al., 2019). Harrison et al. (2019) further demonstrated that increased local within hippocampal correlation, represented by higher regional homogeneity, was associated with decreased cortico-hippocampal connectivity, suggesting that both age and AD pathology may be associated with increasing hippocampal functional disconnection and isolation. In contrast, our findings provide evidence that aerobic activity and physically active lifestyle may constitute a neuroprotective factor in face of this aspect of hippocampal dysfunction. In turn, these results extend previous studies which demonstrated a relationship between physical activity and increased DMN connectivity (Voss et al., 2010; Boraxbekk et al., 2016). Reduced functional connectivity of the DMN is associated not only with aging (Salami et al., 2014) but also with early biomarkers of AD pathology, as being highly sensitive regions to early Aβ accumulation (Palmqvist et al., 2017). Given the evidence pointing at the potential role that aerobic activity may have in increasing the glymphatic removal of Aβ deposition from the interstitial space, it may underlie, at least partially, the observed relationship with higher functional connectivity of the two core hubs of DMN with the hippocampus. In addition, one of the hallmarks of exercise-induced mechanisms observed in animal models is the upregulation of brain and hippocampal brain-derived neurotrophic factor (BDNF) (Oliff et al., 1998; Vaynman et al., 2004; Berchtold et al., 2005). Among its versatile functions, BDNF promotes neurite outgrowth and synaptogenesis, plays a significant role in synaptic plasticity, and is involved in learning and memory processes (Binder and Scharfman, 2004; Leal et al., 2015). In human older adults, increased serum levels of BDNF were associated with increased parahippocampal functional connectivity following 1 year of aerobic intervention, supporting the potential role of BDNF as a neurobiological mediator of exercise-induced changes in brain function (Voss et al., 2013). It is important to note that although $Vo_2$peak was associated with some of the hippocampal measures we examined in this study, it did not explain all the between-group differences observed, especially in terms of distant and local hippocampal connectivity. Although it may support a potential mediating role of $Vo_2$peak in some of the exercise-related hippocampal function effects, it also suggests that other potential mechanisms play a role in mediating this relationship.

This study adds evidence regarding the functional neuroprotective potential of aerobic exercise which is in line with previous models that aim to explain neurocognitive differences in older adults. The ability to successfully perform a cognitive task while recruiting less neural resources, or increased neural efficiency, has been suggested to constitute a mechanism, which may underlie the superior cognitive performance observed in some older individuals compared with others (Barulli and Stern, 2013). Increased neural efficiency has been previously shown to be associated with favorable cognitive performance in aging (Steffener et al., 2011; Hakun et al., 2015) and was also demonstrated to be expressed in healthy older adults compared with neurodegenerative patients (Sole-Padulles et al., 2009). In this study, since the physically active group also demonstrated higher memory performance, in addition to the observed lower hippocampal activation, these findings may suggest that these individuals may be able to use more efficiently hippocampal resources in order to cope with memory demands.

## Study Limitations

The main limitation of this study lies in its cross-sectional nature. Although previous evidence from animal models and human participants support the observed relationship between aerobic exercise and hippocampal function from a neurobiological mechanistic point of view, we cannot state that the physically active lifestyle is, in fact, the causal mediator of the attenuation

in hippocampal dysfunction observed in the current sample of cognitively intact older adults. Instead, these results should serve as a starting point for future longitudinal and interventional studies that are needed to explore the time-dependency between aerobic exercise and functional adaptations of the hippocampus in human aging and to establish a causal effect. Another issue that should be kept in mind is that other factors that have not been evaluated in this study could potentially contribute to the explanation of the relationship observed. These include, but are not limited to, differences in genetic background and latent pathological processes. Although we excluded participants with unbalanced medical conditions, this population is prone to age-related pathologies, and it is possible that at least some of the included participants had ongoing pathological processes that are still not symptomatically expressed and therefore they were not aware of.

## CONCLUSION

While the relationship between physical activity and hippocampal function in human aging has been sparsely investigated, this study provides evidence for a potential relationship between lifestyle habits of aerobic exercise and attenuation of different aspects of hippocampal dysfunction, normally observed in older individuals, namely alteration in patterns of hippocampal activity and connectivity. By that, the current research extends previous studies demonstrating the relationship between physical activity and aging brain in general and specifically the neuroprotective effect of aerobic exercise on the aged hippocampus. In addition, our results suggest that although $Vo_2$peak may be associated with some aspects of hippocampal function in older adults, other factors may also contribute to the relationship between aerobic exercise and distinct hippocampal functions.

## DATA AVAILABILITY STATEMENT

Due to medical confidentiality and since participants did not consent to having their data publicly published, the unidentified data (e.g., data spreadsheet) and code that support the findings of this study are available from the corresponding author without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Studies Committee of Tel Aviv Sourasky Medical Center. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

TE: conceptualization, investigation, methodology, software, formal analysis, writing—original draft, writing—review & editing, project administration, and visualization. NG: supervision and conceptualization. TH: resources and funding acquisition. OH: project administration. YL: conceptualization, methodology, supervision, writing—review & editing, project administration, resources, and funding acqusition. All authors contributed to the article and approved the submitted version.

## FUNDING

This study has been funded from the grant of the Israel Science Foundation (ISF) provided to YL (Grant No. 1573/18) and the financial support of the Sagol Family Foundation for Brain Research provided to Sagol Brain Institute. The funding sources were not involved in the conduction of the research.

## ACKNOWLEDGMENTS

We thank Prof. Dafna Ben Bashat for her consultation during the research process. We thank Dr. Moran Artzi for the help with planning the acquisition sequences and Prof. Yuval Nir for his thoughtful advice. We also thank Dr. Avraham Man for his assistance with conducting the cardiopulmonary testing. This manuscript has been previously uploaded to bioRxiv (Eisenstein et al., 2021).

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.720990/full#supplementary-material

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 25 October 2021
doi: 10.3389/fnagi.2021.716638

# Arterial Stiffening Moderates the Relationship Between Type-2 Diabetes Mellitus and White Matter Hyperintensity Burden in Older Adults With Mild Cognitive Impairment

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[†]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

**Received:** 28 May 2021
**Accepted:** 06 September 2021
**Published:** 25 October 2021

**Citation:**
Werhane ML, Thomas KR, Bangen KJ, Weigand AJ, Edmonds EC, Nation DA, Sundermann EE, Bondi MW and Delano-Wood L (2021) Arterial Stiffening Moderates the Relationship Between Type-2 Diabetes Mellitus and White Matter Hyperintensity Burden in Older Adults With Mild Cognitive Impairment. Front. Aging Neurosci. 13:716638. doi: 10.3389/fnagi.2021.716638

**Background:** Cerebrovascular dysfunction has been proposed as a possible mechanism underlying cognitive impairment in the context of type 2 diabetes mellitus (DM). Although magnetic resonance imaging (MRI) evidence of cerebrovascular disease, such as white matter hyperintensities (WMH), is often observed in DM, the vascular dynamics underlying this pathology remain unclear. Thus, we assessed the independent and combined effects of DM status and different vascular hemodynamic measures (i.e., systolic, diastolic, and mean arterial blood pressure and pulse pressure index [PPi]) on WMH burden in cognitively unimpaired (CU) older adults and those with mild cognitive impairment (MCI).

**Methods:** 559 older adults (mean age: 72.4 years) from the Alzheimer's Disease Neuroimaging Initiative were categorized into those with diabetes (DM+; CU = 43, MCI = 34) or without diabetes (DM-; CU = 279; MCI = 203). Participants underwent BP assessment, from which all vascular hemodynamic measures were derived. T2-FLAIR MRI was used to quantify WMH burden. Hierarchical linear regression, adjusting for age, sex, BMI, intracranial volume, CSF amyloid, and APOE ε4 status, examined the independent and interactive effects of DM status and each vascular hemodynamic measure on total WMH burden.

**Results:** The presence of DM ($p$ = 0.046), but not PPi values ($p$ = 0.299), was independently associated with greater WMH burden overall after adjusting for covariates. Analyses stratified by cognitive status revealed a significant DM status x PPi interaction within the MCI group ($p$ = 0.001) such that higher PPi values predicted greater WMH burden in the DM + but not DM- group. No significant interactions were observed in the CU group (all $p$s > 0.05).

**Discussion:** Results indicate that higher PPi values are positively associated with WMH burden in diabetic older adults with MCI, but not their non-diabetic or CU counterparts. Our findings suggest that arterial stiffening and reduced vascular compliance may have a role in development of cerebrovascular pathology within the context of DM in individuals at risk for future cognitive decline. Given the specificity of these findings to MCI, future exploration of the sensitivity of earlier brain markers of vascular insufficiency (i.e., prior to macrostructural white matter changes) to the effects of DM and arterial stiffness/reduced vascular compliance in CU individuals is warranted.

**Keywords: mild cognitive impairment, white matter hyperintensity volume, blood pressure, arterial stiffness, diabetes**

## INTRODUCTION

Type 2 diabetes (hereby referred to as "diabetes" or DM) has been repeatedly linked to an increased risk for developing dementia in late life (Arvanitakis et al., 2004; Crane et al., 2013). Given that both diabetes and dementia represent chronic, debilitating conditions that are extremely common in our rapidly aging population (Alzheimer's Association [AA], 2019; Centers for Disease Control and Prevention [CDCP], 2020), there has been a critical push for research aimed at disentangling the nature of their association in order to aid in prognosis and identify potential treatment targets. Cerebrovascular dysfunction remains a putative mechanism by which poor cognitive outcomes occur in diabetes. Dementia in the context of diabetes has been linked to increased cerebrovascular pathology at autopsy, which stands in contrast to dementia without diabetes that on average has greater evidence of other neuropathological changes (e.g., amyloid beta and tau accumulation; Sonnen et al., 2009). Well-aligned with such findings is the observation that the most common neuroradiological finding associated with diabetes is the presence of increased white matter hyperintensity (WMH) burden in the brain (Van Harten et al., 2006). Thought to reflect a highly prevalent form of cerebrovascular disease (i.e., small vessel ischemic damage to deep white matter regions; DeCarli et al., 2005), the presence of increased WMH burden on imaging is associated with greater risk for age-related cognitive decline, mild cognitive impairment (MCI), and dementia (Delano-Wood et al., 2008, 2009; Debette and Markus, 2010; Nation et al., 2013; Bangen et al., 2018).

Structural neuroimaging studies have also demonstrated *in vivo* evidence of cerebral atrophy and accumulation of neurodegenerative pathology in individuals with diabetes, which in turn predict poorer cognitive performance across domains including memory, executive functioning, and processing speed (Tiehuis et al., 2009; Hayashi et al., 2011; Moran et al., 2013). Critically, these white and gray matter alterations observed in individuals with diabetes likely represent end-stage pathological changes to brain parenchyma attributable to chronic cerebrovascular dysfunction, as suggested by prior work reporting links between cognitive functioning and alterations in regional cerebral blood flow (an indicator of cerebral perfusion), but not cortical thickness or regional brain volume, in older adults without dementia (Bangen et al., 2018). Combined, this research highlights the need to identify sensitive, early markers of cerebrovascular dysfunction prior to the development of irreversible brain pathology and cognitive impairment in individuals with diabetes.

While hypertension, specifically, has shown the most consistent association with increased WMH burden (de Leeuw et al., 2002; de Havenon et al., 2019), there is accumulating evidence for arterial stiffness—the decreased elasticity of the arterial wall that occurs in the context of aging—as a sensitive predictor of risk for cerebrovascular disease and dementia. Particularly notable are longitudinal findings that show that increased arterial stiffness at baseline in cognitively unimpaired older adults predicts future accumulation of concomitant white matter disease and neurodegenerative pathology (Ohmine et al., 2008; Mitchell et al., 2011), as well as increased risk for cognitive impairment, functional decline, and dementia diagnosis (Nation et al., 2013, 2016; Werhane et al., 2018). Importantly, arterial stiffness represents one of the earliest indicators of change to vascular wall structure and function in the progression of cardiovascular and cerebrovascular disease (Cohn et al., 2005), and is accelerated in health conditions such as diabetes that negatively impact the integrity of the vascular system (Xu et al., 2016; Chirinos et al., 2019).

Taken together, this literature highlights the potential role of vascular-induced white matter pathology in the development of poor cognitive outcomes in aging individuals with diabetes. Indeed, vascular disease, alterations to white matter integrity, and cognitive impairment are all highly prevalent in older adults, regardless of diabetes status. However, few studies to date have characterized differential relationships between vascular and white matter pathologies, especially in relation to the presence of cognitive impairment, in older adults with and without diabetes. Therefore, we explored relationships between diabetes status (i.e., diabetes absent vs. present) and different vascular hemodynamic measures (i.e., diastolic and systolic BP [BP], pulse pressure index [PPi], and mean arterial BP [MABP]) to the presence of MRI evidence of small vessel cerebrovascular disease (i.e., WMH) in a large sample of well-characterized older adults without dementia. Of particular interest was PPi as an indicator of systemic vascular pathology, given literature to suggest its utility as an easily obtainable blood-pressure based measure of arterial stiffness and reduced vascular compliance (Peng-Lin and Yue-Chun, 2009). In order to understand how relationships between different vascular hemodynamic measures, diabetes status, and WMH burden may vary across the spectrum of cognitive aging to early stages of

cognitive impairment, these variables were examined in both cognitively unimpaired older adults as well as those with a diagnosis of MCI.

We hypothesized the following: (1) greater arterial stiffness, as indicated by greater PPi values, would predict greater WMH volume on neuroimaging across cognitive groups, and (2) any observed relationship would be more pronounced in individuals with MCI versus cognitively unimpaired. Additionally, we also predicted that (3) older adults with both diabetes and greater arterial stiffening would demonstrate greater white matter pathology burden compared to those with one or no risk factors (i.e., no diabetes and/or reduced arterial stiffening); and (4) this interactive effect will be observed to a lesser extent in older adults with no evidence of cognitive impairment (i.e., cognitively unimpaired [CU] older adults). These hypotheses were evaluated using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

# MATERIALS AND METHODS

## The ADNI Dataset

Data used for the present study were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations. The main goal of ADNI has been to determine whether MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. The Principal Investigator of ADNI is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and participants have been recruited from over 50 sites across the United States and Canada. ADNI has been followed by ADNI-GO and ADNI-2. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. Data used in the present study were acquired in ADNI-2. For up-to-date information, see www.adni-info.org.

## Participants

The sample comprised 559 dementia-free older adults with or without MCI from ADNI. All participants were between the ages of 55 and 90 years old, had completed at least six years of education, were fluent in Spanish or English, and were free of any significant neurological or psychiatric disease. Information about each participant's medical history and medications was collected at baseline. All participants underwent neuropsychological testing and brachial BP assessment at baseline. Full criteria for ADNI eligibility and diagnostic classifications are described in detail at http://www.adni-info.org/Scientists/ADNIGrant/ProtocolSummary.aspx.

Participant selection was as follows: Of the 2,952 ADNI participants who completed neuropsychological assessment, 2,393 participants were identified as having no dementia at baseline based on ADNI's criteria for dementia. Consistent with previous work, we excluded individuals with functional dependence (based on a Functional Assessment Questionnaire [FAQ] score $> 5$) to ensure that that the final study sample consisted of older adults who could independently complete their activities of daily living (e.g., Thomas et al., 2017; Werhane et al., 2018). Of this sample, 559 participants had available WMH volume data. Within this subsample, the comprehensive neuropsychological criteria for MCI (Jak et al., 2009; Bondi et al., 2014) were used to identify cognitive status, yielding a final analytic sample of 322 CU older adults and 237 with MCI. Participants were then classified as either diabetic (DM+; CU = 43, MCI = 34) or non-diabetic (DM-; CU = 279; MCI = 203) based on their self-reported diabetes diagnosis, presence of glucose-lowering agents in their medical history, and/or fasting blood glucose above American Diabetes Association cutoff values for a diagnosis of diabetes (i.e., $> 125$ mg/dL). Consistent with our previous work in ADNI (Thomas et al., 2020), the following search terms were used to identify participants with DM at their initial study visit from medical history: diabetes, diabetic, insulin, insulin-dependent diabetes mellitus, and non-insulin dependent diabetes mellitus.

## White Matter Imaging

All participants underwent baseline MR imaging from which total WMH volume was derived. A detailed description of ADNI MR imaging data acquisition and processing can be found online[1]. Briefly, participants were scanned using a 3T MRI scanner. A T1-weighted sequence was acquired using the following parameters: TR = 2300 ms; TE = 2.98 ms; TI = 900 ms; 170 sagittal slices; within plane FOV = 256 × 240 $mm^2$; voxel size = 1.1 × 1.1 × 1.2 $mm^3$; flip angle = 9; bandwidth = 240 Hz/pix. T2 FLAIR scans were also obtained using an echo-planar imaging sequence with the following parameters: TR = 9000ms; TE = 90ms; TI = 2500ms; 42 slices at a thickness 5 mm. T1-weighted and T2 FLAIR scans were both pre-processed through a standardized pipeline and co-registered using cross-correlation. Brain and non-brain tissues were separated via skull-stripping. WMHs were detected using the previously validated, semi-automated Bayesian Markov-Random Field (MRF) method (DeCarli et al., 1999). The skull-stripped T1-weighted image was then non-linearly aligned to a minimum deformation template (MDT), to which the T1, T2 FLAIR, and map of ground-truth FLAIR-based WMH pixels were then warped using the non-linear alignment.

## Blood Pressure Assessment

Seated brachial artery systolic and diastolic BPs were obtained from ADNI participants at their initial study visit. PPi values were calculated for each participant by dividing pulse pressure values (systolic BP – diastolic BP) by systolic BP. PPi allows for the evaluation of the effects of pulse pressure, a common proxy for arterial stiffening, while also removing the effects of systolic pressure. This measure was derived to help disambiguate the potential effects of arterial stiffening versus hypertension in

[1]http://adni.loni.usc.edu/methods/mri-tool/mri-acquisition/

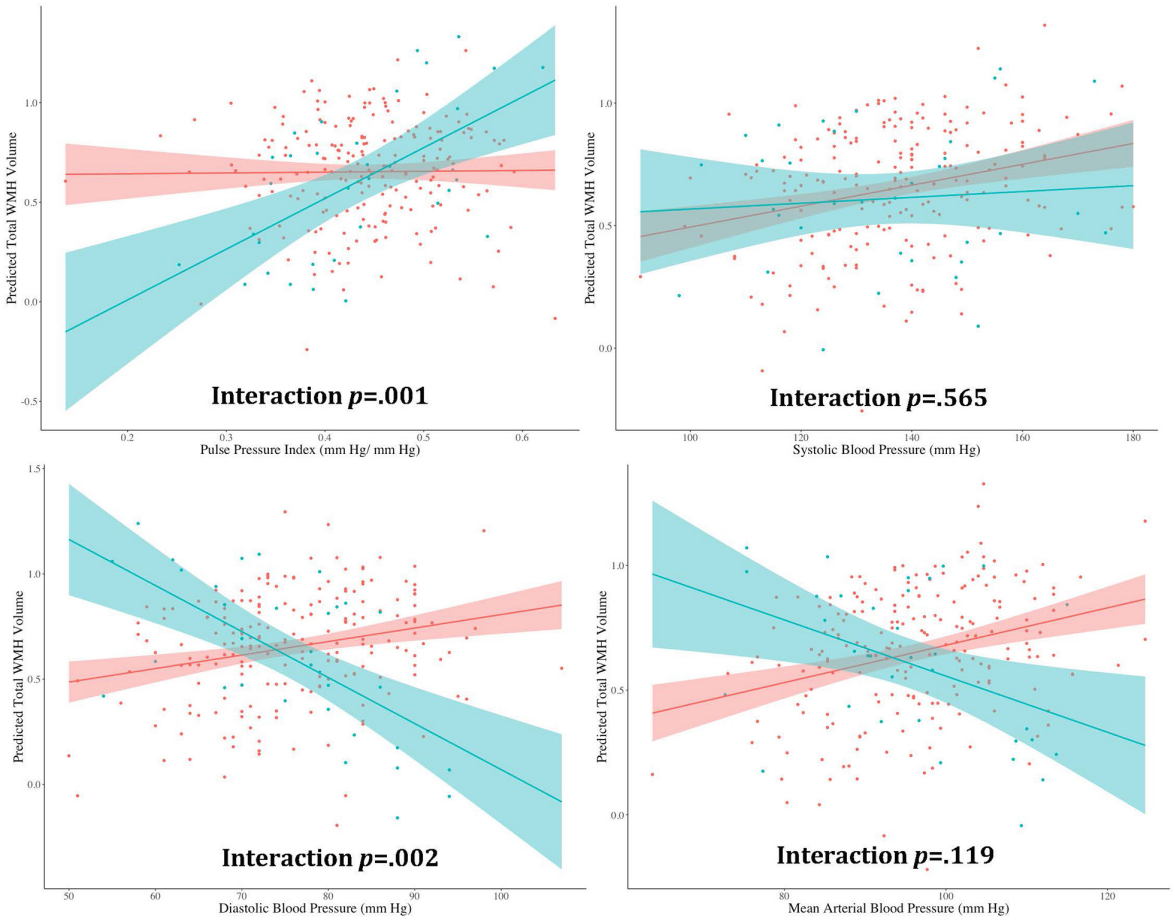


**FIGURE 1 |** The effect of different vascular hemodynamic measures on the relationship between diabase status and total white matter hyperintensity burden in older adults with mild cognitive impairment. *Note.* DM, diabetes mellitus; WMH, white matter hyperintensity. Within the MCI group, separate hierarchical multiple linear regression models evaluated the interactive effect of diabetes status and each vascular hemodynamic measure on total WMH volumes. All models were adjusted for age, sex, body mass index, intracranial volume, cerebrospinal fluid amyloid beta positivity, and apolipoprotein E ε4 status. PPi significantly modified the relationship between diabetes status and total WMH burden (interaction $p = 0.001$), such that PPi values were associated with greater WMH burden in older adults with MCI and diabetes (β = 1.99, S.E. = 0.943, 95% CI: 0.051–3.928; $p = 0.045$, partial $r = 0.382$), but not their non-diabetes counterparts ($p > 0.05$). Diastolic BP also significantly interacted with diabetes status on total WMH volume (interaction $p = 0.002$). Here, greater diastolic BP values were associated with greater WMH volumes in non-diabetic older adults with MCI (β = 0.008, S.E. = 0.003, 95% CI: 0.155, 2.438; $p = 0.016$, partial $r = 0.382$). In contrast, no significant association was observed between diastolic BP values and WMH burden in their diabetic counterparts ($p > 0.05$). No significant interaction effects were observed with systolic BP or MABP (interaction $p$s $> 0.05$).

study findings, and allows for the improved evaluation of arterial stiffness and vascular compliance in the context of pathological vascular aging (Peng-Lin and Yue-Chun, 2009). Mean arterial pressure was calculated as diastolic pressure plus one-third the pulse pressure. All arterial BP measurements were taken using a calibrated mercury sphygmomanometer and BP cuff. BP readings were taken from the dominant arm while the participant was in a seated position, with their forearm held horizontally at the level of the fourth intercostal space at the sternum (i.e., the level of the heart).

## Statistical Analyses

Demographic and clinical characteristics by diabetes and cognitive status were examined using linear regression and chi-square tests for continuous and categorical variables, respectively. Hierarchical multiple linear regression was used in order to assess the independent and interactive effects of diabetes status and each vascular hemodynamic measure on total WMH volume within the overall and then within cognitive normal and MCI groups, separately. Parameters of interest in the models included vascular hemodynamic variables (systolic BP, diastolic BP, PPi, and MABP; all continuous and mean centered) and diabetes status (dichotomous; type 2 diabetes absent/present). The outcome of interest was total WMH volumes (continuous), which was log-transformed in order to improve distributional normality. At the first level of each model, age, sex, BMI, amyloid beta 1-42 positivity (Hansson et al., 2018), apolipoprotein E (APOE) ε4 status, and intracranial volume were all entered given well-established associations with vascular aging and WMH volume in the literature. Diabetes status, a vascular hemodynamic

variable, and their interaction term were then entered on the second level. Again, separate models were generated for each vascular hemodynamic measure, stratified by cognitive status. Effect sizes were indexed semi-partial r values. The Bonferroni method was used to control for familywise error inflation due to multiple comparisons (statistical significance threshold: $p < 0.05/8$; Bonferroni corrected $p$-value = 0.006). All analyses were performed using R Studio Version 1.1.453 (2009-2018 RStudio, Inc.).

## RESULTS

Participant demographics and clinical characteristics are presented in **Table 1**. The mean age of the overall sample was 72.4 years (SD: 6.94 years; range: 55.1 to 91.4 years). Mean physiological (i.e., BP [systolic, diastolic], arterial stiffness, MABP) and psychometric scores were in the non-clinical range[2] both across the entire sample and within diabetes status groups, confirming that the sample was generally healthy with respect to vascular, psychiatric, cognitive, and functional symptomatology. Diabetes status did not significantly differ by cognitive group (CU vs. MCI, $p = 0.591$). The bivariate association between DM status and WMH burden was not significant in the overall sample; however, a significant positive association was observed between diabetes status and WMH burden once covariates were included in an adjusted model ($p = 0.045$). Both bivariate and adjusted associations between PPi and WMH burden were not statistically significant in the sample overall, nor within cognitive subgroups ($ps > 0.05$). Within the CU group, participants with diabetes had fewer years of formal education at the level of a statistical trend ($p = 0.060$) and performed more poorly on a brief screen of global cognitive functioning (Mini Mental Status Exam [MMSE]; $p = 0.028$) relative to non-diabetic participants. Comparatively, within the MCI group, participants with diabetes on average were significantly younger ($p = 0.005$) and had significantly greater BMI values ($p < 0.001$) relative to those without diabetes. No other significant differences by diabetes status were observed within CU or MCI groups across all other demographic characteristics, parameters of interest (PPi, WMH total volume), or variables related to increased vascular and dementia risk (e.g., BP values, depressive symptomology, everyday functioning, genetic risk for dementia, cerebrospinal fluid amyloid beta positivity).

Separate hierarchical multiple linear regression analyses examined the relationship between diabetes status and each vascular hemodynamic measure (i.e., systolic BP, diastolic BP, MABP, and PPi) on total WMH volume in both CU (**Table 2**) and MCI (**Table 3**) older adults. Covariates included in all models included age, sex, BMI, amyloid beta positivity, APOE ε4 status, and intracranial volume. Within CU older adults, the relationship vascular hemodynamic measures and WMH burden did not vary depending on diabetes status (all interaction $ps > 0.05$). In contrast, within the MCI group, diabetes status significantly interacted with PPi (β = 3.48, 95% CI: 1.52, 5.44; $p = 0.001$, partial $r = 0.226$) and diastolic blood pressure (β = –0.025, 95% CI: –0.04, –0.009; $p = 0.002$, semi-partial $r = -0.202$) on total WMH volume (**Figure 1**). Specifically, PPi significantly modified the relationship between diabetes status and total WMH burden (interaction $p = 0.001$), such that PPi values were associated with greater WMH burden in older adults with MCI and diabetes (β = 1.99, S.E. = 0.943, 95% CI: 0.051-3.928; $p = 0.045$, semi-partial $r = 0.382$), but not their non-diabetes counterparts ($p > 0.05$). In comparison, higher diastolic BP values were associated with greater WMH volumes in non-diabetic older adults with MCI (β = 0.008, S.E. = 0.003, 95% CI: 0.155, 2.438; $p = 0.016$, semi-partial $r = 0.382$), but not their diabetic counterparts ($p > 0.05$). There were no other significant interaction effects observed between other vascular hemodynamic measures (i.e., systolic BP, MABP) and diabetes status on total WMH burden in older adults with MCI.

## DISCUSSION

We examined the interactive effects of different vascular hemodynamic measures and diabetes on the white matter hyperintensity burden in a sample of well-characterized older adults with and without MCI. Pulse pressure index, a proxy measure for arterial stiffening and vascular non-compliance, significantly interacted with diabetes status in its association white matter hyperintensity burden, such that cognitively impaired older adults with diabetes and higher PPi values had more extensive white matter hyperintensity pathology compared to those with one or no vascular risk factors. Interestingly, these effects were only observed in older adults with MCI, and not their cognitively unimpaired counterparts. Taken together, these findings suggest that arterial stiffening and reduced vascular compliance may have a role in the presence of cerebrovascular pathology in older adults with diabetes who have objective evidence of cognitive impairment, highlighting the need for further research parsing apart the nature of the association between arterial stiffening, white matter hyperintensity burden, and diabetes status on cognitive decline in this potentially high-risk aging subgroup.

The *a priori* focus of this study was PPi given prior findings using both pulse pressure and PPi as a measure of arterial stiffness and vascular non-compliance (Peng-Lin and Yue-Chun, 2009; Nation et al., 2013, 2015, 2016), which have importance to pathological vascular aging within the context of both diabetes and cognitive impairment in late life. We also repeated all primary analyses using other vascular hemodynamic measures (i.e., systolic, diastolic, and mean arterial BP) to determine whether findings were specific to PPi. The pattern of findings observed with PPi were not observed for any other vascular hemodynamic measures, suggesting that increased arterial stiffness, but not other blood pressure measures of vascular risk, may have a unique link to the presence of greater cerebrovascular pathological burden in cognitively symptomatic

[2]Clinical cut points: hypertension, BP > 140/90 in older adults < 60 years of age and 150/90 in older adults of 60 + years of age (James et al., 2014); functional dependence, FAQ ≥ 6 (Teng et al., 2010); presence of depressive symptoms, GDS > 9 (Yesavage and Sheikh, 1986); cognitive impairment, MMSE < 24 (Folstein et al., 1975).

**TABLE 1 |** Sample characteristics by diabetes status and cognitive diagnosis.

| | | DM + | DM- | Differ by DM status? | Differ by cognitive dx? |
|---|---|---|---|---|---|
| **Variable** | **Cognitive dx** | **Mean (SD)** | **Mean (SD)** | ***p* or $\chi^2$ value** | ***p* or $\chi^2$ value** |
| *N* | MCI | *N* = 34 | *N* = 203 | – | **–** |
| | CU | *N* = 43 | *N* = 279 | – | – |
| Age (*years*) | MCI | 73.1 (6.89) | 69.5 (7.41) | **0.005** | 0.358 |
| | CU | 72.0 (6.82) | 72.2 (6.30) | 0.852 | – |
| Education (*years*) | MCI | 16.4 (2.54) | 15.7 (3.05) | 0.182 | 0.055 |
| | CU | 16.5 (2.52) | 15.7 (2.50) | 0.060 | – |
| Sex *(% male*) | MCI | 69.23% | 53.55% | 0.129 | 0.168 |
| | CU | 58.62% | 48.46% | 0.297 | – |
| Systolic BP (*mm Hg*) | MCI | 137.3 (16.27) | 135.1 (19.80) | 0.490 | 0.320 |
| | CU | 135.6 (16.96) | 134.2 (14.14) | 0.781 | – |
| Diastolic BP (*mm Hg*) | MCI | 76.0 (9.92) | 75.4 (10.63) | 0.736 | 0.383 |
| | CU | 75.2 (9.62) | 74.9 (8.07) | 0.831 | – |
| Pulse Pressure Index (*mm Hg/mm Hg*) | MCI | 0.4 (0.07) | 0.4 (0.09) | 0.600 | 0.924 |
| | CU | 0.4 (0.07) | 0.4 (0.08) | 0.984 | – |
| Mean Arterial BP (*mm Hg*) | MCI | 95.27 (11.50) | 96.41 (10.32) | 0.560 | 0.275 |
| | CU | 94.9 (98.27) | 95.4 (10.26) | 0.774 | – |
| BMI ($kg/m^2$) | MCI | 27.0 (4.92) | 31.1 (6.36) | < 0.001 | 0.846 |
| | CU | 27.4 (4.77) | 28.3 (5.70) | 0.245 | – |
| GDS Total Score | MCI | 1.6 (1.45) | 2.0 (1.62) | 0.082 | **0.002** |
| | CU | 1.3 (1.40) | 1.0 (1.02) | 0.289 | – |
| MMSE Score | MCI | 27.8 (1.80) | 27.8 (1.94) | 0.968 | **< 0.001** |
| | CU | 28.9 (1.20) | 28.4 (2.18) | **0.028** | – |
| FAQ Score | MCI | 3.6 (4.30) | 4.0 (4.33) | 0.642 | **< 0.001** |
| | CU | 0.6 (1.15) | 0.58 (1.16) | 0.973 | – |
| APOE ε4 status *(%*ε4 +) | MCI | 50.00% | 51.66% | 0.977 | **< 0.001** |
| | CU | 44.83% | 34.81% | 0.092 | **–** |
| CSF amyloid beta (*% positive)* | MCI | 65.38% | 65.88% | 0.960 | **< 0.001** |
| | CU | 37.93% | 36.18% | 0.851 | – |
| WMH total volume† | MCI | 0.6 (0.66) | 0.6 (0.48) | 0.138 | **< 0.001** |
| | CU | 0.5 (0.45) | 0.4 (0.49) | 0.256 | – |
| ICV | MCI | 1405.9 (142.10) | 1417.0 (147.02) | 0.178 | 0.125 |
| | CU | 1393.1 (129.20) | 1367.8 (132.50) | 0.235 | – |

*Abbreviations: DM, diabetes mellitus; dx, diagnosis; MCI, mild cognitive impairment; CU, cognitively unimpaired; BP, blood pressure; BMI, body mass index; CDR, clinical dementia rating; GDS, Geriatric Depression Scale; MMSE, Mini Mental State Exam; FAQ, Functional Assessment Questionnaire; APOE, apolipoprotein E; WMH, white matter hyperintensity; ICV, intracranial volume.*

†*This variable was log-transformed in order to improve the normality of the distribution. Bold values indicate for p ≥ 0.05.*

older adults with diabetes. While diastolic BP was observed to significantly modify the relationship between diabetes and WMH burden, this interaction effect was such that diastolic BP was positively associated with WMH burden in non-diabetic older adults with MCI, but negatively associated (although this was statistically non-significant) with WMH burden in their diabetic counterparts. A possible explanation for this unexpected finding is that the etiology of high vs. low diastolic BP values in older adults with and without diabetes differs. For example, while high diastolic BP likely reflects general hypertension in older adults without diabetes, low diastolic blood pressure values could be more indicative of cardiac dysfunction and associated with the greater prevalence of isolated systolic hypertension due to arterial stiffening in older adults with diabetes (Franklin et al., 2011). This would represent an intriguing area for further exploration in future studies that are well-equipped to explore associations with diastolic BP and other health and brain aging variables in older adults with and without diabetes. Findings from such work would help inform how diastolic BP contributes to neurocognitive aging in an often medically complex clinical population (i.e., older adults with diabetes and cognitive impairment).

There are a variety of vascular risk factors (e.g., hypertension, atherosclerosis, hyperlipidemia, metabolic syndrome, diabetes) that have been linked to pathological brain aging processes, such as evidence of cerebrovascular disease on neuroimaging (e.g., white matter hyperintensity burden, altered cerebral perfusion), neuropathological changes on brain autopsy, cognitive impairment, and functional decline (Arvanitakis et al., 2004; de la Torre, 2010; Crane et al., 2013; Bangen et al., 2018; Werhane et al., 2018; Thomas et al., 2020). There is a growing

**TABLE 2 |** Final Multiple Linear Regression Models for CU Older Adults.

**Systolic Blood Pressure**

| | Estimate | SE | t-value | p-value | 95%CI | Semi-partial r |
|---|---|---|---|---|---|---|
| Intercept | −3.827 | 0.521 | −7.343 | **< 0.001** | −4.853, −2.802 | – |
| DM | 0.373 | 0.686 | 0.544 | 0.587 | −0.977, 1.723 | 0.031 |
| SYS BP | 0.004 | 0.002 | 2.520 | **0.012** | 0.001, 0.007 | 0.141 |
| SYS BP x DM | −0.002 | 0.005 | −0.328 | 0.743 | −0.012, 0.008 | −0.019 |
| Age | 0.025 | 0.004 | 6.499 | **< 0.001** | 0.017, 0.032 | 0.345 |
| Gender | 0.158 | 0.063 | 2.528 | **0.012** | 0.035, 0.281 | 0.142 |
| BMI | 0.007 | 0.005 | 1.312 | 0.191 | −0.003, 0.017 | 0.074 |
| CSF Aβ + | 0.174 | 0.055 | 3.145 | **0.002** | 0.065, 0.282 | 0.175 |
| APOE ε4 + | −0.019 | 0.055 | −0.343 | 0.732 | −0.127, 0.089 | −0.019 |
| ICV | 0.001 | 0.000 | 4.813 | **< 0.001** | 0.001, 0.002 | 0.263 |

**Diastolic Blood Pressure**

| | Estimate | SE | t-value | p-value | 95%CI | Semi-partial r |
|---|---|---|---|---|---|---|
| Intercept | −3.950 | 0.548 | −7.202 | **< 0.001** | −5.029, −2.870 | – |
| DM | 0.414 | 0.668 | 0.619 | 0.536 | −0.901, 1.729 | 0.035 |
| DIA BP | 0.006 | 0.003 | 2.249 | **0.025** | 0.001, 0.012 | 0.126 |
| DIA BP x DM | −0.004 | 0.009 | −0.398 | 0.691 | −0.021, 0.014 | −0.023 |
| Age | 0.028 | 0.004 | 7.182 | **< 0.001** | 0.020, 0.035 | 0.377 |
| Gender | 0.173 | 0.063 | 2.748 | **0.006** | 0.049, 0.296 | 0.154 |
| BMI | 0.006 | 0.005 | 1.187 | 0.236 | −0.004, 0.016 | 0.067 |
| CSF Aβ + | 0.158 | 0.056 | 2.826 | **0.005** | 0.048, 0.268 | 0.158 |
| APOE ε4 + | −0.007 | 0.055 | −0.132 | 0.895 | −0.116, 0.101 | −0.007 |
| ICV | 0.001 | 0.000 | 4.723 | **< 0.001** | 0.001, 0.002 | 0.258 |

**Mean Arterial Blood Pressure**

| | Estimate | SE | t-value | p-value | 95%CI | Semi-partial r |
|---|---|---|---|---|---|---|
| Intercept | −4.067 | 0.546 | −7.444 | **< 0.001** | −5.142, −2.992 | – |
| DM | 0.493 | 0.820 | 0.601 | 0.548 | −1.120, 2.105 | 0.034 |
| MABP | 0.007 | 0.003 | 2.781 | **0.006** | 0.002, 0.012 | 0.156 |
| MABP x DM | −0.004 | 0.009 | −0.418 | 0.676 | −0.021, 0.013 | −0.024 |

*(Continued)*

**TABLE 2 |** (Continued)

**Mean Arterial Blood Pressure**

| | Estimate | SE | t-value | p-value | 95%CI | Semi-partial r |
|---|---|---|---|---|---|---|
| Age | 0.026 | 0.004 | 7.030 | **< 0.001** | 0.019, 0.034 | 0.370 |
| Gender | 0.169 | 0.062 | 2.698 | **0.007** | 0.046, 0.291 | 0.151 |
| BMI | 0.006 | 0.005 | 1.134 | 0.258 | −0.004, 0.016 | 0.064 |
| CSF Aβ + | 0.159 | 0.056 | 2.853 | **0.005** | 0.049, 0.268 | 0.159 |
| APOE ε4 + | −0.013 | 0.055 | −0.244 | 0.808 | −0.121, 0.095 | −0.014 |
| ICV | 0.001 | 0.000 | 4.764 | **< 0.001** | 0.001, 0.002 | 0.260 |

**Pulse Pressure Index**

| | Estimate | SE | t-value | p-value | 95%CI | Semi-partial r |
|---|---|---|---|---|---|---|
| Intercept | −3.464 | 0.509 | −6.801 | **< 0.001** | −4.466, −2.462 | – |
| DM | 0.139 | 0.482 | 0.289 | 0.773 | −0.810, 1.089 | 0.016 |
| PPi | 0.155 | 0.378 | 0.409 | 0.683 | −0.590, 0.899 | 0.023 |
| PPi x DM | 0.011 | 1.080 | 0.010 | 0.992 | −2.113, 2.135 | 0.001 |
| Age | 0.025 | 0.004 | 6.380 | **< 0.001** | 0.018, 0.033 | 0.340 |
| Gender | 0.158 | 0.063 | 2.489 | **0.013** | 0.033, 0.283 | 0.140 |
| BMI | 0.008 | 0.005 | 1.556 | 0.121 | −0.002, 0.018 | 0.088 |
| CSF Aβ + | 0.186 | 0.056 | 3.331 | **0.001** | 0.076, 0.295 | 0.185 |
| APOE ε4 + | −0.012 | 0.056 | −0.212 | 0.832 | −0.121, 0.098 | -0.012 |
| ICV | 0.001 | 0.000 | 4.775 | **< 0.001** | 0.001, 0.002 | 0.261 |

*Abbreviations: DM, diabetes; SYS, systolic; DIA, diastolic; BP, blood pressure; MABP, mean arterial blood pressure; PPi, pulse pressure index; BMI, body mass index; CSF Aβ +, cerebrospinal fluid amyloid beta positivity; APOE ε4 +, apolipoprotein E ε4 positivity; ICV, intracranial volume. Bold values indicate for p ≥ 0.05.*

body of evidence to suggest a robust association between arterial stiffness and pathological changes associated with advanced age, including gray and white matter degradations, accumulation of AD neuropathology, and cognitive decline (Nation et al., 2015; Saji et al., 2016). It is thought that arterial stiffness gives rise to these changes by inducing a deleterious systemic hypertensive state, causing downstream damage to vulnerable microvasculature and associated tissue. The brain is especially susceptible to these effects given the high density and low impedance of its microvasculature, which allows for the increased pulsatile load that occurs in the context of arterial stiffening to deeply penetrate the microvascular bed and cause damage to the vessels (particularly in watershed areas with low perfusion), ultimately leading to chronic

**TABLE 3 |** Final Multiple Linear Regression Models for MCI Older Adults.

**Systolic Blood Pressure**

| | Estimate | SE | t-value | p-value | 95%CI | Semi-partial r |
|---|---|---|---|---|---|---|
| Intercept | −2.420 | 0.584 | −4.142 | **< 0.001** | −3.571, −1.269 | – |
| DM | −0.239 | 0.609 | −0.392 | 0.696 | −1.438, 0.961 | −0.026 |
| SYS BP | 0.000 | 0.002 | 0.149 | 0.882 | −0.004, 0.004 | 0.010 |
| SYS BP x DM | 0.003 | 0.004 | 0.576 | 0.565 | −0.006, 0.011 | 0.038 |
| Age | 0.030 | 0.005 | 6.577 | **< 0.001** | 0.021, 0.039 | 0.400 |
| Gender | 0.061 | 0.074 | 0.825 | 0.410 | −0.085, 0.208 | 0.055 |
| BMI | −0.010 | 0.006 | −1.690 | 0.092 | −0.021, 0.002 | −0.111 |
| CSF Aβ + | 0.122 | 0.069 | 1.773 | 0.078 | −0.014, 0.257 | 0.117 |
| APOE ε4 + | −0.055 | 0.066 | −0.829 | 0.408 | −0.185, 0.076 | −0.055 |
| ICV | 0.001 | 0.000 | 2.839 | **0.005** | 0.000, 0.001 | 0.185 |

**Diastolic Blood Pressure**

| | Estimate | SE | t-value | p-value | 95%CI | Semi-partial r |
|---|---|---|---|---|---|---|
| Intercept | −2.894 | 0.585 | −4.950 | **< 0.001** | −4.046, −1.742 | – |
| DM | 1.975 | 0.605 | 3.264 | **0.001** | 0.783, 3.167 | 0.212 |
| DIA BP | 0.007 | 0.003 | 2.243 | **0.026** | 0.001, 0.013 | 0.147 |
| DIA BP x DM | −0.025 | 0.008 | −3.105 | **0.002** | −0.04, −0.009 | −0.202 |
| Age | 0.030 | 0.004 | 6.977 | **< 0.001** | 0.022, 0.039 | 0.420 |
| Gender | 0.060 | 0.074 | 0.809 | 0.419 | −0.086, 0.205 | 0.054 |
| BMI | −0.010 | 0.006 | −1.695 | 0.092 | −0.021, 0.002 | −0.112 |
| CSF Aβ + | 0.090 | 0.068 | 1.333 | 0.184 | −0.043, 0.223 | 0.088 |
| APOE ε4 + | −0.051 | 0.065 | −0.797 | 0.426 | −0.179, 0.076 | -0.053 |
| ICV | 0.001 | 0.000 | 2.809 | **0.005** | 0.000, 0.001 | 0.183 |

**Mean Arterial Blood Pressure**

| | Estimate | SE | t-value | p-value | 95%CI | Semi-partial r |
|---|---|---|---|---|---|---|
| Intercept | −2.792 | 0.603 | −4.632 | **< 0.001** | −3.980, −1.604 | – |
| DM | 1.232 | 0.720 | 1.712 | 0.088 | −0.186, 2.650 | 0.113 |
| MABP | 0.005 | 0.003 | 1.509 | 0.133 | −0.001, 0.011 | 0.100 |
| MABP x DM | −0.012 | 0.008 | −1.567 | 0.119 | −0.027, 0.003 | −0.103 |

*(Continued)*

**TABLE 3 |** (Continued)

**Mean Arterial Blood Pressure**

| | Estimate | SE | t-value | p-value | 95%CI | Semi-partial r |
|---|---|---|---|---|---|---|
| Age | 0.029 | 0.004 | 6.629 | **< 0.001** | 0.021, 0.038 | 0.403 |
| Gender | 0.063 | 0.075 | 0.843 | 0.400 | −0.084, 0.210 | 0.056 |
| BMI | −0.009 | 0.006 | −1.608 | 0.109 | −0.021, 0.002 | −0.106 |
| CSF Aβ + | 0.107 | 0.068 | 1.564 | 0.119 | −0.028, 0.242 | 0.103 |
| APOE ε4 + | −0.049 | 0.066 | −0.745 | 0.457 | −0.178, 0.080 | −0.049 |
| ICV | 0.001 | 0.000 | 2.851 | **0.005** | 0.000, 0.001 | 0.186 |

**Pulse Pressure Index**

| | Estimate | SE | t-value | p-value | 95%CI | Semi-partial r |
|---|---|---|---|---|---|---|
| Intercept | −2.042 | 0.549 | −3.722 | **< 0.001** | −3.123, −0.961 | – |
| DM | −1.398 | 0.439 | −3.184 | **0.002** | −2.263, −0.533 | −0.207 |
| PPi | −0.952 | 0.447 | −2.130 | **0.034** | −1.832, −0.071 | −0.140 |
| PPi x DM | 3.480 | 0.994 | 3.501 | **0.001** | 1.521, 5.438 | 0.226 |
| Age | 0.033 | 0.004 | 7.301 | **< 0.001** | 0.024, 0.041 | 0.436 |
| Gender | 0.059 | 0.073 | 0.816 | 0.415 | −0.084, 0.203 | 0.054 |
| BMI | −0.011 | 0.006 | −1.962 | 0.051 | −0.022, 0.000 | −0.129 |
| CSF Aβ + | 0.098 | 0.067 | 1.457 | 0.146 | −0.034, 0.230 | 0.096 |
| APOE ε4 + | −0.064 | 0.064 | −0.989 | 0.324 | −0.191, 0.063 | −0.065 |
| ICV | 0.001 | 0.000 | 2.769 | **0.006** | 0.000, 0.001 | 0.181 |

*Abbreviations: DM, diabetes; SYS, systolic; DIA, diastolic; BP, blood pressure; MABP, mean arterial blood pressure; PPi, pulse pressure index; BMI, body mass index; CSF Aβ +, cerebrospinal fluid amyloid beta positivity; APOE ε4 +, apolipoprotein E ε4 positivity; ICV, intracranial volume. Bold values indicate for $p \geq 0.05$.*

hypoperfusion and ischemia that harms the surrounding brain tissue (Watson et al., 2011; Wardlaw et al., 2013; Nation et al., 2015). Evidence in support of this mechanism comes from studies linking arterial stiffening to morphological and functional brain change as early as young and mid-life (Tsao et al., 2013; Maillard et al., 2016; Pase et al., 2016), highlighting the chronic, insidious contribution of vascular disease to cognitive aging. Our findings extend this literature by demonstrating that elevated arterial stiffness, as measured by pulse pressure index values, is particularly deleterious in the presence of diabetes and MCI.

While the role of white matter alterations in cognitive aging has long been acknowledged, there is a growing body of evidence highlighting their role in the link between diabetes and late-life

cognitive impairment. White matter hyperintensities are more prevalent in populations with increased vascular risk, such as those with diabetes, and several studies have shown that white matter hyperintensity burden predicts cognitive impairment and MCI in older adults (DeCarli et al., 1995; Au et al., 2006; Delano-Wood et al., 2008, 2009; Silbert et al., 2008, 2009; Bangen et al., 2018), more rapid cognitive decline within at-risk populations (Tosto et al., 2014), and the onset and progression of incident AD dementia (Wolf et al., 2000; Brickman et al., 2012; Brickman et al., 2015). Critically, findings from the present study show that, for individuals already at increased risk for developing dementia (i.e., those with MCI), diabetes in the presence of increased systemic vascular pathology is associated with greater white matter hyperintensity burden. Such findings not only suggest that arterial stiffening may contribute to the development of cerebrovascular pathology in at-risk older adults, but moreover underscore its possible utility as an early, potentially modifiable risk factor for cognitive impairment. Given the specificity of these findings to MCI, future exploration of the sensitivity and utility of sensitive brain markers of vascular insufficiency that may precede gross, end stage white matter changes observable on MRI is also warranted, as such markers may allow for the detection of similar interactive effects of arterial stiffness and diabetes within cognitively unimpaired individuals. Such research may lead to a better understanding of the pathophysiological mechanism that underlies the relationship between arterial stiffening and white matter pathogenesis in the context of diabetes, and possible targets for intervention prior to the development of cognitive impairment.

There are several strengths to the present study. This well-characterized older adult sample allowed us to adjust for multiple relevant covariates to increase confidence in the interpretation of the effects of arterial stiffness and diabetes. To this point, we have confidence in the robustness of the reported findings given that they held across various models adjusted for several relevant factors and confounds. We also identified cognitively unimpaired older adults and those with MCI within the ADNI dataset using highly sensitive diagnostic criteria that have shown to be more reliable and stable than the conventional diagnostic criteria for MCI and yield far fewer (∼33%) false positives diagnostic errors (Jak et al., 2009; Bondi et al., 2014; Edmonds et al., 2015, 2016). However, there are some important limitations to the present study that must also be considered. The ADNI exclusion and inclusion criteria yielded a particularly healthy sample (on average, participants were within recommended ranges clinically for all vascular hemodynamic measures) that likely does not adequately mirror the health status of the general population. Indeed, only 9.5% of our sample met criteria for diabetes which, while comparable to diabetes prevalence in the American population, resulted in a relatively small cell size in our final diabetes analytic sample. This sample may therefore reflect a subsample of older adults with and without diabetes that has relatively reduced chronic disease and vascular risk burden compared to the general population. This more restricted range of vascular risk may also explain why PPi was not associated with WMH in our sample overall. Additionally, our sample was highly educated (average was approximately 16 years of education, while the national average for older adults age 65 + is 13 years [Ryan and Bauman, 2016]) and homogeneous with respect to race/ethnicity (predominantly White). This is an important caveat this study, particularly given ample literature documenting differences across racial/ethnics groups in diabetes prevalence and outcomes (Walker et al., 2016). Thus, our findings may apply only to a demographically specific subpopulation (i.e., highly educated older adults who identify as White and are willing and have access to participate in an Alzheimer's disease study) with a relatively restricted range of vascular disease. Additional research using more diverse, multiethnic epidemiological samples would therefore facilitate an enhanced understanding of how relationships between these variables compare across subpopulations, and moreover clarify important mechanisms that may underlie observed differences across demographic and clinical groups. Additionally, there was limited information available for this sample regarding other risk and protective factors for arterial stiffness and vascular disease (e.g., hemoglobin $A_{1C}$ levels, disease characteristics, disease management, health behaviors). Thus, replication of these results in a more representative community sample that is well characterized with respect to vascular risk is needed in order to further elucidate the role of arterial stiffness as a predictor of white matter pathology in aging individuals with DM. Finally, our study design was cross-sectional in nature, and thus did not address questions about directionality of these relationships nor how they might evolve over time. Future research that employs multivariate models to explore more complex associations between longitudinal pulse pressure index measurements, diabetes status, and white matter pathology is needed.

## CONCLUSION

Our results demonstrated that higher pulse pressure index values in the presence of diabetes was associated with small vessel disease as indexed by white matter hyperintensities in older adults with MCI. These findings have important implications for the early identification of individuals at risk for progressive cognitive decline and dementia, as well as the development of treatment targets to potentially stave off cognitive decline in order to optimize independence and quality of life in at-risk older adults. The proportion of people over the age of 65 is rapidly increasing in our population and the number of individuals with dementia are expected to burgeon in tandem with this population expansion. Such demographic changes will stretch resources related to the social, economic, and psychological needs of those who develop cognitive impairment in late life. While we do not yet have therapies that can reliably slow or halt cognitive decline, there are a variety of validated preventative approaches and interventions that can target vascular risk factors. Thus, identifying high-risk individuals using potentially modifiable markers, such as elevated pulse pressure index values (which is a relatively quick, cost-effective, and non-invasive proximate measure of arterial stiffness), prior to the onset of cognitive impairment may help to relieve this burden and promote independence in late adulthood, particularly in populations

where vascular risk is elevated. Future longitudinal studies that include biomarkers are needed in order to clarify the etiology and timeline of the association between pulse pressure index values and different brain aging processes. Moreover, research that extends into middle age (and focuses on earlier disease states such as prediabetes) will assist in further exploring the utility of the pulse pressure index as an early marker of risk for poor cognitive outcomes in aging.

## DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The datasets analyzed for this study can be found in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Investigators must submit an application to access ADNI data. Requests to access these datasets should be directed to the official ADNI website: adni.loni.usc.edu.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committees/institutional review boards that approved the ADNI, including: Albany Medical Center Committee on Research Involving Human Subjects Institutional Review Board, Boston University Medical Campus and Boston Medical Center Institutional Review Board, Butler Hospital Institutional Review Board, Cleveland Clinic Institutional Review Board, Columbia University Medical Center Institutional Review Board, Duke University Health System Institutional Review Board, Emory Institutional Review Board, Georgetown University Institutional Review Board, Health Sciences Institutional Review Board, Houston Methodist Institutional Review Board, Howard University Office of Regulatory Research Compliance, Icahn School of Medicine at Mount Sinai Program for the Protection of Human Subjects, Indiana University Institutional Review Board, Institutional Review Board of Baylor College of Medicine, Jewish General Hospital Research Ethics Board, Johns Hopkins Medicine Institutional Review Board, Lifespan - Rhode Island Hospital Institutional Review Board, Mayo Clinic Institutional Review Board, Mount Sinai Medical Center Institutional Review Board, Nathan Kline Institute for Psychiatric Research and Rockland Psychiatric Center Institutional Review Board, New York University Langone Medical Center School of Medicine Institutional Review Board, Northwestern University Institutional Review Board, Oregon Health and Science University Institutional Review Board, Partners Human Research Committee Research Ethics, Board Sunnybrook Health Sciences Centre, Roper St. Francis Healthcare Institutional Review Board, Rush University Medical Center Institutional Review Board, St. Joseph's Phoenix Institutional Review Board, Stanford Institutional Review Board, The Ohio State University Institutional Review Board, University Hospitals Cleveland Medical Center Institutional Review Board, University of Alabama Office of the IRB, University of British Columbia Research Ethics Board, University of California Davis Institutional Review Board Administration, University of California Los Angeles Office of the Human Research Protection Program, University of California San Diego Human Research Protections Program, University of California San Francisco Human Research Protection Program, University of Iowa Institutional Review Board, University of Kansas Medical Center Human Subjects Committee, University of Kentucky Medical Institutional Review Board, University of Michigan Medical School Institutional Review Board, University of Pennsylvania Institutional Review Board, University of Pittsburgh Institutional Review Board, University of Rochester Research Subjects Review Board, University of South Florida Institutional Review Board, University of Southern, California Institutional Review Board, UT Southwestern Institution Review Board, VA Long Beach Healthcare System Institutional Review Board, Vanderbilt University Medical Center Institutional Review Board, Wake Forest School of Medicine Institutional Review Board, Washington University School of Medicine Institutional Review Board, Western Institutional Review Board, Western University Health Sciences Research Ethics Board, and Yale University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

MW, KB, KT, ES, and LD-W contributed to conception and design of the study. KT and AW organized the database. MW performed the statistical analysis and wrote the manuscript. MB and EE provided consultation regarding MCI diagnosis using Jak et al. diagnostic criteria to identify CU and MCI participants in the ADNI database. DN provided consultation and guidance with respect to the use of PP as a measure for arterial stiffness and its application to the ADNI data. All authors contributed to manuscript revision, read, and approved the submitted version.

## FUNDING

This work was supported by the US Department of Veterans Affairs Clinical Sciences Research and Development Service (Merit Award 1I01CX001842; CDA-2 1IK2CX001865), National Institutes of Health/National Institute of Aging (NIH/NIA) grants (R01 AG063782; R01 AG049810; and R01 AG054049), and the Alzheimer's Association (AARG-18-566254).

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 16 November 2021
doi: 10.3389/fnagi.2021.734866

# Leisure Activities and Their Relationship With MRI Measures of Brain Structure, Functional Connectivity, and Cognition in the UK Biobank Cohort

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**Introduction:** This study aimed to evaluate whether engagement in leisure activities is linked to measures of brain structure, functional connectivity, and cognition in early old age.

**Methods:** We examined data collected from 7,152 participants of the United Kingdom Biobank (UK Biobank) study. Weekly participation in six leisure activities was assessed twice and a cognitive battery and 3T MRI brain scan were administered at the second visit. Based on responses collected at two time points, individuals were split into one of four trajectory groups: (1) stable low engagement, (2) stable weekly engagement, (3) low to weekly engagement, and (4) weekly to low engagement.

**Results:** Consistent weekly attendance at a sports club or gym was associated with connectivity of the sensorimotor functional network with the lateral visual ($\beta = 0.12$, 95%CI = [0.07, 0.18], FDR $q = 2.48 \times 10^{-3}$) and cerebellar ($\beta = 0.12$, 95%CI = [0.07, 0.18], FDR $q = 1.23 \times 10^{-4}$) networks. Visiting friends and family across the two timepoints was also associated with larger volumes of the occipital lobe ($\beta = 0.15$, 95%CI = [0.08, 0.21], FDR $q = 0.03$). Additionally, stable and weekly computer use was associated with global cognition ($\beta = 0.62$, 95%CI = [0.35, 0.89], FDR $q = 1.16 \times 10^{-4}$). No other associations were significant (FDR $q > 0.05$).

**Discussion:** This study demonstrates that not all leisure activities contribute to cognitive health equally, nor is there one unifying neural signature across diverse leisure activities.

**Keywords: leisure activities, brain, MRI, aging, cognition, UK Biobank**



***Edited by:***
*Francesca R. Farina, Trinity College Dublin, Ireland*

***Reviewed by:***
*Nora Bittner, Heinrich Heine University Düsseldorf, Germany*
*Rory Boyle, Trinity College Dublin, Ireland*

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***Received:*** *01 July 2021*
***Accepted:*** *05 October 2021*
***Published:*** *16 November 2021*

***Citation:***
*Anatürk M, Suri S, Smith SM, Ebmeier KP and Sexton CE (2021) Leisure Activities and Their Relationship With MRI Measures of Brain Structure, Functional Connectivity, and Cognition in the UK Biobank Cohort. Front. Aging Neurosci. 13:734866. doi: 10.3389/fnagi.2021.734866*

## INTRODUCTION

By 2050, the total number of older adults (i.e. individuals $\geq$ 60 years old) worldwide is expected to reach 2.1 billion (Prince et al., 2015). While improvements in life expectancy is a significant achievement of the 21st century, population aging represents a major societal challenge (World Health Organization, 2015). This is because older adults are often at a greater risk of developing

certain health conditions than their younger counterparts. For instance, an individual aged 90 or older has 25 times the risk of developing dementia compared to an individual in their late 60s (Yip et al., 2006; Brayne, 2007). Whole population rates of dementia, such as Alzheimer's disease, are projected to triple by 2050 as a consequence of population aging (Patterson, 2018). Consequently, there has been growing scientific interest in identifying modifiable factors that may reduce the risk of developing dementia and contribute to "better" brain health in late life.

Leisure activities (e.g., visiting friends and family, reading, and going to the cinema or museum) represent one set of modifiable factors that potentially support healthy cognitive aging, by promoting brain plasticity (Stern, 2012). For example, higher activity participation has been systematically linked to better cognitive performance, higher regional and global gray matter (GM) volume, fewer volumetric measures of WM lesions and less decline in the quality of white matter (WM) tracts (Fratiglioni et al., 2004; Wang et al., 2012; Sexton et al., 2013; Erickson et al., 2014; Yates et al., 2016; Anatürk et al., 2018; Chan et al., 2018; Evans et al., 2018; Matyas et al., 2019; Wassenaar et al., 2019). Variability in functional connectivity measures also appears to be partly accounted for by activity engagement, particularly for physically demanding activities (Stillman et al., 2019). However, many of these studies have employed composite measures of leisure activities, providing limited insights into the *specific* activities that need to be targeted to promote brain health in older individuals. Targeting non-optimal activities may in part explain the limited efficacy of current randomized-controlled trials (RCTs) on cognitive and neural outcomes (Mortimer et al., 2012; Stephen et al., 2019).

A small number of epidemiological studies have begun to shift away from the composite approach when examining the link between leisure activities and the aging brain, finding that not all activities equally contribute to the risk of cognitive impairment (Krell-Roesch et al., 2017, 2019; Fancourt et al., 2018). For example, Fancourt et al. (2018) examined data collected from 3,911 participants enrolled in the English Longitudinal Study of Aging and found that adults who visited museums, art galleries and exhibitions on a regular basis, had a lower incidence of dementia over the course of 10 years. The association between cultural activities and dementia incidence appeared to be robust, as it remained significant after adjusting for how frequently these individuals were involved in community-based activities (e.g., social clubs, volunteering, sports clubs), alongside sociodemographic (i.e., age, sex, marital status, education, employment status, wealth, and previous occupational classification), and health-related co-variates (i.e., eyesight, depression, hearing, and existing cardiovascular health conditions). Importantly, a study that aims to evaluate whether different activities relate to markers of brain health requires a comparably larger number of univariate tests, relative to when a single composite measure of leisure activity is of interest. A range of key factors also need to be appropriately adjusted for when investigating the association between leisure activities and the aging brain, due to the bias that these confounding variables can otherwise introduce in the results and conclusions of a study, including inflated effect sizes or even spurious findings. For example, education and socio-economic status (SES) are determinants of how often a person engages in cultural activities such as visiting a museum, art gallery and exhibition (Grisolía et al., 2010; Mak et al., 2020). As low levels of education and SES are linked to an increased risk of dementia (Cadar et al., 2018; Livingston et al., 2020), demonstrating an independent relationship between cultural activities and the dementia risk strengthens the argument that these activities potentially contribute to maintaining brain health in older ages. The results of such correlational studies can then help guide randomized controlled trials (RCTs) to focus their intervention programs on a specific subset of activities, to determine whether these reported associations translate to direct effects on the aging brain. With a sample that currently exceeds several thousand well-characterized individuals, the United Kingdom Biobank (UK Biobank) study offers the statistical power to employ a more fine-grained approach to investigate the relationship between activities and markers of brain health, after adjusting for a wide range of confounders. This cohort study also offers measures of activity levels at more than one timepoint, allowing us to capture how longitudinal patterns of activities relate to metrics of brain health.

The aim of this study was to investigate whether individual leisure activities relate to MRI measures of GM volume, WM microstructure, WM lesions, resting-state functional connectivity, and cognitive function in late life. We examined six leisure activities that were available in the UK Biobank: going to a pub or social club, undertaking a religious activity, attending adult education classes, going to a sports club or gym, visiting friends and family and leisure-time computer use. Based on their self-reported activity levels at two timepoints, individuals were divided into one of four groups: (1) stable weekly participation, (2) stable low participation, (3) low to weekly participation, and (4) weekly to low participation. We predicted that weekly activity participation (both stable and increased participation over time) would associate with higher global cognitive function (Brown et al., 2012; Mitchell et al., 2012; Wang et al., 2012; Yates et al., 2016; Evans et al., 2018). We further expected that consistently high or increased participation in each leisure activity would correlate with greater structural integrity, including greater regional GM and higher WM integrity (i.e., higher fractional anisotropy (FA), lower mean diffusivity (MD; Anatürk et al., 2018). Given the limited evidence investigating activity-specific effects on resting-state functional connectivity, no predictions were made regarding this modality, so any results would be exploratory.

# MATERIALS AND METHODS

## Sample Characteristics

Data was provided by participants enrolled in the UK Biobank study, a large-scale prospective cohort study. These individuals were asked to complete a range of assessments including detailed lifestyle questionnaires, cognitive tests, physical measures (e.g., blood pressure and mobility tests), provide biological samples

(e.g., blood, urine, and saliva) and also provide permission to access their National Health Services (NHS) health records. Since 2014, a sub-sample of the original 500,000 participants have been invited back to undergo a single session of MRI scanning of the brain, body and heart, with the goal of reaching 100,000 scanned individuals by 2022. Their recruitment continues, with regular data releases made available to researchers (Miller et al., 2016). At the time of paper preparation, imaging data from a total 15,000 participants had been released (January 2019).

In our analyses, we examine data collected from two study phases: at recruitment (2006–2010) and MRI assessment (2014+). As demonstrated in **Supplementary Figure 1**, leisure activity measures were taken from both timepoints, while MRI and cognitive data was taken at the second timepoint (mean years between timepoints = 8 years, range = 4–11 years). The UK Biobank study received ethical approval from the NHS National Research Ethics Service (Ref 11/NW/0382) and all enrolled participants gave their informed and written consent.

## Inclusion and Exclusion Criteria

The sample consisted of individuals without a diagnosis of stroke or dementia for the study duration, who had completed an MRI assessment and provided complete data on leisure activities and sociodemographic, health, cognitive and lifestyle variables (for flowchart, see **Supplementary Figure 2**).

## Activities

Activity levels were assessed through items displayed on a touch screen tablet. From a list of activities, participants were required to highlight those that they participated in on at least a weekly basis. Accordingly, we coded response option for each activity as (1) weekly or (2) less than weekly participation. A total of six activities were examined, which included going to a pub or social club; undertaking a religious activity; attending adult education classes; going to a sports club or gym; visiting friends and family and leisure-time computer use. Note that visiting friends and family and computer use were measured with different response options (i.e., frequency and hours) and these items were binarized into weekly/less than weekly engagement to harmonize the scales with the remaining activity measures. Further information on these items is provided in the **Supplementary Methods** section "Activity Measures." Individuals were then split into one of four groups: (1) weekly stable engagement, (2) low stable engagement, (3) low to weekly engagement, and (4) weekly to low engagement.

## Cognitive Function

A 15-min study-specific battery of cognitive assessments was administered to participants via a touch screen tablet (Cornelis et al., 2019). The cognitive measures examined are described in **Table 1**, with a detailed description of each measure in the **Supplementary Material**. A measure of global cognitive function was computed by summing across all cognitive measures. Prior to this step, all continuous cognitive scores were standardized, with the outcomes of the alphanumeric and numeric trail making tasks and Pairs Matching test reverse scored to allow higher scores to reflect "better" performance.

**TABLE 1 |** Neuropsychological tests of the UK Biobank battery examined in the present study.

| Cognitive test | Outcome |
|---|---|
| Fluid intelligence | Total number of questions answered correctly (maximum score: 13) |
| Numeric/Alphanumeric Trail making | Time (in seconds) taken to complete the trail |
| Digit span | Maximum number of digits recalled (maximum score: 12) |
| Pairs matching | Number of incorrect matches made |
| Prospective memory | Whether or not participant responded correctly at first attempt |
| Symbol digit matching | Number of correct symbol-digit matches |
| Simple reaction time | Mean response time (in seconds) across the 4 trials containing matching pairs |

## Demographic and Health-Related Variables

Baseline measures of age, sex, education, occupation, frequency of alcohol intake, sleep duration, body mass index (BMI), Mean arterial pressure (MAP), and social isolation (total number of individuals in household) were collected. ICD-10 diagnoses of depressive or anxiety disorders developed over the study duration was also examined. Additional information about these variables can be found in the **Supplementary Material**.

## MRI Data Acquisition and Pre-processing

Participants were scanned using identical protocols with Siemens Skyra 3T (software VB13) and a Siemens 32-channel head coil at one of two study sites (i.e., Stockport or Newcastle).

$T_1$-weighted images, diffusion-weighted images, T2 FLAIR images and resting-state functional images were assessed. Summary measures of brain structure and functional connectivity, or Image Derived Phenotypes (IDPs), have been generated on behalf of UK Biobank (Alfaro-Almagro et al., 2018) and are available from UK Biobank upon data access application. For a detailed description of the imaging protocol and pre-processing steps, please see the **Supplementary Material**. The IDPs generated from this pipeline consisted of total and regional GM volume (142 IDPs), total WM volume and lesions within WM (2 IDPs), WM microstructure (FA and MD in 27 pre-defined tracts, 54 IDPs), and partial correlation functional connectivity between large-scale resting-state networks (210 IDPs). GM and WM IDPs were averaged across left and right hemispheres, resulting in a total of 76 GM outcomes and 63 WM outcomes. For a comprehensive list of all IDPs examined in our study, please see **Supplementary File**: List of MRI Outcomes.

## Statistical Analysis

All analyses were performed in R (version 3.5.2). The lm function in R was used to fit a series of linear models to evaluate the relationship between each type of activity (e.g., going to a sports club or gym; visiting friends and family) and each of the neuroimaging outcomes and global cognition, after adjusting

for a range of co-variates. The co-variates included age, sex, education, occupational status, assessment center, BMI, Mean Arterial Pressure (MAP), frequency of alcohol intake, sleep duration, the presence of depressive or anxiety disorders and the number of individuals living in a household. Mean head motion and head size were also included as co-variates in the analysis of neuroimaging metrics. Six linear models (one for each type of activity) were run across the entire sample for every activity-outcome combination, with 139 MRI outcomes (i.e., 76 GM and 63 WM measures) and 1 cognitive outcome examined. This resulted in a total of 840 linear regressions that were conducted, with an example of the general formulae used for these models provided below:

$y = \beta 0 + \beta 1$ weekly stable activity engagement $+ \beta 2$ low to weekly activity engagement $+ \beta 3$ weekly to low activity engagement $+ \beta 4$ age $+ \beta 5$ sex $+ \beta 6$ education $+ \beta 7$ occupation $+ \beta 8$ assessment center $+ \beta 9$ body mass index $+ \beta 10$ mean arterial pressure $+ \beta 11$ alcohol intake $+ \beta$ 12 sleep duration $+ \beta 13$ depressive/anxiety disorder $+ \beta 14$ number in household $+ \beta 15$ mean head motion (MRI outcomes only) $+ \beta 16$ head size (MRI outcomes only) $+ \varepsilon$.

Prior to the analysis, the distributions of all dependent variables were screened, with the distributions of total WM lesions log-transformed due to non-normality. All continuous variables were also standardized before the analysis, while categorical variables were dummy coded. A total of three dummy variables were used to reflect different engagement patterns for a given activity: (1) weekly stable activity engagement (=1, all other groups = 0), (2) low to weekly activity engagement (=1, all other responses = 0), and (3) weekly to low activity engagement (=1, all other responses = 0). Based on prior evidence indicating that low levels of activity are linked to poorer brain health and cognitive outcomes (Brown et al., 2012; Mitchell et al., 2012; Wang et al., 2012; Yates et al., 2016; Anatürk et al., 2018), individuals in the "low stable" group were chosen as our reference category. Comparisons of age, sex and education and ICD-10 diagnosis of anxiety/depression between each group for a given activity can be found in **Supplementary File:** Group Comparisons.

Due to the number of univariate tests conducted, FDR-corrections were applied. To facilitate these corrections, the p.adjust function in R was applied with a two-tailed FDR $q$ value $< 0.05$ considered significant (Cox et al., 2019). We report standardized beta coefficients (β), 95% confidence intervals and FDR $q$-values in the main text. The results of all associations examined are also included in the **Supplementary File**: Results. Excluded and included participants were compared on age, sex, education and ICD-10 diagnosis of anxiety or depression, which are reported in **Supplementary Table 1**.

# RESULTS

## Participant Demographics

**Table 2** provides a detailed description of the sample demographics. In brief, a total of 7,152 participants were included in the analysis of neuroimaging outcomes. Participants were on average 56.39 years old ($SD$ = 7.31) at baseline and

**TABLE 2 |** Sample characteristics.

| | | Range |
|---|---|---|
| No. of participants | 7,152 | |
| Duration between baseline and MRI scan (years) | 7.55 | 4.29–10.85 |
| **Demographics** | | |
| Age at baseline (years) | 56.39 ± 7.31 | 40–70 |
| Age at MRI scan (years) | 63.94 ± 7.32 | 46–80 |
| No. of females (%) | 3,897 (54.5) | |
| Highest educational qualification (%) | O levels/GCSE = 146 (2%) \| CSE = 771 (10.8%) \| A levels/AS = 398 (5.6%) NVQ/HND/HNC = 2213 (30.9%) \| CU = 3624 (50.7%) | |
| Occupational status n. (%) | 0 = 1480 (20.7%) \| 1 = 17 (0.2%) \| 2 = 29 (0.4%) \| 3 = 37 (0.5%) \| 4 = 58 (0.8%) \| 5 = 154 (2.2%) \| 6 = 513 (7.2%) \| 7 = 1046 (14.6%) \| 8 = 2290 (32%) \| 9 = 1528 (21.4%) | |
| **Activities** | | |
| **No. (%) reporting weekly participation at** | **Baseline** | **Follow-up** |
| Leisure-time computer use | 6,340 (88.7) | 6,778 (94.8) |
| Visiting friends and family | 5,750 (80.4) | 5,874 (82.1) |
| Going to the pub or social club | 2,540 (35.5) | 2,513 (35.1) |
| Undertaking religious activities | 1,723 (24.1) | 1,770 (24.8) |
| Attending educational courses | 903 (12.6) | 775 (10.8) |
| Going to a sports club or gym | 3,852 (50.1) | 3,539 (49.5) |
| **Health and Lifestyle** | | **Range** |
| BMI (kg/m$^2$) | 26.4 ± 4.01 | 16.14–55.07 |
| MAP | 99.57 ± 11.84 | 60–152.83 |
| No. (%) with ICD-10 diagnosis of Depression/Anxiety | 51 (0.71) | |
| Sleep duration (hours/night) | 7.21 ± 0.93 | 2–13 |
| Alcohol (frequency/week) | 0 = 300 (4.2%) \| 1 = 499 (7%) \| 2 = 664 (9.3%) \| 3 = 1,837 (25.7%) \| 4 = 2,183 (30.5%) \| 5 = 1,669 (23.3%) | |
| **Structural MRI measures** | | |
| Total GM (volume, mm$^3$) | 613,301.98 ± 54,614.44 | 443,926–832,927 |
| WM (volume, mm$^3$) | 547,421.16 ± 61,214.82 | 362,561–804,641 |
| CSF (volume, mm$^3$) | 36,479.39 ± 17,032.15 | 7,613.27–157,075 |
| WM hyperintensities (volume, mm$^3$)* | 2,752 (4054.5) | 30–86,534 |
| **Cognitive function ($n$ = 1,734)** | | |
| Fluid intelligence score | 7.04 ± 1.93 | 1–13 |
| Alphanumeric trail making (seconds)* | 47.9 (20.08) | 21.10–242.10 |
| Numeric trail making (seconds)* | 19.9 (6.5) | 9.40–112.90 |
| Pairs matching test (total errors)* | 6 (4) | 0–28 |

*(Continued)*

**TABLE 2 |** (Continued)

| | | Range |
|---|---|---|
| Simple reaction time (seconds) | 0.59 ± 0.1 | 0.37–1.34 |
| No. of correct symbol-digit matches | 19.74 ± 5.14 | 2–36 |
| Backward digit span score | 6.91 ± 1.22 | 2–12 |
| Prospective memory score (No. % correct) | 1,510 (87.1%) | |

*Values are Mean ± Standard deviation and N (%) for categorical variables, unless otherwise stated. *Median (IQR) reported.*
*BMI, body mass index; BP, blood pressure; CSE, certificate of secondary education, CSF, cerebrospinal fluid; CU, college or university degree, GCSE, general certificate of secondary education; GM, gray matter; HNC, higher national certificate; HND, higher national diploma; ICD, international classification of diseases; MAP, mean arterial pressure; MRI, magnetic resonance imaging; OL, O-levels, N, number; NVQ, national vocational qualifications; WM, white matter.*
*Occupational status was coded according to the following scale: 0 = "Unemployed/Retired/Unable to work/Student," 1 = "Elementary Occupations," 2 = "Process, plant and machine operatives," 3 = "Sales and Customer Service Occupations," 4 = "Personal Service Occupations," 5 = "Skilled Trades Occupations," 6 = "Administrative and Secretarial Occupations," 7 = "Associate Professional and Technical Occupations," 8 = "Professional Occupations," and 9 = "Manager and Senior Officials. Alcohol intake was measured on a 5-point scale: 5 = "daily or almost daily," 4 = "three or four times a week," 3 = "once or twice a week," 2 = "one to three times a month," and 1 = "special occasions only" or 0 = "never."*

63.94 years old (*SD* = 7.32) at follow-up. Females represented 54.5% of the sample (*n* = 3,897). A substantially smaller number of individuals had provided complete data for all cognitive measures at follow-up and were therefore analyzed as a sub-set (*n* = 1,734) of the main sample. The percentage of participants in each activity group (along with the percentage of females) are reported in **Table 3**. Comparisons between the analytical samples and excluded participants (**Supplementary Table 1**) suggested that the MRI sample were significantly older, more educated and had a higher occupation status and higher proportion of females than compared to excluded participants. These group differences were also found for sex, education and occupational status in the cognitive sample. No significant group differences were observed in the proportion of individuals with an ICD-10 diagnoses of anxiety/depression in either sample. For group comparisons on these variables between each activity group, please see **Supplementary File**: Group Comparisons.

**TABLE 3 |** Summarizing the number of individuals in each activity group, for the MRI and cognitive samples.

| Activity | Stable low engagement | Weekly to low engagement | Low to weekly engagement | Stable weekly engagement |
|---|---|---|---|---|
| **MRI sample** | | | | |
| **Computer use** | 197 (2.8%); | 177 (2.5%); | 615 (8.6%); | 6163 (86.2%) ; |
| *No. of females (%)* | 129 (65.5%) | 120 (67.8%) | 412 (67%) | 3,236 (52.5%) |
| **Educational classes** | 5804 (81.2%); | 573 (8%); | 445 (6.2%); | 330 (4.6%); |
| *No. of females (%)* | 2,947 (50.8%) | 387 (67.5%) | 312 (70.1%) | 251 (76.1%) |
| **Religious activities** | 5,208 (72.8%) ; | 174 (2.4%); | 221 (3.1%); | 1,549 (21.7%); |
| *No. of females (%)* | 2,659 (51.1%) | 106 (60.9%) | 152 (68.8%) | 980 (63.6%) |
| **Pub/social club** | 3974 (55.6%); | 665 (9.3%); | 638 (8.9%); | 1875 (26.2%); |
| *No. of females (%)* | 2,573 (64.7%) | 347 (52.2%) | 340 (53.3%) | 637 (34%) |
| **Sports club/gym** | 2707 (37.8%); | 906 (12.7%); | 875 (12.2%); | 2664 (37.2%); |
| *No. of females (%)* | 1,408 (52%) | 529 (58.4%) | 525 (60%) | 1,435 (53.9%) |
| **Visiting friends/family** | 685 (9.6%) ; | 593 (8.3%); | 717 (10%); | 5157 (72.1%); |
| *No. of females (%)* | 314 (45.8%) | 277 (46.7%) | 377 (52.6%) | 2,929 (56.8%) |
| **Cognitive sample** | | | | |
| **Computer use** | 45 (2.6%); | 48 (2.8%); | 142 (8.2%); | 1,499 (86.4%); |
| *No. of females (%)* | 31 (68.9%) | 36 (75%) | 89 (62.7%) | 795 (53%) |
| **Educational classes** | 1,385 (79.9%) ; | 161 (9.3%); | 110 (6.3%); | 78 (4.5%); |
| *No. of females (%)* | 704 (50.8%) | 107 (66.5%) | 83 (75.5%) | 57 (73.1%) |
| **Religious activities** | 1,270 (73.2%) ; | 44 (2.5%); | 45 (2.6%); | 375 (21.6%); |
| *No. of females (%)* | 643 (50.6%) | 27 (61.4%) | 34 (75.6%) | 247 (65.9%) |
| **Pub/social club** | 958 (55.2%); | 162 (9.3%); | 169 (9.7%); | 445 (25.7%); |
| *No. of females (%)* | 638 (66.6%) | 87 (53.7%) | 82 (48.5%) | 144 (32.4%) |
| **Sports club/gym** | 621 (35.8%); | 208 (12%); | 241 (13.9%); | 664 (38.3%); |
| *No. of females (%)* | 325 (52.3%) | 119 (57.2%) | 137 (56.8%) | 370 (55.7%) |
| **Visiting friends/family** | 167 (9.6%) ; | 155 (8.9%); | 184 (10.6%) ; | 1,228 (70.8%) ; |
| *No. of females (%)* | 73 (43.7%) | 73 (47.1%) | 92 (50%) | 515 (41.9%) |

*Numbers and percentages are reported as well as the percentage of females in each group. For comparisons of age, sex, education and the presence of ICD-10 diagnoses of anxiety/depression, please see **Supplementary File**: Group Comparisons.*

## Cognitive Function

Stable weekly computer use was linked to higher global cognitive performance, relative to stable low computer use (β = 0.62, 95%CI = [0.35, 0.89], FDR $q = 1.16 \times 10^{-4}$). No other activities were significantly linked to cognitive performance (FDR *q*'s > 0.05).

## Structural MRI

Stable weekly family/friend visits were associated with higher GM volume in the occipital pole, in comparison to individuals consistently reporting infrequent family and friend visits (β = 0.15, 95%CI = [0.08, 0.21], FDR *q* = 0.03). No significant associations were found for any other activity with GM volume, tract-specific FA or MD, total WM volume or lesions (FDR *q*'s > 0.05).

## Functional MRI

Stable weekly engagement at a sports club or gym was associated with stronger absolute connectivity between the sensorimotor network and lateral visual network, relative to stable low engagement (β = 0.12, 95%CI = [0.07, 0.18], FDR $q = 2.04 \times 10^{-2}$; **Figure 1**). Similarly, stronger connectivity was also observed between the sensorimotor and cerebellar networks for this activity (β = 0.12, 95%CI = [0.07, 0.18], FDR $q = 2.04 \times 10^{-2}$; **Figure 1**). The association for sensorimotor-cerebellar network connectivity (β = 0.12, 95%CI = [0.07, 0.18], FDR $q = 1.23 \times 10^{-4}$) and sensorimotor-lateral visual network connectivity (β = 0.12, 95%CI = [0.07, 0.18], FDR $q = 2.48 \times 10^{-3}$) remained significant after adjusting

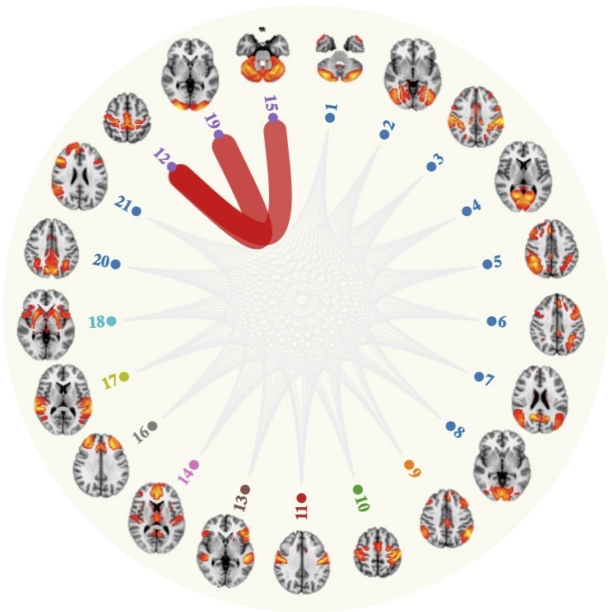


**FIGURE 1 |** Attending a sports club and gym on a weekly basis associated with stronger connectivity (red lines) between the sensorimotor network (node 12) and lateral visual network (node 19) and cerebellar network (node 15).

for physical activity levels (i.e., summed weekly Metabolic equivalent of task (MET) minutes, n. with physical activity information = 6,289) and global GM volume. There were no significant associations between any other activity and resting-state functional connectivity strength (FDR $q > 0.05$).

## DISCUSSION

We present the largest multi-modal study to examine whether patterns of engagement in leisure activities associate with markers of brain structure, functional connectivity, and cognition. We found that stable weekly participation in a sports club or gym correlated positively with connectivity of the sensorimotor network. Additionally, weekly visits to or from family and friends was associated with higher volumetric measures of GM in the occipital pole. However, apart from consistent leisure time computer use, no other activity was significantly linked to global cognition. Each of these results are discussed, in turn.

One of our main findings was that consistent, weekly visits to a gym or sports club correlated with greater absolute connectivity of the sensorimotor network and cerebellar network, relative to infrequent attendance over time. Similar activation patterns at rest and during task execution indicate that both the sensorimotor and cerebellar networks play a role in motor tasks (Smith et al., 2009), potentially interacting with one another to support motor behavior. Subdivisions of the cerebellum are typically found within the sensorimotor network (Habas et al., 2009; Dobromyslin et al., 2012), an observation that was also replicated in our study (**Supplementary Figure 3**). The present findings additionally identified a link between connectivity of the sensorimotor and lateral visual network in individuals reporting consistent gym and sports club attendance across time, suggesting that sustained activity engagement contributes to enhanced visual-motor coupling. Potentially underlying this relationship is the importance of visual information in regulating and updating current behavior during physical exercise (Mallek et al., 2017). Our findings are in line with a previous study reporting strengthened connectivity between regions involved in the sensorimotor network, cerebellar and visual network, following a 13-week cognitive and motor skills training intervention (Demirakca et al., 2016). Task based fMRI has also highlighted a greater BOLD response in regions involved in these networks (Domingos et al., 2021). For example, the supplementary motor areas, precentral gyrus, angular gyrus and supramarginal gyrus were among the areas to demonstrate greater BOLD activation during a famous face recognitions task, in a group of adults (age range = 65 to 85) reporting high physical activity levels ($n$ = 34) relative to a low physical activity group ($n$ = 34, Smith et al., 2011). However, stronger connectivity *between* resting-state networks in an aging sample is not entirely straightforward to interpret. For instance, older adults often exhibit less segregated sensorimotor networks (i.e., lower within-network connectivity and higher between-network connectivity) when compared to younger adults, with these increases in connectivity linked to poorer task performance (e.g., reaction time, dexterity; Cassady et al., 2019). Additionally, physical activity levels did not account for the associations observed across the sensorimotor-visual-cerebellar networks, suggesting that other factors (e.g., physical fitness or socially interacting with others) may support these associations.

A difficulty in interpreting our findings is that while gym/sports club attendance was linked to greater connectivity between the visual and sensorimotor networks, no parallel associations were found between this activity and cognition, despite an established link between physical activity participation and cognitive function (Kelly et al., 2014; Erickson et al., 2019). The absence of a relationship with global cognition may be partly explained by the lower statistical power present in the analyses of cognitive function relative to the MRI analyses, due to the smaller sample size (1,734 individuals versus 7,152 individuals in the MRI sample). As we focused our analyses on global cognition, our study may have also failed to detect specific cognitive domains that are sensitive to gym/sports club participation (e.g., executive function (Erickson et al., 2019). Future studies examining cognitive subdomains could therefore provide novel insights into the cognitive correlates of these types of activities. Additionally, we were only able to generate a crude measure of activity participation based on the measures available in the UK Biobank study, which potentially hampered our ability to detect a link between gym/sports club attendance and cognitive function. Specifically, the granularity of our activity measure may have prevented us from capturing sufficient inter-individual variation in activity levels, such as between individuals who attended a gym/sports club once a week to those who attend it on a more regular basis (e.g., five times a week). Further work would therefore benefit from using more fine-grained assessments of activities (e.g., duration and frequency), as this approach could

offer enhanced sensitivity in detecting associations between gym/sport club attendance and cognitive function. A final and more general consideration is that attending the gym or sports clubs is unlikely to serve as an accurate proxy of overall physical activity levels, as many activities can be performed outside of these settings (e.g., running and cycling). This could explain why our study failed to replicate well-established links between physical activity, GM and WM outcomes (Cheng, 2016; Sexton et al., 2016; Wassenaar et al., 2019).

Another of our key findings was that consistently visiting friends and family on a weekly basis associated with higher GM volume in the occipital pole, relative to low and stable patterns. This finding offers partial support for our second hypothesis. Two previous studies have also reported a relationship between higher social activity levels and higher GM volume within this region (James et al., 2012; Arenaza-Urquijo et al., 2016), consistent with the "brain maintenance" (Nyberg et al., 2012) or "brain reserve" (Stern, 2012) hypotheses. However, other studies have not replicated this association (Foubert-Samier et al., 2012; Seider et al., 2016; Anatürk et al., 2020), or otherwise report associations across frontal, parietal and temporal regions (Valenzuela et al., 2008; Arenaza-Urquijo et al., 2015; Seider et al., 2016). The discrepant findings may be due to the use of a cross-sectional assessment of activities in most of these studies or alternatively a lack of assessment into activity-specific relationships. While the frontal and temporal regions are considered to be the most age-sensitive, GM in the occipital cortex also demonstrates a negative relationship with age (e.g., Allen et al., 2005; Fjell and Walhovd, 2010; Lemaitre et al., 2012; Raz et al., 2005). Sustained interpersonal interactions could potentially prevent age-related neuronal or synaptic loss or otherwise promote synaptic or dendritic plasticity (Anatürk et al., 2018). Animal studies offer support for this interpretation (e.g., Briones et al., 2004; Okuda et al., 2009; Zhao et al., 2011; Jung and Herms, 2014), with one study reporting an increase in the synaptic density of the rat visual cortex after housing in an enriched environment for a month (Briones et al., 2004). At the same time, the selectivity of the occipital cortex needs to be interpreted with caution, given the "blunt" nature of our activity measure. Overall, our results suggest that encouraging middle-aged and older adults to stay engaged with their existing social network could potentially be an important avenue for supporting individuals through their later years of life.

Individuals who consistently reported weekly computer use had higher global cognitive performance, relative to those who consistently reported less frequent participation over time. Despite the small number of individuals in the low and stable group (i.e., reference group; $n$ = 197) this association was one of the few to survive FDR corrections. These results are in line with prior findings indicating a link between frequent computer (Tun and Lachman, 2010) and internet use (Berner et al., 2019) and better cognitive function. Our findings further complement the observation that computerized cognitive training programs lead to improvements in trained cognitive domains, with some findings suggesting transfer to untrained domains (e.g., Kueider et al., 2012; Nguyen et al., 2019). While speculative, the pathway linking computer use to cognition could be through an increased exposure to novelty (e.g., reading articles online), a greater demand on psychomotor skill (through mouse use and typing) and/or the opportunity to engage several domains of cognition at once (e.g., attention and memory when playing computer games; Tun and Lachman, 2010). Nevertheless, we cannot rule out the explanation that individuals who frequently use the computer are more accustomed to using technology and may have had an advantage to non-users on the computerized cognitive assessments administered in the UK Biobank. Reverse causation could alternatively explain our results, such that individuals with higher levels of cognitive function are inclined to spend more of their time using computers relative to individuals with lower levels of global cognition. While no structural or functional correlates were found for this activity, a link with GM volume in the putamen was detected at trend-level ($\beta$ = 0.22, 95%CI = [0.12, 0.33], FDR $q$ = 0.07), **Supplementary File**: Results). The putamen is implicated in both movement preparation and execution and non-motor functions, (e.g., executive control, working and episodic memory and category fluency, Ell et al., 2011) and although the trend reported here needs to be independently validated by future studies, it could represent a potential region of interest for studies investigating potential mediators of the computer-cognition association. Taken together, our results suggest that improving computer use level among middle-aged adults represents an important aim of future RCTs, which will also concurrently establish the directionality of the associations reported here.

Otherwise, contrary to our hypotheses, none of the other activities examined (i.e., going to the pub or social clubs, attending an adult educational class, undertaking religious activities) were associated with markers of GM, WM microstructure, functional connectivity or cognitive function, after FDR corrections. While prior meta-analytic investigations have identified associations with brain structure (Anatürk et al., 2018) and cognition (Kuiper et al., 2016) when composite measures of activities were used, our results suggest that comparatively speaking, they do not uniquely contribute to brain health in early late life. The alternative explanation is that the crude measure of activity levels used in our study potentially attenuated associations between these activities and neural/cognitive outcomes. Therefore, an important next step for this line of work is to examine whether our results are replicated when assessing other dimensions of engagement (i.e., duration and frequency). Considering that the present findings imply dissociable effects between activities in brain-cognition associations, our results are in favor of an approach sensitive to these inter-activity differences when the statical power of a study allows for it. However, it also needs to be considered that cumulative engagement over separate activities is likely necessary for sustained improvement in brain function, especially as only weak associations were found for the individual activities investigated in our study. Accordingly, we repeated our results with the inclusion of cumulative leisure activities (i.e., number of activities engaged in on a weekly basis across the two timepoints) and found that although cumulative activities were not significantly linked to any MRI or cognitive outcomes, a trend (i.e., $\beta$ = 0.03, 95%CI = [0.02, 0.05], FDR $q$ = 0.066,

**Supplementary File**: Results [Posthoc MRI results]) was detected for higher cumulative activity and stronger connectivity between the medial visual and posterior default mode network, which was not observed for any specific activity. Hence, activity-specific associations could serve as complementary to that of composite leisure activity scores. Overall, our results are informative to clinicians and researchers planning intervention studies as we highlight several activities that may play a role in maintaining brain health in older adult populations.

## Strengths and Limitations

The core strength of this study is the use of longitudinal leisure activity data provided by a large cohort of middle-aged and older adults. This design enabled novel insights into the neural and cognitive correlates of life activities, while minimizing the risk of recall errors inherent in retrospective assessments of baseline activity levels (Gow et al., 2017). Furthermore, corrections for multiple comparisons were applied to minimize the risk of type I errors, due to the large number of associations examined. However, we were only able to examine six activities due to limited coverage in the Biobank study. Other common activities, such as reading (Paillard-Borg et al., 2009) were not investigated. There was also a lack of specificity in some of the activity items, for example, no information was collected on the type of social or sports clubs that respondents attended. These highlighted weaknesses in our activity measure reflect a more general limitation in the field, where activity questionnaires are often brief or otherwise include non-specific items on club participation (e.g., Cognitive Activities Scale (Wilson et al., 1999, 2003, 2005); Cognitive Reserve Index Questionnaire (Nucci et al., 2012); Cognitive & Leisure Activity Scale (Galvin et al., 2021). We therefore recommend that the activity measures employed by future studies include a comprehensive list of activities and integrate an open-ended question that allows respondents to clarify the type of sports/social clubs that they participate in during their leisure time.

The observational design is also a major weakness of this study. Due to the opportunistic self-selected nature of the sample, we are unable to rule out reverse causation or residual confounding by a third unaccounted for variable. Additionally, at the time of manuscript preparation only a single timepoint of MRI data was available, meaning that the associations reported between gym/sports club attendance and connectivity of the sensorimotor and lateral network could reflect *pre-existing* differences in visual-motor coupling between individuals who engage frequently in this activity compared to those who do so infrequently. Future releases of longitudinal MRI data from the UK Biobank study will help to delineate the directionality of these associations and RCTs will serve to establish whether the reported associations translate to direct effects. Cohort effects serve as another alternative explanation of our results. For example, while older individuals who are now fully engaged with technology may gain cognitive benefits, the same effects might not be observed in 20 years' time as it becomes more common for individuals to become computer literate from a young age. We also note significant differences between individuals included in the sample to those excluded, with those included generally being older, more educated and from a higher occupational grade and more likely to be female. These comparisons complement the observation that the larger Biobank cohort is not entirely representative of the British general population (Fry et al., 2017). This would suggest that our results are most applicable to those who share similar characteristics to our sample and may not equally generalize to all middle- and older-aged adults.

A final limitation of our study is that while we compared each trajectory group against the "low and stable" group for each activity, we did not compare these trajectory groups against each other, which may have revealed further insights into how differences in activity trajectories relate to brain structure, functional connectivity and cognition. This study therefore represents an initial step toward better characterizing activity-specific associations with the brain but is by no means exhaustive. Further work is required to parse out the specific set of activities that have greater implications for brain aging, generating evidence that may help improve current RCTs designs and retirement programs to ensure that the most promising activities are targeted.

# CONCLUSION

We found that sustained sports club/gym attendance was linked to greater absolute connectivity of the sensorimotor connectivity although no parallel associations with cognition were found. Conversely, consistent family and friend visits over time were associated with higher volumetric measures of GM in the occipital cortex. Only weekly leisure time computer use over time was linked higher levels of global cognition. Overall, this study demonstrates selective associations between different leisure activities, highlighting several that may be relevant for RCTs aiming to promoting cognitive health in late life.

# DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Data access to the UK Biobank will need to requested through a standard data access procedure. Requests to access these datasets should be directed to http://www.ukbiobank.ac.uk/register-apply.

# ETHICS STATEMENT

The studies involving human participants were reviewed and approved by NHS National Research Ethics Service (Ref 11/NW/0382). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

SMS provided the overall scientific strategy for UK Biobank brain imaging. MA planned and conducted the analyses and prepared the manuscript, including all tables and the figures. SS, SMS, CES, and KPE provided feedback and comments on all versions of the manuscript. All authors contributed to the article and approved the submitted version.

## FUNDING

This research was conducted using the UK Biobank Resource under the approved application of 45301. The UK Biobank resource and brain imaging extension was funded by the UK Medical Research Council and the Wellcome Trust. MA was supported by the Clarendon Trust DPhil Fellowship and HDH Wills 1965 Charitable Trust (1117747). SS was supported by a fellowship from the UK Alzheimer's Society (Ref 441), the EU Horizon 2020 Program "Lifebrain" (Grant No. 732592) and WIN (203139/Z/16/Z). SMS receives support from the Wellcome Trust (098369/Z/12/Z, 203139/Z/16/Z). KPE reports support from the UK Medical Research Council (G1001354, MR/K013351/), the HDH Wills 1965 Charitable Trust (1117747), Alzheimer's Research UK (PPG2012A-5), and the European Commission (Horizon 2020 grant "Lifebrain," 732592). SS and CES were supported by the NIHR Oxford Biomedical Research Center located at the Oxford University Hospitals NHS Trust and the University of Oxford, the NIHR Oxford Health BRC. The Wellcome Center for Integrative Neuroimaging was supported by core funding from the Wellcome Trust (203139/Z/16/Z).

## ACKNOWLEDGMENTS

The authors thank all participants of the UK Biobank study who have dedicated their valuable time toward this project and the UK Biobank team for collecting, preparing, and providing data used in this work.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.734866/full#supplementary-material

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**Conflict of Interest:** This research was conducted using the UK Biobank Resource under the approved application of 45301. MA was supported by the Clarendon Trust DPhil Fellowship and HDH Wills 1965 Charitable Trust (1117747). SS reports funding from the Academy of Medical Sciences/the Wellcome Trust/the Government Department of Business, Energy and Industrial Strategy/the British Heart Foundation/Diabetes UK Springboard Award (SBF006\1078). SMS receives support from the Wellcome Trust (098369/Z/12/Z, 203139/Z/16/Z). KPE reports support from the UK Medical Research Council (G1001354, MR/K013351/), the HDH Wills 1965 Charitable Trust (1117747), Alzheimer's Research UK (PPG2012A-5), and the European Commission (Horizon 2020 grant "Lifebrain," 732592). SS and CES were supported by the NIHR Oxford Biomedical Research Center located at the Oxford University Hospitals NHS Trust and the University of Oxford, the NIHR Oxford Health BRC. The Wellcome Center for Integrative Neuroimaging was supported by core funding from the Wellcome Trust (203139/Z/16/Z). CES is now a full-time employee of the Alzheimer's Association.

frontiers in Aging Neuroscience

PERSPECTIVE
published: 08 December 2021
doi: 10.3389/fnagi.2021.783297

# Psychographic Segmentation: Another Lever for Precision Population Brain Health

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Dementia prevention interventions that address modifiable risk factors for dementia require extensive lifestyle and behavior changes. Strategies are needed to enhance engagement and personalization of the experience at a population level. Precision Population Brain Health aims to improve brain health across the lifespan at a population level. Psychographic segmentation is a core component of Precision Population Brain Health with untapped potential. Psychographic segmentation applies behavioral and social sciences to understanding people's motivations, values, priorities, decision making, lifestyles, personalities, communication preferences, attitudes, and beliefs. Integrating psychographic segmentation into dementia care could provide a more personalized care experience and increased patient engagement, leading to improved health outcomes and reduced costs. Psychographic segmentation can enhance patient engagement for dementia and shift the clinical paradigm from "What is the matter?" to "What matters to you?" Similar benefits of psychographic segmentation can be provided for dementia caregivers. Developing dementia prevention programs that integrate psychographic segmentation could become the basis for creating a shared framework for prevention of non-communicable diseases and brain health disorders at a population level. Integrating psychographic segmentation into digital health tools for dementia prevention programs is especially critical to overcome current suboptimal approaches. Applying psychographic segmentation to dementia prevention has the potential to help people feel a sense of empowerment over their health and improve satisfaction with their health experience—creating a culture shift in the way brain health is approached and paving the way toward Precision Population Brain Health.

**Keywords: psychographic segmentation, precision/personalized medicine, population health, dementia prevention, patient engagement**

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***Edited by:***
*Frauke Beyer, Max Planck Institute for Human Cognitive and Brain Sciences, Germany*

***Reviewed by:***
*Ruth Stephen, University of Eastern Finland, Finland*
*Craig Speelman, Edith Cowan University, Australia*

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***Received:*** *25 September 2021*
***Accepted:*** *19 November 2021*
***Published:*** *08 December 2021*

***Citation:***
*Smith E, Ibanez A, Lavretsky H, Berk M and Eyre HA (2021) Psychographic Segmentation: Another Lever for Precision Population Brain Health. Front. Aging Neurosci. 13:783297. doi: 10.3389/fnagi.2021.783297*

## INTRODUCTION

The dearth of clinically established dementia therapeutics emphasizes the importance of prevention approaches (Rabinovici, 2021). The 2020 Lancet Commission on dementia prevention, intervention, and care identified 12 modifiable risk factors for dementia and developed a life-course model of dementia prevention based on these factors (Livingston et al., 2020). The risk factors are less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury (TBI), and air pollution (Livingston et al., 2020). Modifying these 12 risk factors might prevent or delay up to 40% of dementias and maybe even more in low-income and middle-income countries where around two-thirds of people with dementia live (Livingston et al., 2020; Patterson, 2018). Dementia prevention interventions that address modifiable risk factors for dementia, such as the Finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER) (Ngandu et al., 2015), require extensive lifestyle and behavior changes. Consequently, strategies are needed to enhance engagement and personalization of the experience at a population level.

Precision Population Brain Health aims to improve brain health across the lifespan at a population level. It fuses Precision Brain Health (Fernandes et al., 2017; Frisoni et al., 2020) and Population Brain Health (UCSF Center for Population Brain Health, 2021). Engagement and personalization at a population level is key to Precision Population Brain Health. For Precision Population Brain Health to be achieved, insights from various disciplines must be combined. For example, for efforts such as widespread dementia prevention, platform technologies (e.g., telemedicine, apps) and frontier technologies (e.g., genomics, AI, robotics), creative care, culturally competent care, personalization techniques, and behavior design must be combined to address social determinants and other modifiable risk factors for dementia.

Psychographic segmentation is a core component of Precision Population Brain Health with untapped potential. Psychographic segmentation applies behavioral and social sciences to understanding people's motivations, values, priorities, decision making, lifestyles, personalities, communication preferences, attitudes, and beliefs (Samuel, 2016). Complementing demographic and socioeconomic segmentation, psychographic segmentation enables people to be divided into sub-groups based on shared psychological characteristics. Since the 1970s, psychographic segmentation has been used by the world's most successful consumer product and retail companies to understand and influence consumer behavior. It is commonly leveraged by the corporate sector to better understand employees and build more successful organizations. Psychographic segmentation has potential to improve dementia prevention initiatives and to provide a more ecological, decision making-oriented evaluation of both people with dementia and their caregivers.

## PSYCHOGRAPHIC SEGMENTATION FOR HEALTH

Psychographic segmentation has only recently started to be used for healthcare applications. Currently, many healthcare programs are one-size-fits-all or are based on a shared diagnosis. This often does not lead to high adoption rates of recommended behaviors. This highlights a need for personalization, creating an opportunity for psychographic segmentation to increase patient engagement and improve outcomes (Hardcastle and Hagger, 2015). Applying psychographic segmentation to healthcare enables organizations within healthcare to understand—and classify accordingly—if individual consumers take a proactive or reactive approach to health and wellness; want many or few choices; want traditional and/or alternative medicine; prioritize others' health and wellness over their own; and more. For example, if someone lives in the "here and now" and does not prioritize their long-term health, messages from a health system may be sent *via* text instead of email and include language that emphasizes living for today, clear first steps, and immediacy. Companies including Frame Health and PatientBond have been key to actioning and scaling psychographic segmentation within healthcare, including capturing psychographic data and integrating it into electronic health records (EMRs) and customer relationship management platforms (CRMs) (Frame Health, 2021; PatientBond, 2021a). In partnership with Frame Health for example, CVS, UnitedHealthcare, and Cedars-Sinai Medical Center were able to increase patient signups for a medication adherence program by 38% and decrease pharmacy all time by 22% using Frame Health's personalized call strategies and scripts (Frame Health, 2020). As another example, in partnership with PatientBond, a top health system was able to reduce hospital readmissions for congestive heart failure by 90% using PatientBond's digital system (PatientBond, 2020).

However, the use of psychographic segmentation for dementia—along with brain health more broadly—remains nascent. Integrating psychographic segmentation into dementia care could provide a more personalized care experience and increased patient engagement, leading to improved health outcomes and reduced costs (Laurance et al., 2014). Psychographic segmentation has the opportunity to enhance patient engagement for dementia and to "change the clinical paradigm from 'What is the matter?' to 'What matters to you?'" (Edgman-Levitan et al., 2013).

## PSYCHOGRAPHIC SEGMENTATION FOR DEMENTIA PREVENTION

Due to the complex, multifactorial, and heterogeneous nature of dementia, there has been increasing interest in multidomain interventions for dementia prevention (Andrieu et al., 2015). Multidomain interventions target several risk factors and mechanisms simultaneously and may be required for optimal

preventative effects (Rosenberg et al., 2020b). The first large-scale randomized controlled trials (RCTs) of multidomain interventions include the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial and the Multidomain Alzheimer Preventive Trial (MAPT).

In FINGER, participants received a 2-year multidomain lifestyle intervention consisting of physical training, cognitive training, nutritional counseling, and cardiovascular monitoring (Kivipelto et al., 2013; Ngandu et al., 2015). In MAPT, participants received a 3-year multidomain lifestyle intervention consisting of cognitive training, physical activity counseling, and nutritional counseling with either an omega-3 supplement or placebo (Andrieu et al., 2017). For multidomain interventions such as FINGER and MAPT, adherence is key (Coley et al., 2019). Greater personalization, such as considering participant characteristics and motivations and taking a precision prevention approach, is critical to increase adherence (Coley et al., 2019; Rosenberg et al., 2020a; Solomon et al., 2021). In other words, a psychographic segmentation approach to prevention is needed.

Psychographic segmentation has the potential to improve the adherence and effectiveness of multidomain interventions for dementia prevention. For instance, a few example segments of psychographic segmentation include the following (see **Figure 1** for more) (PatientBond, 2021b): (1) Self-achiever, people who are highly receptive to health information; (2) priority juggler, people who are generally not engaged in getting health care information for themselves and whose family or peer influence is important; and (3) Willful endurers, people who live in the here and now and are least engaged with their health. The engagement strategies will need to be varied and personalized for each segment. For example, outreach materials and participation strategies for self-achievers may be centered around the theme of achieving a goal, whereas for priority jugglers, a sense of how the family/other people will benefit and evoking commitment and duty will be essential. For the willful endurers, messages that center around living for today and create a sense of urgency will be important. The method of communication may differ with certain segments preferring text messaging, emails, or physical mail. Different versions of dementia preventions programs could be developed for different psychographic profiles. Since dementia prevention requires multifactorial efforts across the lifespan, these methods of enhancing engagement and personalization through psychographic segmentation are key and a powerful addition to researchers' and health providers' toolkits.

## PSYCHOGRAPHIC SEGMENTATION FOR DIGITAL TECHNOLOGIES FOR DEMENTIA

Both in-person and digital dementia prevention programs could extensively benefit by integrating psychometric segmentation into their approach. With the proliferation of digital health tools for dementia prevention programs, it is especially important to integrate psychographic segmentation into these technologies. When describing hallmarks of digital health initiatives that have not lived up to their potential, Dr. Brennan Spiegel, Director of Health Services Research at Cedars-Sinai Health System, points toward not giving patients optimal messaging,

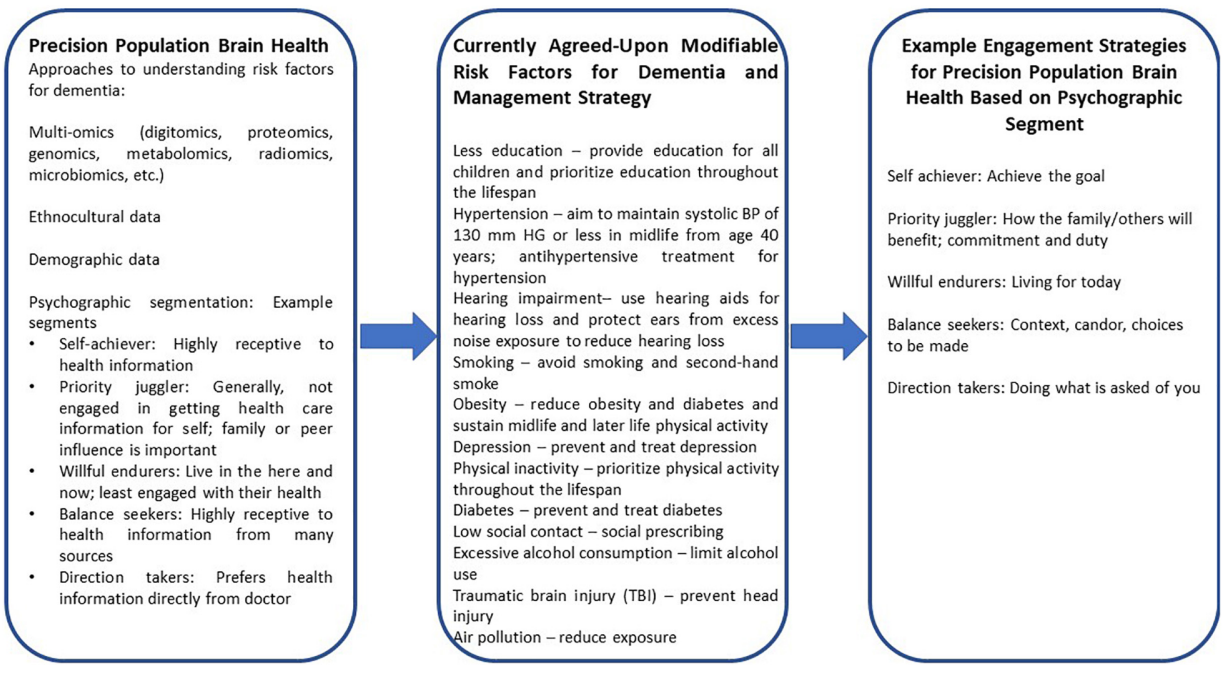


**FIGURE 1 |** Examples of how psychographic segmentation can enable a Precision Population Brain Health approach to care through addressing modifiable risk factors of dementia and enhancing patient engagement.

not inviting patients in the most compelling way, and a lack of patient engagement as being problematic (Fry and Mukherjee, 2018) – all of which could have been helped by psychographic segmentation. He further noted that with digital health tools "Creating the tech isn't the hard part. . .the hard part is using the tech to change patient behavior" (Pagoto and Hekler, 2018). Psychometric segmentation is highly compatible with current applications of behavioral insights across the health system, especially for nudging (Hansen et al., 2016; Benartzi et al., 2017). Such interventions can be boosted by the development behavioral research in policy domains to increase effectiveness, economic growth, and competitiveness (Sunstein, 2016). The combination of technology and psychometry are a powerful force to change behavior that should be ethically addressed to avoid technocracy and "psychocracy" (Feitsma, 2018). Integrating psychometric segmentation into digital health tools for dementia may help address these challenges.

## PSYCHOGRAPHIC SEGMENTATION FOR CAREGIVERS

Psychographic segmentation can also improve the lives of caregivers for people with dementia. For example, a recent study explored how people balance caregiving with other family and employment responsibilities by considering their personal characteristics and their informal caregiving network (Neubert et al., 2018). Applying psychographic segmentation could expand this study and lead to a more comprehensive understanding of a caregiver's needs. Additionally, better understanding of a caregiver's motivations and personality through psychographic segmentation can be used to develop personalized strategies to mitigate caregiver burden and prevent burnout.

## CONCLUSION

Applying psychometric segmentation to dementia prevention endeavors can improve the entire spectrum of care. Psychometric segmentation accounts for an individual's unique values, motivations, priorities, lifestyle, personality, and beliefs as well as behavioral change. Thus, personalization and patient engagement can be at the heart of care. In addition to improved health outcomes and reduced costs due to dementia, developing dementia prevention programs that integrate psychographic segmentation could become the basis for creating a shared framework for prevention of non-communicable diseases and brain health disorders at a population level (O'Neil et al., 2015). Applying psychometric segmentation to dementia prevention endeavors has the potential to help people feel a sense of empowerment over their health and improve satisfaction with their health experience—creating a culture shift in the way brain health is approached and paving the way toward Precision Population Brain Health.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

ES led the manuscript development. ES and HE co-developed the idea that led to the beginning of this manuscript. All authors contributed to the idea development, writing, and editing of this manuscript and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 08 December 2021
doi: 10.3389/fnagi.2021.748888

# Liver Health and Dementia in an Italian Older Population: Findings From the Salus in Apulia Study

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**Objectives:** Non-alcoholic fatty liver disease (NAFLD) currently affects a quarter of the global population. Systemic inflammation, metabolic syndrome, and coronary artery disease, all conditions associated with NAFLD, have also been related to cognitive dysfunction in older age. The present study aimed to investigate the relationship between NAFLD risk and a dementia diagnosis in a large population-based sample aged > 65 years.

**Methods:** We selected 1,542 participants (723 men) from the Salus in Apulia Study. To assess the risk of fat distribution in the liver, we used the Fatty Liver Index (FLI). Dementia was diagnosed according to the American Psychiatric Association criteria (DSM-5).

**Results:** The overall prevalence of dementia was 8.5% [95% confidence interval (CI): 7–10%]. Subjects with dementia were older [effect size (ES): −0.89, 95% CI: −1.07 to −0.70], had a lower level of education (ES:0.88, 95% CI:0.69–1.06), higher levels of gamma-glutamyl transferase (ES: −0.21, 95% CI: −0.39 to −0.03), lower levels of total cholesterol (ES: −0.24, 95% CI: −0.42 to −0.06) and low-density lipoprotein cholesterol (ES: −0.20, 95% CI: −0.38 to 0.02), and a higher FLI (ES: −0.22, 95% CI: −0.39 to −0.04). In the logistic regression model adjusted for age, sex, education, hypertension, diabetes mellitus, alcohol consumption, smoking habits, stroke, cholesterol, and Apo-E, a dementia diagnosis was positively associated with FLI > 60 [odds ratio (OR):1.81; standard error (SE): 0.53; 95% CI: 1.02–3.21].

**Conclusion:** Our findings suggested that an increased NAFLD risk may be associated to dementia and cognitive decline in older age. Considering the high NAFLD prevalence, the possible adverse disease effects on cognitive performance pose a health problem with significant social and economic implications.

**Keywords: NAFLD (non-alcoholic fatty liver disease), aging, dementia, older population, neurodegenerative diseases, liver**

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***Received:*** *28 July 2021*
***Accepted:*** *17 November 2021*
***Published:*** *08 December 2021*

***Citation:***
*Lampignano L, Donghia R, Griseta C, Lagravinese G, Sciarra S, Zupo R, Castellana F, Bortone I, Guerra V, Tirelli S, De Nucci S, Tatoli R, Lozupone M, Sborgia G, Leo A, De Pergola G, Giannelli G, Panza F and Sardone R (2021) Liver Health and Dementia in an Italian Older Population: Findings From the Salus in Apulia Study. Front. Aging Neurosci. 13:748888. doi: 10.3389/fnagi.2021.748888*

## INTRODUCTION

In Western countries, non-alcoholic fatty liver disease (NAFLD) is the most prevalent cause of chronic liver diseases (CLDs), a major cause of multimorbidity and mortality worldwide. The Third National Health and Nutrition Examination Survey (NHANES-III), conducted in the U.S. population between 1988 and 2008, showed that the prevalence of CLDs increased from 12 to 15% (Younossi et al., 2011). In Western countries, this tendency is mainly driven by the rising impact of NAFLD, and, as the populations age, the number of patients affected by this condition is expected to increase. NAFLD is common in older adults, and its prevalence rises with age, reaching 30% from the age of seventy onward (Bertolotti et al., 2014). During aging, the concomitance and increasing weight of several biomarker (i.e., metabolic syndrome, obesity, dyslipidemia, type 2diabetes) and lifestyle risk factors (i.e., Western diet pattern and sedentary habits) predisposing to NAFLD can partly explain this rising prevalence (Bertolotti et al., 2014; Younossi et al., 2021).

The rapid growth of the global population aged 65 and older has driven recent scientific interest in cognitive aging (World Health Organization [WHO], 2021). Indeed, severe cognitive impairments, such as dementia, lead to substantial cognitive dysfunction that impairs performance in daily living and global functional status activities. Dementia is defined by the WHO as a syndrome featuring the deterioration of cognitive and social functions such as memory, attention, problem-solving, and judgment (World Health Organization [WHO], 2021). Dementia has several physical, psychological and social repercussions both on people with dementia and their families, and on the whole population. A classic way to conceptualize dementia is to consider two major categories of disease: "neurodegenerative" [i.e., Alzheimer's disease (AD)] and "non-neurodegenerative" (i.e., cerebrovascular disease). This dichotomy is a valuable heuristic, although it is constrained by its simplicity (Gale et al., 2018). Most dementia in the elderly have a neurodegenerative nature (Gale et al., 2018). Diseases can impair cognition without causing a decline in daily functioning, whether at the time of diagnosis or later. Mild neurocognitive disorder and mild cognitive impairment are two terms that have been used to describe these conditions (Gale et al., 2018).

In Europe, dementia affects approximately 10 million people, while in Italy, its prevalence ranges between 5 and 7% among older people over 65 years (Niu et al., 2017). People living with dementia lose their autonomy over time and need assistance to accomplish even the simplest activities, such as personal care. The need for ongoing care causes increased healthcare costs to enable appropriate management and care of these patients.

Starting from these concepts, prevention appears to play a central role in the optimal management of cognitive aging, recognizing potentially modifiable risk factors to reduce the risk of cognitive decline and achieving early recognition of individuals at risk of dementia to slow the progression to more severe conditions. Based on a growing body of scientific evidence, the 2017 Lancet Commission identified nine risk factors for dementia: less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes mellitus, sleep deprivation, and chronic isolation/loneliness (Livingston et al., 2017; Wu et al., 2019). In 2020, the Lancet Commission added excessive alcohol consumption, traumatic brain injury, and air pollution to the "life-course model" of dementia to be prevented (Livingston et al., 2020). The 12 risk factors listed above are responsible for about 40% of the world dementia cases. By modifying these both biomarkers and lifestyle risk factors, dementia could be prevented or delayed.

A link between NAFLD and brain health has been suggested (Yilmaz and Ozdogan, 2009). Liver steatosis may be linked with brain structure and function, at least partly, through shared risk factors including diabetes mellitus, obesity, and physical inactivity, which are established risk factors for dementia (Gorelick et al., 2011), as well as for brain aging (Debette et al., 2011). Interestingly, both NAFLD and dementia share two important biological risk factors, such as Apolipoprotein E (APO-E) (Yang et al., 2005; Rasmussen, 2016) and Adiponectin (ADPN) (Buechler et al., 2011; Rizzo et al., 2020). Nevertheless, although both NAFLD and the degree of liver fibrosis are linked to a wide range of adverse health outcomes, their link to cognitive performance in older people is unclear (Weinstein et al., 2019). However, in a study that compared cognitive performance in 874 NAFLD and healthy controls, the NAFLD group performed less well in activities requiring memory and attention (Seo et al., 2016). A deterioration in the cognitive performance of NAFLD subjects was also found in other smaller cross-sectional studies (Kjærgaard et al., 2021). Nevertheless, another report from the NHANES did not show specific cognitive impairment in NAFLD, and nor did other studies (Weinstein et al., 2018). Recent Italian population-based results suggest that advanced liver fibrosis could be a long-term predictor for overall dementia in people with physical frailty (Solfrizzi et al., 2020).

The present study investigated the cross-sectional relationships between a non-invasive risk score for NAFLD (fatty liver index, FLI) and a dementia diagnosis in an older population (aged over 65 years) from Southern Italy selected from the large population-based Salus in Apulia Study.

## MATERIALS AND METHODS

### Study Population and Design

Participants of the present study were recruited from the electoral rolls of Castellana Grotte, Bari, Southern Italy. The sampling framework was the health registry office list until December 31, 2014, which included 19,675 subjects, 4,021 of whom were aged 65 years or more. All subjects belonged to the "Salus in Apulia Study," a public health initiative funded by the Italian Ministry of Health and Apulia Regional Government and conducted at IRCCS "S. De Bellis" Research Hospital. From the whole sample of 4,021 subjects, only 1,542 who underwent the physical and neurological assessment, and complete blood tests, enrolled from 2015 to 2018, were included in this analysis. The subjects had the neurological and blood evaluation in the same week, contextually. The exclusion criteria were to have no complete data about neuropsychological examination. physical

examination and blood biomarkers (complete case analysis). All participants signed informed consent before their examination. The Internal Review Board (IRB) approved the study of the head institution, the National Institute of Gastroenterology and Research Hospital "S. de Bellis" in Castellana Grotte, Italy, in 2014. The present study adhered to the "Standards for Reporting Diagnostic Accuracy Studies" (STARD) guidelines[1], the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines[2] and is in accordance with the Helsinki Declaration of 1975.

## Clinical and Socio-Demographic Characteristics

Smoking status was assessed with the single question, "Are you a current smoker?" The level of education is expressed in years of schooling. Alcohol consumption was evaluated by a validated food frequency questionnaire (FFQ) (Leoci et al., 1993). A sphygmomanometer YTON and a stethoscope FARMAC-ZARBAN were used to measure blood pressure by nurses with professional qualifications in Italy. Blood pressure was determined in a sitting position after rest. The final blood pressure values (systolic and diastolic blood pressure) were the mean of the last two of three measurements. Body mass index (BMI) was calculated as kg/m$^2$. Height and weight measurements were performed using a Seca 220 stadiometer and a Seca 711 scale. Waist circumference was measured at the narrowest part of the abdomen or in the area between the tenth rib and the iliac crest (minimum circumference). Blood samples were collected from each subject in the morning after an overnight fast. Plasma glucose was determined using the glucose oxidase method (Sclavus, Siena, Italy), while the concentrations of plasma lipids [triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol] were quantified by an automated colorimetric method (Hitachi; Boehringer Mannheim, Mannheim, Germany). Low-density lipoprotein (LDL) cholesterol was calculated by applying the Friedewald equation. Blood cell count, glutamyl oxaloacetic transaminase (GOT), glutamyl pyruvic transaminase (GPT), and gamma-glutamyl transferase (GGT) were measured using automatic enzyme procedures. The platelets count was determined using an XT-2000i hematology analyzer (Sysmex, Dasit, Cornaredo, Italy). Genomic DNA was manually purified from 4 mL of frozen blood samples by organic protein extraction and ethanol precipitation in accordance with standard methods (Kirby, 1957). The APO-E genotype was established by polymerase chain reaction (PCR) and agarose gel electrophoresis, as described in detail elsewhere (Seripa et al., 2006). Genotypes were considered according to the presence of at least one allele. For the apoE polymorphism, we reported ε2 (ε2/) and ε4 (ε4/) carriers. ε2 carriers were distinct as those participants showing at least one ε2 allele, that is, having a ε2/ε2, a ε2/ε3, or a ε2/ε4 genotype. Likewise, ε4 carriers were defined as those participants showing at least one ε4 allele, that is, having a ε4/ε2, a ε4/ε3, or a ε4/ε4 genotype (Seripa et al., 2006). We considered APO-E ε2 carriers as at decreased risk and APO-E ε4 carriers as at increased risk for late-life cognitive decline (Verghese et al., 2011).

In addition, the following pathological conditions were assessed, as described in detail elsewhere (Castellana et al., 2021). In accordance with the American College of Cardiology American Heart Association criteria, hypertension status was evaluated as values $\geq$ 130/80 mmHg (Whelton et al., 2018). Diabetes mellitus was diagnosed as fasting blood glucose $\geq$ 126 mg/dL. The presence of stroke was ascertained during a complete medical history questionnaire administered by a certified neurologist.

## Assessment of Non-alcoholic Fatty Liver Disease Risk

To assess the risk of fat distribution in the liver, Bedogni et al. (2006) developed an index, the FLI, that is accurate and easy to employ to predict NAFLD in the general population, applying BMI, waist circumference, triglycerides and GGT as routine measurements in clinical practice (Bedogni et al., 2006). An algorithm based on BMI, waist circumference, triglycerides, and GGT had an accuracy of 0.84 [95% confidence interval (CI): 0.81–0.87] in detecting NAFLD. This index ranges between 0 and 100, whereby NAFLD is ruled out with FLI $<$ 30 and ruled in with FLI $\geq$ 60.

## Neurological and Neuropsychological Assessment

A standard neurological examination was carried out by a licensed neurologist, exploring perception, deambulation, cranial nerves, motor function (muscle tone, erectness of posture, and tropism), pathological gestures, sensory function, cerebellar and sphincter functions, deep tendon reflexes, and signs of diffuse cerebral distress. The Clinical Dementia Rating Scale (CDR) was administered to stage cognitive decline (Hughes et al., 1982). The diagnosis of dementia was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria (DSM-4) (American Psychiatric Association [APA], 2000), as detailed elsewhere (Sardone et al., 2020). Global cognitive performance was assessed by the Mini-Mental State Examination (MMSE), a measure that includes 10 items to determine spatial and temporal orientation, attention, memory, language, and visuospatial functions (Measso et al., 1993).

## Statistical Analysis

The whole sample was subdivided according to the parameter: dementia vs. non-dementia. Normal distributions of quantitative variables were tested using the Kolmogorov-Smirnov test. Data are reported as mean $\pm$ standard deviations (M $\pm$ SD) for continuous measures and frequency and percentages (%) for all categorical variables. In order to focus on the practical differences, a statistical approach based on the effect size rather than the null hypothesis significance test (NHST) was adopted. Differences in the prevalence of exposure groups (FLI categories) and other categorical variables and their 95% CIs were calculated and used to assess essential differences in the magnitude of association, i.e., effect size (ES). Differences between continuous

[1]http://www.stard-statement.org/

[2]https://www.strobe-statement.org/

variables were calculated using Cohen's *d* difference between means, Hedge's *g* when the assumption of a similar variance was violated, and their ES using the CIs (Grissom and Kim, 2005). Three nested logistic regression multivariable models were built to estimate the odds ratio (OR) for dementia of all the principal variables. The goodness of fit of the models was assessed using pseudo-R squared (Pseudo-R2) and Akaike Information Criteria (AIC), measuring the amount of variance explained by the regression model. It ranges in (0,1), with a larger value indicating that the model explains more variance (higher value is better). In detail, its measure shows how much Logistic Regression model reduces the error vs. simply guessing the average probability of occurrence for each observation. Probability estimators were expressed as Odds Ratios (OR) and 95% CI. The multicollinearity of models was evaluated through the variance inflation factor (VIF), using the score of 2 as a cut-off for exclusion of the covariates with a high probability of convergence in the model. In addition, the load of every single covariate was assessed using standard error (se) to control for overfitting of the adjusted models. Confounders were selected among the retained factors related both to exposure (FLI categories) and to the probability of dementia, i.e., the risk factors: age, sex, education, hypertension, diabetes mellitus, alcohol consumption, smoking habit, stroke, cholesterol, and Apo-E (Cheng et al., 2012; Licher et al., 2019).

## RESULTS

In the present study, conducted on 1,542 older individuals (53% women), the mean age of the whole sample was 73.51 ± 6.25 years. The prevalence of dementia was 8.5% (95% CI: 7–10%) People with dementia were older on average (ES: −0.89, 95% CI: −1.07 to −0.70), had a lower level of education (ES: 0.88, 95% CI: 0.69–1.06) and MMSE (ES: 3.19, 95% CI: 2.98–3.40), and a higher FLI score (ES: −0.22, 95% CI: −0.39 to −0.04). As to the metabolic biomarkers, subjects with dementia had lower levels of total cholesterol (ES: −0.24, 95% CI: −0.42 to −0.06) and LDL cholesterol (ES: −0.20, 95% CI: −0.38 to 0.02) and higher levels of GGT (ES: 0.2, 95% CI: 0.03–0.039) (**Table 1**).

In the logistic regression models, a dementia diagnosis was positively associated with a FLI > 60 in the unadjusted model (**Table 2**). Subjects with a FLI > 60 showed almost twice the probability of dementia compared to subjects with lower FLI, ceteris paribus of the other confounders, in the fully adjusted model (OR:1.81; se:0.53; 95% CI: 1.02–3.21) (**Table 1**). The goodness of fit was assessed using pseudo R2, that showed an absolute good fit of the model (pseudo R2 = 0.1337); considering the small increase of the adjusted Pseudo-R2 in the models before and after the implementation of the confounders, we could be confident in that results, despite the presence of several variables. Moreover, overfitting was quite low considering the single standard errors (<1) of the model covariates (**Table 1**).

## DISCUSSION

In the present study, we found a positive association between dementia and NAFLD risk assessed with the FLI in a large,

**TABLE 1 |** Sociodemographic and clinical variables in cognitively normal subjects and patients with dementia.

| Variables | Dementia (*n = 131*) (8.5%) | Cognitively normal (*n* = 1411) (91.5%) | Effect size* (95% CI) |
|---|---|---|---|
| **Sociodemographic** | | | |
| Age (years) | 78.85 ± 6.53 | 73.39 ± 6.12 | 0.89 (0.70–1.07) |
| Females | 77 (9.40) | 742 (90.60) | −0.06 (−0.15 to 0.03) |
| Males | 54 (7.47) | 669 (92.53) | 0.06 (−0.03 to 0.15) |
| Education (years) | 3.76 ± 3.07 | 7.06 ± 3.81 | −0.88 (−1.06 to −0.69) |
| Smoking (yes) | 8 (6.11) | 110 (7.80) | 0.44 (−0.03 to 0.06) |
| BMI (Kg/m$^2$) | 29.37 ± 4.24 | 28.92 ± 4.38 | 0.10 (−0.08 to 0.28) |
| Waist circumference (cm) | 102.96 ± 9.85 | 102.93 ± 10.54 | 0.002 (−0.18 to 0.18) |
| MMSE | 16.76 ± 5.01 | 27.10 ± 3.02 | −3.19 (−3.40 to −2.98) |
| Low physical activity (Yes) | 107 (81.68) | 1,165 (82.57) | 0.01 (−0.06 to 0.08) |
| Alcohol consumption (>20 g/die) | 14 (16.28) | 209 (19.05) | 0.03 (−0.05 to 0.11) |
| **Biomarkers** | | | |
| FBG (mg/dl) | 108.44 ± 31.53 | 105.64 ± 29.11 | 0.09 (−0.08 to 0.27) |
| Total cholesterol (mg/dl) | 176.08 ± 39.48 | 184.95 ± 36.91 | −0.24 (−0.42 to −0.06) |
| HDL cholesterol (mg/dl) | 47.08 ± 12.99 | 49.35 ± 12.90 | −0.18 (−0.35 to 0.003) |
| LDL cholesterol (mg/dl) | 107.50 ± 31.71 | 113.83 ± 31.07 | −0.20 (−0.38 to −0.02) |
| Triglycerides (mg/dl) | 108.72 ± 52.12 | 104.37 ± 59.74 | 0.07 (−0.10 to 0.25) |
| GGT | 41.03 ± 42.61 | 33.49 ± 35.56 | 0.21 (0.03–0.39) |
| AST | 32.55 ± 22.37 | 32.15 ± 28.39 | 0.01 (−0.16 to 0.19) |
| ALT | 25.44 ± 16.74 | 25.67 ± 20.66 | −0.01 (−0.19 to 0.17) |
| ***Apo-E genotype*** | | | |
| Apo-E ε3/ε3 carriers | 100 (76.09) | 1,043 (73.99) | −0.02 (−0.15 to 0.11) |
| Apo-E ε2 carriers | 20 (15.22) | 173 (12.28) | −0.03 (−0.14 to 0.08) |
| Apo-E ε4 carriers | 11 (8.70) | 194 (13.73) | 0.05 (−0.03 to 0.13) |
| ***Clinical variables*** | | | |
| Hypertension (Yes) | 89 (67.94) | 988 (70.02) | 0.02 (−0.06 to 0.10) |
| Diabetes mellitus (Yes) | 22 (16.79) | 172 (12.19) | −0.05 (−0.11 to 0.02) |
| Stroke (Yes) | 6 (7.23) | 31 (3.06) | −0.04 (−0.10 to 0.01) |
| FLI | 59.12 ± 25.43 | 53.81 ± 24.46 | 0.22 (0.04–0.39) |
| **FLI-Code** | | | |
| <30 | 21 (16.03) | 276 (19.56) | 0.03 (−0.03 to 0.10) |
| 30–60 | 38 (29.01) | 552 (39.12) | 0.10 (0.02–0.18) |
| >60 | 72 (54.96) | 583 (41.32) | −0.14 (−0.22 to −0.05) |

*The Salus in Apulia Study (n = 1,542). *Hedges' effect size; CI, confidence interval. Data are shown as mean and standard deviation for continuous variables and as percentage (%) for proportions.*

*BMI, body mass index; MMSE, Mini Mental State Examination; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GGT, γ-glutamyl transferase; AST, aspartate transaminase; ALT, alanine amino transferase, FLI Fatty Liver Index; APO-E, Apolipoprotein E.*

**TABLE 2 |** Logistic regression multivariable models in cognitively normal subjects and patients with dementia.

| Parameters | Unadjusted model | | | | Partially adjusted model 1 | | | |
|---|---|---|---|---|---|---|---|---|
| | OR | se (OR) | 95% CI | $R^2$ | OR | se (OR) | 95% CI | $R^2$ |
| | | | | 0.0101 | | | | 0.0979 |
| FLI (> 60) | 1.73 | 0.32 | 1.21–2.48 | | 1.68 | 0.32 | 1.16–2.43 | |
| Age | – | – | – | | 1.89 | 0.14 | 1.63–2.19 | |
| Sex | – | – | – | | 1.33 | 0.25 | 0.92–1.94 | |
| Education | – | – | – | | – | – | – | |
| Hypertension | – | – | – | | – | – | – | |
| Diabetes mellitus | – | – | – | | – | – | – | |
| Alcohol consumption | – | – | – | | – | – | – | |
| Smoking habit | – | – | – | | – | – | – | |
| Stroke | – | – | – | | – | – | – | |
| Cholesterol | – | – | – | | – | – | – | |
| Apo-E | – | – | – | | – | – | – | |
| **Parameters** | **Partially adjusted model 2** | | | | **Fully adjusted model** | | | |
| | OR | se (OR) | 95% CI | $R^2$ | OR | se (OR) | 95% CI | $R^2$ |
| | | | | 0.1313 | | | | 0.1337 |
| FLI (> 60) | 1.79 | 0.42 | 1.12–2.85 | | 1.81 | 0.53 | 1.02–3.21 | |
| Age | 1.74 | 0.17 | 1.44–2.11 | | 1.66 | 0.20 | 1.31–2.12 | |
| Sex | 1.15 | 0.30 | 0.69–1.92 | | 1.38 | 0.46 | 0.72–2.67 | |
| Education | 0.35 | 0.09 | 0.21–0.56 | | 0.29 | 0.10 | 0.15–0.57 | |
| Hypertension | 0.72 | 0.19 | 0.44–1.20 | | 1.04 | 0.35 | 0.54–2.00 | |
| Diabetes mellitus | 0.85 | 0.29 | 0.44–1.66 | | 0.56 | 0.26 | 0.23–1.39 | |
| Alcohol consumption | 1.01 | 0.35 | 0.51–1.99 | | 1.13 | 0.46 | 0.51–2.49 | |
| Smoking habit | – | – | – | | 2.12 | 1.26 | 0.66–6.83 | |
| Stroke | – | – | – | | 2.08 | 1.22 | 0.65–6.60 | |
| Cholesterol | – | – | – | | 0.99 | 0.004 | 0.98–1.00 | |
| Apo-E | – | – | – | | 0.54 | 0.27 | 0.20–1.44 | |

*The Salus in Apulia Study (n = 1,542). OR, odds ratio; se (OR), standard error of OR; CI, confidence interval; $R^2$, pseudo $R^2$; FLI, Fatty Liver Index.*

older population-based sample. This association persisted after controlling for possible confounders such as age, sex, education, hypertension, diabetes mellitus, alcohol consumption, smoking habit, and stroke.

Although there is a wealth of evidence about the risk of a declining cognitive performance of older people with diabetes mellitus (Palta et al., 2014), studies of the cognitive performance in subjects with NAFLD are lacking. In a large cross-sectional study involving more than 4,000 American adults aged 20–59 years, NAFLD was independently associated with lower cognitive performance, independently of cerebrovascular disease (CVD) and its risk factors (Seo et al., 2016). Individuals with NAFLD and diabetes mellitus had a lower cognitive function, according to a large population-based cohort study (Weinstein et al., 2018). However, the presence of NAFLD without diabetes mellitus did not appear to be linked to poor cognitive function (Weinstein et al., 2018). Another study found that participants in the community-based Framingham Study with NAFLD had a cognitive function that was not statistically different from those without NAFLD (Weinstein et al., 2019). Insulin resistance may play a significant role in the link between NAFLD and cognitive function. Insulin resistance is widespread in people with NAFLD, diabetes mellitus, and cognitive impairment diseases, such as Alzheimer's disease (AD) (Targher et al., 2005; Craft, 2007). A study on animal models suggested that increased insulin resistance (induced by nitrosamine) may result in non-alcoholic steatohepatitis (NASH) and AD (Tong et al., 2009). The role of metabolic disorders in the pathophysiology of AD is shown by the consistent correlations of serum-based liver function markers with cognitive performance and amyloid β (Aβ), tau protein, and other AD neurodegeneration biomarkers (Nho et al., 2019).

AD is the most prevalent cause of dementia in older people (No Authors Listed, 2021). The liver physiological role includes various processes engaged in pathways that contribute to the development and progression of AD. Both functional and structural deterioration of the liver reduces its ability to efficiently remove and degrade Aβ (Wang et al., 2017). A low hepatic expression of low-density lipoprotein receptor-related protein 1 (LRP1) and high levels of circulating Aβ have been reported in patients with CLDs. This is due to diminished Aβ clearance with low hepatic LRP1 activity (Wang et al., 2017). According to a recent epidemiological study, NAFLD, cirrhosis, CVD, or type 2 diabetes mellitus were the most common comorbidities associated with dementia caused by AD (Bassendine et al., 2020). Diet-induced hepatic insulin resistance is closely linked to NAFLD (Kumashiro et al., 2011). In a healthy condition, insulin enhances LRP1 translocation to the cell membrane in hepatocytes, favoring Aβ clearance by LRP1. Therefore, insulin

resistance hampers or prevents this process, leading to increased Aβ levels (Tamaki et al., 2007). Furthermore, liver damage is correlated with Aβ deposition in the brain. Besides, NAFLD and NASH enhance the level of hematic cholesterol, particularly of 27-hydroxycholesterol, the form that can pass freely through the blood-brain barrier. This accumulation of cholesterol in the brain favors the production of Aβ in lipid rafts, contributing to the vicious circle supporting AD progression (Tamaki et al., 2007).

The AD pathogenesis is characterized by synaptic and neuronal degeneration and amyloid plaques, mostly consisting of Aβ peptide (Estrada et al., 2019). Through metabolic detoxification, the liver plays a critical role in the clearance of peripheral circulating Aβ. The absorption of Aβ into hepatocytes and subsequent excretion in the bile may be impaired in the presence of hepatic inflammation, especially in more advanced stages such as cirrhosis, resulting in greater Aβ levels in the circulation (Kanekiyo and Bu, 2014; Gehrke and Schattenberg, 2020). Moreover, failing autophagy (Nixon, 2013) predisposes to amyloidosis, which in turn sets the stage for microglial activation/phenotype change, increased CNS inflammation, and microglial toxicity, as well as an emerging tauopathy (modification of tau via excessive phosphorylation or disruption of phosphatase/kinase balance). These alterations may be due to both compensations for amyloidosis and systemic inflammation (Nixon, 2013), and thus metabolic alterations contributing to NAFLD.

Furthermore, evidence suggests that both NAFLD and dementia share two important biological risk factors, such as Apolipoprotein E (APO-E) and Adiponectin (ADPN). APO-E has been linked to a variety of diseases as well as altered lipid profiles (Nascimento et al., 2020). In particular, some studies suggest that the apoE ε4 allele is a risk factor for NAFLD pathogenesis (Yang et al., 2005). Moreover, the ε4 allele is a major genetic risk factor for late onset Alzheimer's disease (Rasmussen, 2016). This association was first recognized in 1993 (Corder et al., 1993) and then has been validated worldwide. The APO-E polymorphism is undoubtedly the strongest genetic risk factor implicated in late-life Alzheimer's disease (Hort et al., 2010). Even though APO-E was considered as a covariate in our models, it does not modify the effect of the association. This finding may be due to the presence of several epigenetic factors (i.e., environmental factors, lifestyle and gut microbiota) that may have influenced both NAFLD (Frank et al., 2021) and cognitive impairment in aging subjects (Morris et al., 2019) and then could have a hidden confounding effect or interplay between apoe4 and dementia.

Adiponectin (ADPN) is a pleiotropic plasma protein produced by adipose tissue with anti-diabetic, anti-atherogenic, and anti-inflammatory functions (Roy and Palaniyandi, 2021). Initially, it was considered that the principal function was to regulate metabolism. ADPN receptors were later discovered in the central nervous system as well (CNS) (Rizzo et al., 2020). Overall, ADPN appears to have neuroprotective effects through lowering inflammatory markers such as C-reactive protein (PCR), interleukin 6 (IL6), and Tumor Necrosis Factor a, based on its central and peripheral actions (TNFa). High levels of inflammatory cascade components, on the other hand, appear to suppress ADPN synthesis, implying bidirectional modulation. Furthermore, ADPN appears to have an insulin-sensitizing effect. As stated previously, the decline in insulin signaling is known to be linked to both cognitive impairment and liver diseases (Buechler et al., 2011; Rizzo et al., 2020).

In the present study, we observed lower levels of total cholesterol (TC) and LDL cholesterol and higher levels of GGT in subjects with dementia. In a meta-analysis including 23,338 participants, total cholesterol was not associated with cognitive outcomes or dementia in any analyses or in any of the extensive individual studies conducted in late-life, and the authors concluded that there is no biological association between late-life lipids and brain health, even though evidence suggests that high midlife TC increases risk of late-life AD, and may correlate with the onset of AD (Anstey et al., 2017). In the Honolulu-Asia Aging Study (HAAS) cohort, total cholesterol was reported to be consistently lower in men who developed dementia (Stewart et al., 2007). Nevertheless, there are still considerable gaps in the literature about associations between total cholesterol and late-life dementia (Peters et al., 2020). It is difficult to predict whether an isolated reading indicates cognitive decline without knowing an individual's total cholesterol trajectory over time. It is also plausible that participants with high LDL cholesterol (and not HDL cholesterol) were lost from our cohort due to mortality or other multimorbidity associated with cardiovascular diseases. Very long-term cohort follow-ups with AD biomarkers, which the field currently lacks, will be needed to disentangle the impact of lipids on late-life brain health (Anstey et al., 2017).

GGT is a biomarker produced mostly by the liver and present in human epithelial cells. It's an oxidative stress marker linked to an elevated risk of cardiovascular disease (Oni et al., 2020). Elevated GGT levels have also been linked with hepatic steatosis and liver cancer (Loomba et al., 2013). Since evidence suggests that smoking may also cause elevated GGT levels (Oni et al., 2020), we adjusted our analysis for smoking habits. Interestingly, several studies highlighted that baseline GGT level and GGT variability were independent predictors of incident dementia, confirming our findings (Kunutsor and Laukkanen, 2016; Lee et al., 2020). The present results could also reflect the fact that the GGT value is included in the formula for calculating the FLI.

## Strengths and Limitations

The strengths of the present study include its well-defined population-based sample, the standardized and clinically based evaluations. Moreover, this study benefits from good internal validity, as the subjects with dementia were older and had lower MMSE scores. Furthermore, in our population study, the prevalence of dementia reflects that of the European population (OECD and European Union, 2018), corroborating a good external validity of the dementia findings. Of note, the FLI has been validated to detect NAFLD in an Italian population and reflects the prevalence of the disease (Bedogni et al., 2005, 2006).

However, we must acknowledge some limitations. Firstly, the cross-sectional nature of the study did not allow us to establish causality in the relationship between NAFLD and dementia. Secondly, we cannot introduce any variables about the use of drugs (statins, NSAIDs, corticosteroids) because

we don't have access to that information. Moreover, our subjects did not have a diagnosis of AD but an overall diagnosis of dementia (unspecified) that could also include vascular forms with an entirely different etiopathogenesis from AD. In addition, we do not have any data about subjects with severe dementia (CDR greater than 1). They could not come to visit because of substantial impairment, generating a typical selection bias. Besides, we used MMSE that shown less sensitivity to mild cognitive impairment and lesser degrees of a cognitive deficit than other assessments. Furthermore, we did not use a gold standard method to confirm liver fat presence such as ultrasonography or biopsy, since the risk of having NAFLD was based on the FLI score.

## CONCLUSION

In conclusion, NAFLD may be a possible independent risk factor for dementia. Such a link might shed light on the contribution of NAFLD to late-life cognitive impairment and support a more effective management of older people with the disease. Particularly, if we consider NAFLD as a precursor stage of clinical diabetes, this finding could highlight an early role of metabolic alterations in the pathogenesis of dementia. This is especially important in light of the increasing prevalence of obesity and metabolic syndrome, which might signal increased NAFLD rates. In the near future, the NAFLD clinical assessment may well be included in the comprehensive geriatric assessment (CGA) with the aim of increasing the accuracy of determining a dementia risk in older age, and thus modifying the prevention trajectories in a primary care setting.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## AUTHOR CONTRIBUTIONS

RS and LL: conceptualization. RD, FP, and RS: methodology. RD and VG: formal analysis. CG, GL, SS, RZ, FC, IB, ST, SD, RT, and ML: investigation. LL: writing—original draft preparation. CG, FP, and RS: writing—review and editing. GS, AL, GD, FP, and RS: supervision. RS and GG: project administration. GG: funding acquisition. All authors have read and agreed to the published version of the manuscript.

## FUNDING

This study was funded by the Italian Ministry of Health with the "Ricerca Corrente 2019" Grant. The Salus in Apulia Study was funded by Apulia Government and Italian Ministry of Health, under the Studies on Aging Network, at Italian Research Hospitals (IRCCS).

## ACKNOWLEDGMENTS

We thank the "Salus in Apulia" Research Team. This manuscript is the result of the research work on frailty undertaken by the "Research Network on Aging" team, supported by the resources of the Italian Ministry of Health—Research Networks of National Health Institutes. We thank M. V. Pragnell, B.A., for her precious help as native English language supervisor. We thank the General Practitioners of Castellana Grotte, for their fundamental role in supporting the recruitment of participants in these studies: Campanella Cecilia Olga Maria, Daddabbo Annamaria, Dell'aera Giosue', Giustiniano Rosalia Francesca, Guzzoni Iudice Massimo, Lomuscio Savino, Lucarelli Rocco, Mazzarisi Antonio, Palumbo Mariana, Persio Maria Teresa, Pesce Rosa Vincenza, Puzzovivo Gabriella, Romano Pasqua Maria, Sgobba Cinzia, Simeone Francesco, Tartaglia Paola, and Tauro Nicola.

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frontiers in Aging Neuroscience

SYSTEMATIC REVIEW
published: 28 January 2022
doi: 10.3389/fnagi.2021.755926

# Prevalence and Associated Risk Factors of Cognitive Frailty: A Systematic Review and Meta-Analysis

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**Edited by:**
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**Specialty section:**
*This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience*

**Received:** *09 August 2021*
**Accepted:** *27 December 2021*
**Published:** *28 January 2022*

**Citation:**
*Zhang T, Ren Y, Shen P, Jiang S, Yang Y, Wang Y, Li Z and Yang Y (2022) Prevalence and Associated Risk Factors of Cognitive Frailty: A Systematic Review and Meta-Analysis. Front. Aging Neurosci. 13:755926. doi: 10.3389/fnagi.2021.755926*

**Objective:** Currently, the prevalence of CF (Cognitive Frailty) is not very clear, and the relationship between CF and its associated risk factors has not been accurately evaluated. Therefore, it is necessary to conduct a systematic review and meta-analysis further to understand CF's prevalence and associated factors.

**Methods:** Embase, PubMed, Web of Science, Ovid, and Cochrane were systematically searched for articles exploring the prevalence of CF, the deadline of searching date was up to March 2021. For the prevalence of CF, the events of CF and the total number of patients in every included study were extracted to estimate the prevalence of CF. For associated factors of CF, Odds Ratios (ORs) with (corresponding) 95% confidence intervals (CIs) were used for estimations.

**Results:** Firstly, the estimated prevalence of CF I (Cognitive Frailty in the model I) was 16%, 95% CI (0.13–0.19), and the estimated prevalence of CF II (Cognitive Frailty in model II) was 6%, 95% CI (0.05–0.07). Secondly, both lower engagement in activities and age were calculated to be independent risk factors of CF, and the OR (95% CI) was 3.31 (2.28–4.81) and 1.10 (1.04–1.16), respectively. Finally, depression was also a prominent risk factor of CF, with the overall OR (95% CI) as 1.57 (1.32–1.87).

**Conclusion:** CF was a high prevalence in community older. The various assessment scales and the different cutoff values of diagnostic criteria would affect the prevalence of CF. Lower engagement in activities, age, and depression was the risky factor of CF.

**Systematic Review Registration:** http://www.crd.york.ac.uk/PROSPERO/, identifier: CRD42019121369.

**Keywords: cognitive frailty (CF), associated factor, prevalence, frailty, cognitive**

## INTRODUCTION

Frailty, a critical intermediate status of the aging process and a reversible condition, is a multidimensional clinical syndrome that includes physical, cognitive, social, and psychological dimensions or phenotypes (Clegg et al., 2013; Rodríguez-Mañas et al., 2013; Sugimoto et al., 2018). Numerous studies have confirmed that cognitive impairment is significantly associated with physical frailty, as both cognitive impairment and physical frailty often co-occur in older people (Avila-Funes et al., 2009; Boyle et al., 2010; Auyeung et al., 2011; Malmstrom and Morley, 2013; Shimada et al., 2013). Based on previous research, the consensus from the International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics (IANA-IAGG) proposed the operational definition of cognitive frailty (CF) as the co-existence of physical frailty and mild cognitive impairment (MCI) in the absence of dementia (Kelaiditi et al., 2013). Individuals with CF carry a higher risk of developing dementia and mortality in comparison to healthy older adults (Solfrizzi et al., 2017a), as well as a higher risk than older adults with either physical frailty or cognitive impairment alone (Avila-Funes et al., 2009; Feng et al., 2017; Shimada et al., 2018; Zhang et al., 2021). Notably, CF is a potentially reversible condition, unlike dementia (Clegg et al., 2013). It is a state of reduced cognitive reserve, occurring at an intermediate stage between age-related cognitive changes and neurodegenerative diseases (Dorner et al., 2013; Morley et al., 2013). However, CF by itself may still lead to the following adverse outcomes: decline in physiological function, disability, hospitalization, and dementia (Avila-Funes et al., 2009; Solfrizzi et al., 2017a,b; Shimada et al., 2018). Therefore, CF preventive and health promotion strategies need to be implemented in the early stages or the reversible stage.

Owing to different assessment measures and diagnostic criteria, the prevalence of CF varies significantly among studies. There is currently no gold standard for diagnosing CF and no evident estimated prevalence of CF in community-dwelling individuals.

Moreover, in recognition of the importance of CF and the perniciousness of adverse health, a significant number of studies have focused on the risk factors for it. However, the main associated factors of CF have also varied in different studies, and results have been controversial. For example, Katayama et al. (2021) reported that sex was independently associated with CF. However, Chu et al. (2019) reported that sex did not show a significant association with CF. Furthermore, Xie et al. (2021) reported that depression was independently associated with CF, but Chu et al. (2019) reported that depression was not. Therefore, it is crucial to objectively evaluate the risk factors of CF with more rigorous scientific methods.

**Abbreviations:** CF I, Cognitive Frailty in model I; CF II, Cognitive Frailty in model II; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; HDS-R, Revised Hasegawa's dementia scale; CI testing, Cognitive Impairment testing; TICS-10, Telephone Interview of Cognitive Status-10 items; SPMSQ, Short Portable Mental Status Questionnaire; MiniCog, Minimal Cognition; CDR, Clinical Dementia Rating Scale.

Given those as mentioned earlier, we have conducted a systematic review and meta-analysis to clarify CF's prevalence and associated risk factors in community-dwelling older adults.

## METHODS

### Inclusion Criteria

1) We defined CF as the co-existence of frailty and cognitive impairment, so included studies must evaluate cognition level and frailty.
2) The original study must include the number of individuals with CF and the total population size.
3) The included population is community-dwelling.
4) Multiple papers were generated from the same data set; only the most relevant study and the larger sample were included.

### Exclusion Criteria

1) The original study did not involve or could not calculate the number of those diagnosed with CF.
2) Data cannot be obtained, even after contacting the corresponding author of a study.
3) Literature reviews, case reports, animal studies, or conference abstracts.
4) Non-English studies.

### Data Sources and Search Strategy

Two researchers (Tao Zhang and Yan Ren) independently searched the following electronic databases: Cochrane, PubMed, Web of Science, Ovid, and EMBASE, the deadline of searching date was up to March 2021. Search terms were as follows: [(frailty [Mesh Terms]) OR (frail*[Title/Abstract])] AND (cogniti*[Title/Abstract]). After removing duplicates, 9,198 articles were screened, and the screening process of included studies is shown in **Figure 1**.

### Data Extraction and Study Selection

Firstly, two reviewers (Tao Zhang and Yan Ren) screened the titles and abstracts from searches and independently selected relevant studies, which met the inclusion criteria. Secondly, Tao Zhang and Yan Ren decided on the studies for final inclusion after reviewing the full text of potential studies. Thirdly, once the quantitative data in the original study met the inclusion criteria, we extracted the number of events of CF and other important information. Fourth, we also collected the adjusted OR and 95% (CI), which evaluated the associated risk factors of CF. Lastly, any disagreement in selection was referred to the arbitrator (Ying Yang). We also contacted the corresponding author of the original studies for additional information if required.

### Risk of Bias (Quality) Assessment

Two reviewers (Ping Shen and Yan Ren) independently assessed the risk of bias of the included studies by using a tool explicitly designed for assessing the risk of bias of prevalence studies (Hoy et al., 2012) (The full details of this tool are presented in **Supplementary Table 4**). In brief, it involves a total of 10 items that contain three domains: measurement bias, selection bias, and analysis bias. The answer to each item was, "Yes (low risk)," or

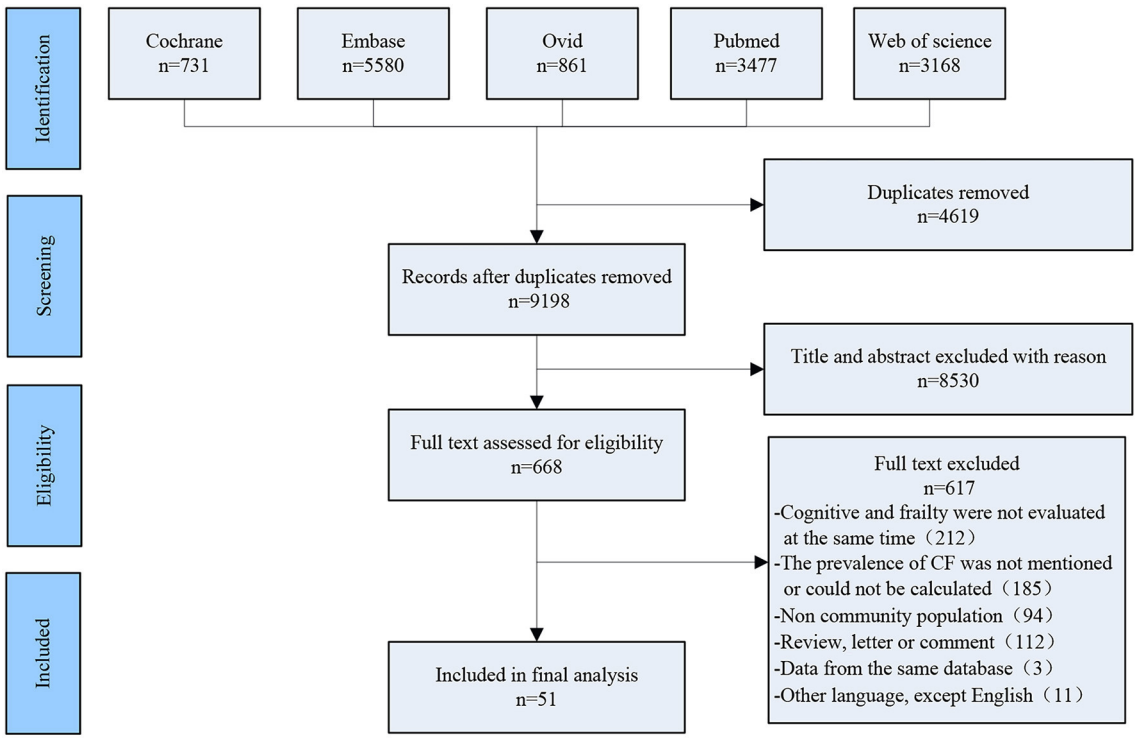


**FIGURE 1 |** The PRISMA diagram of the study selection.

"No (high risk)." When ≥ 8 items answered, "Yes (low risk)," low risk of bias was considered, a moderate risk of bias when 6 to 7 items were answered as "YES (low risk)"; and a high risk of bias when ≤5 items were answered as "YES (low risk)." Any disagreement among the reviewers was discussed with the arbitrator (Ying Yang).

## Strategy for Data Synthesis

Firstly, the actual events of CF and the total number of patients in every included study were extracted to estimate the prevalence of CF. Secondly, we collected the adjusted OR (95% CI), which evaluated the associated risk factors of CF. Finally, we adopted a random-effects model if the heterogeneity test significantly detected statistical difference ($I^2 > 50\%$) or otherwise used a fixed-effects model. All analyses were performed using STATA software (version 16.0, STATA Corp., College Station, TX, USA).

# RESULTS

## Included Studies and Demographics

A total of 51 studies and 123,771 patients were included in our analysis (**Supplementary Table 2**), and 64,784 were observed to be female. All the patients were recruited from the community. Thirty-three among the included 51 studies were pooled by meta-analysis. Patients were included from different countries, including France, Mexico, Australia, Netherlands, Spain, Italy, England, Malaysia, Singapore, India, Thailand, Japan, Korea, China, Brazil, Canada, and the United States. Among the included studies, 20 were considered moderate quality, which involves a moderate risk of bias, and 31 studies were considered high quality, with a lower risk of bias.

## Meta-Analysis Results

### Prevalence of Cognitive Frailty

Our review found that the Fried criteria were most commonly used to define frailty in community residents. A total of 35 studies reported the prevalence of Fried-defined frailty. Otherwise, 5 included studies applied the FRAIL scale to define frailty, and 3 included studies applied the FI (Frailty index). The remaining evaluation tools were not very common or standardized assessment tools. Moreover, the assessment tools of cognitive function are also observed to be varied. Twenty-seven studies used the MMSE (Mini-Mental State Examination) to evaluate cognition, 5 studies utilized the MoCA (Montreal Cognitive Assessment), 3 studies took advantage of the NCGG-FAT (National Center for Geriatrics and Gerontology-Functional Assessment Tool) to assess cognitive function, 2 studies applied the CDR (Clinical Dementia Rating Scale), and 2 studies used the HDS-R (Revised Hasegawa's Dementia Scale). In this case, the prevalence of CF is quite different because of the ununified assessment scale and various cutoff values, which from the lowest prevalence 0.71% (Solfrizzi et al., 2017b) to the highest prevalence 58% (Sharma et al., 2020). To minimize the heterogeneity, we combined data using the Fried-defined frailty; however, given different cutoff values, further categorization was conducted; therefore, we divided them into CF I (cutoff value ≥ 1 in Fried

Criteria Scale) and CF II (cutoff value ≥ 3 in Fried Criteria Scale) to conduct our meta-analysis. We found that the estimated prevalence of CF I was 16%, 95% CI (0.13–0.19) (**Figure 2**), and the estimated prevalence of CF II was 6%, 95% CI (0.05–0.07) (**Figure 3**). There are three reasons why we divided into CF Model I and CF Model II. Firstly, CF was composed of cognitive impairment (MCI) and frailty. CF Model I included the whole population classified as MCI with frailty, and CF Model I emphasized the overall prevalence in the globally high risky population. Secondly, the CF Model II represents a more strict cutoff value, and CF Model II has excluded someone diagnosed with pre-frailty. Therefore, CF Model II could emphasize the severity of CF. Thirdly, internal inconsistency is more evident in terms of validity and credibility if we consider model III (cutoff value from 1 to 3 in Fried Criteria Scale) (Hao et al., 2018; Sharma et al., 2020). Thereby, we adopt CF Model I and CF Model II to assess the prevalence of CF.

## Associated Risk Factors of Cognitive Frailty

### Age

Eight studies revealed that the prevalence of CF increased with age (Ma et al., 2017; Chu et al., 2019; Kim et al., 2019; Navarro-Pardo et al., 2020; Rivan et al., 2020; Ruan et al., 2020; Katayama et al., 2021; Xie et al., 2021). Among them, three studies mentioned that the prevalence of CF in elderly individuals over 80 years of age was significantly higher than in younger groups (Navarro-Pardo et al., 2020; Ruan et al., 2020; Xie et al., 2021). Notably, Ruan et al. (2020) reported that individuals aged 80 years were at a higher risk than those aged 60–69 years (OR 19.71, 95% CI 13.49–28.79). Moreover, 3 other studies reported that age per 1-year increment was an associated risk factor of CF (the pool data: $I^2$ 63%, OR 1.10, 95% CI 1.04–1.16) (Kim et al., 2019; Rivan et al., 2020; Katayama et al., 2021). However, in one study, Navarro-Pardo found that in comparison with those aged 60–64 years, age was not a risk factor for CF in those younger than 80 years of age (**Figure 4**; **Supplementary Table 3**).

### Gender

Two of the included studies reported an association between gender and CF (Chu et al., 2019; Ruan et al., 2020). One of them reported that gender was an independent risk factor of CF (Chu et al., 2019). However, the pooled data indicated that gender was not found to be an independent risk factor for CF ($I^2$ 96.9%, OR 0.52, 95% CI 0.14–1.95) (**Figure 4**; **Supplementary Table 3**).

### Physical Activity

Because the quantitative index of activity varied significantly between studies, we divided them into two groups: the more active group and the less active group, according to the description of the study. Two included studies addressed the relationship between activities and CF ($I^2$ 26.5%, OR 3.31, 95% CI 2.28–4.81) (Katayama et al., 2021; Xie et al., 2021). One of the studies (Katayama et al., 2021) reported that different types of activities (such as going-out activities, cognitive and physical activities, and multidomain activities) had different effects on the prevalence of CF (OR 1.76, 95% CI 1.47–2.11; OR 2.80, 95% CI 1.97–3.97; OR 3.94, 95% CI 2.58–6.03; respectively) (**Figure 4**; **Supplementary Table 3**).

### Negative Emotional State

Results are presented in **Figure 5** and **Supplementary Table 3**. The meta-analysis of the 7 studies included suggested that negative emotion was associated with a statistically significant increased risk of the prevalence of CF ($I^2$ = 94.2%, OR = 1.57, 95% CI 1.32–1.87) (Liu et al., 2018; Chu et al., 2019; Li et al., 2020; Navarro-Pardo et al., 2020; Rivan et al., 2020; Katayama et al., 2021; Xie et al., 2021). Of them, five studies revealed that patients with depression had a higher prevalence of CF (Liu et al., 2018; Navarro-Pardo et al., 2020; Rivan et al., 2020; Katayama et al., 2021; Xie et al., 2021). The pooled data showed that depression assessed by GDS was an independent risk factor of CF ($I^2$ = 92.3%, OR = 1.47, 95% CI 1.09–1.97). However, Chu et al. (2019) reported that depression assessed by PHQT was not a risk factor for CF prevalence. In addition, depression with anxiety also was found to have a higher prevalence of CF (Li et al., 2020).

### Education

Four included studies addressed the relationship between education level and CF (Chu et al., 2019; Navarro-Pardo et al., 2020; Ruan et al., 2020; Katayama et al., 2021). Due to severe heterogeneity among standards for evaluating education levels, a meta-analysis could not be performed. One included study (Chu et al., 2019) revealed that the incidence of CF was lower in those with a high school degree and higher in those with <8 years of education. However, education for more than 1–4 years did not significantly reduce the prevalence of CF. Nevertheless, another included study found that people with 6–12 years of education have a lower prevalence of CF than those under 6 years of education (Ruan et al., 2020). Navarro-Pardo et al. (2020) reported that those with lower years of education had an increased risk of CF compared with those with more than 7 years. When treated as continuous data, education per 1-point increment was positively associated with CF (OR 0.95, 95% CI 0.91–0.99) (Katayama et al., 2021) (**Supplementary Table 3**). Further original studies may focus on the relationship between education level and risk of CF, especially the dose-response relationship between CF and continuous data of education level.

### Marital Status

One included study (Ruan et al., 2020) suggested that marital status, whether married (OR 0.995, 95% CI 0.327–3.025) or widowed (OR 1.802, 95% CI 0.564–5.757), possessed no correlation with the prevalence of CF compared with those who are single (**Supplementary Table 3**).

### Social Participation and Sleep Problems

Xie et al. (2021) proposed that more social participation was a protective factor for CF (OR 0.61, 95% CI 0.39–0.96). The study also found that insomnia was a risk factor for CF. Moreover, daily insomnia was observed to be more harmful than occasional insomnia (OR 2.38, 95% CI 1.33–4.26; OR 1.84, 95% CI 1.07–3.17; respectively) (**Supplementary Table 3**).

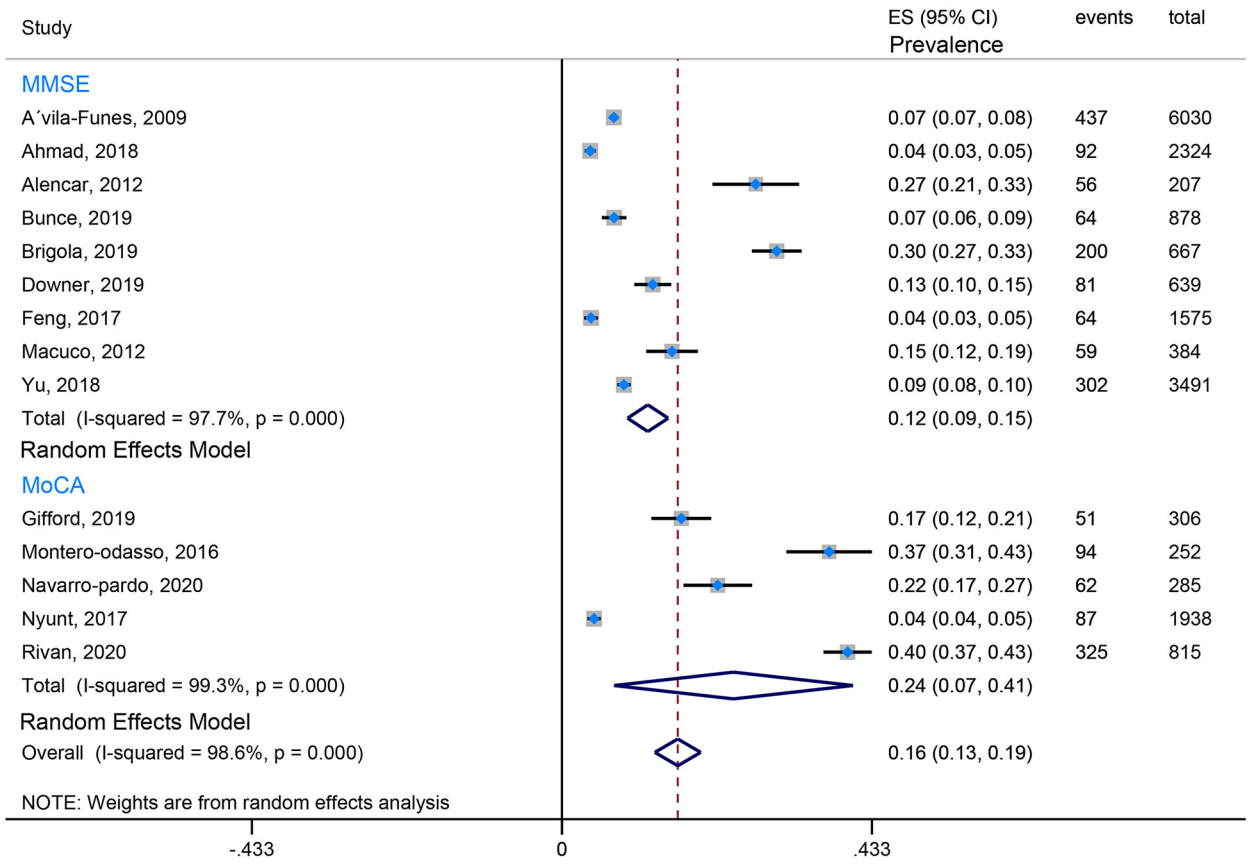


**FIGURE 2 |** The forest plot pooled the prevalence of CF I.

### Nutrition

Four of the included studies reported an association between nutrition and CF (Liu et al., 2018; Kim et al., 2019; Rivan et al., 2020; Katayama et al., 2021). One study (Liu et al., 2018) defined malnutrition according to the Mini-Nutritional Assessment (MNA), another one (Kim et al., 2019) evaluated nutrition by the CNAQ (Council on Nutrition Appetite Questionnaire). Finally, Katayama et al. (2021) used skeletal muscle mass index (ASM) to correlate nutritional status indirectly. These assessment tools indicated that the lower the nutritional status, the higher the prevalence of CF (OR 0.869, 95% CI 0.766–0.986; OR 0.736, 95% CI 0.628–0.863; OR 0.82, 95% CI 0.78–0.87; respectively). There are also different anthropometric results (Kim et al., 2019; Katayama et al., 2021) (calf circumference, total body fat, and body mass index) and biochemical (Rivan et al., 2020; Katayama et al., 2021) indicators (albumin and vitamin D) that may be used to reflect the nutritional status. Individuals who had a thinner calf circumference, higher total body fat, lower albumin, and lower vitamin D showed an increased CF prevalence (OR 0.748, 95% CI 0.625–0.895; OR 1.04, 95% CI 1.01–1.07; OR 0.45, 95% CI 0.34–0.59; OR 0.362, 95% CI 0.141–0.930; respectively). Body mass index was not a risk factor associated with CF (**Supplementary Table 3**).

## Sensitivity Analysis

When calculating the prevalence of CF, a Begg's test and an Egger's test were employed, indicating some evidence for publication bias. However, we used the command to test the robustness of our results. By excluding one study at a time, our results were robust. Begg's test showed no publication bias regarding the OR for subgroup analysis of various depression assessment scales. However, Egger's test ($p$-value for Egger's test = 0.045) indicated some evidence for publication bias. Next, we performed a non-parametric trim-and-fill method to evaluate the effects of any potential missing studies on the overall results (Zhu and Carriere, 2018). We identified 4 studies, and the corresponding result was not significantly altered (OR = 1.109, 95% CI: 1.082–1.137), suggesting that our results were robust (**Figure 6**).

# DISCUSSION

Our manuscript is the first systematic review and meta-analysis to focus on CF's prevalence and associated risk factors among community residents. Based on 51 studies with 123,771 cases, the pooled prevalence of CF in the model I was 16%, 95% CI

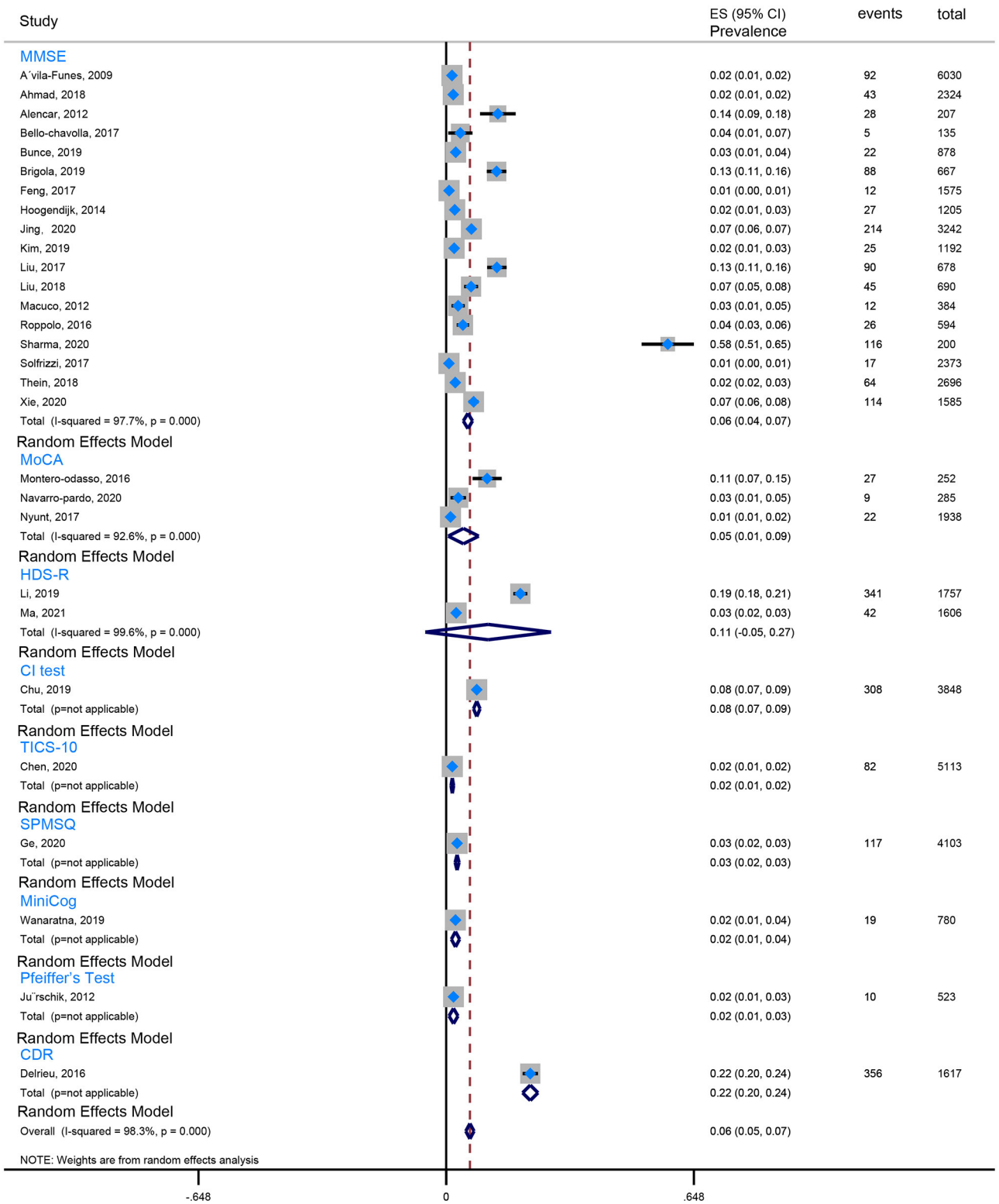


**FIGURE 3 |** The forest plot pooled the prevalence of CF II.

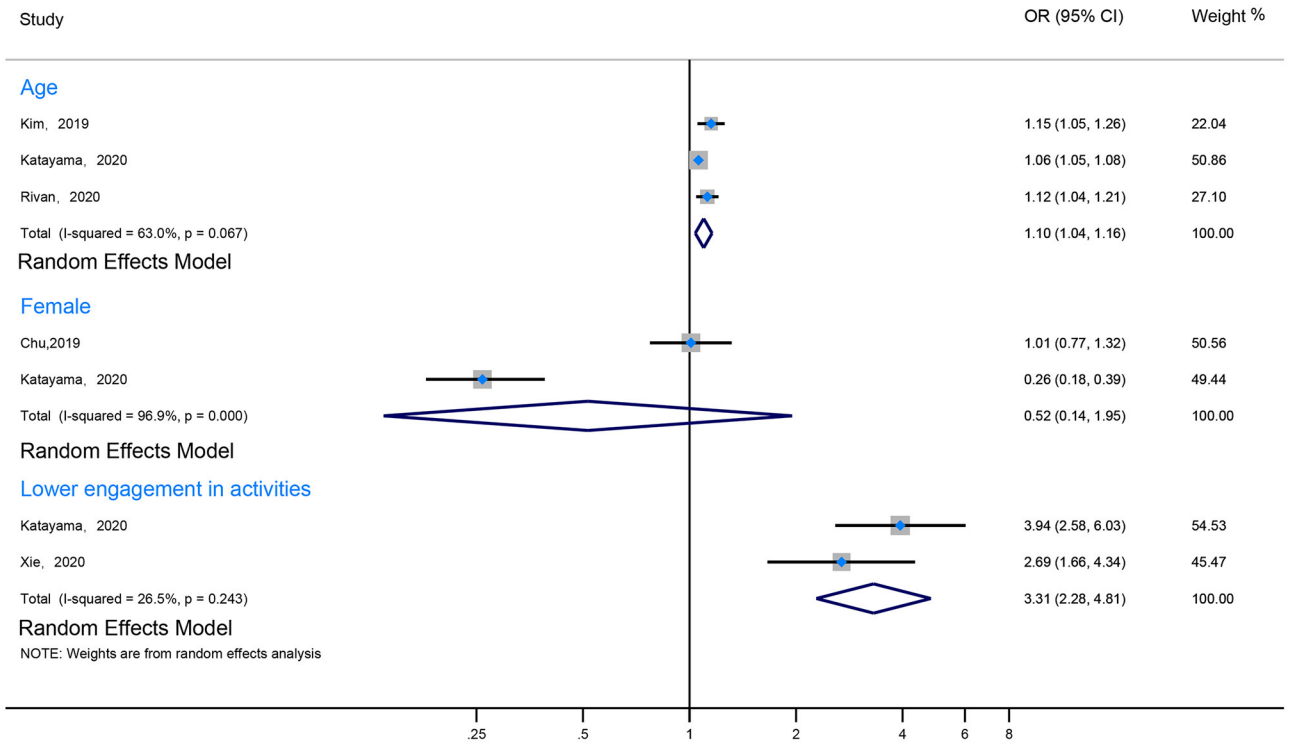


**FIGURE 4 |** The forest plot illustrated the associated risk factors about CF.

(0.13–0.19), and the pooled prevalence of CF in model II was 6%, 95% CI (0.05–0.07). The pooled analysis demonstrated that engagement in age, activities, negative emotional state, especially depression appeared to be independent risk factors of CF. It was unclear whether gender or marital status were independently associated with CF. Additionally, limited evidence suggested that education level, social participation, sleeping problems, calf circumference, body fat, albumin, and vitamin D may be associated with CF. However, there appears to be no direct correlation between marital status or body mass index with CF.

Multiple instruments exist to screen for frailty, but there is no unified consensus about its predictive value and no gold standard measure utilized in clinical settings currently (Walston et al., 2018; Lee H. et al., 2020). However, there are two commonly used frailty assessment tools. One is "physical frailty," which views frailty as a syndrome, such as the Fried criteria, whereas the other approach views frailty as a spectrum of aging, such as FI. The FI is known to predict death better than the frailty phenotype. Nevertheless, when constructing FI, the domain composed of a physical performance-based measure does not necessarily possess predictive power superior to self-reported items (Lee H. et al., 2020).

Similarly, various assessment tools are available for cognitive impairment. Because these tools have different sensitivity and validity values influenced by education, language, culture, and variable cutoffs, some findings highlight the lack of appropriate validated cognitive assessment tools. However, a screening tool is still crucial for cognitive recognition (Rosli et al., 2016; Ranjit et al., 2020). Among the studies we included, the two studies (Hao et al., 2018; Sharma et al., 2020) with the highest prevalence of CF were evaluated by FI and Fried criteria, respectively. The MMSE was used to evaluate cognition. Notably, though, the main reason for the high prevalence of CF was that the included population involved the most elderly. In contrast, studies that reported the lowest prevalence included relatively younger individuals and were found to lack data of the elderly over age 84 (Solfrizzi et al., 2017a). In addition, the vast majority of studies divide frailty into pre-frailty and frailty, which are two different severities and thus may cause variability in prevalence in these groups.

Frailty is a clinical syndrome driven by age-related biologic changes (Lee H. et al., 2020). Cognitive impairment represented by dementia is mainly a disease of the elderly (Scheltens et al., 2016; Ranjit et al., 2020). Among several geriatric syndromes, cognitive impairment and frailty are common problems in the elderly, and these two entities have a close relationship. The deterioration of one element can affect the other and may form a vicious cycle (Arai et al., 2018). The positive rate of Alzheimer's Disease-like CSF (Cerebrospinal Fluid) and amyloid lesion on PET-CT (Positron Emission Tomography-Computed Tomography) increase with age, which may be the basis for age-related pathological mechanisms of CF (Parnetti et al., 2019). Our results also demonstrated that age is an independent risk factor for CF, consistent with the above standpoints.

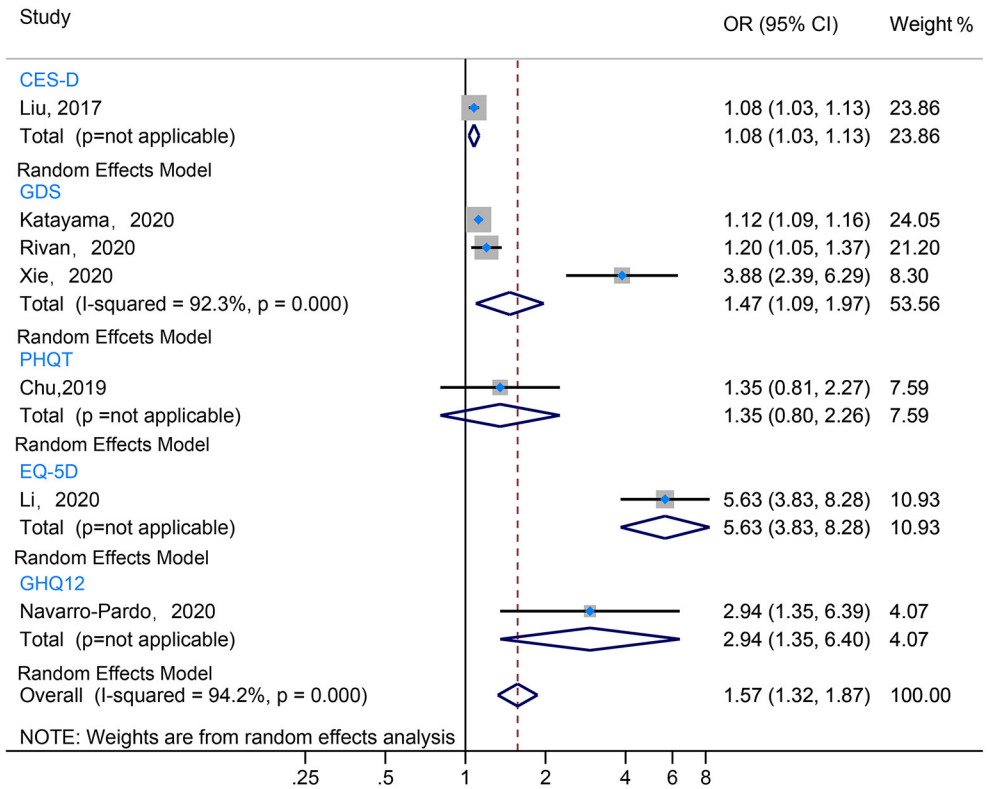


**FIGURE 5 |** The forest plot illustrated the OR for various depression assessment scales estimating risk factor of CF.

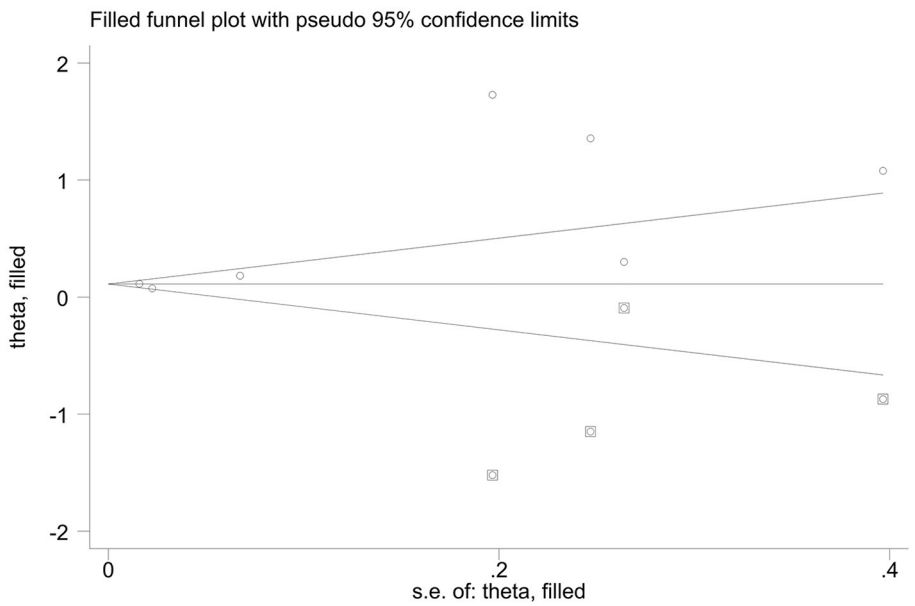


**FIGURE 6 |** Funnel plots of non-parametric trim-and-fill method regards the OR for various depression assessment scales estimating risk factor of CF.

Our study found that people who engaged in less physical activity or social participation had a higher prevalence of CF. First, sarcopenia characterized by unintentional loss of muscle mass is a critical pathophysiological component of frailty (Shen et al., 2019). Previous studies have demonstrated that a certain degree and intensity of resistance training significantly

enhanced muscle strength, muscle power, muscle morphology, and functional outcomes (Dedeyne et al., 2017; Lopez et al., 2018). A meta-analysis provided evidence that physical exercise positively affects most frail older adults (De Labra et al., 2015). Second, Scheltens conducted a study that proposed that exercise also can improve cognitive reserves (Ballard et al., 2011).

Additionally, resistance training may mitigate cognitive impairment due to evidence suggesting a positive effect in verbal fluency, cognitive flexibility, and response inhibition aspects of executive function (Zhang et al., 2020). Previous studies have demonstrated that some cognitive brain networks are disrupted in aging and cognitive disorder patients, and physical exercise may remediate the function of these brain networks effectively (Huang et al., 2016). Last but not least, people with more social participation have a higher physical activity or cognitive training opportunities. One study confirmed similar positive effects of cognitive and physical activity treatments in mitigating the cognitive decline in patients diagnosed with cognitive impairment (Fonte et al., 2019).

Our study also suggests that depression is closely related to cognitive impairment and physical frailty, consistent with recent studies (Soysal et al., 2017). First, these reciprocal associations may be shared among similar risk factors, such as cerebrovascular disease, oxidative stress, chronic inflammation, and mitochondrial dysfunction (Arai et al., 2018; Silva et al., 2019). Additionally, inflammatory cytokines may play an important role, such as interleukin-6 (IL-6), which was also elevated in individuals with CF or those with moderate to severe depression (Franceschi et al., 2000; Soysal et al., 2017). These inflammatory markers are associated with muscle strength and mass and negatively affect central dopaminergic function, resulting in fatigue, motoric slowing, depressive affect, and cognitive impairment (De Labra et al., 2015; Soysal et al., 2017). Third, mitochondrial dysfunction can be identified in numerous neurodegenerative diseases and depression, which may be an essential pathway in the pathophysiology of depression and CF (Mantzavinos and Alexiou, 2017). An influential study mentioned that depression might be a potentially treatable disorder that contributes significantly to cognitive impairment (Ballard et al., 2011). Marcos mentioned that middle-aged patients with depression displayed hippocampal atrophy and Aβ peptide deposition observed by PET-CT, indicating that protein metabolism may be altered in patients with depression (Silva et al., 2019). The importance of depression cannot be ignored when focusing on cognition and frailty in managing elderly individuals in the community.

When analyzing preventative measures, one element that can increase cognitive reserve involves education level (Silva et al., 2019). A study conducted by Philip et al. indicated that education could improve cognitive reserve (Ballard et al., 2011). Furthermore, Martin et al. analyzed the relationship between education level and cognition carefully, suggesting that the number of years of formal education completed by individuals was positively correlated with their cognitive function in adulthood and predicted a lower risk of dementia later in life (Lovden et al., 2020). Consensus guidelines for the intervention of frailty state that cognitive training is a fundamental part of frailty management (Marcucci et al., 2019). Therefore, providing more educational opportunities for the elderly in the community may be an effective measure for CF prevention.

Regarding gender, our review and analysis did not elucidate any significant difference in the prevalence of CF within community-dwelling residents. This finding is in congruence with recent systematic reviews. Shen found no significant gender differences regarding the prevalence of sarcopenia in nursing home residents (Shen et al., 2019). In another meta-analysis, Lucilla also mentioned that gender was not significantly associated with preclinical Alzheimer's Disease prevalence (Parnetti et al., 2019). This study also suggested that both elderly males and females in the community are at similar risk of developing CF.

The relationship between sleep deficits and cognitive function has been studied in detail. Omonigho proved that individuals with insomnia had a 1.65 times higher risk of developing cognitive impairment when compared to individuals without sleep problems. This study additionally estimated that approximately 15% of cognitive impairment might be attributed to sleeping problems, including insomnia (Sun et al., 2020). Hiroki reinforced this concept by reporting that patients with frailty often experience more inferior sleep quality (Nishikawa et al., 2020). A meta-analysis reported that interventions on circadian rhythms might have significant clinical implications in the frail elderly (Gallione et al., 2019). We implemented strategies to address sleep deficits that should be included in any CF preventative strategy.

Finally, nutritional status and its relation to the risk of developing CF is a salient point of discussion. Malnutrition and CF share some clinical features, such as fatigue and weight loss; therefore, it is clear that there is a correlation between them. As mentioned above, there is a distinct correlation between CF and aging. Aging is a physiological process known to produce changes in body composition, affecting the musculature and decreasing muscle volume and strength (Planella-Farrugia et al., 2019). In addition, resistance training and dietary guidance, especially foods with anti-inflammatory and antioxidant properties, can inhibit aging by reducing waist circumference and body fat percentage and increasing arm circumference and calf circumference (Lopes et al., 2020). Specific markers may be utilized to assess for malnutrition as such. Shen suggested that albumin and prealbumin rather than the body mass index may be beneficial for assessing malnutrition (Shen et al., 2019). Different studies have shown that cognitive impairment and frailty are affected by vitamin D levels (Zhou et al., 2016; Lee D. H. et al., 2020). Given the literature, there are reasons to suggest that thinner calf circumference, higher total body fat, and lower albumin content appear to be linked to a higher prevalence of CF. Body mass index alone may not be appropriate for estimating the occurrence of CF as well.

Besides, previous fall history is also a risk factor of CF. For instance, a Japanese cross-sectional survey in a total of 7,614 older people age $>$ 70 years reported that falls associated with CF were (OR 1.132, 95% CI 1.002–1.280) (Kim et al., 2019). Another Chinese multiple-center study found that fall is an independent risk factor of CF (OR 6.653, 95% CI

2.651–16.697) (Ma et al., 2017). Furthermore, the adverse complication of fall indeed promoted sarcopenia because of the prolonged bed rest. On the other hand, fall also caused hospitalacquired pneumonia (HAP) because patients extended hospitalized days. As usual, the pathogenic microbes of HAP are multi-resistant pathogens and deteriorate the poor prognosis of CF.

## LIMITATION

This review has several limitations. Firstly, we only included studies written in English, which may introduce selection bias or reporting bias to our results. Secondly, our focus was on the prevalence of CF. Our analysis of all the studies involved various assessment tools related to cognition and frailty with inconsistent cutoff values. As such, this level of heterogeneity likely affected our results. However, many of these studies did provide supporting evidence regarding the validity of such assessment tools for global use. Thirdly, due to the significant heterogeneity in study designs and lack of uniformly reported risk factors in every study (such as gender, marital status, sleeping deficits), we could not perform a conglomerate meta-analysis of all risk factors of CF. However, our sensitivity analysis demonstrated that the individual study did not significantly influence the pooled results. Finally, most of the included studies were retrospective observational studies, which cannot provide a higher strength of evidence when compared to prospective cohort studies. Therefore, there are significant opportunities to expand our understanding of CF by performing further well-designed prospective cohort studies to search for effective and predictive diagnostic tools and to verify the risk factors of CF in the future.

## CONCLUSION/FUTURE DIRECTION

CF is highly prevalent in community residents. Furthermore, different definitions of CF have different prevalence rates. A multi-modal intervention for CF, including the combination of increased exercise, nutritional support, depression prevention, sleeping disorder adjustments, increased social opportunities, and multi-component strategies, may be effective for the prevention of CF. Prospective studies of a large sample size should be conducted to establish a consensus to assess CF's various reported diagnostic criteria. Additionally, the measurement of various clinical outcomes (e.g., progression to dementia, morbidity, mortality) cannot be thoroughly conducted without such studies. More well-designed randomized controlled trials are also needed to determine the types of nutritional support, the choice of exercise methods, and the measures of emotional regulation required for community residents to prevent CF.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

YiY conceived and collected the preliminary data. TZ and YiY performed and designed the study. TZ and YR gathered and analyzed the original studies, extracted the data independently and ensured congruence with the inclusion and exclusion criteria. TZ, YR, and YiY wrote the first draft of the manuscript. TZ conceived all the figures and tables. YR and PS also independently evaluated the risk bias of all included studies. YaY completed the **Supplementary Material**. YW and ZL participated and guided in the discussion of an overall framework of the article. SJ and YiY corrected and validated the manuscript in its entirety. The manuscript has been read and approved by all authors.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.755926/full#supplementary-material

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frontiers in Aging Neuroscience

SYSTEMATIC REVIEW
published: 11 February 2022
doi: 10.3389/fnagi.2022.804341

# Association of Headache Disorders and the Risk of Dementia: Meta-Analysis of Cohort Studies

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**Objectives:** The purpose of this meta-analysis is to assess whether there is an association between headache disorders and all-cause dementia, Alzheimer's disease (AD), and vascular dementia (VaD).

**Methods:** PubMed, Cochrane Library, Embase, and Web of Science were searched for cohort studies published from database inception to October 8, 2021, using medical subject headings (MeSH) and keywords. All statistical analyses were performed using Stata statistical software version 14.0. If $P > 0.1$ and $I^2 \leq 50\%$, a fixed-effects model was adopted. If $I^2 > 50\%$ (which indicated great heterogeneity), a random-effects model was adopted. The funnel plot and Egger's test were used to evaluate publication bias.

**Results:** This meta-analysis included 12 cohort studies covering 465,358 individuals, which were published between 2001 and 2020. The pooling analysis shows that a history of any headache disorder is associated with an increased risk of all-cause dementia (OR = 1.35; 95% CI: 1.21–1.50; $I^2 = 81.6\%$, $P < 0.001$). The history of any headache was associated with an increased risk of AD (OR = 1.49; 95% CI: 1.08–2.05; $I^2 = 70.0\%$, $P = 0.003$) and VaD (OR = 1.72; 95% CI: 1.32–2.25; $I^2 = 0\%$, $P < 0.001$). In the subgroup analysis, females with a history of headache have a slightly higher risk of dementia than males (OR = 1.32; 95% CI: 1.16–1.51; $I^2 = 88.3\%$, $P < 0.001$) and the risk of dementia in the retrospective cohort was slightly higher than in the prospective cohort (OR = 1.38; 95% CI: 1.22–1.56; $I^2 = 83.4\%$, $P < 0.001$).

**Conclusions:** Our meta-analysis shows that any headache disorder increases the risk of all-cause dementia, AD, or VaD. These findings provide evidence that headache should be recognized as an independent risk factor for dementia, AD, or VaD.

**Keywords: headache, dementia, Alzheimer's disease, vascular dementia, meta-analysis**

OPEN ACCESS

***Edited by:***
*Omar Yaxmehen Bello-Chavolla, Instituto Nacional de Geriatría, Mexico*

***Reviewed by:***
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***Specialty section:***
*This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience*

***Received:*** *29 October 2021*
***Accepted:*** *19 January 2022*
***Published:*** *11 February 2022*

***Citation:***
*Qu H, Yang S, Yao Z, Sun X and Chen H (2022) Association of Headache Disorders and the Risk of Dementia: Meta-Analysis of Cohort Studies. Front. Aging Neurosci. 14:804341. doi: 10.3389/fnagi.2022.804341*

## BACKGROUND

Dementia is a neurological disorder characterized by cognitive, behavioral, social, and emotional deterioration. It is a major public health problem in the world and has a high incidence rate (Van Der Steen et al., 2018). Although significant progress has been made in molecular neuroimaging, clinical pathology, and the development of biomarkers of dementia in the last decade, the results are slightly disappointing. Clinicians are still waiting for disease modification therapy of dementia

(Gale et al., 2018). Therefore, if we can identify the risk factors associated with dementia early, the development of dementia might be prevented. A previous study has explored the risk factors of dementia, including age, gender, family history, rural residents, low educational level, marital status, smoking, hypertension, hyperlipidemia, diabetes, heart disease, and cerebrovascular disease (Jia et al., 2020). The impact of headache on dementia has not been noted.

Headaches (including migraine, tension headache, and drug overuse headache) are associated with a high incidence rate, low quality of life, low productivity, and high economic costs. A global disease burden study listed headache as the second largest cause of disability in the world. Among people aged 15–49, the incidence of migraine is the third highest (Saylor and Steiner, 2018). Migraine can be regarded as a high signal of white matter-related risk factors (Kruit et al., 2004). Patients with headache are more likely to have extensive white matter hyperintensity (WMH) than patients without headache (Honningsvåg et al., 2018). White matter hyperintensity may be associated with dementia. Therefore, we speculate that headache may be associated with an increased risk of dementia, and we systematically reviewed the existing population-based longitudinal evidence to determine the association between headache disorder and the risk of all-cause dementia, Alzheimer's disease (AD), or vascular dementia (VaD).

# METHODS

This meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021). The protocol was pre-registered in the International Prospective Register of Systematic Reviews (PROSPERO) platform, and the approval number is CRD42021283921.

## Data Sources and Searches

PubMed, Cochrane Library, Embase, and Web of Science were searched for cohort studies published from database inception to October 8, 2021. There were no language restrictions, and the search strategy combined the use of medical subject headings (MeSH) and keywords. The search terms included dementia, AD, VaD, headache, head pain, migraine, and cohort studies. The full search strategy of PubMed is included in **Supplementary Table 1.** The reference lists of included cohort studies and other published meta-analyses were also examined to identify relevant trials.

## Eligibility Criteria

The trials were included on the basis of the following eligibility criteria: (1) cohort studies or nested case-control studies based on cohort trials; (2) investigations of the association of headache disorders with the risk of incident all-cause dementia, AD, or VaD. In this meta-analysis, "any headache" was defined as "patients who suffered from any type of primary headache in the past." All-cause dementia was chosen as the primary outcome, AD, and VaD as the secondary outcomes.

Trials were excluded if they did not provide an odds ratio (OR) estimate with corresponding 95% confidence interval (CI). If more than one study reported data from the same cohort, we included the study with the longest follow-up or the largest number of participants. Furthermore, the following articles were also excluded: conference abstracts, study protocols, duplicate publications, and studies with no outcomes of interest.

## Study Selection

Study selection was performed by two reviewers (HLQ and ZCY) who independently screened the literature based on the eligibility and exclusion criteria. Duplicate and irrelevant articles were first excluded according to their titles and abstracts. Thereafter, the full texts of the potentially eligible articles were downloaded and read to identify all eligible studies. Any disagreements were resolved by the third reviewer (SDY), who acted as an arbiter.

## Data Extraction

Data extraction was performed independently by the two above-mentioned reviewers (HLQ and ZCY) who consulted the guidelines on data extraction for systematic reviews and meta-analysis (Taylor et al., 2021). They used predesigned forms for extracting data including the first author, year of publication, study type, sample size, follow-up years, age, diagnosis of migraine/dementia, headache type, dementia type, and confounders adjusted. Disagreements were resolved by discussion with SDY to reach a consensus.

## Risk of Bias Assessment

The Newcastle-Ottawa scale (NOS) was used to assess the quality of cohort studies (Wells et al., 2014). Stars ranged from 0 to 9 points for cohort studies, four stars for selection of participants and measurement of exposure, two stars for comparability, and three stars for assessment of outcomes and adequacy of follow-up, with more stars indicating higher quality of study. Scores of 0–3, 4–6, and 7–9 were considered to indicated low, moderate, and high quality, respectively.

## Statistical Analysis

The adjusted OR and 95% CI from each trial were used to assess the association between headache disorders and risk of dementia, AD, or VaD. The $\chi^2$-test and the $I^2$-values were used to evaluate heterogeneity. If $P > 0.1$ and $I^2 \leq 50\%$, a fixed-effects model was adopted. If $I^2 > 50\%$ (which indicated great heterogeneity), a random-effects model was adopted. The sensitivity analysis was performed by excluding one study each time and rerunning to verify the robustness of the overall effects. The funnel plot was visually inspected to confirm publication bias, and Egger's regression test was used to statistically assess publication bias. We conducted a subgroup analysis based on gender and research type. All statistical analyses were performed using Stata statistical software version 14.0 (Stata Corp, College Station, Texas).

# RESULTS

## Literature Search

The systematic search of cohort studies published before October 8, 2021, identified 1,176 results. After title and abstract screening, 20 articles were considered potentially relevant. Twelve studies (Tyas et al., 2001; Chuang et al., 2013; Hagen et al., 2014; Røttereng et al., 2015; Yang et al., 2016; Tzeng et al., 2017; Yin

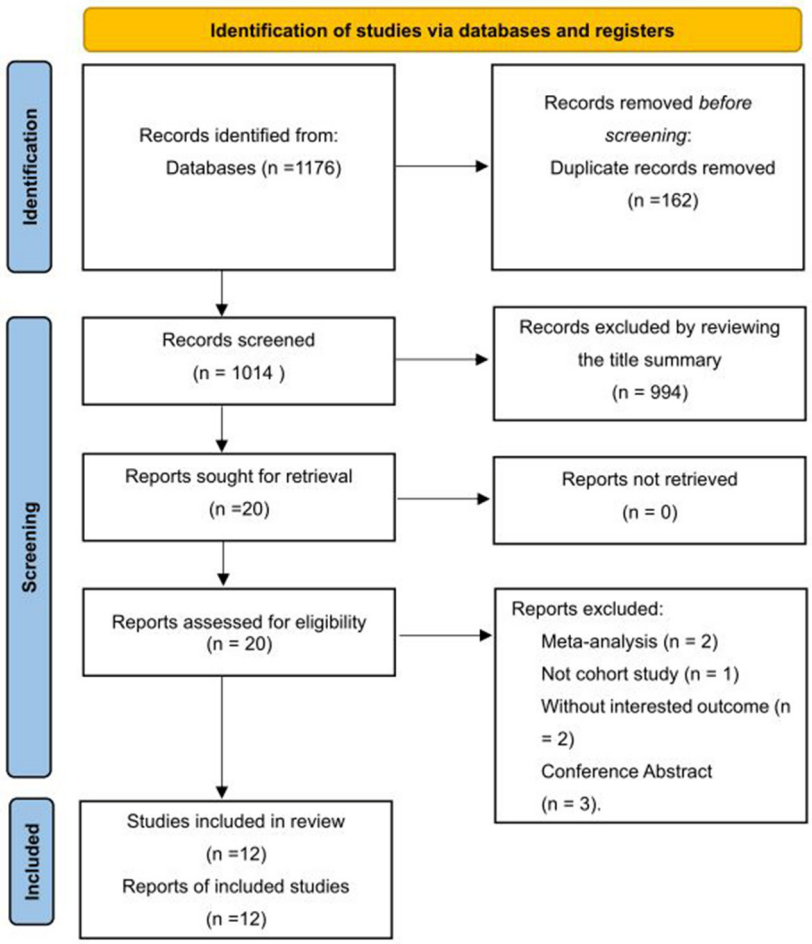


**FIGURE 1 |** Studies screening process.

et al., 2018; Kostev et al., 2019; Lee et al., 2019; Morton et al., 2019; George et al., 2020; Islamoska et al., 2020) were included after full text review, of which 11 reported the incidence of dementia or composite of AD or VaD on follow-up, and one study (Tyas et al., 2001) reported the incidence of AD only. The selection process is presented in **Figure 1**.

## Study Characteristics

This meta-analysis included 12 cohort studies covering 465,358 individuals, which were published between 2001 and 2020. Four studies were retrospective cohort studies, while the other eight were prospective cohort studies. All individuals in these cohorts were at least 20 years old at the beginning of follow-up, and had clear diagnostic criteria for dementia. The average follow-up time ranged from 5 to 22 years. The adjusted estimates were available for almost all studies even though the adjusted confounders are slightly different. The main characteristics of the included trials are shown in **Table 1**.

## Quality Assessment

According to NOS criteria, the average score was 7.67 of all included cohort studies, and the score for each trail was 7 or above, indicating that all cohort studies were of high quality in this meta-analysis. The scores of the included studies are shown in **Table 1**.

## Any Headache Disorders and Risk of All-Cause Dementia

Eleven cohort studies (Chuang et al., 2013; Hagen et al., 2014; Røttereng et al., 2015; Yang et al., 2016; Tzeng et al., 2017; Yin et al., 2018; Kostev et al., 2019; Lee et al., 2019; Morton et al., 2019; George et al., 2020; Islamoska et al., 2020) explored the association between a history of headache and the risk of all-cause dementia. The pooling analysis shows that a history of any headache disorder is associated with an increased risk of all-cause dementia (OR = 1.35; 95% CI: 1.21–1.50; $I^2$ = 81.6%, $P < 0.001$; **Figure 2**). Sensitivity analysis showed that none of the individual studies reversed the pooled-effect size, which means that the results are robust (**Supplementary Figure A**).

## Any Headache Disorders and Risk of AD

Seven included studies (Tyas et al., 2001; Hagen et al., 2014; Røttereng et al., 2015; Yang et al., 2016; Yin et al., 2018; Kostev et al., 2019; Morton et al., 2019) assessed the association between

**TABLE 1 |** Basic characteristics of the included studies.

| Author | Year | Country | Study type | Sample size | Follow-up years | Age (years) | Diagnosis of migraine/ dementia | Headache type | Dementia type | Confounders adjusted | NOS scores |
|---|---|---|---|---|---|---|---|---|---|---|---|
| George et al. (2020) | 2020 | USA | Prospective cohort | Total: 11,252 Migraine: 1,397, No migraine: 9,855 | 21 averages | 51∼70 | ICHD-II/ICD-9 | Migraine/ Severe Non-migraine Headache | All-cause dementia | Age, sex, race, center, APOE ε4, income, education, BMI, smoking status, hypertension, diabetes, prevalent CHD, drinking status, HDL cholesterol, and total cholesterol | 9 |
| Islamoska et al. (2020)) | 2020 | Denmark | Retrospective cohort | Total: 62,578 Migraine: 10857, No migraine: 51721 | 3.6∼11.2 | 49 averages | ICD-8/ICD-10 | Migraine | All-cause dementia | Sex, country of origin, marital status, educational level, headache diagnoses, psychiatric morbidities, and Charlson Comorbidity Index (CCI) | 8 |
| Morton et al. (2019) | 2019 | Canada | Prospective cohort | Total: 679 | 5 averages | ≥65 | ICHD-II/DSM-IV | Migraine | All-cause dementia, Alzheimer's disease (AD), Vascular dementia (VaD) | Age and education | 7 |
| Lee et al. (2019) | 2019 | Korea | Retrospective cohort | Total:56,309 Migraine: 45,752, No migraine: 10,557 | 11 averages | ≥60 | ICD-10 | Migraine | All-cause dementia | Age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia | 7 |
| Kostev et al. (2019) | 2019 | Germany | Retrospective cohort | Total: 7,454 Migraine: 3,727, No migraine: 3,727 | 10 averages | 60∼80 | ICD-10 | Migraine | All- cause dementia, Alzheimer's disease (AD), Vascular dementia (VaD) | No report | 8 |
| Yin et al. (2018) | 2018 | China | Retrospective cohort | Total:6,730 PHDs:1,346, No migraine: 5,384 | 5 averages | 47.38 averages | ICD-9 | Primary headache | All-cause dementia, Alzheimer's disease (AD), Vascular dementia (VaD) | Age, sex, hypertension, DM, IHD, hyperlipidemia, AF, TUD, alcoholism, obesity, PD, CVA, depression, CKD, and CAI | 8 |
| Tzeng et al. (2017) | 2016 | China | Retrospective cohort | Total: 14,480 Headache: 3,620 No headache: 10,860 | 10 averages | ≥20 | ICD-9 | Migraines, tension-type headaches | All-cause dementia, Alzheimer's disease (AD), Vascular dementia (VaD) | Gender, age, monthly income, urbanization level, geographic region of residence, and comorbidities | 7 |
| Yang et al. (2016) | 2016 | China | Retrospective cohort | Total: 69,540 TTH: 13,908 No TTH: 55,632 | 8.14 averages | ≥20 | ICD-9 | Tension-type headaches | All-cause dementia, Alzheimer's disease (AD), Vascular dementia (VaD) | Age, sex, diabetes, dyslipidemias, COPD, hypertension, IHD, AF, HF, stroke, depression, head injury, Parkinson's disease, and migraine | 8 |

*(Continued)*

**TABLE 1** | Continued

| Author | Year | Country | Study type | Sample size | Follow-up years | Age (years) | Diagnosis of migraine/ dementia | Headache type | Dementia type | Confounders adjusted | NOS scores |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Røttereng et al. (2015) | 2015 | Norway | Retrospective cohort | Total: 16,443 Any headache: 8,676 No headache: 7,767 | 11 averages | ≥55 | ICHD-I | Any headache | All-cause dementia, Alzheimer's disease (AD), Vascular dementia (VaD) | Age, gender, level of education, comorbidity, smoking, and anxiety and depression | 7 |
| Hagen et al. (2014) | 2013 | Norway | Prospective cohort | Total: 51,859 Any headache: 21,871 No headache: 29,988 | 15 averages | ≥20 | ICHD-I | Any headache Migraine Non-migraine headache | All-cause dementia | Age, sex, education, total HADS score, and smoking | 8 |
| Chuang et al. (2013) | 2013 | China | Retrospective cohort | Total: 167,340 Migraine: 33,468 No migraine: 133,872 | 12 longest | 42.2 means | ICD-9 | Migraine | All-cause dementia | Age, sex, diabetes, hypertension, depression, head injury, and CAD | 8 |
| Tyas et al. (2001) | 2001 | USA | Prospective cohort | Total: 694 Migraine: 36 No migraine: 658 | 5 averages | 74 means | NINCDS–ADRDA | Migraine | Alzheimer's disease (AD) | Age, education, and sex, occupational exposure | 7 |

any headache and the risk of AD. Overall, the history of any headache was associated with an increased risk of AD (OR = 1.49; 95% CI: 1.08–2.05; $I^2 = 70.0\%$, $P = 0.003$; **Figure 3**). Sensitivity analysis showed that none of the individual studies had reversed the pooled-effect size, which means that the results are robust (**Supplementary Figure B**).

## Any Headache Disorders and Risk of VaD

Five studies (Hagen et al., 2014; Røttereng et al., 2015; Yin et al., 2018; Kostev et al., 2019; Morton et al., 2019) assessed the association between a history of headache and the risk of VaD. Pooled results showed that a history of any headache disorder is associated with an increased risk of VaD (OR = 1.72; 95% CI: 1.32–2.25; $I^2 = 0\%$, $P < 0.001$; **Figure 4**).

## Subgroup Analysis

We conducted a subgroup analysis of gender and research type, but still did not find the origin of the high heterogeneity. In the subgroup analysis, females with a history of headaches have a slightly higher risk of dementia than males; in the prospective cohort design, there is no direct relationship between the history of headaches and the increased risk of dementia. Meanwhile, a history of migraine is associated with a higher risk of dementia (OR = 1.32; 95% CI: 1.13–1.40; $I^2 = 75.6\%$, $P < 0.001$), but the risk is lower than that of non-migraine headache patients (**Table 2**).

## Publication Bias

A visual inspection of the funnel plot showed no evidence of a significant publication bias in the outcome of any headache disorders and risk of all-cause dementia (**Figure 5**). Egger's regression test ($P = 0.087$) likewise indicated no publication bias in our meta-analysis.

# DISCUSSION

## Main Findings

This meta-analysis included 12 cohort studies covering 465,358 individuals, which provided a comprehensive evaluation on the association between headache and dementia. We found a significant increase in the risk of all-cause dementia, AD, or VaD among individuals with headache, with an overall 1.35-fold, 1.49-fold, or 1.72-fold increase in risk, respectively, compared with non-headache controls. This indicates that headache might be an independent risk factor for dementia.

## Interpretation of Findings

A previous review investigated the relationship between headache and dementia (Wang et al., 2018). The results showed that any headache increased the risk of all-cause dementia. However, it does not mean that headache is associated with an increased risk of all types of dementia. Moreover, it did not find a relationship between any headache and AD. In contrast, in the current analysis, we added more recent studies and analyzed the data according to the type and subgroup of dementia, so as to provide strong evidence for the association between headache and all-cause dementia, AD, or VaD. Another meta-analysis

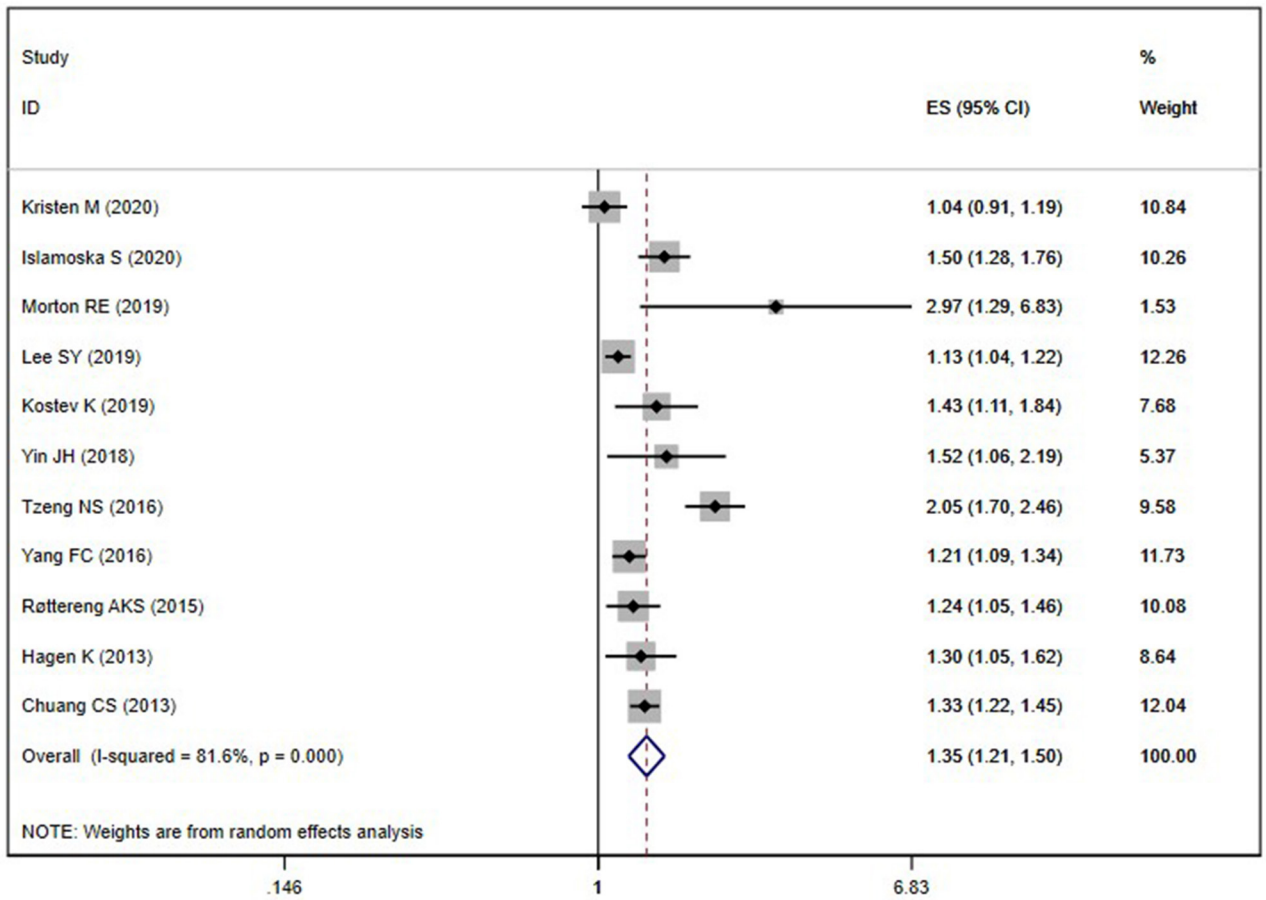


**FIGURE 2 |** Meta-analysis of the risk of all-cause dementia caused by any headache.

revealed that migraine is a potential risk indicator for AD and all-cause dementia (Wang et al., 2021). However, they did not find any association between migraine and the risk of VaD, which may be reasonably associated with the low number of studies included in their meta-analysis. Only five published cohort studies were identified in the review mentioned above. So, we re-analyzed the relationship between any type of headache and all-cause dementia, AD, or VaD. Our study found that any type of headache increases the risk of all-cause dementia, AD, or VaD, and the previous meta-analysis did not show these meaningful conclusions.

So far, there are few studies on the pathophysiological mechanism of the association between headache and dementia. Several brain structures involved in the pain network, such as the thalamus, insula, anterior cingulate gyrus, amygdala, and temporal cortex, also play an important role in the memory network (Apkarian et al., 2005; Svoboda et al., 2006). The overlap of the pain and memory network regions explains the potential correlation between chronic pain and memory impairment in patients with headache. The changes of hippocampal function and structure may play an important role in the pathophysiology of migraine (Maleki et al., 2013). The hippocampus is involved in memory consolidation, spatial navigation, and the stress response. Migraine is a paroxysmal disease. Each attack is accompanied by or causes many physiological and emotional stressors. Therefore, migraine attack can be regarded as a repeated stressor, causing changes in hippocampal structure and function. Some research showed that WMH is associated with an increased risk of all-cause dementia and AD (Godin et al., 2008; Bos et al., 2018; Garnier-Crussard et al., 2020). However, only a few studies have investigated the changes of the white matter microstructure and structural connectivity in migraine patients. The pathophysiology of migraine-related WMH is still poorly understood. In the current study, chronic headache may change the network of white matter by changing the mode and number of connections, resulting in the destruction of network topology. Therefore, the brain structural network of migraine patients shows abnormal overall integration between different migraine-related brain circuits adapted to long-term pain (Liu et al., 2013). Therefore, the white matter fibers of migraine patients will have abnormal changes, which may be related to the occurrence of dementia. Migraine is an independent risk factor for ischemic stroke, which may be related to the pathogenesis of VaD (Paemeleire, 2009). Migraine patients are more likely to develop psychiatric diseases, such as depression (Breslau et al., 1994; Chen et al., 2012; Rammohan et al., 2019). In particular, early depression (or depressive symptoms) has been associated with a more than two-fold increase in the risk of dementia

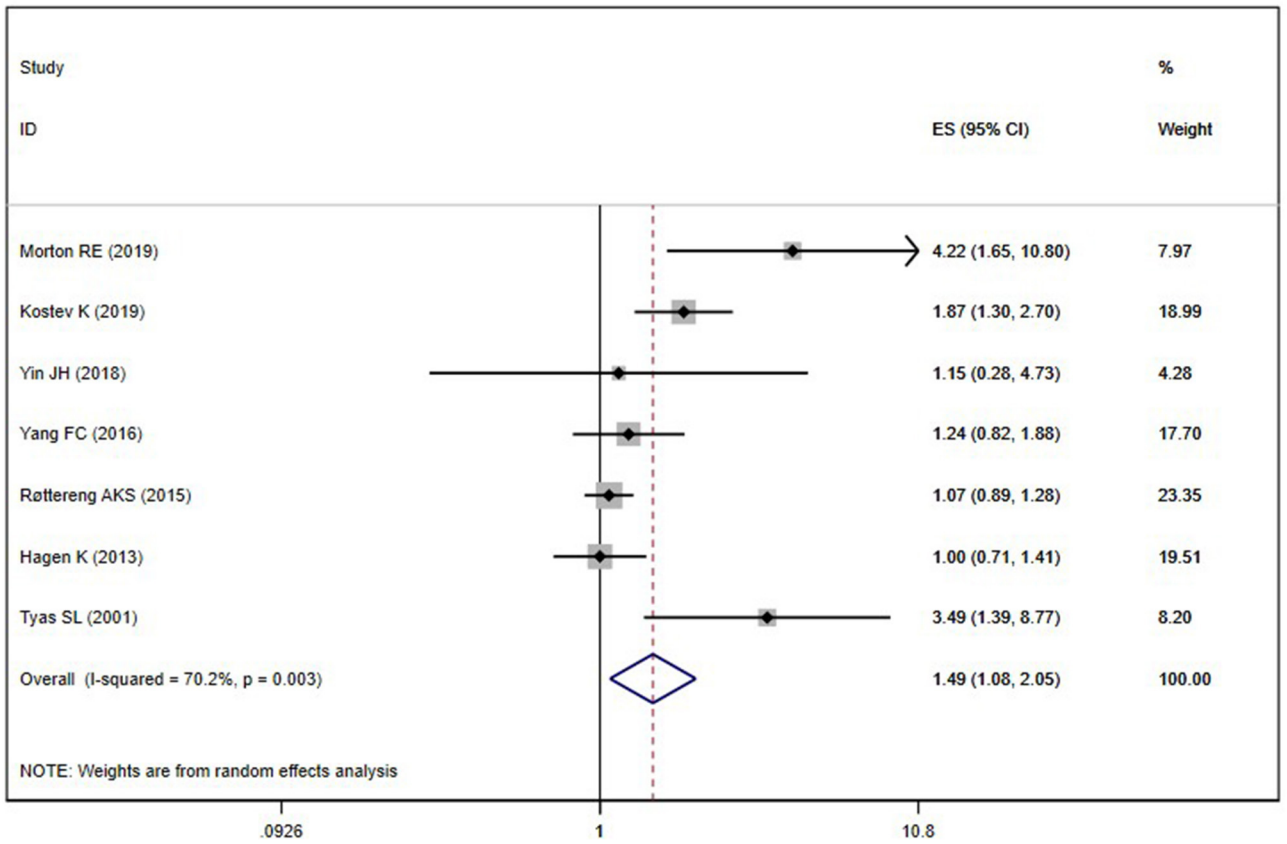


**FIGURE 3 |** Meta-analysis of the risk of Alzheimer's disease caused by any headache.

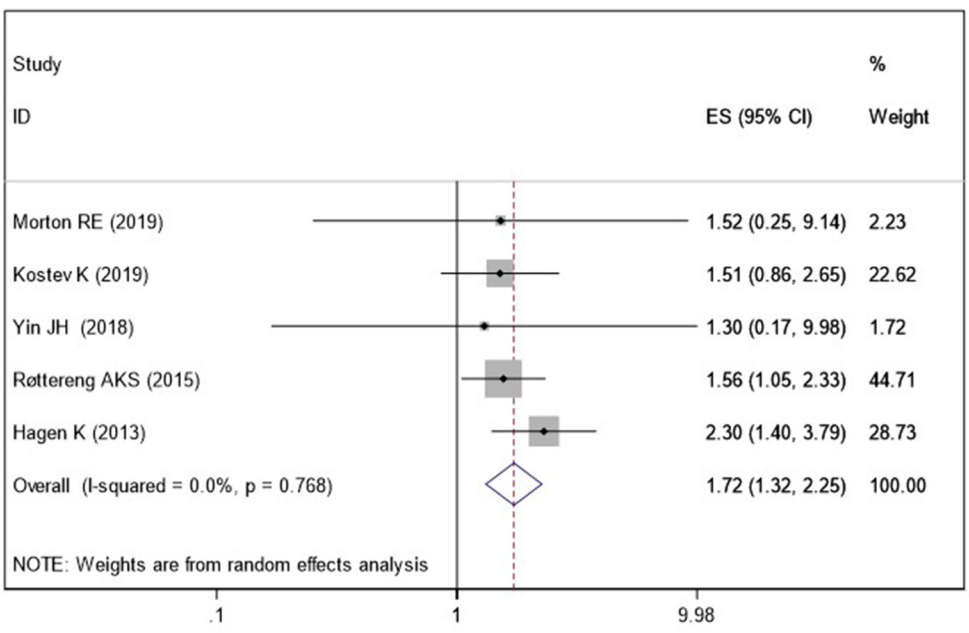


**FIGURE 4 |** Meta-analysis of the risk of vascular dementia caused by any headache.

**TABLE 2 |** Subgroup analysis for the risk of dementia in patients with headache.

| Subgroups | Included studies | OR] (95% CI) | Heterogeneity | |
|---|---|---|---|---|
| | | | $I^2$ (%) | *P*-values |
| **Sex** | | | | |
| Female | 7 | 1.32 (1.16–1.51) | 88.3 | 0.000 |
| Male | 9 | 1.28 (1.09–1.50) | 80.5 | 0.000 |
| **Study type** | | | | |
| Retrospective cohort | 8 | 1.38 (1.22–1.56) | 83.4 | 0.000 |
| Prospective cohort | 3 | 1.28 (0.94–1.76) | 75.5 | 0.017 |
| **Headache type** | | | | |
| Migraine | 7 | 1.26 (1.13–1.40) | 75.6 | 0.000 |
| Non-migraine | 4 | 1.50(1.15–1.95) | 83.1 | 0.003 |

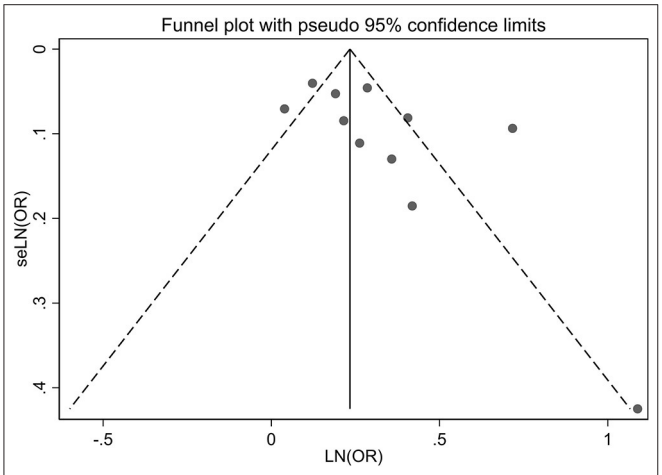


**FIGURE 5 |** Publication bias of the risk of all-cause dementia caused by any headache.

(Katon et al., 2015; Lin et al., 2017). The possible biological mechanisms linking depression with dementia include vascular disease, changes in glucocorticoid levels, hippocampal atrophy, increased amyloid β plaque deposition, inflammatory changes, and nerve growth factor deficiency (Byers and Yaffe, 2011). In other words, patients with depression have a higher risk of dementia (Rapp et al., 2006; Wint, 2011). The number of neuritic plaques and neurofibrillary tangles in the hippocampus of AD patients with major depressive disorder confirmed by neuropathology is higher than that of AD patients who have never had a major depressive disorder in their life (Ringman et al., 2008).

In the subgroup analysis, females with a history of headaches have a slightly higher risk of dementia than males. Female are significantly more susceptible to migraine. The role of sex hormone fluctuations in promoting migraine attacks is well-known. This may be related to female sex hormones and their physiological fluctuations, which may play a role in women's susceptibility to pain hypersensitivity (Gazerani et al., 2005). In most clinical studies, migraine patients show impaired cognitive function during the interictal period (Cady and Farmer, 2013). An apolipoprotein E (ApoE) genotype is equally common in men and women, but plays a stronger role in women (Rocca et al., 2014). Apolipoprotein E is positively correlated with headache (Miao et al., 2015), which may explain why females with a history of headaches have a slightly higher risk of dementia than males.

## Implications and Limitations

Our meta-analysis summarizes the existing evidence of the association between a history of headache and the risk of all-cause dementia and shows that any headache is a risk factor for all-cause dementia. It suggests that we need to pay more attention to the dementia risk of headache patients, which is also conducive to the early identification of high-risk groups of dementia. Meanwhile, this study also has certain limitations. We only included cohort studies. This controls many confounders and hence the conclusion is reliable. Future studies can consider including case-control studies and cross-sectional studies to enrich the research types. Moreover, we did not include covariate analysis in this meta-analysis. However, the included cohort studies have controlled the adjusted confounders and thus have a well-controlled confounding bias, making the conclusions of this study reliable and facilitating translation to the clinic.

# CONCLUSIONS

This meta-analysis suggests that any headache disorder increases the risk of all-cause dementia, AD, or VaD. However, more studies are still needed to confirm the pathophysiological mechanisms underlying this phenomenon. The results of our meta-analysis can be very useful in the development of new dementia prevention and treatment strategies.

# DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/ **Supplementary Material**.

# AUTHOR CONTRIBUTIONS

XS and HC conceived the study. HQ and ZY collected the data and drafted the manuscript. SY revised the manuscript and language. HQ conducted the subgroup analysis. All authors have read and approved the manuscript.

# FUNDING

This study was supported by the Doctoral Research Start-Up Fund Project of Liaoning (No. 2019-BS-234) and the Young and Middle-Aged Scientific and Technological Innovation Talents Support Program of Shenyang (No. RC210374).

# SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.804341/full#supplementary-material

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 23 March 2022
doi: 10.3389/fnagi.2022.771486

# Association Between Antibiotic Treatment of Leptospirosis Infections and Reduced Risk of Dementia: A Nationwide, Cohort Study in Taiwan

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**Specialty section:**
*This article was submitted to Alzheimer's Disease and Related Dementias, a section of the journal Frontiers in Aging Neuroscience*

**Received:** *06 September 2021*
**Accepted:** *14 February 2022*
**Published:** *23 March 2022*

**Citation:**
*Chao P-C, Chien W-C, Chung C-H, Huang C-K, Li H-M and Tzeng N-S (2022) Association Between Antibiotic Treatment of Leptospirosis Infections and Reduced Risk of Dementia: A Nationwide, Cohort Study in Taiwan. Front. Aging Neurosci. 14:771486. doi: 10.3389/fnagi.2022.771486*

**Background:** To explore the association between leptospirosis, the risk of dementia, and the potential protective role of antibiotic treatment.

**Methods:** We conducted a retrospective cohort nationwide, population-based study, from Taiwan's National Health Insurance Research Database (NHIRD). We enrolled 1,428 subjects aged 50 years or above, in the index year of 2000, which included those retrieved from the NHIRD record. Dementia diagnosis and incidence over 16 years follow-up was retrieved from the NHIRD records. The Fine and Gray survival analysis was used to determine the risk of dementia, and the results were presented as a sub-distribution hazard ratio (SHR) with a 95% confidence interval.

**Results:** In the study period, 43 of the 357 leptospirosis patients developed dementia, as compared to 103 of the control group (930.90 vs. 732.49 per $10^5$ person-years). By the Fine and Gray survival analysis, the leptospirosis was associated with the risk of dementia, and the adjusted SHR was 1.357 (95% confidence interval [CI]: 1.213–1.519, $P < 0.001$), across 16-year of the follow-up period. To exclude the protopathic bias, the sensitivity analysis was conducted. This analysis revealed that the leptospirosis was associated with the increased risk of dementia, even after excluding the dementia diagnosis within the first year (adjusted SHR = 1.246, 95%CI: 1.114–1.395, $P < 0.001$) or within the first 5 years (adjusted SHR = 1.079, 95%CI: 1.023–1.152, $P = 0.028$), antibiotic treatment for leptospirosis was associated with the reduced risk of dementia ($P = 0.001$).

**Conclusion:** Leptospirosis was associated with an increased risk for dementia, and antibiotic treatment was associated with a reduced risk. Further research will be necessary to explore the underlying mechanisms of this association.

**Keywords: leptospirosis, antibiotic, dementia, time-dependent, risk**

## INTRODUCTION

In Taiwan, 4–8% of those aged 65 years or over have dementia (Sun et al., 2014), which is a heavy burden for the patients, their caregivers, and the community. Alzheimer's dementia (AD) is the most common type of dementia, which is a progressive condition that principally affects the elderly. Even though the underlying etiology of AD is not known, there are extensive beta-amyloid (Aβ) deposits in the brain of individuals with no signs of cognitive impairment (Rodrigue et al., 2009). In addition, Aβ may play a role in response to several types of infection (Soscia et al., 2010; Moir et al., 2018). Several recent studies have focused on the possibility that infectious agents might be predisposed to the AD development (Itzhaki et al., 2016). Research has focused on pathogens, such as herpes viruses, yeasts, or bacteria, notably including spirochetes (Miklossy, 2011).

The spirochetes pathogens are generally acquired by the exposure to wild animal secretions or arthropod bites, which are the most prevalent spirochetosis worldwide, particularly in wet tropical and subtropical regions (Levett, 2001). A broad spectrum of clinical manifestations may occur in humans, ranging from subclinical infections and self-limited anicteric febrile illnesses to the severe and potentially fatal icteric disease including Weil's disease. Antibiotics, especially penicillin, are the mainstay of treatment for suspected or confirmed cases of leptospirosis, and treatment with the appropriate antibiotics should be initiated immediately (Center for Disease Control and Prevention [CDCP], 2018). Although some infected individuals display fulminant disease, it is suspected that the chronic carriage in others can remain subclinical. The treatment of leptospirosis differs depending on the severity and duration of the symptoms at the time of presentation, and patients with mild, flu-like symptoms may require only symptomatic treatment.

A possible relationship between *Leptospira* infection and neuropsychiatric disorders has been previously discussed, including dementia, depression, mania, and psychosis (Marshall and Scrimgeour, 1978; Semiz et al., 2005; Chiu et al., 2019). Importantly, it was recently reported that patients with a history of leptospirosis were at a moderately increased risk of developing dementia (Chiu et al., 2019). In addition, since the allelic variants of Apolipoprotein E4 (*APOE4*) allele are a risk factor not only for AD (Strittmatter et al., 1993) but also for a disease caused by the herpes simplex virus (HSV)-1 (Burgos et al., 2006), human immunodeficiency virus (HIV)-1 (Burt et al., 2008), and bacteria including *Chlamydia pneumoniae* (Gerard et al., 2005), we hypothesize that there might be a link between leptospirosis infections and dementia. For this reason, we have conducted a retrospective cohort study so as to investigate the association between leptospirosis and dementia, and the role of the antibiotic treatment in the risk of dementia in the leptospirosis group.

## MATERIALS AND METHODS

### Data Sources

The National Health Insurance (NHI) Program was launched in Taiwan in 1995, and as of June 2009, includes contracts with 97% of medical providers, up to 23 million beneficiaries, and covers more than 99% of the entire population (Ho Chan, 2010). Several previous studies have documented the details of this program (Chen et al., 2020; Tzeng et al., 2020; Wan et al., 2020). We used the Taiwan NHI Research Database (NHIRD) to investigate the association between leptospirosis diagnosis and dementia over a 16-year period (2000–2015) for all outpatients and hospitalizations recorded in the NHIRD.

Diagnosis of leptospirosis was performed according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) (Chinese Hospital Association [CHA], 2000). Typical clinical findings indicative of leptospirosis were confirmed in all cases by a culture of *Leptospira* spp. and/or serology (Chiu et al., 2019). For the culture, blood and urine collected during the first 10 days of the disease were sent for microbiological analysis. For the serological diagnosis, paired acute and convalescent sera were analyzed by a microscopic agglutination test (MAT). The MAT titer is obtained by incubating serial dilutions of a patient's serum with different *Leptospira* serovars; the serovar that reacts most strongly is suggested to be the infecting serovar. A positive laboratory diagnosis of leptospirosis required one of the following two criteria: (i) positive culture isolation, and/or (ii) a fourfold rise in MAT titer between the acute phase and the convalescent phase and a titer $\geq$1:400 in a single serum. Laboratory studies were performed at the Taiwan Centers for Disease Control [TCDC] (2017).

Dementia diagnosis was performed by board-certified neurologists or psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition and its text-revised edition (American Psychiatric Association [APA], 1994, 2000). Licensed medical records technicians review and verify the diagnostic coding before claiming reimbursements (Chen et al., 1995). The NHI Administration randomly reviews the records of 1 in 100 ambulatory care visits and 1 in 20 in-patient claims to verify the accuracy of the diagnoses (Ministry of Justice, 2019). Several studies have demonstrated the accuracy and validity of the diagnoses in the NHIRD (Cheng et al., 2011; Liang et al., 2011; Chou et al., 2013).

### Study Design and Sampled Participants

This study was of a retrospective matched-cohort design. Patients with a history of leptospirosis, spirochetal disease, or syphilis, dementia diagnosis before the index date, who were aged <50 years, or where relevant information was missing were excluded from this study. Patients with leptospirosis were selected from January 1 to December 31, 2000, according to ICD-9-CM code 100 (100.0, 100.8, or 100.9). This included 357 patients first diagnosed with leptospirosis during the index year. A control group ($n$ = 1038) matched for age and sex with no diagnosis of leptospirosis was also selected for study (**Figure 1**).

Covariates included gender, age group (50–64, $\geq$65 years), marital status, years of education, geographical area of residence (north, center, south, and east of Taiwan), urbanization level of residence area (levels 1 to 4), level of hospital as medical centers, regional and local hospitals, and insurance premiums (in New Taiwan Dollars [NT$]; <18 000, 18 000–34 999, $\geq$35

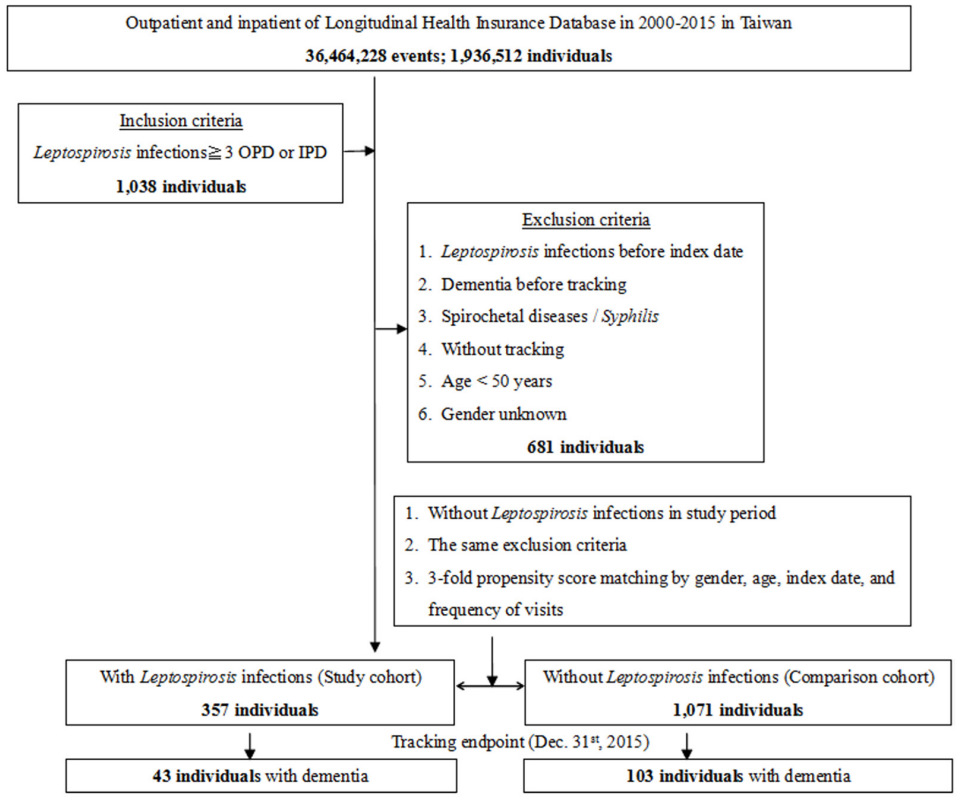



**FIGURE 1 |** The flowchart of study sample selection.

000). The urbanization level of residence was defined according to the total population and indicators of the level of development (Chiu et al., 2014). The comorbidities included diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, obesity, cancer, depressive disorder, bipolar disorder, anxiety disorder, alcohol usage disorder, substance usage disorder, sleep disorder, septicemia (ICD-9-CM codes listed in **Supplementary Table 1**). We also used the Charlson Comorbidity Index (CCI, scores of 0, 1, 2, 3, ≧4), which is the most widely used comorbidity index in the literature (Charlson et al., 1987; de Groot et al., 2003).

The antibiotics used in the treatment for the leptospirosis includeβ-lactams, cephalosporins, and doxycycline, and the data on the usage of these antibiotics were collected. The data of the defined daily dose (DDD) were obtained from the WHO Collaborating Centre for Drug Statistics Methodology[1], and the duration of the usage of antibiotics was calculated by dividing the cumulative dosages by the DDD of the antibiotics. The duration of the antibiotic treatment is usually 7 days (Charan et al., 2013; Day, 2021), therefore, we divided the treatment durations as 7, 8–14, 15–21, 22–28, and >28 days, respectively.

## Outcome Measures

All the study participants were followed from the index date until the onset of dementia including Alzheimer's dementia, vascular dementia, and other degenerative dementias, withdrawal from the NHI program, or the end of 2015. To ensure accuracy, each patient diagnosed with dementia was required to have made at least three outpatient visits during 1 year within the study period (Chiu et al., 2018).

## Statistical Analysis

All analyses were performed using the SPSS software version 22 (SPSS Inc., Chicago, IL, United States). $\chi^2$ and *t*-tests were used to evaluate the distributions of the categorical and continuous variables, respectively. The Fisher exact test for categorical variables was used to statistically examine the differences between the two cohorts. The Fine and Gray survival analysis was used to determine the risk of dementia, and the results were presented as a sub-distribution hazard ratio (SHR) with a 95% confidence interval (CI). The difference in the incidence of dementia between the study and control groups was estimated using the Kaplan–Meier method with log-rank test. A two-tailed *P*-value of <0.05 was considered so as to indicate the statistical significance.

# RESULTS

## Sample Characteristics

The flowchart for enrollment of the leptospirosis patients and the controls is as presented in **Figure 1**. A total of 1428 patients

[1]https://www.whocc.no/

**TABLE 1 |** Characteristics of study at the baseline.

| *Leptospirosis* infections | With | | Without | | *P* |
|---|---|---|---|---|---|
| **Variables** | ***n*** | **%** | ***n*** | **%** | |
| Total | 357 | 25.00 | 1,071 | 75.00 | |
| Gender | | | | | 0.999 |
| Male | 249 | 69.75 | 747 | 69.75 | |
| Female | 108 | 30.25 | 324 | 30.25 | |
| Age (years) | 63.35 ± 8.68 | | 63.68 ± 8.67 | | 0.532 |
| Age groups (years) | | | | | 0.999 |
| 50–64 | 220 | 61.62 | 660 | 61.62 | |
| ≧65 | 137 | 38.38 | 411 | 38.38 | |
| Marital status | | | | | 0.927 |
| Without | 159 | 44.54 | 480 | 44.82 | |
| With | 198 | 55.46 | 591 | 55.18 | |
| Education (years) | | | | | 0.903 |
| <12 | 183 | 51.26 | 545 | 50.89 | |
| ≧12 | 174 | 48.74 | 526 | 49.11 | |
| Insured premium (NT$) | | | | | 0.005 |
| <18,000 | 348 | 97.48 | 1,063 | 99.25 | |
| 18,000–34,999 | 9 | 2.52 | 6 | 0.56 | |
| ≧35,000 | 0 | 0.00 | 2 | 0.19 | |
| Diabetes mellitus | 54 | 15.13 | 149 | 13.91 | 0.600 |
| Hypertension | 57 | 15.97 | 216 | 20.17 | 0.087 |
| Hyperlipidemia | 8 | 2.24 | 38 | 3.55 | 0.298 |
| Coronary artery disease | 20 | 5.60 | 109 | 10.18 | 0.008 |
| Obesity | 2 | 0.56 | 0 | 0.00 | 0.062 |
| Cancer | 18 | 5.04 | 101 | 9.43 | 0.008 |
| Depressive disorder | 2 | 0.56 | 3 | 0.28 | 0.604 |
| Bipolar disorder | 0 | 0.00 | 2 | 0.19 | 0.414 |
| Anxiety disorder | 131 | 36.69 | 251 | 23.44 | <0.001 |
| Alcohol use disorder | 0 | 0.00 | 6 | 0.56 | 0.346 |
| Substance use disorder | 0 | 0.00 | 2 | 0.19 | 0.414 |
| Sleep disorder | 4 | 1.12 | 4 | 0.37 | 0.113 |
| Septicemia | 51 | 14.29 | 28 | 2.61 | <0.001 |
| CCI_R | | | | | 0.002 |
| 0 | 272 | 76.19 | 703 | 65.64 | |
| 1 | 67 | 18.77 | 258 | 24.09 | |
| 2 | 10 | 2.80 | 62 | 5.79 | |
| 3 | 6 | 1.68 | 27 | 2.52 | |
| ≧4 | 2 | 0.56 | 21 | 1.96 | |
| Season | | | | | <0.001 |
| Spring (Mar–May) | 85 | 23.81 | 291 | 27.17 | |
| Summer (Jun–Aug) | 133 | 37.25 | 246 | 22.97 | |
| Autumn (Sep–Nov) | 78 | 21.85 | 220 | 20.54 | |
| Winter (Dec–Feb) | 61 | 17.09 | 314 | 29.32 | |
| Location | | | | | <0.001 |
| Northern Taiwan | 89 | 24.93 | 439 | 40.99 | |
| Middle Taiwan | 59 | 16.53 | 280 | 26.14 | |
| Southern Taiwan | 43 | 12.04 | 284 | 26.52 | |
| Eastern Taiwan | 166 | 46.50 | 65 | 6.07 | |
| Outlets islands | 0 | 0.00 | 3 | 0.28 | |
| Urbanization level | | | | | <0.001 |
| 1 (The highest) | 81 | 22.69 | 404 | 37.72 | |
| 2 | 240 | 67.23 | 437 | 40.80 | |
| 3 | 13 | 3.64 | 68 | 6.35 | |
| 4 (The lowest) | 23 | 6.44 | 162 | 15.13 | |
| Level of care | | | | | <0.001 |
| Medical center | 257 | 71.99 | 396 | 36.97 | |
| Regional hospital | 96 | 26.89 | 380 | 35.48 | |
| Local hospital | 4 | 1.12 | 295 | 27.54 | |

*P: Chi-square/Fisher exact test on category variables and t-test on continue variables; NT$, New Taiwan Dollars; CCI_R, Charlson Comorbidity Index, dementia removed.*

were enrolled including 357 subjects with leptospirosis and 1071 controls without leptospirosis. The ratio of leptospirosis cohort and the control cohort was 1:3. These two cohorts were matched for age, sex, and index year (**Figure 1** and **Table 1**). The prevalence of leptospirosis was 18.44 per $10^5$ (357 from an eligible population of 1 936 512) during the 16 years of follow-up; none of the control group received a diagnosis of leptospirosis during the study period. There were no differences between the groups in sex, age, marital status, or insurance premiums. In the leptospirosis cohort, there was a higher percentage of anxiety and septicemia and a lower percentage of coronary artery disease and cancer.

## Kaplan–Meier Model for the Cumulative Incidence of Dementia

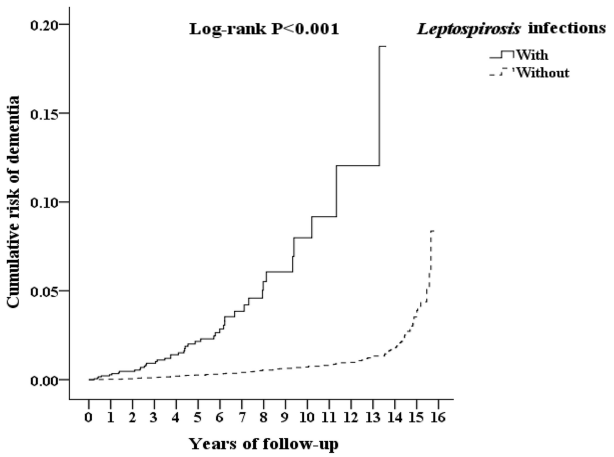
In the overall study period, 43 of the 357 leptospirosis patients (930.90 per $10^5$ person-years) developed dementia as compared to 103 of the control group ($n$ = 1071, 732.49 per $10^5$ person-years); the Kaplan–Meier analysis indicated that the difference was statistically significant (log-rank, $P < 0.001$, **Figure 2**).

## Hazard Ratio Analysis of Dementia in Patients With Leptospirosis

Fine and Gray's competing risk model analysis revealed that the leptospirosis group was more likely to develop dementia (crude SHR = 1.350; 95% CI 1.211–1.496; $P < 0.001$). After adjustment for sex, age, monthly insurance premiums, urbanization level, geographic region, and comorbidities, the adjusted SHR over the 16-year period was 1.357 (95% CI 1.213–1.519; $P < 0.001$) (**Table 2**).

## The Risk and Sensitivity Analysis of Different Types of Dementia After Leptospirosis

As shown in **Table 3**, leptospirosis was associated with different types of dementia, including AD (adjusted SHR = 1.300 [95% CI: 1.162–1.455, $P < 0.001$]), VaD (adjusted SHR = 1.243 [95% CI: 1.111–1.391, $P < 0.001$]), or other degenerative dementia (adjusted SHR = 1.459 [95% CI: 1.305–1.634, $P < 0.001$]), respectively.




| *Leptospirosis* infections | **With** (n = 357) | **Without** (n = 1,071) | ***P*** |
|---|---|---|---|
| **In the tracking of x year(s)** | **Numbers of dementia** | | |
| **1** | 5 | 2 | 0.142 |
| **2** | 8 | 4 | 0.083 |
| **3** | 14 | 9 | 0.041 |
| **4** | 19 | 15 | 0.020 |
| **5** | 25 | 19 | 0.004 |
| **6** | 29 | 22 | 0.002 |
| **7** | 33 | 28 | <0.001 |
| **8** | 37 | 35 | <0.001 |
| **9** | 38 | 40 | <0.001 |
| **10** | 40 | 43 | <0.001 |
| **11** | 41 | 47 | <0.001 |
| **12** | 42 | 54 | <0.001 |
| **13** | 42 | 64 | <0.001 |
| **14** | 43 | 75 | <0.001 |
| **15** | 43 | 97 | <0.001 |
| **16** | 43 | 103 | <0.001 |

**FIGURE 2 |** Kaplan–Meier for cumulative incidence of dementia aged 50 and over stratified by *Leptospirosis* infections with log-rank test.

To exclude the protopathic bias, the sensitivity analysis was conducted. This analysis revealed that the leptospirosis was associated with the increased risk of dementia, even after excluding dementia diagnosis within the first year (adjusted SHR = 1.246, 95% CI: 1.114–1.395, $P < 0.001$) or within the first 5 years (adjusted SHR = 1.079, 95% CI: 1.023–1.152, $P = 0.028$). However, after excluding the diagnosis within the first and first 5 years, leptospirosis was associated with AD and other degenerative dementia, but not VaD.

**TABLE 2 |** Antibiotics usage and the risk of dementia by using Fine and Gray's competing risk model.

| | **Competing risk in the model** | | | |
|---|---|---|---|---|
| **Variables** | **Adjusted SHR** | **95% CI** | **95% CI** | ***P*** |
| *Leptospirosis* infections (reference: without) | 1.357 | 1.213 | 1.519 | <0.001 |
| Severe infections | 1.400 | 1.257 | 1.598 | <0.001 |
| Non-severe infections | 1.326 | 1.202 | 1.483 | <0.001 |
| CCI_R = 1 (reference: CCI_R = 0) | 3.098 | 1.124 | 8.012 | 0.003 |
| CCI_R = 2 (reference: CCI_R = 0) | 4.501 | 1.188 | 14.562 | 0.001 |
| Winter (reference: spring) | 6.532 | 1.397 | 33.012 | 0.001 |

*P: Chi-square/Fisher exact test on category variables and t-test on continue variables; SHR, sub-distribution hazard ratio; CI, confidence interval; Adjusted SHR, Adjusted variables listed in* ***Table 1****; CCI_R, Charlson Comorbidity Index, dementia removed.*

## Subgroup Analysis for the Risk of Dementia After Leptospirosis

As shown in **Table 4**, the subgroup analysis revealed that the differential risk stratified by sex, age, marital status, educational level, monthly insurance premiums, comorbidities, urbanization and region of residence, CCI score, season, and level of medical care (possible exceptions include higher insured premiums). The subgroup analysis found that the leptospirosis patients with nearly all the covariates were associated with a higher risk of dementia, with the exceptions of insured premium of NT$18,000–34,999 and NT$ ≧35,000. In addition, the patients with or without most of these comorbidities were associated with a higher risk of dementia, with the exceptions of obesity, depression, bipolar disorder, alcohol usage disorder, other substance usage disorder, sleep disorder, and CCI as 3 and ≧4.

**TABLE 3 |** Dementia types and sensitivity analysis using Fine and Gray's competing risk model.

| | *Leptospirosis* infections | Competing risk in the model | | | |
|---|---|---|---|---|---|
| **Sensitivity test** | **Dementia subgroup** | **Adjusted SHR** | **95% CI** | **95% CI** | ***P*** |
| Overall | Overall | 1.357 | 1.213 | 1.519 | <0.001 |
| | AD | 1.300 | 1.162 | 1.455 | <0.001 |
| | VaD | 1.243 | 1.111 | 1.391 | <0.001 |
| | Other degenerative dementia | 1.459 | 1.305 | 1.634 | <0.001 |
| In the first 1 year excluded | Overall | 1.246 | 1.114 | 1.395 | <0.001 |
| | AD | 1.220 | 1.091 | 1.366 | 0.001 |
| | VaD | 1.104 | 0.987 | 1.236 | 0.180 |
| | Other degenerative dementia | 1.352 | 1.208 | 1.513 | <0.001 |
| In the first 5 years excluded | Overall | 1.079 | 1.023 | 1.152 | 0.028 |
| | AD | 1.117 | 1.058 | 1.195 | 0.009 |
| | VaD | 0.938 | 0.881 | 1.041 | 0.334 |
| | Other degenerative dementia | 1.142 | 1.076 | 1.222 | 0.002 |

*P: Chi-square/Fisher exact test on category variables and t-test on continue variables; PYs, Person-years; Adjusted SHR, Adjusted sub-distribution Hazard ratio: Adjusted for the variables listed in this table. CI, confidence interval; AD, Alzheimer's dementia; VaD, vascular dementia.*

## Effect of Leptospirosis Antibiotic Treatment and Risk of Dementia

Although the majority of patients diagnosed with leptospirosis were recorded as having received antibiotic treatment (β-lactams, cephalosporins, and doxycycline), a small number were not treated. **Figure 3** shows the flowchart of the study sample selection with or without antibiotic treatment. These subgroups differed in their risk of developing dementia. Of the leptospirosis patients with antibiotic treatment, 36 of 321 (916.52 per $10^5$ person-years) developed dementia compared to seven of 36 (938.04 per $10^5$ person-years) patients without antibiotic treatment; the difference was statistically significant in the Kaplan–Meier analysis (log-rank, $P < 0.001$; **Figure 4**). The risk of dementia development was lower in patients treated for a longer time or with higher antibiotic dosages (adjusted SHR = 0.685, 95%CI: 0.534–0.950, $P = 0.001$, **Table 5**).

## Time-Dependence of Risk of Dementia Development

Patients with a diagnosis of leptospirosis showed an overall increased risk of dementia development over the 16-year follow-up period (adjusted SHR = 1.357). However, the SHR evolved with time. The greatest differential was in the years immediately following the leptospirosis development, and the cumulative unnormalized relative incidences of dementia development were 3.96 at 6 years, 2.61 at 11 years, and 1.25 at 16 years. Cumulative SHR values adjusted for sex, age, monthly insurance premium, urbanization level, geographic region, and comorbidity were 1.296 at 6 years, to 1.331 at 11 years, to 1.357 at 16 years. Linear regression predicts that the SHR for dementia development between the two groups declines to 1.0 at 18–19 years following the leptospirosis development (**Table 6**).

## The Interaction Term Analysis Between Anxiety and Leptospirosis

**Table 7** shows the subgroup analysis for the factors of dementia using the Fine and Gray's competing risk model. The adjusted SHR of leptospirosis with anxiety was 2.806 (95% CI: 2.407–3.305, $P < 0.001$) and the adjusted SHR of leptospirosis without anxiety was 1.237 (95% CI: 1.095–1.386, $P < 00.001$) The *P*-values of the interaction term analysis of anxiety × leptospirosis was 0.001 in the non-competing risk model and <0.001 in the competing risk model.

# DISCUSSION

## Association Between Leptospirosis, Antibiotic Treatment, and the Risk of Dementia

We have reported that the individuals with a previous diagnosis of leptospirosis had an increased risk of developing any type of dementia, including AD and VaD ($P < 0.001$). When individuals with a diagnosis of dementia within the first year or the first 5 years were excluded, the leptospirosis patients were still associated with an increased risk of AD and related dementias. The results of our study (adjusted SHR = 1.357; 95% CI 1.213–1.519; $P < 0.001$; 16 years follow-up) are comparable to the conclusions of an earlier study on leptospirosis patients (adjusted SHR = 1.89; 95% CI 1.72–2.08; 10 years follow-up) (Chiu et al., 2019). In addition, leptospirosis was associated with AD, VaD, and other degenerative dementia. We also reported that treatment of the leptospirosis patients with antibiotic medications, such as β-lactams, cephalosporin, and doxycycline, for the first time, was associated with a reduced risk of dementia (adjusted SHR = 0.685) in a dose-dependent manner ($P = 0.001$).

The adjusted SHR increased from the sixth year and, as the Linear regression predicts, declined after the 16-years of follow-up (**Table 6**). This finding might hint that the risk of dementia would be higher between six and 16 years after the leptospirosis.

In the leptospirosis groups, there was a significant higher incidence of anxiety disorders ($N = 131$, 36.69%) as compared to the control group ($N = 251$, 23.44%). As previously reported, anxiety has been associated with all types of dementia (Santabarbara et al., 2020). Thus, we have conducted an interaction term analysis, which revealed an interaction between anxiety and leptospirosis in the contribution of the risk of dementia (**Table 7**).

## Possible Mechanisms of Association Between Leptospirosis and the Risk of Dementia

The underlying mechanisms of the association between leptospirosis infections and dementia remain unclear.

**TABLE 4 |** Subgroup analysis stratified by variables listed in the table by using Fine and Gray's competing risk model.

| *Leptospirosis* infections | Competing risk in the model | | | |
|---|---|---|---|---|
| **Stratified** | **Adjusted SHR** | **95% CI** | **95% CI** | ***P*** |
| Total | 1.357 | 1.213 | 1.519 | <0.001 |
| Male | 1.429 | 1.278 | 1.600 | <0.001 |
| Female | 1.219 | 1.089 | 1.364 | <0.001 |
| Age 50–64 | 1.266 | 1.131 | 1.417 | <0.001 |
| Age group≧65 | 1.464 | 1.308 | 1.638 | <0.001 |
| Married | 1.332 | 1.190 | 1.491 | <0.001 |
| Not married | 1.102 | 0.985 | 1.233 | 0.121 |
| Education (years) < 12 | 1.328 | 1.187 | 1.487 | <0.001 |
| Education (years)≧12 | 1.507 | 1.347 | 1.687 | <0.001 |
| Insured premium (NT$) < 18,000 | 1.357 | 1.213 | 1.519 | <0.001 |
| Insured premium (NT$) 18,000–34,999 | – | – | – | – |
| Insured premium (NT$) 35,000 | – | – | – | – |
| Without DM | 1.212 | 1.084 | 1.357 | <0.001 |
| With DM | 1.664 | 1.487 | 1.862 | <0.001 |
| Without HTN | 1.309 | 1.170 | 1.466 | <0.001 |
| With HTN | 1.468 | 1.312 | 1.643 | <0.001 |
| Without Hyperlipidemia | 1.357 | 1.213 | 1.519 | <0.001 |
| With Hyperlipidemia | – | – | – | – |
| Without CAD | 1.285 | 1.148 | 1.438 | <0.001 |
| With CAD | 1.883 | 1.683 | 2.107 | <0.001 |
| Without Obesity | 1.357 | 1.213 | 1.519 | <0.001 |
| With Obesity | – | – | – | – |
| Without Cancer | 1.246 | 1.114 | 1.394 | <0.001 |
| With Cancer | 3.154 | 2.819 | 3.530 | <0.001 |
| Without Depression | 1.357 | 1.213 | 1.519 | <0.001 |
| With Depression | – | – | – | – |
| Without Bipolar | 1.357 | 1.213 | 1.519 | <0.001 |
| With Bipolar | – | – | – | – |
| Without Anxiety | 1.246 | 1.114 | 1.395 | <0.001 |
| With Anxiety | 1.459 | 1.305 | 1.634 | <0.001 |
| Without Alcohol use disorder | 1.357 | 1.213 | 1.519 | <0.001 |
| With Alcohol use disorder | – | – | – | – |
| Without other substance use disorder | 1.357 | 1.213 | 1.519 | <0.001 |
| With other substance use disorder | – | – | – | – |
| Without Sleep disorder | 1.540 | 1.377 | 1.724 | <0.001 |
| With Sleep disorder | 0.000 | – | – | 0.885 |
| Without Septicemia | 1.189 | 1.063 | 1.331 | <0.001 |
| With Septicemia | 2.361 | 2.111 | 2.643 | <0.001 |
| CCI_R 0 | 1.183 | 1.057 | 1.324 | <0.001 |
| CCI_R 1 | 1.431 | 1.279 | 1.602 | <0.001 |
| CCI_R 2 | 3.438 | 3.073 | 3.848 | <0.001 |
| CCI_R 3 | – | – | – | – |
| CCI_R≧4 | – | – | – | – |
| Spring | 1.141 | 1.020 | 1.277 | 0.030 |
| Summer | 1.226 | 1.096 | 1.372 | <0.001 |
| Autumn | 1.490 | 1.332 | 1.668 | <0.001 |
| Winter | 2.182 | 1.950 | 2.443 | <0.001 |
| **Urbanization level** | | | | |
| Urbanization level 1 (the highest) | 1.208 | 1.080 | 1.352 | <0.001 |
| Urbanization level 2 | 1.330 | 1.189 | 1.488 | <0.001 |
| Urbanization level 3 | – | – | – | – |
| Urbanization level 4 (the lowest) | 1.704 | 1.524 | 1.908 | <0.001 |
| Level of care Hospital center | 1.454 | 1.299 | 1.627 | <0.001 |
| Level of care Regional hospital | 1.274 | 1.139 | 1.426 | <0.001 |
| Level of care Local hospital | 1.144 | 1.023 | 1.281 | 0.029 |

*P: Chi-square/Fisher exact test on category variables and t-test on continue variables; PYs, Person-years; Adjusted HR, Adjusted sub-distribution Hazard ratio: Adjusted for the variables listed in* ***Table 1****; CI, confidence interval; NT$, New Taiwan Dollars; CCI_R, Charlson Comorbidity Index, dementia removed.*

Nonetheless, inflammatory changes in the brain have been reported in studies on the pathogenesis of dementia (Daulatzai, 2016; Stefaniak and O'Brien, 2016). Previous researchers have found that infectious diseases, such as hepatitis C, viral infection, Helicobacter pylori infection, cytomegalovirus infections, chronic osteomyelitis, or even sepsis, were associated with an increased risk of dementia (Barnes et al., 2015; Kao et al., 2015). Other antibiotic-susceptible bacterial species were widely present in both the control and AD brain (Branton et al., 2013; Emery et al., 2017). In 2019, Chiu first reported that patients with leptospirosis were associated with higher risks of dementia, pointing out the role of endothelial damage and vascular hypo-perfusion in subsequent chronic diseases such as dementia (Chiu et al., 2019).

*Leptospira* may cause cytokine storm, endothelial damage, vascular hypo-perfusion, and subsequent organ failure (Cagliero et al., 2018). AD is the most common cause of dementia. The major hypothesis on the etiology of AD is the amyloid cascade hypothesis (Barage and Sonawane, 2015). In addition, there is also growing evidence indicating that vascular dysfunction plays a pivotal role in the development of AD, and several vascular risk factors, such as hypertension, atherosclerosis, hyperlipidemia, and stroke, are associated with AD-type dementia (Launer et al., 2000; Fratiglioni et al., 2007). The significant association between vascular diseases and AD suggests that dementia associated with AD may be caused by vascular mechanisms.

However, the specific role of spirochetes is uncertain. For *Leptospira* spp., only 1.4% of United States army soldiers deployed in disease-endemic countries, and 2.5% of United States veterinarians, were reported to be seropositive (Lettieri et al., 2004; Whitney et al., 2009). In the United Kingdom, fewer than 100 cases of acute leptospirosis were recorded each year (Forbes et al., 2012). In addition, serological testing may not detect many individuals infected with *Borrelia* spp. (Lloyd and Hawkins, 2018). Several studies have found that, in the countries closer to the equator where *Leptospira* spp. seroprevalence rates closer to 40% (Gonwong et al., 2017; Garba et al., 2018; Sohail et al., 2018). Therefore, the role of the difference of seroprevalence of the *Leptospira* spp. in different countries might well need to be further studied.

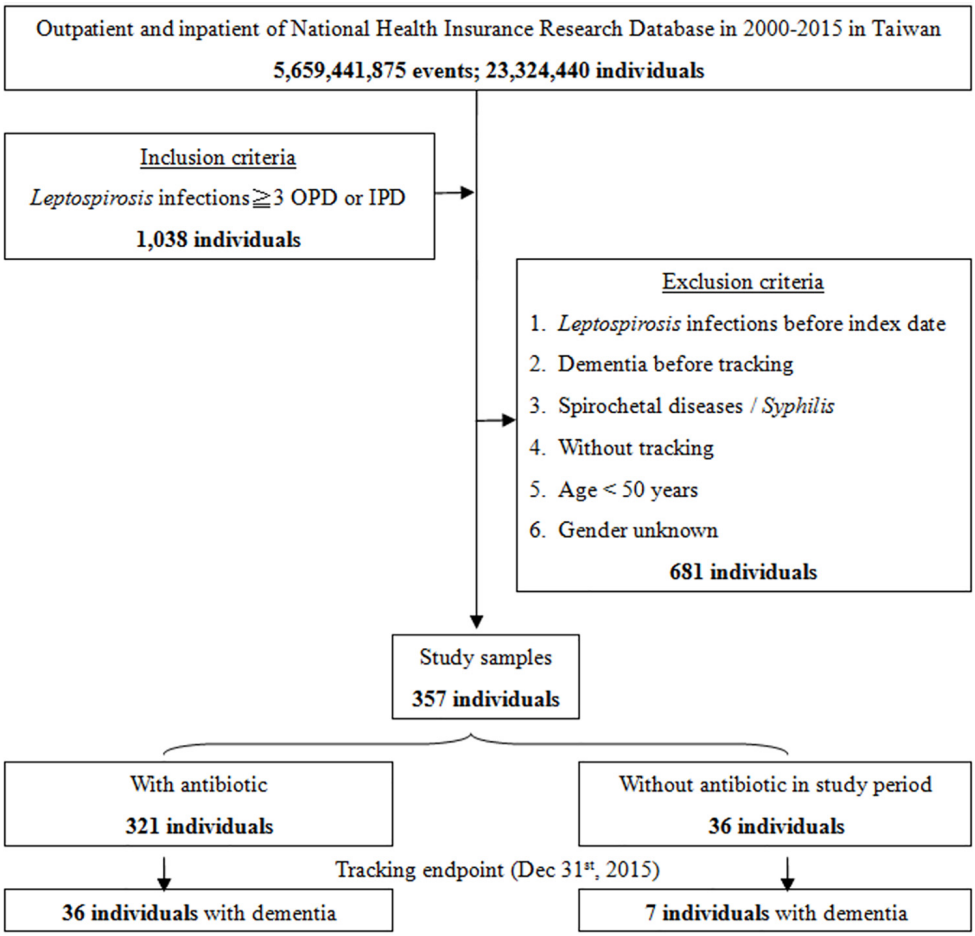



**FIGURE 3 |** The flowchart of study sample selection with or without antibiotic treatment.

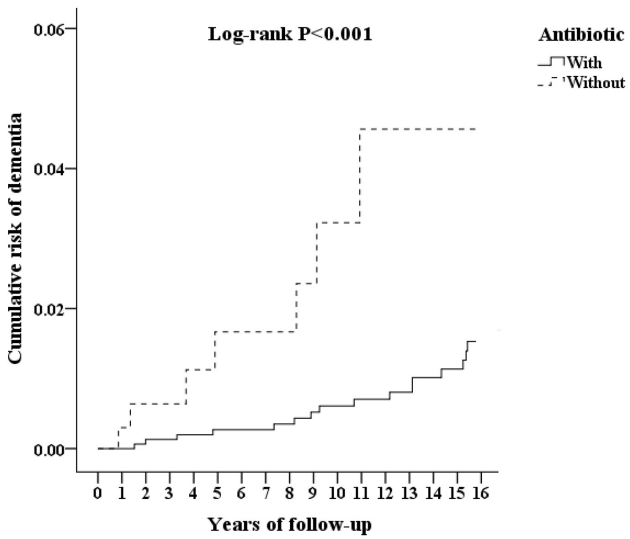



**FIGURE 4 |** Kaplan–Meier for cumulative incidence of dementia aged 50 and over stratified by *Leptospirosis* infections with or without antibiotics, with log-rank test.

**TABLE 5 |** Percentage, duration, percentage of decrease of risk by days, and adjusted sub-distribution hazard ratios of antibiotic among *Leptospirosis* infections patients.

| Antibiotic | | | | | With *vs.* without antibiotic *(Reference)* | | |
|---|---|---|---|---|---|---|---|
| **Type** | ***n*** | **%** | **Duration (days)** | | **Competing risk in the model** | | |
| | | | **Mean** | **SD** | ***n*% decrease of risk by day** | **Adjusted SHR (95% CI)** | ***P*** |
| Overall | 321 | | 25.33 | 22.20 | 1.24 | 0.685 (0.534–0.950) | 0.001 |
| Beta-lactam | 113 | 35.20 | 26.71 | 23.89 | 1.16 | 0.689 (0.542–0.962) | 0.009 |
| 7 days | 11 | 3.43 | 7.00 | 0.00 | 3.01 | 0.789 (0.604–1.102) | 0.152 |
| 8–14 days | 19 | 5.92 | 12.12 | 10.34 | 1.45 | 0.824 (0.608–1.189) | 0.288 |
| 15–21 days | 23 | 7.17 | 18.65 | 15.25 | 1.47 | 0.725 (0.592–0.978) | 0.024 |
| 22–28 days | 29 | 9.03 | 25.27 | 23.21 | 1.44 | 0.635 (0.489–0.929) | <0.001 |
| >28 days | 31 | 9.66 | 49.98 | 47.72 | 0.83 | 0.584 (0.415–0.827) | <0.001 |
| Cephalosporin | 130 | 40.50 | 24.73 | 21.17 | 1.33 | 0.672 (0.513–0.955) | 0.001 |
| 7 days | 21 | 6.54 | 7.00 | 0.00 | 3.54 | 0.752 (0.586–1.067) | 0.134 |
| 8–14 days | 18 | 5.61 | 12.35 | 10.25 | 1.34 | 0.835 (0.712–1.234) | 0.294 |
| 15–21 days | 30 | 9.35 | 18.51 | 15.11 | 1.63 | 0.698 (0.526–0.959) | 0.007 |
| 22–28 days | 25 | 7.79 | 25.98 | 23.72 | 1.38 | 0.641 (0.502–0.952) | 0.001 |
| >28 days | 36 | 11.21 | 45.58 | 42.25 | 0.88 | 0.599 (0.442–0.863) | <0.001 |
| Doxycycline | 119 | 37.07 | 24.67 | 21.71 | 1.29 | 0.681 (0.494–0.938) | <0.001 |
| 7 days | 20 | 6.23 | 7.00 | 0.00 | 3.26 | 0.772 (0.594–1.083) | 0.148 |
| 8–14 days | 18 | 5.61 | 12.13 | 10.98 | 1.31 | 0.841 (0.726–1.248) | 0.304 |
| 15–21 days | 25 | 7.79 | 18.72 | 15.34 | 1.51 | 0.718 (0.555–0.964) | 0.012 |
| 22–28 days | 25 | 7.79 | 25.19 | 23.08 | 1.47 | 0.629 (0.472–0.915) | <0.001 |
| >28 days | 31 | 9.66 | 47.72 | 45.97 | 0.86 | 0.588 (0.421–0.834) | <0.001 |

*P: Chi-square/Fisher exact test on category variables and t-test on continue variables; Adjusted SHR, Adjusted sub-distribution Hazard ratio: Adjusted for the variables listed in* ***Table 1****; CI, confidence interval; NT$, New Taiwan Dollars.*

**TABLE 6 |** Factors of dementia by using Fine and Gray's competing risk model.

| | ***Leptospirosis* infections (reference: without)** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Tracking period** | **Crude SHR** | **95% CI** | **95% CI** | ***P*** | **Adjusted SHR** | **95% CI** | **95% CI** | ***P*** |
| Overall (In 16-year tracking) | 1.647 | 1.315 | 2.103 | <0.001 | 1.357 | 1.213 | 1.519 | <0.001 |
| In 1-year tracking | 1.486 | 0.867 | 2.085 | 0.106 | 1.225 | 0.645 | 1.402 | 0.267 |
| In 6-year tracking | 1.569 | 1.047 | 2.117 | 0.002 | 1.296 | 1.030 | 1.426 | 0.009 |
| In 11-year tracking | 1.629 | 1.211 | 1.997 | <0.001 | 1.331 | 1.176 | 1.798 | <0.001 |

*P: Chi-square/Fisher exact test on category variables and t-test on continue variables; Adjusted HR, Adjusted sub-distribution Hazard ratio: Adjusted for the variables listed in* ***Table 1****; CI, confidence interval.*

## Possible Mechanisms of Association Between Antibiotics and the Lower Risk of Dementia in Patients With Leptospirosis

We also found that the antibiotic treatment was associated with a lower risk of dementia in patients with leptospirosis infections, and the adjusted SHR was 0.685. The leptospirosis-infected subjects treated with the antibiotics of beta-lactam, cephalosporin, and doxycycline showed a decreased risk of dementia, when compared to the group without antibiotic medications. Moreover, once the treatment duration was more than 14 days, the risk of dementia decreased subsequently with the treatment duration prolonged.

The role of the antibiotic treatment of leptospirosis infections for the prevention of dementia has not, as yet, been studied. The association between antibiotic usage and Alzheimer's disease had only been studied in animal models before. Ceftriaxone may restore the glial glutamate transporter and further ameliorate tau pathology, and the cognitive decline in Alzheimer's disease (Zumkehr et al., 2015). Neuroinflammation is a chronic event whose perpetuation leads to the continuous

**TABLE 7 |** The interaction between *Leptospirosis* infections and anxiety for the risk of dementia.

| ***Leptospirosis* infections** | **Anxiety** | **Adjusted SHR** | **95% CI** | **95% CI** | ***P*** |
|---|---|---|---|---|---|
| Without | Without | Reference | | | |
| Without | With | 1.354 | 1.288 | 1.518 | <0.001 |
| With | Without | 1.237 | 1.095 | 1.386 | <0.001 |
| With | With | 2.806 | 2.407 | 3.305 | <0.001 |

*Adjusted SHR, Adjusted sub-distribution hazard ratio: Adjusted for the variables listed in* ***Table 1****; CI, confidence interval.*
*Interaction term (Joint Effect): Leptospirosis infections × Anxiety, P < 0.001.*

release of pro-inflammatory cytokines, promoting neuronal cell death and gross brain atrophy. Doxycycline emerged as a promising preventive strategy in prion diseases and gave compelling pre-clinical results in mouse models of AD against Aβ oligomers and neuroinflammation (Balducci and Forloni, 2019). Our present study might be the first to report on the role of antibiotic medication treatment in attenuating the risk of developing dementia for patients with leptospirosis infections in a nationwide, population-based study. However, in the leptospirosis group, only 10.1% (36 in 357) did not receive antibiotic treatment. This suggests that further study is needed so as to clarify whether antibiotic usage plays a role in reducing the risk of dementia for leptospirosis-infected patients.

### Strengths of This Study

The present study has several strengths: First, we used Taiwan's NHIRD, which is a valuable resource to cover a nationwide population, to address this issue. Second, one previous study has demonstrated the accuracy and validity of several diagnoses of psychiatric disorders in the NHIRD, including major depressive disorder, schizophrenia, and dementia (Wu et al., 2020). Besides, the in-hospital licensed medical records technicians and NHI Administration would have verified the diagnoses in the claims dataset (Hsieh et al., 2019; Ministry of Justice, 2019), for the diagnosis. Third, previous studies have also demonstrated the concordance between Taiwan's National Health Survey and the NHIRD on a variety of diagnoses (Wu et al., 2014), medication usage (Wu et al., 2014), and health system utilization (Yu et al., 2009; Wu et al., 2014).

### Limitations of This Study

This study has several limitations. First, regarding the antibiotic treatment, only 10.1% (36 of 357) of the leptospirosis group did not receive antibiotic treatment, and of these only seven went on to develop dementia. Although our results point to statistical significance, further investigations with a larger number of subjects will be essential to clarify whether the antibiotic treatment truly plays a role in reducing the risk of dementia for the leptospirosis-infected patients. Second, patients with dementia were identified using the insurance claims data, but data on severity or stage were not available, and we could only estimate the treatment durations of each antibiotic medication by dividing the cumulative doses of individual medications by the defined daily dose. Third, other confounding factors such as genetics and dietary factors are also not included in the NHIRD. Because no imaging findings or other laboratory data are included in the NHIRD, we relied on the professional diagnosis of dementia by board-certified psychiatrists or neurologists according to the ICD-9-CM codes from the NHIRD, and the leptospirosis cases that were presented as mild symptoms may not have been recorded and were thus not enrolled in this study. Nevertheless, because our analysis is based on a large cohort of patients (1428 subjects: 357 leptospirosis and 1071 controls) as well as internationally recognized diagnostic codes, and furthermore corroborates previous work on leptospirosis and AD risk (Chiu et al., 2019), our central results may be reliable – and raise three important issues concerning causation and the pathogen(s) that might be involved.

## CONCLUSION

Patients with leptospirosis infections have an increased risk of developing dementia, and the antibiotic treatment was associated with a diminished risk of dementia. These findings might well be considered as an indicator to clinicians caring for patients with leptospirosis infections. Further research will be necessary so as to explore the underlying mechanism(s) of this association.

## DATA AVAILABILITY STATEMENT

The datasets on the study population that were obtained from the NHIRD (http://nhird.nhri.org.tw/en/index.html) are maintained in the NHIRD (http://nhird.nhri.org.tw/). The National Health Research Institutes (NHRI) is a nonprofit foundation established by the government. Only citizens of Taiwan who fulfill the requirements for conducting research projects are eligible to apply for the NHIRD. The use of the NHIRD is limited to research purposes only. Applicants must follow the Computer-Processed Personal Data Protection Act (https://dep.mohw.gov.tw/dos/lp-2506-113.html) and the related regulations of the National Health Insurance Administration and NHRI, and an agreement must be signed by the applicant and their supervisor upon application submission. All applications are reviewed for approval of data release.

## ETHICS STATEMENT

Since the identifiable database of individuals included in the NHIRD were all encrypted in order to protect individual privacy, the NHI Administration has given general approval for their data to be used in this research. Because the NHIRD has the advantage of providing a large-scale, longitudinal, reliable dataset, leading to extensive use for population-based researches in Taiwan, the Institutional Review Board of Tri-Service General Hospital was aware of this and approved the research to proceed, and also agreed that the benefit justified waiving the need for individual written informed consent in such a study (IRB No. 1-106-05-169).

## AUTHOR CONTRIBUTIONS

P-CC and N-ST contributed to the study concept and design. W-CC, C-HC, and N-ST contributed to the acquisition of data. W-CC, C-HC, C-KH, H-ML, P-CC, and N-ST contributed to the analysis and interpretation of data. P-CC contributed to the drafting of the manuscript. N-ST contributed to the critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

## FUNDING

This work was supported by the Medical Affairs Bureau, the Ministry of Defense of Taiwan (MAB-107-084 and MND-MAB-D-111-075), the Tri-Service General Hospital Research

Foundation (TSGH-C108-003, TSGHC108-027, TSGH-C108-151, TSGH-B-109-010, TSGH-B-111-018, and TSGH-D-111-121), and the Taoyuan Armed Forces General Hospital (TYAFGH-A-110-020).

## ACKNOWLEDGMENTS

We appreciate Taiwan's Health and Welfare Data Science Center and Ministry of Health and Welfare (HWDC, MOHW) for providing the National Health Research Database. We also appreciate Richard Lathe for his help in the writing of this article.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.771486/full#supplementary-material

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 28 March 2022
doi: 10.3389/fnagi.2022.804842

# The Relative Importance of Vascular Risk Factors on Early Cognitive Aging Varies Only Slightly Between Men and Women

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**Objective:** To investigate the sex-specific course and impact of vascular risk factors on cognitive aging in a rather young and healthy community-dwelling cohort.

**Methods:** We used data from a population-based cohort study, collected three times during 6 years, comprising 1,911 examinations from 798 participants aged 35–66 years at baseline. Cognitive performance on the Color-Word-Interference-Test, the Trail Making Tests (TMT) A&B, the Word Fluency Test, a 12-item word list, the Purdue Pegboard Test and a principal component global score were used as outcomes in linear mixed models. We evaluated (1) sex differences in cognitive trajectories, (2) the mediating role of hypertension, diabetes, smoking and obesity [body mass index (BMI) > 30] on sex differences and (3) in sex-stratified analyses, potential sex-specific effects of these risk factors on cognition.

**Results:** For all cognitive tests, we observed cognitive decline with age. Rates of decline slightly differed across sexes, showing a later but steeper decline for women in tests of memory (word list) and word fluency, but a steeper decline for men in tests of psychomotor speed and mental set shifting (TMT A&B) in older age. Women generally scored better on cognitive tests, but the slightly higher prevalence of classical vascular risks factors in men in our cohort could not explain these sex differences. Sex-stratified analyses revealed a generally small, concordantly negative, but quantitatively slightly different impact of diabetes, smoking and obesity on cognitive functions but mixed effects for arterial hypertension, depending on the blood pressure values, the treatment status and the duration of arterial hypertension.

**Conclusion:** Cognitive sex differences in this rather young and healthy cohort could not be explained by a differing prevalence of vascular risks factors across sexes. The association of cardiovascular risk factors with cognition, however, slightly differed between men and women, whereby effects were generally small. Whereas longtime diabetes, obesity and smoking had a sex-specific, but concordantly negative impact on

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***Edited by:***
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***Specialty section:***
*This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience*

***Received:*** *29 October 2021*
***Accepted:*** *16 February 2022*
***Published:*** *28 March 2022*

***Citation:***
*Bonberg N, Wulms N, Berger K and Minnerup H (2022) The Relative Importance of Vascular Risk Factors on Early Cognitive Aging Varies Only Slightly Between Men and Women. Front. Aging Neurosci. 14:804842. doi: 10.3389/fnagi.2022.804842*

psychomotor speed, executive and motor functions, we found some opposing effects for arterial hypertension. Our results can help to identify sex-specific susceptibilities to modifiable risk factors, to attract attention to potential information bias and to stimulate further research into alternative causes and mechanism of sex differences in cognitive aging.

**Keywords: sex, cognitive aging, cardiovascular risk factors, bias, susceptibility**

## INTRODUCTION

Sex differences in cognition have been observed over many domains and populations (McCarrey et al., 2016; Reas et al., 2017; Fu et al., 2020; Levine et al., 2021; Nichols et al., 2021). Most studies in high-income countries show that men outperform women in some spatial tasks, while women usually outperform men in most other domains, particularly verbal tasks (McCarrey et al., 2016; Reas et al., 2017). However, the causes for this sex difference are not fully revealed yet and are presumably multifactorial (Levine et al., 2021; Nichols et al., 2021). Besides biological reasons, such as differences in brain reserve, hormone profiles and the prevalence of potentially brain-damaging risk factors, several environmental (e.g., education and socioeconomic factors) as well methodological factors (e.g., age and selection of the population), have to be acknowledged in the analysis and interpretation of cognitive sex differences (Reas et al., 2017; Volgman et al., 2019; Bloomberg et al., 2021; Nichols et al., 2021; van Zutphen et al., 2021). When examining cognitive aging, i.e., the trajectories of cognitive performance over time, even more challenges arise, such as selective attrition and test-retest effects (Salthouse, 2019; Rouanet et al., 2021).

Regarding modifiable risk factors, it is established that cardiovascular risk factors are associated with vascular and degenerative brain damage and an increased risk of cognitive decline and dementia (Debette et al., 2011; Gorelick et al., 2011; Gottesman et al., 2017; Boots et al., 2019; Livingston et al., 2020). Arterial hypertension and diabetes mellitus, particularly when acquired in midlife, are probably the single most important adversaries of cognitive aging, having been consistently associated with declines in executive functions, attention, memory as well as processing and motor speed (Biessels et al., 2008; Monette et al., 2014; Gottesman et al., 2017; Biessels and Despa, 2018; Iadecola and Gottesman, 2019). Besides, systemic low-grade inflammation, obesity and smoking have been identified as risk factors for cognitive decline, though the evidence is less consistent (Beeri et al., 2009; Hajjar et al., 2018; Zheng and Xie, 2018; Vintimilla et al., 2019; Walker et al., 2019).

The question that arises from this evidence on sex differences on the one hand, and vascular risk factors, on the other hand, is, whether the former can at least partially be explained by the latter in the context of cognitive aging. It is known that men and women have different vascular risk profiles. For example, the midlife prevalence of classical vascular risk factors in women is generally lower compared to men of the same age and socio-economic background (Lerner and Kannel, 1986), and women differ from men with regard to hormonal and inflammatory status (Khera et al., 2005; Lakoski et al., 2006).

Besides differences in the prevalence of vascular and metabolic risk factors, men and women might differ regarding the susceptibility to the damage these risk factors potentially cause in the brain. Studies on this aspect are rather rare, but there is recent evidence that suggests that specific risk factors, such as smoking and diabetes, might have a differential impact on men and women and thus might further explain some of the sex differences in cognitive aging (Appelman et al., 2015; Biessels and Despa, 2018; van Zutphen et al., 2021).

Based on 6-year longitudinal data from the population-based cohort of the BiDirect Study, the goal of the current analysis was to reveal sex-specific cognitive trajectories for a variety of distinct neuropsychological tests and to evaluate the role of cardiovascular risk factors on the specific test performances. We also examined the effect of potential biases, such as test-retest effects and selective attrition, in the association between risk factors and cognitive aging.

## MATERIALS AND METHODS

### Study Population

The BiDirect Study is a cohort study conducted in Münster, Germany (Teismann et al., 2014). The primary aim of the study is to investigate the bidirectional relationship between depression and (subclinical) atherosclerosis. It is based on the examination of three distinct cohorts comprising (1) patients with an acute episode of depression, (2) patients with a recent cardiovascular event and (3) population-based controls, who had been randomly recruited by use of the population register of the city of Münster. In the current analysis, three examinations of the population-based control participants were used. The baseline examination of 911 population-based controls aged 35–66 years took place between 2010 and 2013, 800 participants returned for a second examination between 2013 and 2016 after a mean follow-up time of 2.7 years and 680 for the third examination between 2016 and 2018 after a mean follow-up time of another 2.7 years. At all examinations, participants underwent a computer-guided interview, self-administered questionnaires, sensory and neuropsychological assessments, clinical examinations (e.g., anthropometry, vascular status and blood sampling), as well as magnetic resonance imaging of the brain (Teismann et al., 2014; Teuber et al., 2017). The data acquisition was conducted by a trained study team. For the current analyses, we applied several exclusion criteria. We excluded participants with neurological disorders and limited German language skills, as well participants with missing or invalid neuropsychological test results resulting

in a total of 798 out of 911 participants in our analysis. This study was approved by the Ethics Committee of the University of Münster and the Westphalian Chamber of Physicians in Münster, North-Rhine-Westphalia, Germany. All participants gave their written informed consent for study participation.

## Assessment of Sociodemographic and Health Status

Smoking status, socio-demographic characteristics and data on participants' health status and histories, such as physician's diagnosis of diabetes and hypertension, were assessed in a personal interview at baseline and follow-ups. Education was documented in the four categories (1) primary or general secondary school, (2) intermediate secondary school, (3) high school and (4) university graduates. Current medications were denoted and blood pressure as well as body weight and height were measured in a standardized way (Teismann et al., 2014). For analysis, a categorical variable "arterial hypertension" was defined as a combination of current hypertensive treatment (yes/no) and measured blood pressure (controlled/uncontrolled) and therefore labeled as (1) untreated, controlled, (2) untreated, uncontrolled, (3) treated, controlled and (4) treated, uncontrolled blood pressure. Uncontrolled blood pressure was defined as a systolic blood pressure of at least 140 mmHg and/or a diastolic blood pressure of at least 90 mmHg. For sensitivity analysis, we used another definition of hypertension given as physician's diagnosis (no diagnosis, diagnosed $\leq$ 10 years, diagnosed $>$ 10 years). A history of diabetes was classified into "no physician diagnosis," "diagnosed $\leq$ 7 years" and "diagnosed $>$ 7 years." Body mass index (BMI) was calculated from measured weight and height (kg/m$^2$) and categorized into no obesity (BMI $<$ 30 kg/m$^2$) and obesity (BMI $\geq$ 30 kg/m$^2$). Smoking status was defined categorically as never vs. former vs. current smoking. Self-reported depressive symptoms were assessed by the Center for Epidemiological Studies Depression-Scale (CES-D) at baseline and follow-up examinations (Teismann et al., 2014). A CES-D score $\geq$ 16 was used to define clinically relevant depressive symptoms (Radloff, 1977).

## Neuropsychological Assessment

Five validated tests were administered to all study participants at BiDirect baseline and follow-ups (Teismann et al., 2014).

(1) *Color–Word Interference Test (CWIT)*: Participants performed a paper-pencil version with three task sets (words, color, color–word) with 36 items each. The reaction time was measured for each task set (Stroop, 1935). We focused on the second and third condition (color and color–word) and calculated the time difference of these conditions (interference time) to measure interference control, a measure of working memory capacity.

(2) *Trail Making Test (TMT) A&B*: In TMT A participants were asked to connect consecutive numbers from 1 to 25 as fast as possible to measure attention and psychomotor speed. In TMT B, they have to connect consecutive numbers and letters in an alternating sequence (1-A-2-B-3-C, etc.) to measure working memory and mental set shifting (Reitan, 1992). The time needed to complete each part was recorded.

(3) *Regensburg Word Fluency Test ("animal naming test")*: Participants were asked to name as many animals as possible within 60 s to measure categorical association (semantic) fluency as a measure or executive function (Morris et al., 1989; Tombaugh et al., 1999).

(4) *Word List*: To measure verbal retentiveness and memory, a recorded 12-item emotional word memory list was presented via loudspeaker to the participants (Kissler et al., 2006). After the presentation of the word list, the participants were asked to reproduce as many words as possible. A second presentation of the word list with immediate recall followed. After these two presentations, a third free recall followed after an interval of 15 min.

(5) *Purdue Pegboard Test*: Participants were asked to place as many pegs as possible into a wooden board within 30 s, first with the right hand, followed by the left hand, to measure fine motor skills (Tiffin and Asher, 1948).

We calculated a Z-score for each test or subtest result using the respective test mean and standard deviation (*SD*) of the female baseline control group for standardization. Test results from TMT A and B as well as the reaction times and the interference time from CWIT were log-transformed before standardization. All Z-scores were scaled in a way, that higher values represent better results. Afterwards, we averaged the scores for the three runs of the word list and the scores for the right and left hand from the Purdue Pegboard Test.

### Assessment of a Global Cognitive Score

We made a principal component analysis with baseline data (Z-scores from word list, Pegboard, interference time from CWIT, TMT A&B, word fluency test) by using the R-package "psych" [function principal ()] (Revelle, 2021) and extracted one component as a global score. Based on the estimates of this analysis, we calculated the global score for the follow-ups and standardized the score with the mean and SD of the female baseline values.

## Statistical Analyses

We first present the cognitive trajectories for men and women. After these descriptive analyses, we test for a mediating role of cardiovascular risk factors in the association between sex and cognitive performance. Finally, using sex-stratified analyses we estimate the individual effects of several vascular risk factors on cognition for men and women separately. All statistical analyses were performed with R 4.1.0 (R Core Team, 2021) and RStudio Version 1.4.1717 (RStudio Team, 2021). We used the lmer function from the R-package lme4 (Bates et al., 2015) for linear mixed models and produced plots with the R-package interactions (Long, 2019). Analyses were conducted with a 2-tailed alpha of 0.05 referred as a statistically significant level.

### Trajectories of Standardized Neuropsychological Test Results

We assessed trajectories for the different standardized neuropsychological test results using linear mixed models

with random intercepts. In each model, age at study participation was used as a time variable. To account for possible nonlinear trends, we included age as a natural spline with two degrees of freedom (df) in our models. Additionally, sex and interaction of sex and age (as spline) were included, because we expected different slopes for men and women. Furthermore, we added the "number of study participations" to account for possible practice effects. In the model for memory (word list), we included the interaction of age (as spline) and the number of study participations to allow for a variation of the practice effect with age. All models were adjusted for potential selective attrition (see below).

### Adjustment for Selective Attrition

To account for potential sex differences in outcome-related dropouts (i.e., study dropouts due to impaired cognition) we used inverse probability weighting (IPW) in our models (Rouanet et al., 2021). We calculated probabilities for study participation at the two follow-ups with logistic regression models. These logistic regression models comprise age, sex, sociodemographic variables, distance to study center and variables describing the health condition in prior surveys, including the most recent cognitive global score. The inverse values of these probabilities were used as weights in the mixed models described above. Further information on IPW can be found here (Seaman and White, 2013; Hernán and Robins, 2020). As sensitivity analyses, we re-analyzed all models using the same cohort without IPW.

### The Mediating Role of Cardiovascular Risk Factors in the Association Between Sex and Cognitive Performance

Weighted linear mixed models were used to assess the association of sex with standardized neuropsychological test results. We performed two models with different adjustments for every neuropsychological test. In addition to sex, models of type one comprise age (spline, 2 df), number of study participations and education. Models of type two were additionally adjusted for hypertension, diabetes, CES-D score, smoking status and obesity. Models for memory (word list) additionally include the interaction of age and number of study participations, and models for the Purdue Pegboard Test include body height as a proxy for hand size. IPW was used to account for potential selective attrition (see above).

### Sex-Specific Effects of Risk Factors on Cognition

We built weighted linear mixed regression models with IPW for the standardized neuropsychological test results stratified by sex and added age (spline, 2 df), education and the number of study participations (and for memory the interaction of these), diabetes, CES-D score, obesity, smoking status and hypertension as explaining variables. In the models for the Purdue Pegboard Test, we also added body height as a proxy for hand size.

## RESULTS

We used longitudinal data (baseline and two follow-ups) consisting of 1,911 examinations from 798 participants of the BiDirect study for analysis. **Table 1** shows the characteristics of the study population at baseline and follow-ups. At baseline, 47% of participants were male. Median age at baseline was 53 years (range: 35–66 years), at first follow-up 57 years (range: 37–69) and at second follow-up 60 years (range: 40–71 years). In all, 76 (22%) men and 82 (21%) women were current smokers at baseline and 137 men (39%) and 218 women (55%) had untreated and controlled blood pressure, while 115 men (33%) and 88 women (22%) had an untreated and uncontrolled, 31 (9%) men and 38 (10%) women a treated and controlled and 66 (19%) men and 50 (13%) women a treated and uncontrolled blood pressure. A CES-D score of at least 16 was documented for 47 (13%) men and 84 (21%) women at baseline.

## Trajectories of Standardized Neuropsychological Test Results

**Figure 1** shows trajectories for the standardized cognitive test results at first study participation as results of weighted linear mixed regression models. For all cognitive tests, we observed a cognitive decline with age. Descriptively viewed, women, on average, outperformed men, especially in memory (word list), the Pegboard Test, the Word Fluency Test (at least in some age regions) and the global score. Trajectories for the different conditions of the CWIT showed a lesser superiority of women and the TMTs showed only a slight superiority of women at later ages. Also descriptively, the trajectories for women showed a later, but steeper cognitive decline in tests of memory (word list), word fluency and the global score, but steeper declines for men in tests of psychomotor speed and mental set shifting (TMT A&B) in older age.

## The Mediating Role of Cardiovascular Risk Factors in the Association Between Sex and Cognitive Performance

Significant sex differences were found before and after further adjustments for vascular risk factors (**Table 2**). Adjusted for education, number of study participations and age, female sex was positively associated with memory [$\widehat{\beta}$ = 0.57, 95% CI = (0.47, 0.67)], Pegboard [0.39, (0.24, 0.54)], interference time of CWIT [0.18, (0.07, 0.30)], TMT B [0.20, (0.08, 0.32)], Word Fluency Test [0.21, (0.09, 0.33)] and the global score [0.48, (0.36, 0.59)]. Additional adjustments for smoking status, obesity, hypertension, CES-D score and diabetes resulted in significant positive and only slightly lower associations of female sex with the cognitive test results (**Table 2**).

## Practice Effects

Sex-specific trajectories for memory (word list) at all three study participations are shown in **Figure 2**. A decline with age can be observed for men and women for all participations, as well as a distinct practice effect, that slightly decreases with age. Smaller practice effects could be also observed for the interference time of CWIT, TMT A, TMT B (women), Word Fluency Test (women) and the global score (**Table 3B**).

**TABLE 1 |** Study population at baseline and two follow-ups.

| | Baseline | | First follow-up | | Second follow-up | |
|---|---|---|---|---|---|---|
| | **Men *N* = 349** | **Women *N* = 394** | **Men *N* = 311** | **Women *N* = 361** | **Men *N* = 228** | **Women *N* = 268** |
| **Age (years)** | | | | | | |
| (Median, range) | 53 (35–66) | 54 (35–66) | 56 (38–69) | 57 (37–69) | 59 (40–71) | 61 (40–71) |
| **Education, *N* (%)** | | | | | | |
| Primary or general secondary school | 74 (21%) | 68 (17%) | 62 (20%) | 61 (17%) | 37 (16%) | 48 (18%) |
| Intermediate secondary school | 48 (14%) | 112 (28%) | 40 (13%) | 98 (27%) | 32 (14%) | 63 (24%) |
| High school | 63 (18%) | 75 (19%) | 51 (16%) | 71 (20%) | 36 (16%) | 53 (20%) |
| University graduates | 164 (47%) | 139 (35%) | 158 (51%) | 131 (36%) | 123 (54%) | 104 (39%) |
| **Diabetes, *N* (%)** | | | | | | |
| No | 335 (96%) | 380 (96%) | 292 (94%) | 346 (96%) | 216 (95%) | 259 (97%) |
| 0-7 years | 7 (2%) | 7 (2%) | 11 (4%) | 9 (2%) | 4 (2%) | 5 (2%) |
| > 7 years | 7 (2%) | 7 (2%) | 8 (3%) | 6 (2%) | 8 (4%) | 4 (1%) |
| **Hypertension, *N* (%)** | | | | | | |
| Untreated, controlled | 137 (39%) | 218 (55%) | 121 (39%) | 198 (55%) | 93 (41%) | 148 (55%) |
| Untreated, uncontrolled | 115 (33%) | 88 (22%) | 88 (28%) | 73 (20%) | 45 (20%) | 50 (19%) |
| Treated, controlled | 31 (9%) | 38 (10%) | 48 (15%) | 43 (12%) | 57 (25%) | 40 (15%) |
| Treated, uncontrolled | 66 (19%) | 50 (13%) | 54 (17%) | 47 (13%) | 33 (14%) | 30 (11%) |
| **CES-D score, *N* (%)** | | | | | | |
| < 16 | 302 (87%) | 310 (79%) | 279 (90%) | 294 (81%) | 207 (91%) | 229 (85%) |
| ≥ 16 | 47 (13%) | 84 (21%) | 32 (10%) | 67 (19%) | 21 (9%) | 39 (15%) |
| **Smoking status, *N* (%)** | | | | | | |
| Never | 140 (40%) | 164 (42%) | 116 (37%) | 146 (40%) | 79 (35%) | 114 (43%) |
| Former | 133 (38%) | 148 (38%) | 131 (42%) | 153 (42%) | 106 (46%) | 117 (44%) |
| Current | 76 (22%) | 82 (21%) | 64 (21%) | 62 (17%) | 43 (19%) | 37 (14%) |
| **Obesity, *N* (%)** | | | | | | |
| No (BMI < 30 kg/m$^2$) | 270 (77%) | 315 (80%) | 243 (78%) | 297 (82%) | 176 (78%) | 220 (82%) |
| Yes (BMI ≥ 30 kg/m$^2$) | 79 (23%) | 79 (20%) | 68 (22%) | 64 (18%) | 52 (22%) | 48 (18%) |

## Sex-Specific Effects of Risk Factors on Cognition

The sex-specific impact of vascular risk factors on standardized cognitive test results are shown in **Tables 3A**, **3B**. Diabetes ≤ 7 years was negatively associated with TMT A in men [−0.46 (−0.86, −0.06)]. Diabetes > 7 years was negatively associated with Pegboard in men (−0.91 [−1.34, −0.48]), interference time of CWIT in men [−0.73, (−1.20, −0.25)], TMT A in men [−0.67, (−1.25, −0.20)] and the global score in men [−0.76, (−1.17, −0.35)]. A treated and controlled blood pressure was positively associated with Pegboard in men [0.18, (0.004, 0.36)] and negatively associated with TMT B in women (−0.25, [−0.43, −0.07]). As a sensitivity analysis, we performed the same analysis but used the physician's diagnosis to define hypertension (**Supplementary Tables 1A,B**). A diagnosis of hypertension > 10 years was positively associated with Pegboard in men [0.26, (0.05, 0.47)]. No further significant results for this definition of hypertension were found. Smoking was negatively associated with Pegboard in men [former: −0.19, (−0.35, −0.03), current: −0.36, (−0.55, −0.18)] and women [former: −0.22, (−0.36, −0.08), current: −0.30, (−0.48, −0.12)], the interference time of CWIT in women [current: −0.19, (−0.38, −0.001)] and with the global score in women [current: −0.21, (−0.37, −0.04)]. Obesity was negatively associated with the global score in women [−0.15, (−0.29, −0.01)]. Of the potential confounding variables, higher education was positively associated with all cognitive tests apart from Pegboard (women) where no significant association was found. Moreover, a CES-D score ≥ 16 was negatively associated with Pegboard in men [−0.17, (−0.33, −0.02)] and women [−0.16, (−0.29, −0.04)], TMT A in women [−0.22, (−0.36, −0.08)] and TMT B in men [−0.29, (−0.46, −0.11)].

## Sensitivity Analyses

For all above-mentioned analyses, the re-analyses on the unweighted data showed similar results (data not shown).

# DISCUSSION

The presented work investigated sex differences in early cognitive aging from multiple perspectives. First, a descriptive approach presents sex-specific trajectories for various cognitive functions. Second, the influence of vascular risk factors on cognitive sex differences is elucidated by investigating their mediating role as well as differing susceptibilities across men and women. Third, the role of selective attrition and information bias is investigated.

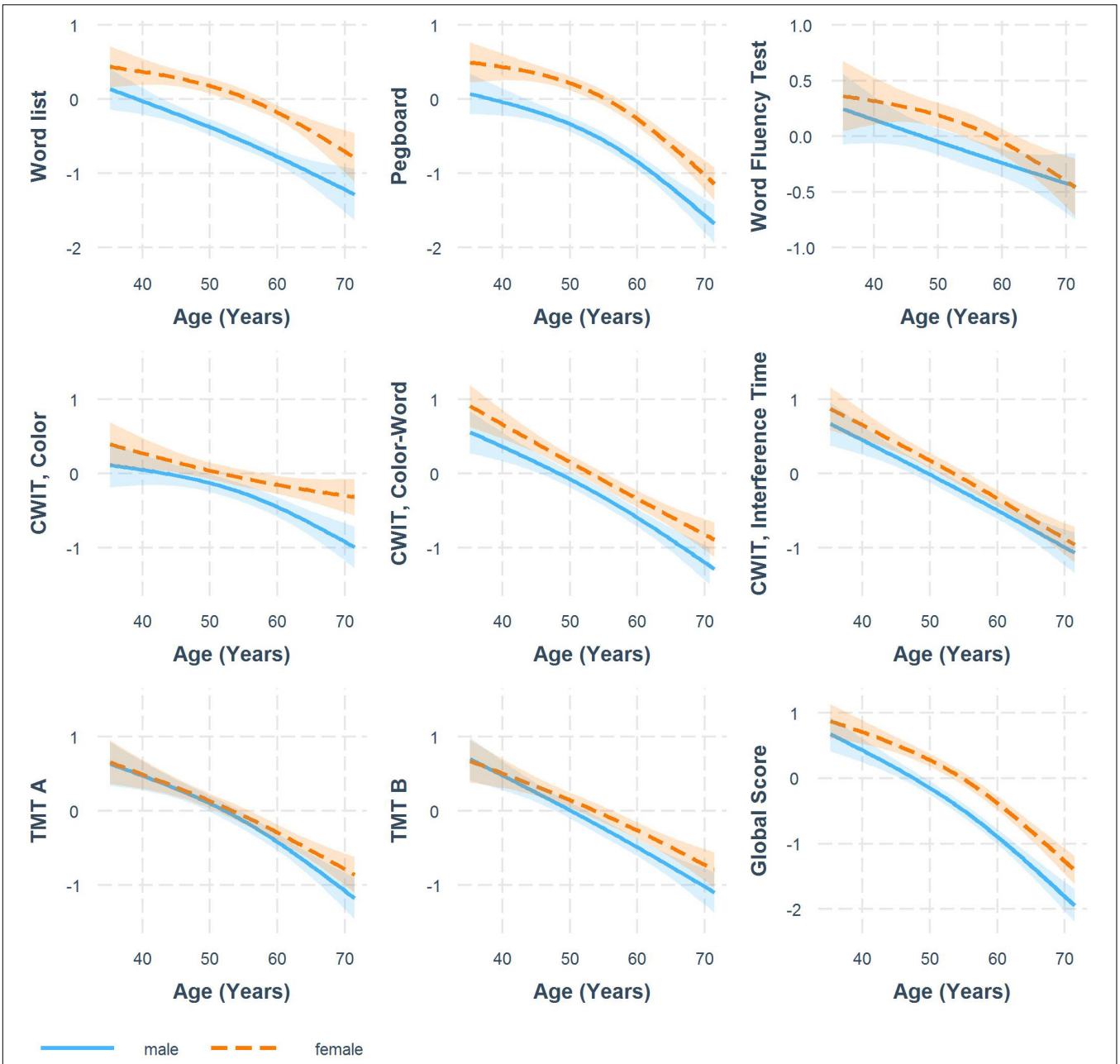


**FIGURE 1 |** Comparison of sex-specific trajectories for standardized neuropsychological test results shown at first study participation with 95% confidence intervals (CI). Results from weighted linear mixed models.

## Cognitive Trajectories

Using a large population-based cohort, we were able to show sex-specific trajectories for a large battery of neuropsychological tests reflecting a broad spectrum of cognitive abilities. As expected, and adding to the growing body of evidence, we generally found cognitive decline with age in our cohort (Reas et al., 2017; van Zutphen et al., 2021). We also observed that women, except for the TMT A, outperformed men for most age ranges. We observed the most pronounced effect of sex in the reproduction of the 12-item word list (short-term memory) with an effect size of $\beta = 0.57$ (adjusted for age, education and study participation). Our findings here corroborate and expand prior work on mostly older cohorts that also reported sex differences in tasks of memory, executive function and attention (Van der Elst et al., 2006; McCarrey et al., 2016; Reas et al., 2017; Luck et al., 2018; Fu et al., 2020; Levine et al., 2021; Nichols et al., 2021; van Zutphen et al., 2021). Regarding sex differences of the Purdue Pegboard Test in a normal aging population, there are only few and conflicting reports (Peters et al., 1990;

**TABLE 2 |** Association of sex with neuropsychological test results (z-scores) with and without adjustment for cardiovascular risk factors.

| | Word list[c] | Pegboard[d] | CWIT (interference time) | TMT A | TMT B | Word fluency test | Global score |
|---|---|---|---|---|---|---|---|
| | $\hat{\beta}$ (95% CI) | $\hat{\beta}$ (95% CI) | $\hat{\beta}$ (95% CI) | $\hat{\beta}$ (95% CI) | $\hat{\beta}$ (95% CI) | $\hat{\beta}$ (95% CI) | $\hat{\beta}$ (95% CI) |
| **Models 1[a]** | | | | | | | |
| **Sex (Ref.: male)** | | | | | | | |
| Female | 0.57*** | 0.39*** | 0.18** | 0.10 | 0.20*** | 0.21*** | 0.48*** |
| | (0.47, 0.67) | (0.24, 0.54) | (0.07, 0.30) | (−0.01, 0.22) | (0.08, 0.32) | (0.09, 0.33) | (0.36, 0.59) |
| **Models 2[b]** | | | | | | | |
| **Sex (Ref.: male)** | | | | | | | |
| Female | 0.56*** | 0.37*** | 0.16** | 0.11 | 0.20** | 0.20** | 0.46*** |
| | (0.46, 0.66) | (0.22, 0.52) | (0.05, 0.28) | (−0.01, 0.22) | (0.08, 0.31) | (0.08, 0.33) | (0.35, 0.57) |
| **Diabetes (Ref: no)** | | | | | | | |
| 0–7 years | 0.07 | −0.09 | −0.10 | −0.20 | −0.01 | −0.03 | −0.04 |
| | (−0.16, 0.29) | (−0.33, 0.16) | (−0.37, 0.17) | (−0.48, 0.08) | (−0.27, 0.24) | (−0.32, 0.25) | (−0.25, 0.17) |
| > 7 years | 0.02 | −0.61*** | −0.54** | −0.37* | −0.42* | −0.32 | −0.53*** |
| | (−0.26, 0.30) | (−0.91, −0.30) | (−0.87, −0.21) | (−0.70, −0.03) | (−0.75, −0.10) | (−0.67, 0.04) | (−0.81, −0.25) |
| **Hypertension (Ref: untreated, controlled)** | | | | | | | |
| Untreated, uncontrolled | −0.05 | 0.02 | −0.11* | −0.001 | −0.04 | 0.01 | −0.05 |
| | (−0.13, 0.03) | (−0.07, 0.11) | (−0.21, −0.01) | (−0.10, 0.10) | (−0.13, 0.05) | (−0.09, 0.12) | (−0.12, 0.02) |
| Treated, controlled | −0.05 | 0.08 | −0.02 | 0.003 | −0.12 | 0.06 | −0.04 |
| | (−0.16, 0.07) | (−0.04, 0.21) | (−0.15, 0.12) | (−0.14, 0.14) | (−0.25, 0.01) | (−0.08, 0.20) | (−0.14, 0.07) |
| Treated, uncontrolled | −0.07 | −0.01 | 0.01 | −0.001 | 0.003 | −0.09 | −0.05 |
| | (−0.19, 0.04) | (−0.14, 0.11) | (−0.13, 0.14) | (−0.14, 0.14) | (−0.13, 0.14) | (−0.23, 0.06) | (−0.16, 0.06) |
| **Smoking (Ref.: never)** | | | | | | | |
| Former | −0.02 | −0.22*** | −0.09 | −0.03 | −0.04 | −0.01 | −0.11* |
| | (−0.12, 0.07) | (−0.33, −0.12) | (−0.21, 0.02) | (−0.14, 0.09) | (−0.16, 0.07) | (−0.14, 0.11) | (−0.21, −0.01) |
| Current | −0.07 | −0.35*** | −0.07 | −0.12 | −0.18* | −0.12 | −0.20** |
| | (−0.19, 0.05) | (−0.48, −0.22) | (−0.21, 0.07) | (−0.26, 0.02) | (−0.32, −0.04) | (−0.27, 0.03) | (−0.32, −0.07) |
| **Obesity (Ref: no)** | | | | | | | |
| Yes | −0.06 | −0.10 | −0.13* | −0.04 | −0.10 | −0.07 | −0.13** |
| | (−0.16, 0.04) | (−0.21, 0.01) | (−0.25, −0.004) | (−0.17, 0.08) | (−0.21, 0.02) | (−0.20, 0.06) | (−0.24, −0.03) |
| Marginal R-squared models 2 | 0.30 | 0.28 | 0.19 | 0.15 | 0.20 | 0.12 | 0.40 |
| Conditional R-squared models 2 | 0.71 | 0.69 | 0.62 | 0.58 | 0.68 | 0.62 | 0.85 |

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a]*Adjusted for age (spline, 2 df), number of study participations and education.*
[b]*Adjusted for age (spline, 2 df), number of study participations, education and CES-D score.*
[c]*Word List: averaged z-scores for the three runs of the Word List. Results are additionally adjusted for the interaction of age and number of study participations.*
[d]*Pegboard: averaged z-scores for the right and left hand from Purdue Pegboard Test. Results are additionally adjusted for body height.*
*Results from weighted linear mixed models with 1,911 examinations from 798 participants.*

Schmidt et al., 2000; Sivagnanasunderam et al., 2015). Though motors skills are known to diminish with age and correlate with cognitive decline (Kluger et al., 1997; Hamilton et al., 2017), to our knowledge this is the first study to show persistent sex differences in a prospective population-based study.

Though not statistically tested for, we also observed sex differences in the longitudinal rates of change, with women showing steeper declines for memory, verbal fluency and fine motor skills, beginning at the age of around 55 years (**Figure 1**). On tests of psychomotor speed in contrast (TMT A and B, CWIT color task), men declined faster beginning at 50 years. The evidence so far is rather inconsistent with reports of later and steeper declines in men or women (McCarrey et al., 2016; Reas et al., 2017; Bloomberg et al., 2021; Levine et al., 2021; van Zutphen et al., 2021). Reasons for these inconsistencies might lay in the use of different tests, but also in differing age periods and age cohorts under study, as well as in methodological differences regarding the modeling of cognitive decline. In general, comparable to our findings, reported sex differences in the rates of cognitive decline were generally small in other studies and mostly affected only some cognitive domains (McCarrey et al., 2016; Reas et al., 2017; Bloomberg et al., 2021; Levine et al., 2021; van Zutphen et al., 2021).

## Comparison of Risk Factor Profiles

Men, on average, were slightly better educated, showing a higher proportion of university graduates. Regarding cardiovascular risk factors, we did not observe large sex differences. Men more often reported to be active smokers, particularly during

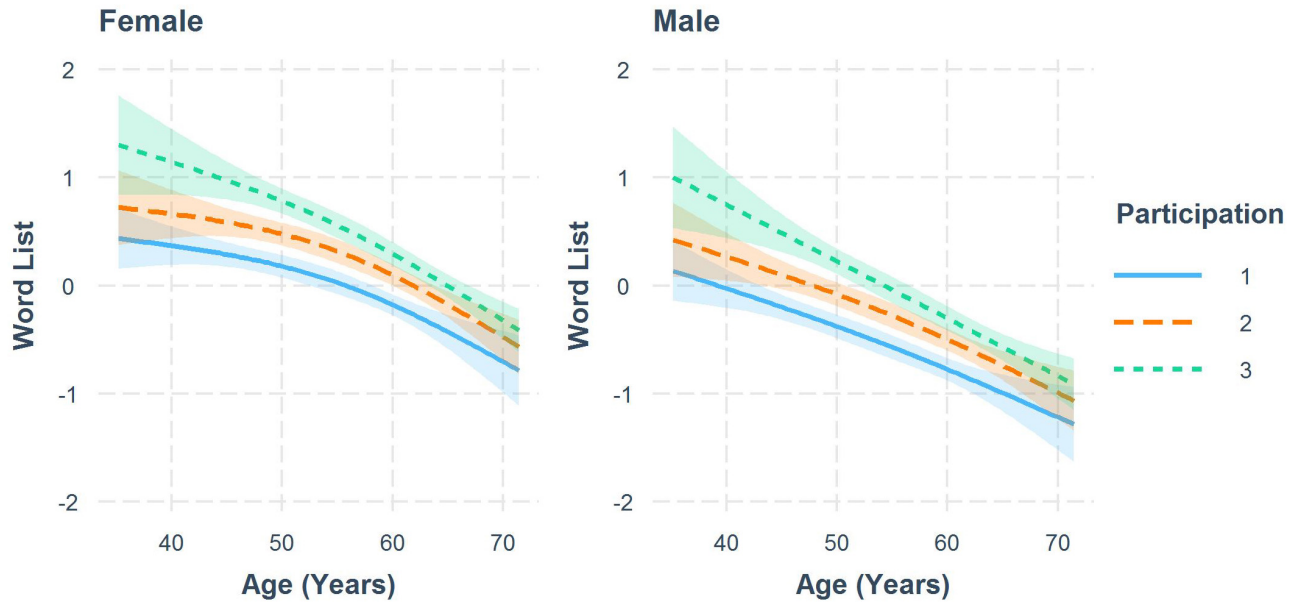


**FIGURE 2 |** Trajectories for standardized test results of the word list by number of study participations to visualize the practice effect for women and men with 95% CI. Results from a weighted linear mixed model.

follow-up examinations. Moreover, men more often showed uncontrolled blood pressures, though the absolute percentage and the sex discrepancy diminished during follow-up. The prevalence of obesity was comparable across sexes, as was diabetes. Self-reported depressive symptoms were more pronounced in women.

Taken together, our cohort represents a rather well-educated and healthy population (Teismann et al., 2014; Schneider et al., 2021) with only small sex discrepancies in the prevalence of cardiovascular risk factors. Nevertheless, as expected and generally observed in populations from high-income countries, men showed a slightly worse cardiovascular risk factor profile, whereas women reported more depressive symptoms (Lerner and Kannel, 1986; Seedat et al., 2009). Moreover, we observed a decline in the prevalence of risk factors and depressive symptoms over time, which might be due to selective attrition (healthy study adherer). We thus used IPW to account for differential loss-to-follow-up.

## The Role of Risk Factors in the Association of Sex and Cognition

The examined risk factors explained next to nothing of the variation in cognition across sexes, as similar effect sizes of sex on cognitive performances were seen before and after adjustment in the linear mixed models (**Table 2**). The mere difference in the prevalence of cardiovascular risk factors across sexes thus did not explain the observed sex differences in cognition. This was expected in our cohort of relatively young and healthy participants, as there was hardly any sex difference in the distribution of vascular risk factors. Nevertheless, these findings corroborate earlier work in mainly older cohorts, that also found only small mediating effects of cardiovascular risk factors on the association between sex and cognition, suggesting that alternative biological mechanisms play a role in cognitive sex differences (Levine et al., 2021; van Zutphen et al., 2021).

Looking at the sex-stratified analyses and thus the impact of the different risk factors on cognitive test results in men and women separately, we found evidence of a slight sex-specific susceptibility: tough most of the risk factors showed a concordantly negative impact on cognitive test performance, the size of the effects slightly differed across sexes. Longtime diabetes was associated with worse performance in many cognitive processes, such as psychomotor speed and mental set switching (TMT A & B), interference control (CWIT) and fine motor functions (Pegboard), however, only in men. This agrees with findings from van Zutphen et al. (2021) who reported sex differences in the impact of diabetes on processing speed. No clear sex discrepancies emerged for former and current smoking, which were about equally associated with worse performances in the Pegboard Test, whereas there was a slightly stronger association of current smoking with the global score and the CWIT in women and the word fluency test in men. For obesity, we found an association with the global score in women only. Taken together, effect sizes differed between men and women, but they were generally small and there is no clear preference of one sex over the other sex. One can assume multiple reasons for varying susceptibilities across men and women, such as differing genetic profiles with varying gene-environment interactions or differences in structural and functional brain reserve (Marrocco and McEwen, 2016;

**TABLE 3A |** Sex-specific effects of potential risk factors on standardized test results from the word list and Purdue pegboard test.

| | Word list[a] | | Pegboard[b] | |
|---|---|---|---|---|
| | Men $\hat{\beta}$ (95% CI) | Women $\hat{\beta}$ (95% CI) | Men $\hat{\beta}$ (95% CI) | Women $\hat{\beta}$ (95% CI) |
| **Diabetes (Ref: no)** | | | | |
| 0-7 years | 0.09 (−0.24, 0.43) | −0.004 (−0.31, 0.30) | −0.27 (−0.63, 0.09) | 0.05 (−0.29, 0.39) |
| > 7 years | −0.01 (−0.41, 0.40) | 0.04 (−0.35, 0.43) | −0.91*** (−1.34, −0.48) | −0.28 (−0.71, 0.14) |
| **Hypertension (Ref: untreated, controlled)** | | | | |
| Untreated, uncontrolled | −0.07 (−0.19, 0.04) | −0.04 (−0.16, 0.07) | 0.03 (−0.09, 0.16) | −0.01 (−0.14, 0.11) |
| Treated, controlled | 0.04 (−0.13, 0.21) | −0.13 (−0.28, 0.02) | 0.18* (0.004, 0.36) | −0.01 (−0.18, 0.15) |
| Treated, uncontrolled | −0.09 (−0.26, 0.07) | −0.05 (−0.21, 0.12) | 0.04 (−0.13, 0.22) | −0.09 (−0.27, 0.09) |
| **Smoking (Ref.: never)** | | | | |
| Former | −0.09 (−0.25, 0.06) | 0.05 (−0.08, 0.18) | −0.19* (−0.35, −0.03) | −0.22** (−0.36, −0.08) |
| Current | −0.11 (−0.29, 0.07) | −0.02 (−0.18, 0.14) | −0.36*** (−0.55, −0.18) | −0.30*** (−0.48, −0.12) |
| **Obesity (Ref: no)** | | | | |
| Yes | −0.04 (−0.18, 0.11) | −0.07 (−0.21, 0.07) | −0.07 (−0.22, 0.09) | −0.11 (−0.26, 0.05) |
| Marginal R-squared | 0.26 | 0.26 | 0.28 | 0.24 |
| Conditional R-squared | 0.71 | 0.66 | 0.69 | 0.65 |

*$p < 0.05$, *$p < 0.01$, ***$p < 0.001$.
*Weighted linear mixed models with 888 examinations from 373 men and 1,023 examinations from 425 women, respectively, adjusted for education, CES-D score, age (natural spline, df = 2), number of study participations, the interaction of age and number of study participations (word list), and body height (pegboard).*
[a]*Averaged z-scores for the three runs of the Word List Test.*
[b]*Averaged z-scores for the right and left hand from Purdue Pegboard Test.*
*Results from linear mixed models stratified by sex.*

McEwen and Milner, 2017; Levine et al., 2021). However, this is by now highly speculative and should stimulate further studies including brain imaging, hormone measurements and genetic data.

Most interestingly, for arterial hypertension we observed mixed effects on cognition for men and women. Treated and controlled arterial hypertension showed a positive association with fine motor skills in men and a negative association with TMT B in women - both compared to participants without hypertension. The exposure "arterial hypertension" is prone to misclassification due, for example, to unknown periods of undiagnosed hypertension, the impact of treatment, the age at onset, and the type of hypertension (systolic vs. diastolic). We have included the treatment status as well as the actual blood pressure in our primary definition. We also used an alternative definition defining arterial hypertension as a known physician's diagnosis and additionally accounting for the period of known hypertension. Here again, we found a diagnosis of hypertension > 10 years to be positively associated with the Pegboard Test in men. So taken together, a long-lasting and adequately treated arterial hypertension, respectively, is associated with better motor performance even compared to normotensive men and non-diagnosed men, respectively. One potential explanation might be that this group presents a highly health-conscious sample with early and optimal interventions of not only hypertension but several vascular risk factors. Interestingly, other studies also reported positive effects of hypertension on cognition (Forte et al., 2019; van Zutphen et al., 2021), but our study also found sex differences in this association. Effects were opposite in women showing worse performance in the TMT B in women with treated and controlled arterial hypertension. There are several potential explanations for these contrasting findings across sexes, such as sex disparities in the initiation, vigor or response to antihypertensive treatment (Lefort et al., 2018; Iadecola and Gottesman, 2019; Kalibala et al., 2020), or an interaction of blood pressure or treatment with sex hormones, especially around the time of menopause (Volgman et al., 2019). All these mechanisms should be further elucidated in future studies.

## Strengths and Limitations

Several limitations must be considered in the interpretation of our data. Although we analyzed nearly 800 participants in a longitudinal design, the number of participants with risk factors, particularly diabetes was relatively low. Given the small effect of vascular risk factors and the only minor sex differences in this relatively young and healthy cohort our analyses from a post hoc view were probably underpowered to detect some statistically significant sex differences. Nevertheless, focusing on the effect sizes this does not considerably affect the interpretation that the estimates slightly varied across sexes and that a major proportion of sex differences in cognitive aging is not explained by cardiovascular risk factors in this population. As methodological challenges, we focused on potential biases like selective attrition and information bias. In this study population, not every participant participated in all surveys. That could lead to biased results due to selective loss to follow-up, particularly when dropout due to cognitive decline is different across sexes. To reduce this selection bias, we calculated models with IPW. We also performed sensitivity analyses with unweighted models and observed stable results. Thus, we can assume that selective attrition is very low in this study. Another problem was the definition of hypertension. The exposure "arterial hypertension" is generally prone to misclassification due to unknown periods of undiagnosed hypertension, the impact of treatment, the age at onset, the type of hypertension (systolic vs. diastolic) etc. We have included the treatment status as well as the actual blood pressure and additionally used a second definition using the physician's diagnosis to define hypertension as accurate as possible. The longitudinal design by itself is a clear strength, but we had to deal with strong practice effects especially in the analysis for memory, that even dominated the age-related decline leading to successive improvements of memory performance over time.

**TABLE 3B |** Sex-specific effects of risk factors on standardized test results of Color–Word Interference Test (CWIT, interference time), Trail Making Test (TMT) A, TMT B, Word Fluency and the PCA-derived global score.

| | CWIT (interference time) | | TMT A | | TMT B | | Word fluency test | | Global score | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Men $\hat{\beta}$ (95% CI) | Women $\hat{\beta}$ (95% CI) | Men $\hat{\beta}$ (95% CI) | Women $\hat{\beta}$ (95% CI) | Men $\hat{\beta}$ (95% CI) | Women $\hat{\beta}$ (95% CI) | Men $\hat{\beta}$ (95% CI) | Women $\hat{\beta}$ (95% CI) | Men $\hat{\beta}$ (95% CI) | Women $\hat{\beta}$ (95% CI) |
| **Study participation (Ref: first)** | | | | | | | | | | |
| Second | 0.26*** | 0.17*** | 0.01 | 0.05 | 0.02 | 0.08 | 0.04 | 0.19*** | 0.16*** | 0.22*** |
| | (0.16, 0.36) | (0.08, 0.27) | (−0.09, 0.11) | (−0.05, 0.14) | (−0.07, 0.11) | (−0.01, 0.17) | (−0.06, 0.14) | (0.09, 0.29) | (0.09, 0.23) | (0.15, 0.28) |
| Third | 0.36*** | 0.37*** | 0.14* | 0.14* | 0.05 | 0.14* | −0.02 | 0.24*** | 0.23*** | 0.38*** |
| | (0.24, 0.48) | (0.25, 0.48) | (0.01, 0.27) | (0.03, 0.26) | (−0.07, 0.16) | (0.03, 0.24) | (−0.14, 0.11) | (0.12, 0.36) | (0.13, 0.32) | (0.29, 0.46) |
| **Diabetes (Ref: no)** | | | | | | | | | | |
| 0–7 years | −0.09 | −0.12 | −0.46* | 0.07 | −0.07 | 0.02 | −0.22 | 0.08 | −0.27 | 0.14 |
| | (−0.48, 0.31) | (−0.50, 0.25) | (−0.86, −0.06) | (−0.31, 0.46) | (−0.45, 0.30) | (−0.34, 0.38) | (−0.63, 0.19) | (−0.31, 0.47) | (−0.58, 0.04) | (−0.14, 0.42) |
| > 7 years | −0.73** | −0.27 | −0.67** | −0.05 | −0.41 | −0.43 | −0.49 | −0.23 | −0.76*** | −0.32 |
| | (−1.20, −0.25) | (−0.74, 0.20) | (−1.15, −0.20) | (−0.53, 0.43) | (−0.87, 0.04) | (−0.89, 0.03) | (−0.99, 0.01) | (−0.73, 0.27) | (−1.17, −0.35) | (−0.70, 0.06) |
| **Hypertension (Ref: untreated, controlled)** | | | | | | | | | | |
| Untreated, uncontrolled | −0.13 | −0.10 | −0.04 | 0.02 | 0.002 | −0.08 | −0.03 | 0.07 | −0.08 | −0.03 |
| | (−0.27, 0.004) | (−0.23, 0.04) | (−0.18, 0.10) | (−0.13, 0.16) | (−0.13, 0.13) | (−0.21, 0.05) | (−0.18, 0.11) | (−0.08, 0.21) | (−0.18, 0.02) | (−0.13, 0.07) |
| Treated, controlled | −0.11 | 0.08 | 0.11 | −0.09 | 0.03 | −0.25** | 0.16 | −0.01 | 0.07 | −0.12 |
| | (−0.30, 0.09) | (−0.11, 0.26) | (−0.09, 0.32) | (−0.28, 0.10) | (−0.15, 0.22) | (−0.43, −0.07) | (−0.05, 0.36) | (−0.20, 0.19) | (−0.08, 0.23) | (−0.26, 0.02) |
| Treated, uncontrolled | −0.04 | 0.07 | −0.01 | 0.01 | 0.10 | −0.07 | −0.08 | −0.07 | −0.04 | −0.05 |
| | (−0.23, 0.16) | (−0.13, 0.27) | (−0.21, 0.19) | (−0.20, 0.22) | (−0.09, 0.28) | (−0.27, 0.12) | (−0.28, 0.13) | (−0.28, 0.14) | (−0.19, 0.11) | (−0.21, 0.10) |
| **Smoking (Ref.: never)** | | | | | | | | | | |
| Former | −0.09 | −0.08 | −0.02 | −0.01 | −0.10 | 0.02 | −0.07 | 0.02 | −0.11 | −0.07 |
| | (−0.26, 0.09) | (−0.23, 0.07) | (−0.19, 0.16) | (−0.17, 0.15) | (−0.27, 0.07) | (−0.14, 0.17) | (−0.25, 0.12) | (−0.15, 0.18) | (−0.26, 0.04) | (−0.21, 0.06) |
| Current | 0.05 | −0.19* | −0.08 | −0.14 | −0.19 | −0.15 | −0.22 | −0.04 | −0.16 | −0.21* |
| | (−0.15, 0.26) | (−0.38, −0.001) | (−0.28, 0.13) | (−0.34, 0.06) | (−0.39, 0.01) | (−0.35, 0.04) | (−0.43, 0.001) | (−0.25, 0.16) | (−0.33, 0.02) | (−0.37, −0.04) |
| **Obesity (Ref: no)** | | | | | | | | | | |
| Yes | −0.08 | −0.16 | −0.06 | −0.04 | −0.15 | −0.03 | −0.03 | −0.11 | −0.11 | −0.15* |
| | (−0.26, 0.09) | (−0.33, 0.01) | (−0.23, 0.12) | (−0.22, 0.13) | (−0.32, 0.01) | (−0.19, 0.14) | (−0.21, 0.16) | (−0.29, 0.07) | (−0.25, 0.04) | (−0.29, −0.01) |
| Marginal R-squared | 0.20 | 0.19 | 0.19 | 0.13 | 0.22 | 0.18 | 0.09 | 0.15 | 0.38 | 0.39 |
| Conditional R-squared | 0.66 | 0.58 | 0.62 | 0.56 | 0.70 | 0.67 | 0.64 | 0.60 | 0.86 | 0.83 |

*$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.*

*Weighted linear mixed models with 888 examinations from 373 men and 1,023 examinations from 425 women, respectively, adjusted for age (natural spline, df = 2), education and CES-D score. PCA, principal component analysis.*

*Results from linear mixed models stratified by sex.*

This discrepancy between cross-sectional and longitudinal age-cognition relations, especially for the cognitive domain of memory, and the inherent difficulty of avoiding or eliminating the practice effect, was also described by others (Salthouse, 2019). Other strengths of this study are the repeated risk factor and neuropsychological assessment allowing for time-dependent modeling, as well as the relatively young cohort and the use of the Pegboard Test.

## CONCLUSION

In conclusion, cognitive trajectories differ between men and women. However, cardiovascular risk factors seem to play only a minor role in the explanation of these sex differences in this cohort of rather healthy younger to middle-aged men and women. Whereas diabetes, smoking and obesity had a negative but quantitatively slightly different impact on psychomotor speed, executive and motor functions across sexes, we found no adverse effects of any of the risk factors on memory. For arterial hypertension, we found opposing effects on mental set shifting and motor skills across sexes. Corroborating other work, we also found significant and persistent sex differences for most cognitive tests, that could not be explained by differing risk factor profiles, which should stimulate further investigations into the development and maintenance of the brain and cognitive reserve in even younger adults or adolescents. Our results might help to classify cognitive test results and identify sex-specific susceptibilities to modifiable risk factors. On the methodological side, they might stimulate deeper investigations into the assessment and definition of risk factors, and the development of strategies to avoid or overcome the practice effects in repeated test situations.

## DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because investigators must submit an application to access BiDirect data. Requests to access the datasets should be directed to the Institute of Epidemiology and Social Medicine, University of Münster, Germany.

## ETHICS STATEMENT

The study involving human participants were reviewed and approved by Ethics Committee of the University of Münster and the Westphalian Chamber of Physicians in Münster, North-Rhine-Westphalia, Germany. The participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

NB drafted the manuscript, conducted, and programmed all statistical analyses. HM came up with the research question, supervised the analyses, and supported the drafting of the manuscript. KB and NW made substantial contributions to the data acquisition and revised the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

## FUNDING

This study was supported by the German Federal Ministry of Education and Research (BMBF grants 01ER1205, 01ER0816, and 01ER1506). The funding source was not involved in the writing of the manuscript or in the decision to submit it for publication.

## ACKNOWLEDGMENTS

We thank everybody involved in the BiDirect study, particularly the study nurses doing the data acquisition and the data managers importing and cleaning the data. Most important, we want to thank the BiDirect participants who made this research possible.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.804842/full#supplementary-material

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frontiers | Frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 11 May 2022
doi: 10.3389/fnagi.2022.810296

# Sex-Specific Causes and Consequences of White Matter Damage in a Middle-Aged Cohort

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OPEN ACCESS

**Edited by:**
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**Reviewed by:**
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**Specialty section:**
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

**Received:** 06 November 2021
**Accepted:** 14 March 2022
**Published:** 11 May 2022

**Citation:**
Bonberg N, Wulms N, Dehghan-Nayyeri M, Berger K and Minnerup H (2022) Sex-Specific Causes and Consequences of White Matter Damage in a Middle-Aged Cohort. Front. Aging Neurosci. 14:810296. doi: 10.3389/fnagi.2022.810296

**Objective:** To evaluate potential sex-specific effects of multiple cardiovascular risk factors on white matter pathology in normal aging men and women, as well as potential sex-differences in the association of white matter pathology and cognitive functions.

**Methods:** We analyzed cross-sectional data of 581 participants (median age: 53 years, 54% women) of the population-based cohort of the BiDirect Study who completed clinical examinations, five neuropsychological tests, and an 3T MRI examination. White matter pathology was determined by the extent of white matter hyperintensities (WMH) on FLAIR images as well as the magnitude of global fractional anisotropy (FA) based on diffusion tensor imaging. Main effects, interaction as well as sex-stratified generalized linear regression models were used to evaluate the moderating effect of sex on the association of hypertension, diabetes mellitus, smoking, and obesity with WMH and FA, respectively. Associations of imaging markers with cognitive test results were determined with linear regression models.

**Results:** Hypertension showed stronger associations with more extensive WMH and less FA in women compared to men. Current smoking was associated with more severe WMH in women only. Adjusted for age and education, WMH were not significantly associated with cognitive tests, but higher FA was associated with better performance in motor function in both sexes and with executive functions in men, even after adjustment for cardiovascular risk factors.

**Conclusion:** We observed a stronger association of hypertension and smoking with white matter damage in women, suggesting a higher susceptibility for vascular pathology in women. However, there was no association of WMH with cognition, and FA was associated with executive function tests only in men, suggesting a higher cognitive reserve in women.

**Keywords: sex, white matter damage, white matter hyperintensities (WMH), fractional anisotropy, vascular risk factors, cognition, cognitive reserve**

## INTRODUCTION

White matter hyperintensities (WMH) on T2-weighted magnetic resonance images (MRI) are common in elderly people (Wen and Sachdev, 2004). Being strongly associated with vascular risk factors they are recognized as a marker of cerebral small vessel disease and as such with an increased risk of cognitive decline and dementia (Debette and Markus, 2010; Wardlaw et al., 2013; Kloppenborg et al., 2014).

Nevertheless, the etiology and pathogenesis of WMH is not well understood and most probably encompasses genetic as well as environmental factors (Gouw et al., 2011). Of those, sex seems one obvious factor as sex differences are known in the etiology of vascular disease (Förster et al., 2009; Fatemi et al., 2018) as well as in normal cognitive aging (McCarrey et al., 2016) and the development of pathological cognitive decline (Li et al., 2014). Men usually show a higher prevalence of cardiovascular risk factors (Fatemi et al., 2018), whereas there is increasing evidence that women have higher WMH volumes (Leeuw et al., 2002; van den Heuvel et al., 2004; Wen and Sachdev, 2004; Sachdev et al., 2009; Fatemi et al., 2018), and sex differences in cognition generally tend toward a better cognitive performance in women (McCarrey et al., 2016; Reas et al., 2017; Levine et al., 2021; Nichols et al., 2021). Given that WMH are presumed to mediate part of the association between cardiovascular risk factors and cognitive performance (Chen et al., 2021), a lower prevalence of vascular risk factors in women contrasting a higher burden of WMH suggests a higher susceptibility to white matter damage in women. Moreover, better cognitive performance despite a higher lesion load calls for investigations into sex-differences in cognitive and brain reserve (O'Dwyer et al., 2012; Stern et al., 2020; Levine et al., 2021; Subramaniapillai et al., 2021). Another approach to solving this apparent paradox might be the evaluation of alternative or more subtle markers of white matter damage. Diffusion tensor based measures, such as fractional anisotropy (FA) have been established as sensitive markers of brain and cognitive aging (Salat et al., 2005; Zavaliangos-Petropulu et al., 2019; Veldsman et al., 2020). Whereas WMH are defined by their macroscopic appearance on FLAIR-images and are highly heterogeneous regarding their underlying pathophysiology, FA reflects the microstructural integrity of the white matter (Le Bihan and Johansen-Berg, 2012) and might therefore be a more sensitive surrogate of risk-factor-associated damage (Wassenaar et al., 2019; Williams et al., 2019; Veldsman et al., 2020). Studies regarding sex-differences in diffusion tensor imaging (DTI) measures are inconsistent, mainly reporting higher FA in men (Inano et al., 2011; Kanaan et al., 2014; Takao et al., 2014).

Taken together, the moderating effect of sex in the association between modifiable risk factors and cognition is increasingly investigated. However, to our knowledge, there is only one study, that investigated sex-differences in cardiovascular risk factors, WMH and cognition simultaneously in a rather small cross-sectional study (Sachdev et al., 2009). The authors found different causes and consequences of white matter hyperintensities across sexes (Sachdev et al., 2009). We expand this multidimensional evidence by a larger cohort with additional evaluation of fractional anisotropy, and a broad battery of neuropsychological tests. The present study thus offers a broad perspective on sex-differences in white matter pathology based on a large community-dwelling cohort. First, the influence of multiple vascular risk factors on WMH and global FA is evaluated for middle-aged men and women. Second, the sex-specific impact of white matter pathology on several cognitive functions is analyzed, while considering potential mediating effects of vascular risk factors.

## MATERIALS AND METHODS

### Subjects

We analyzed baseline data from 581 community-dwelling participants of the longitudinal BiDirect Study in Münster, Germany. All participants underwent a computer-guided interview, self-administered questionnaires, sensory and neuropsychological assessments, clinical examinations (e.g., anthropometry, vascular status, and blood sampling), as well as magnetic resonance imaging (MRI) of the brain (Teismann et al., 2014; Teuber et al., 2017). The data acquisition was conducted by a trained study team. For the present analysis, we applied several exclusion criteria. We excluded participants with clinical or imaging evidence of severe neurological disorders (stroke, Parkinson's Disease, epilepsy, and multiple sclerosis), missing or invalid neuropsychological data including reduced German language skills, and missing or invalid MRI data, respectively. The BiDirect study was approved by the ethics committee of the University of Münster and the Westphalian Chamber of Physicians in Münster, North Rhine-Westphalia, Germany. All participants gave their written informed consent for study participation.

### Assessment of Education, Cardiovascular Risk Factors, and Depression

In personal interviews we assessed socio-demographic characteristics, participants' smoking status, and participants' health status and history. Education was documented in the four categories (1) primary or general secondary school, (2) intermediate secondary school, (3) high school and (4) university graduates. Current medications (e.g., hypertensive treatments) were recorded and body size and height as well as blood pressure were measured in a standardized way (Teismann et al., 2014). For analysis, uncontrolled blood pressure was defined as a systolic blood pressure $\geq$140 mmHg and/or a diastolic blood pressure $\geq$90 mmHg. A combination of current hypertensive treatment (yes/no) and measured blood pressure (controlled/uncontrolled) was used to define the categorical variable "arterial hypertension." A history of diabetes was classified into "no physician diagnosis," "diagnosed $\leq$7 years," and "diagnosed >7 years". Body mass index (BMI) was calculated from measured weight and height (kg/m$^2$) and categorized into obesity (BMI $\geq$ 30 kg/m$^2$) and no obesity (BMI < 30 kg/m$^2$) according to the definition from the World Health Organization. The self-reported presence

of depressive symptoms was measured by the Center for Epidemiological Studies Depression-Scale (CES-D) (Teismann et al., 2014) and categorized into CES-D score <16 (no clinically relevant depressive symptoms) and ≥16 (clinically relevant depressive symptoms) (Radloff, 1977). Smoking status was defined categorically as never vs. former vs. current smoking.

## Neuropsychological Assessment

The following five validated neuropsychological tests were administered to all participants:

(1) *Color-Word-Interference-Test (CWIT)*: A paper-pencil version with three task sets (words, color, and color-word) consisting of 36 items each, was administered to the participants and the reaction time was measured for each task set (Stroop, 1935). To measure interference control, a measure of working memory capacity, we calculated the interference time as the time difference of the second (color) and third (color-word) task set of the CWIT test.
(2) *Trail Making Test (TMT) A and B*: In TMT A, the time that was needed to connect consecutive numbers from 1 to 25 was recorded to measure attention and psychomotor speed. In TMT B, the time that was needed to connect consecutive numbers and letters in an alternating sequence (1-A-2-B-3-C, etc.) was recorded to measure working memory and mental set shifting (Reitan, 1992).
(3) *Regensburg Word Fluency Test ("animal naming test")*: The number of animals that were named by the participants in 60 s were denoted to measure categorical association (semantic) fluency as a measure of executive function (Morris et al., 1989; Tombaugh et al., 1999).
(4) *Word List*: A recorded 12-item emotional word list was presented via loudspeaker two times to the participants. After each of the two presentations the participants were asked to reproduce as many words as possible. A third free recall followed after an interval of 15 min. This test was used to measure verbal retentiveness and memory (Kissler et al., 2006).
(5) *Purdue Pegboard Test*: The number of pegs that were placed by the participants in a wooden board within 30 s, first with the right hand, followed by the left hand, were used to measure fine motor skills (Tiffin and Asher, 1948).

A *Z*-score was calculated for each test or subtest using the respective test mean and standard deviation of the female subgroup for standardization. Test results from TMT A and B and the interference time from CWIT were log-transformed before standardization. All *Z*-scores were scaled, so that higher values represent better test results. Afterward, the scores for the three runs of the word list and the scores for the right and left hand from the Purdue Pegboard Test were averaged for analysis.

## Magnetic Resonance Imaging Acquisition

Magnetic resonance imaging was performed with the following protocol (Teuber et al., 2017) on the same 3.0 T MRI scanner (Intera with Achieva update; Philips Medical Systems, Best, Netherlands). The structural MRI protocol included a T1-weighted 3D TFE sequence with preceding inversion pulse, a T2 weighted FFE sequence, a TSE-FLAIR sequence, and a diffusion weighted sequence. The T1-weighted images were acquired in sagittal orientation with the following parameters: repetition time (TR)/echo time (TE) of 7.26/3.56 ms; flip angle of 9°; matrix size of 256 × 256; field of view (FOV) of 256 mm × 256 mm; reconstructed to pixel size of 1.00 mm × 1.00 mm; 160 slices with slice thickness of 2.0 mm with no gap between slices. The FLAIR images were acquired in axial orientation with TR/TE/TI of 11,000/120/2,600 ms; flip angle of 90°; matrix size of 352 × 206; FOV of 230 mm × 186 mm; reconstructed to pixel size of 0.45 mm × 0.45 mm; 27 slices with slice thickness of 4.0 mm with 1.0 mm gap. The diffusion weighted images were acquired with echo planar imaging (Single Shot SE-EPI, TR/TE = 5,900/95 ms); 36 slices with slice thickness of 3.6 mm with no gap, FOV of 240 mm × 240 mm, reconstructed to pixel size of 0.94 mm × 0.94 mm. Diffusion gradients were applied along 20 non-collinear directions at a *b* value of 1,000 s/mm$^2$ and an additional undirected b0 image with 0 s/mm$^2$.

## Image Analysis

Diffusion tensor imaging data were processed using the FSL v6.0.3 (Jenkinson et al., 2012) software library developed at the Oxford Centre for Functional MRI of the Brain (FMRIB). The pipeline of the PSMD marker tool provided at http://www.psmd-marker.com was used to process all images (Baykara et al., 2016). First, eddy current-induced distortion and motion artifacts in the DTI dataset were corrected using eddy tool in FSL. After skull-stripping using the Brain Extraction Tool (BET), a diffusion tensor model for each subject was fitted to the data by calculating diffusion tensor parameters using the FMRIB Diffusion Toolbox (FDT). The tract-based spatial statistics (TBSS) tool available in FSL [described in detail previously (Smith et al., 2006)] was used separately on each time point for the complete cohort to calculate the skeletonized mean FA images. First, FA images were normalized using the nonlinear registration algorithm in FSL. The individual normalized FA masks for each subject were then projected onto the TBSS skeleton of the PSMD marker tool to derive the individual skeletonized FA masks. These were then used to extract the mean whole-brain skeletonized FA value of each participant (excluding the cerebellum). FA is dimensionless and assumes values between 0 and 1. Higher FA values indicate higher anisotropy reflecting a higher structural integrity of white matter. The workflow described here was wrapped with R 4.1.1 (R Core Team, 2021).

Volumes of white matter hyperintensities were calculated using BIANCA which is implemented in FSL (Griffanti et al., 2016). We used 121 manually delineated FLAIR images and a training sample of 40 subjects for the training of BIANCA to adapt the program to the challenge of low volume extraction (Wulms et al., 2022). The WMH volume was extracted choosing a threshold of 0.8.

## Statistical Analyses

Relative WMH values were calculated by dividing the WMH volume by white matter (WM) volume. Categorical variables used in the regression analyses described below were included in the models as factors and reference categories were revealed in the corresponding tables. As statistical significance level we used a two-tailed alpha of 0.05.

All statistical analyses were performed with R 4.1.0 (R Core Team, 2021) and RStudio Version 1.4.1717 (RStudio Team, 2021).

### Association of Sex With White Matter Pathology

The logarithm of relative and absolute WMH values approximately followed a normal distribution. We therefore used a generalized linear model with Gamma distribution and log-link function to assess the age-adjusted association of sex with WMH volumes. Ordinary least squares (OLS) regressions were conducted to obtain the age-adjusted association of sex with FA. Age was included linearly in the models.

### Association of Vascular Risk Factors With Markers of White Matter Pathology

To examine the association of potential risk factors and markers of white matter pathology (absolute WMH, rel. WMH, and FA, respectively), main effects models, including sex, age (linear, in years), education, smoking, hypertension, diabetes, and obesity, were built. The model for absolute WMH was additionally adjusted for intracranial volume (ICV). To identify the moderation effect of sex, interaction models were conducted separately for each risk factor by including an interaction term between sex and each risk factor. These analyses were controlled for all other risk factors listened above. Additionally, sex-stratified regression models were built. Since WMH volumes approximately showed a log-normal distribution, generalized linear models with Gamma distribution and log-link function were used. For FA, an OLS regression analysis was performed.

### Association of Magnetic Resonance Imaging Markers With Cognitive Functions

To examine the association of markers of white matter pathology with cognitive functions, sex-stratified OLS regression analyses were performed for every cognitive test (*Z*-Score). Analyses were adjusted for age (natural spline with 2 df) and education. Analyses were repeated and adjusted for age (natural spline with 2 df), education, smoking, hypertension, diabetes, obesity, and CES-D score ($</\geq$16).

# RESULTS

**Table 1** shows the characteristics of our study population. In all, 265 men and 316 women aged 35–66 years were included (**Figure 1**). From these participants, 92 men (35%) and 71 women (22%) had an untreated and uncontrolled hypertension and 11 (4%) men, and 11 women (3%) had a diagnosed diabetes mellitus. A high CES-D score $\geq$16 could be observed in 33 men (12%) and 65 women (21%) and obesity in 55 men (21%) and 68 women (22%). Additionally, 53 (20%) men and 63 (20%) women were current smokers.

## Sex-Differences in Markers of White Matter Pathology

Distributions of MRI markers are shown in **Figure 2** and **Table 1**. The age-adjusted associations of sex with MRI markers are shown in **Table 2**. Absolute WMH volumes showed a geometric mean of 0.682 ml (range: 0.029–22.442 ml) for men and geometric mean of 0.668 ml (range: 0.011–26.406 ml) for women. The age adjusted association of sex with absolute WMH values was not statistically significant ($\hat{\beta}$ for female sex = 0.025, $p$ = 0.824). Relative WMH volumes were lower in men (geometric mean: 0.124% of WM volume) than in women (geometric mean: 0.138% of WM volume), with an age-adjusted association of $\hat{\beta}$ (women) = 0.151 and $p$ = 0.171. For FA, a mean value of 0.358 (range: 0.275–0.417) for men and 0.360 (range: 0.292–0.409) for women could be observed. Adjusted for age, female sex was associated with higher FA values ($\hat{\beta}$ = 0.003, $p$ = 0.061).

## Association of Risk Factors With Markers of White Matter Pathology

The main effects models (**Table 2**) showed significant positive associations of age with WMH (rel. WMH: $\hat{\beta}$ = 0.050, $p$ = 1.53e-13, abs. WMH: $\hat{\beta}$ = 0.048, $p$ = 3.06e-12) and a negative association with FA ($\hat{\beta}$ = −0.001 $p$ = 8.03e-16). Additionally, hypertension was positively associated with rel. WMH (treated, controlled: $\hat{\beta}$ = 0.371, $p$ = 0.049; treated, uncontrolled: $\hat{\beta}$ = 0.419, $p$ = 7.71e-3), abs. WMH (treated, controlled: $\hat{\beta}$ = 0.401, $p$ = 0.037; treated, uncontrolled: $\hat{\beta}$ = 0.434, $p$ = 6.56e-3) and negatively associated with FA (treated, controlled: $\hat{\beta}$ = −0.006, $p$ = 0.030; treated, uncontrolled: $\hat{\beta}$ = −0.008, $p$ = 3.86e-4). Current smoking was negatively associated with FA ($\hat{\beta}$ = −0.005, $p$ = 0.014).

**Table 3** shows the moderation effect of sex. For relative WMH the interaction of female sex with former smoking was $\hat{\beta}$ = 0.426 ($p$ = 0.039) and with current smoking $\hat{\beta}$ = 0.791 ($p$ = 1.76e-3). Similar results could be found for absolute WMH volumes (female sex, former smoking: $\hat{\beta}$ = 0.407, $p$ = 0.051; female sex, current smoking: $\hat{\beta}$ = 0.851, $p$ = 8.19e-4). The interaction of female sex with a treated and controlled hypertension resulted in $\hat{\beta}$ = 0.634 ($p$ = 0.071) for rel. WMH and $\hat{\beta}$ = 0.649 ($p$ = 0.069) for abs. WMH.

**Table 4** shows the association of cardiovascular risk factors with MRI markers stratified by sex (abs. WMH, rel. WMH, and FA, respectively). Higher age was associated with higher WMH volumes and lower FA for both, men and women. Current smoking was associated with higher WMH volumes in women (rel. WMH: $\hat{\beta}$ = 0.513, $p$ = 0.004, abs. WMH: $\hat{\beta}$ = 0.530, $p$ = 0.003). Additionally, hypertension was associated with higher relative WMH volumes in women (treated and controlled: $\hat{\beta}$ = 0.538, $p$ = 0.024, treated and uncontrolled: $\hat{\beta}$ = 0.576, $p$ = 0.007), higher absolute WMH volumes in women (treated and controlled: $\hat{\beta}$ = 0.568, $p$ = 0.019, treated and uncontrolled: $\hat{\beta}$ = 0.580, $p$ = 0.007) and lower FA in women (untreated and uncontrolled:

**TABLE 1 |** Characteristics of study participants.

| | **Total** ***N*** **= 581 (100%)** | **Men** ***N*** **= 265 (46%)** | **Women** ***N*** **= 316 (54%)** |
|---|---|---|---|
| **Baseline** | | | |
| *Age (years)* | | | |
| Median (range) | 53.1 (35.2–66.2) | 52.5 (35.3–66.2) | 53.5 (35.2–66.1) |
| *Hypertension, N* (%) | | | |
| Untreated, controlled | 282 (49%) | 108 (41%) | 174 (55%) |
| Untreated, uncontrolled | 163 (28%) | 92 (35%) | 71 (22%) |
| Treated, controlled | 51 (9%) | 22 (8%) | 29 (9%) |
| Treated, uncontrolled | 85 (15%) | 43 (16%) | 42 (13%) |
| *Diabetes, N* (%) | | | |
| No | 559 (96%) | 254 (96%) | 305 (97%) |
| Yes | 22 (4%) | 11 (4%) | 11 (3%) |
| *CES-D, N* (%) | | | |
| <16 | 483 (83%) | 232 (88%) | 251 (79%) |
| ≥16 | 98 (17%) | 33 (12%) | 65 (21%) |
| *Education*, *N* (%) | | | |
| Primary or general secondary school | 105 (18%) | 51 (19%) | 54 (17%) |
| Intermediate secondary school | 124 (21%) | 35 (13%) | 89 (28%) |
| High school | 103 (18%) | 46 (17%) | 57 (18%) |
| University graduates | 249 (43%) | 133 (50%) | 116 (37%) |
| *Smoking status*, *N* (%) | | | |
| Never | 249 (43%) | 112 (42%) | 137 (43%) |
| Former | 216 (37%) | 100 (38%) | 116 (37%) |
| Current | 116 (20%) | 53 (20%) | 63 (20%) |
| *Obesity*, *N* (%) | | | |
| No, BMI < 30 kg/m$^2$ | 458 (79%) | 210 (79%) | 248 (78%) |
| Yes, BMI ≥ 30 kg/m$^2$ | 123 (21%) | 55 (21%) | 68 (22%) |
| *Brain volume (ml)* | | | |
| Arithm. mean | 1455 | 1550 | 1375 |
| Range | 1000–1906 | 1281–1906 | 1000–1758 |
| *Relative brain volume (% of ICV)* | | | |
| Arithm. mean | 75.80 | 75.10 | 76.39 |
| Range | 61.63–84.75 | 61.63–84.38 | 65.59–84.75 |
| *Abs. WMH (ml)* | | | |
| *N* | 579 | 264 | 315 |
| Geom. mean | 0.674 | 0.682 | 0.668 |
| Range | 0.011–26.406 | 0.029–22.442 | 0.011–26.406 |
| *Rel. WMH (% of WM volume)* | | | |
| Geom. mean | 0.131 | 0.124 | 0.138 |
| Range | 0.003–4.701 | 0.006–4.013 | 0.003–4.701 |
| *FA* | | | |
| *N* | 578 | 262 | 316 |
| Arithm. mean | 0.359 | 0.358 | 0.360 |
| Range | 0.275–0.417 | 0.275–0.417 | 0.292–0.409 |
| *Word list (Z-score)* | | | |
| Mean (SD) | −0.22 (0.92) | −0.48 (0.9) | 0 (0.87) |
| *Pegboard (Z-score)* | | | |
| Mean (SD) | −0.20 (0.94) | −0.44 (0.97) | 0 (0.87) |
| *CWIT, interference time (Z-score)* | | | |
| Mean (SD) | −0.09 (1) | −0.19 (0.99) | 0 (1) |
| *TMT A (Z-score)* | | | |
| Mean (SD) | −0.01 (1.02) | −0.02 (1.04) | 0 (1) |
| *TMT B (Z-score)* | | | |
| Mean (SD) | −0.04 (1.02) | −0.09 (1.04) | 0 (1) |
| *Word fluency test (Z-score)* | | | |
| Mean (SD) | 0.01 (1) | 0.03 (1) | 0 (1) |

*ICV, intracranial volume; WM, white matter; WMH, white matter hyperintensities; SD, standard deviation.*

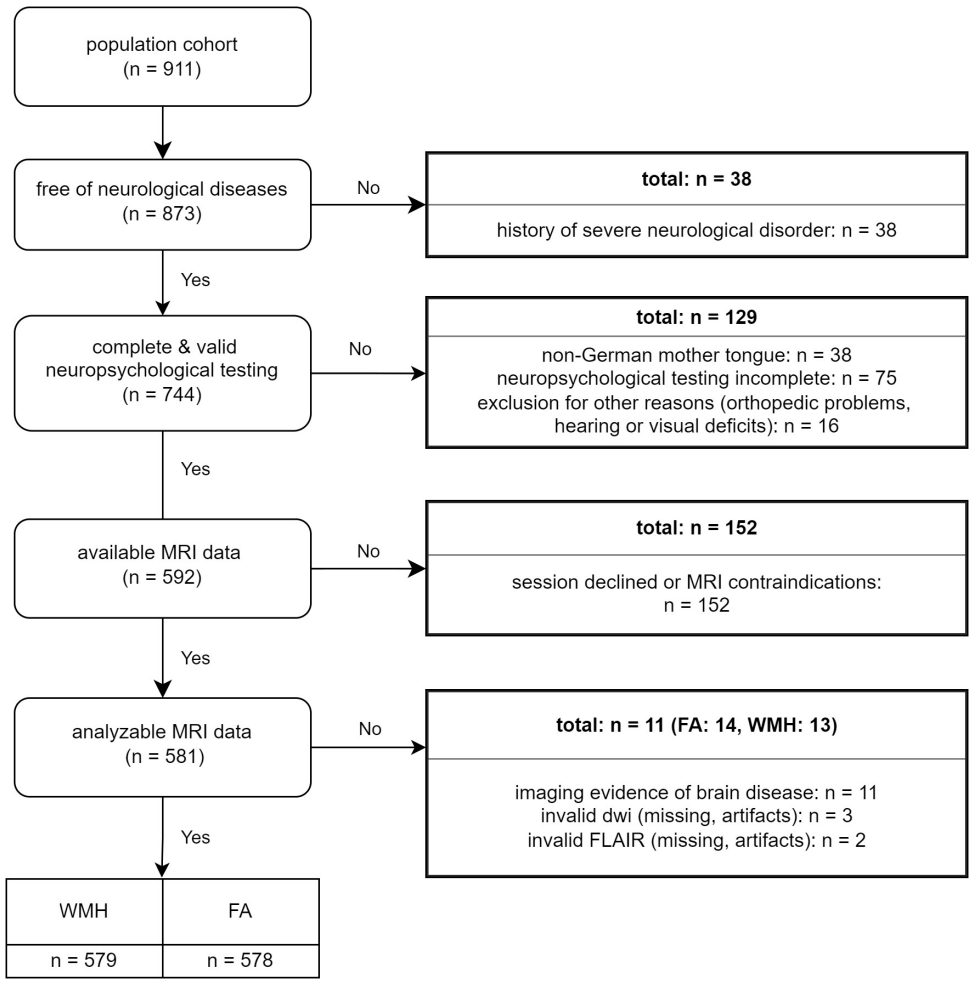


**FIGURE 1 |** Flow chart.

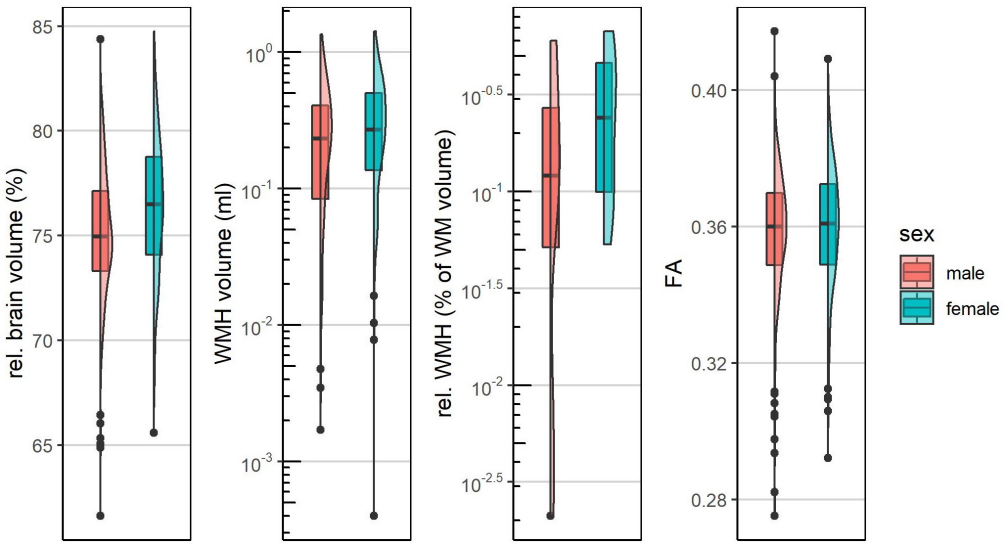


**FIGURE 2 |** Distributions of MRI markers stratified by sex.

**TABLE 2 |** Associations (main effects) of risk factors with MRI markers.

| | Rel. WMH[1] (*N* = 579) | Abs. WMH[1,2] (*N* = 579) | FA[3] (*N* = 578) |
|---|---|---|---|
| | $\hat{\beta}$ (*p*-value) | $\hat{\beta}$ (*p*-value) | $\hat{\beta}$ (*p*-value) |
| **Model 1** | | | |
| *Constant* | −4.79*** (<2e-16) | −3.051*** (3.19e-15) | 0.406*** (<2e-16) |
| *Sex (Ref: Male)* | | | |
| Female | 0.151 (0.171) | 0.025 (0.824) | 0.003 (0.061) |
| Age (In years) | 0.061*** (<2e-16) | 0.061*** (<2e-16) | −0.001*** (<2e-16) |
| **Model 2**[4] | | | |
| *Constant* | −4.189*** (<2e-16) | −4.550*** (8.42e-10) | 0.402*** (<2e-16) |
| *Sex (Ref: Male)* | | | |
| Female | 0.100 (0.321) | 0.228 (0.063) | 0.002 (0.154) |
| Age (In years) | 0.050*** (1.53e-13) | 0.048*** (3.06e-12) | −0.001*** (8.03e-16) |
| *Smoking (Ref: Never)* | | | |
| Former | −0.004 (0.969) | −0.024 (0.830) | −0.002 (0.224) |
| Current | 0.221 (0.099) | 0.213 (0.118) | −0.005* (0.014) |
| *Diabetes (Ref: No)* | | | |
| Yes | 0.207 (0.431) | 0.237 (0.374) | −0.004 (0.264) |
| *Hypertension (Ref: Untreated, controlled)* | | | |
| Untreated, uncontrolled | −0.127 (0.293) | −0.134 (0.273) | −0.003 (0.057) |
| Treated, controlled | 0.371* (0.049) | 0.401* (0.037) | −0.006* (0.030) |
| Treated, uncontrolled | 0.419** (7.71e-3) | 0.434** (6.56e-3) | −0.008*** (3.86e-4) |
| *Obesity (Ref: No)* | | | |
| Yes | 0.204 (0.105) | 0.195 (0.128) | 0.0002 (0.900) |

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[1]*Results from generalized linear models with Gamma distribution and log-link function.*
[2]*Additionally adjusted for intracranial volume in Model 2.*
[3]*Results from ordinary least squares (OLS) regression analysis.*
[4]*Additionally adjusted for education.*

**TABLE 3 |** Moderation effects of sex on the association of potential risk factors with WMH and FA.

| | Rel. WMH[1] (*N* = 579) | Abs. WMH[1,2] (*N* = 579) | FA[3] (*N* = 578) |
|---|---|---|---|
| | $\hat{\beta}$ (*p*-value) | $\hat{\beta}$ (*p*-value) | $\hat{\beta}$ (*p*-value) |
| *Sex × smoking* | | | |
| Women; former | 0.426* (0.039) | 0.407 (0.051) | −0.001 (0.729) |
| Women; current | 0.791** (1.76e-3) | 0.851*** (8.19e-4) | 0.003 (0.367) |
| *Sex × diabetes* | | | |
| Women; yes | 0.434 (0.391) | 0.392 (0.447) | −0.008 (0.251) |
| *Sex × hypertension* | | | |
| Women; untreated, uncontrolled | 0.061 (0.793) | 0.052 (0.823) | −0.004 (0.266) |
| Women; treated, controlled | 0.634 (0.071) | 0.649 (0.069) | −0.006 (0.225) |
| Women; treated, uncontrolled | 0.438 (0.125) | 0.399 (0.169) | −0.006 (0.144) |
| *Sex × obesity* | | | |
| Women; yes | 0.106 (0.660) | 0.102 (0.676) | −0.004 (0.211) |

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
*A separate model was built for each interaction. All results were adjusted for the main effects age, sex, smoking, diabetes, hypertension, obesity, and education.*
[1]*Results from generalized linear models with Gamma distribution and log-link function.*
[2]*Additionally adjusted for intracranial volume.*
[3]*Results from ordinary least squares (OLS) regression analysis.*

**TABLE 4 |** Associations of risk factors with MRI markers. Results from sex-stratified analysis.

| | Rel. WMH[1] | | Abs. WMH[1,2] | | FA[3] | |
|---|---|---|---|---|---|---|
| | Men (*N* = 264) | Women (*N* = 315) | Men (*N* = 264) | Women (*N* = 315) | Men (*N* = 262) | Women (*N* = 316) |
| | $\hat{\beta}$ (*p*-value) | $\hat{\beta}$ (*p*-value) | $\hat{\beta}$ (*p*-value) | $\hat{\beta}$ (*p*-value) | $\hat{\beta}$ (*p*-value) | $\hat{\beta}$ (*p*-value) |
| *Constant* | −3.658*** (1.77e-12) | −4.622*** (<2e-16) | −4.335*** (8.0e-06) | −4.730*** (3.15e-07) | 0.400*** (<2e-16) | 0.405*** (<2e-16) |
| *Age (in years)* | 0.050*** (4.90e-08) | 0.053*** (4.71e-09) | 0.048*** (1.2e-07) | 0.051*** (2.52e-08) | −0.001*** (7.7e-09) | −0.001*** (2.4e-08) |
| *Smoking (Ref: Never)* | | | | | | |
| Former | −0.216 (0.163) | 0.156 (0.266) | −0.227 (0.143) | 0.135 (0.343) | −0.002 (0.543) | −0.002 (0.312) |
| Current | −0.306 (0.104) | 0.513** (0.004) | −0.350 (0.062) | 0.530** (0.003) | −0.006 (0.058) | −0.003 (0.211) |
| *Diabetes (Ref: No)* | | | | | | |
| Yes | −0.041 (0.909) | 0.273 (0.437) | −0.004 (0.992) | 0.286 (0.420) | −0.001 (0.904) | −0.007 (0.147) |
| *Hypertension (Ref: untreated, controlled)* | | | | | | |
| Untreated, uncontrolled | −0.146 (0.359) | −0.048 (0.770) | −0.150 (0.344) | −0.054 (0.744) | −0.001 (0.583) | −0.005* (0.035) |
| Treated, controlled | 0.145 (0.591) | 0.538* (0.024) | 0.179 (0.501) | 0.568* (0.019) | −0.003 (0.463) | −0.009* (0.015) |
| Treated, uncontrolled | 0.162 (0.445) | 0.576** (0.007) | 0.191 (0.363) | 0.580** (0.007) | −0.004 (0.206) | −0.011*** (4.03e-4) |
| *Obesity (Ref: No)* | | | | | | |
| Yes | 0.151 (0.394) | 0.182 (0.258) | 0.143 (0.416) | 0.173 (0.289) | 0.002 (0.516) | −0.001 (0.766) |

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[1]*Results from generalized linear models with Gamma distribution and log-link function, additionally adjusted for education.*
[2]*Additionally adjusted for intracranial volume.*
[3]*Results from ordinary least squares (OLS) regression analysis, additionally adjusted for education.*

**TABLE 5 |** Association of WMH and FA, respectively, with cognitive test results (*Z*-scores).

| | Word list | Pegboard | CWIT, interference time | TMT A | TMT B | Word fluency |
|---|---|---|---|---|---|---|
| | $\hat{\beta}$ (*p*-value) | $\hat{\beta}$ (*p*-value) | $\hat{\beta}$ (*p*-value) | $\hat{\beta}$ (*p*-value) | $\hat{\beta}$ (*p*-value) | $\hat{\beta}$ (*p*-value) |
| **Rel. WMH in % (adjusted for age and education)** | | | | | | |
| Men (*N* = 264) | −0.140 (0.305) | −0.001 (0.995) | 0.051 (0.740) | 0.025 (0.878) | −0.038 (0.806) | −0.071 (0.670) |
| Women (*N* = 315) | 0.093 (0.321) | 0.098 (0.302) | 0.030 (0.781) | −0.009 (0.935) | −0.073 (0.505) | 0.174 (0.115) |
| **FA (adjusted for age and education)** | | | | | | |
| Men (*N* = 262) | 0.684 (0.815) | 10.661*** (5.08e-4) | 2.569 (0.438) | 12.068*** (4.92e-4) | 7.890** (0.018) | 0.328 (0.928) |
| Women (*N* = 316) | 2.456 (0.366) | 7.064** (0.012) | 5.085 (0.107) | 1.224 (0.711) | 4.924 (0.122) | 0.937 (0.771) |
| **FA (adjusted for age, education, smoking, diabetes, hypertension, CES-D, obesity)** | | | | | | |
| Men (*N* = 262) | 0.360 (0.905) | 9.926** (0.0013) | 3.440 (0.310) | 11.493** (0.0012) | 6.527 (0.053) | 0.052 (0.989) |
| Women (*N* = 316) | 1.458 (0.603) | 6.104* (0.035) | 4.311 (0.182) | 0.145 (0.966) | 3.099 (0.344) | 0.670 (0.841) |

*Results were calculated via linear regression models.*
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

$\hat{\beta} = -0.005$, $p = 0.035$, treated and controlled: $\hat{\beta} = -0.009$, $p = 0.015$, treated and uncontrolled: $\hat{\beta} = -0.011$, $p = 4.03e\text{-}4$).

## Association of Magnetic Resonance Imaging Markers With Cognitive Functions

The associations of markers of white matter pathology with cognitive test results are shown in **Table 5**. Adjusted for age and education, no significant association of any of the cognitive test results (Z-scores) were found with WMH, but higher FA values were positively associated with the Pegboard Test in men ($\hat{\beta} = 10.661$, $p = 5.08e\text{-}4$) and women ($\hat{\beta} = 7.064$, $p = 0.012$) and with the TMT A and B in men (TMT A: $\hat{\beta} = 12.068$, $p = 4.92e\text{-}4$, TMT B: $\hat{\beta} = 7.890$, $p = 0.018$). These results remain significant when adjusting for further potential risk factors, with exception of the TMT B in men ($p = 0.053$ after multiple adjustments).

# DISCUSSION

The present study reveals interesting sex differences in the association of cardiovascular risk factors and white matter pathology: Women show a lower prevalence of cardiovascular risk factors but a slightly higher burden of white matter damage than men. The impact of hypertension and smoking on white matter was also stronger in women. This leads to the assumption of a higher susceptibility for microvascular damage in women. Regarding potential consequences of white matter damage, we observed no association of WMH with any of the cognitive tests. There was, however, an association of FA with motor functions in

both sexes and with executive functions in men only, indicating a higher cognitive reserve in women.

## Sex-Differences in White Matter Pathology

Relative WMH volumes were lower in men (geometric mean: 0.124% of WM volume) than in women (geometric mean: 0.138% of WM volume). Though just not statistically significant on the individual level we observed a pattern of more severe white matter damage in women compared to men comprising slightly higher WMH volumes and lower FA values. These findings are largely in line with previous studies in older cohorts reporting a higher WMH-load in women (Leeuw et al., 2002; van den Heuvel et al., 2004; Wen and Sachdev, 2004; Sachdev et al., 2009; Fatemi et al., 2018; *Alqarni et al., 2021*).

## Sex-Differences in the Association of Risk Factors With White Matter Pathology

Interestingly, we found no significant main effect of sex on WMH or FA, respectively. Significant main effects emerged for age on all white matter lesion phenotypes, current smoking on FA, and treated but uncontrolled hypertension as well as treated and controlled hypertension for WMH and FA. The interaction as well as the stratified analyses showed that current smoking was associated with higher WMH volumes only in women, whereas there was a non-significant trend toward an opposite effect for men. We also observed a more negative impact of hypertension on MRI markers in women. These findings are in line with current evidence that shows hypertension and smoking to be predictors of white matter damage (Dickie et al., 2016). However, the few studies examining sex-difference in the associations of cardiovascular risk factors with white matter pathology show conflicting results regarding sex-preferences as well as potential risk factors. Hypertension has mainly been shown to have a greater impact on WMH in men (Sachdev et al., 2009; Assareh et al., 2014; Filomena et al., 2015; Alqarni et al., 2021). Smoking has been associated with higher WMH in women (Sachdev et al., 2009). Other studies did not find any association with hypertension or smoking in neither men nor women, but, for example sex-specific effects of body mass index on deep white matter lesions (Alqarni et al., 2021). Reasons for these inconsistencies might be differing age-ranges, small sample sizes, varying definitions of risk factors and white matter damage, as well as high a co-linearity of risk factors.

From our results, we conclude, that hypertension and smoking seem to be main risk factors of early brain aging particularly in women. Looking at the effect sizes, treated and/or uncontrolled hypertension as well as current smoking in women have a comparable impact on WMH and FA as up to 10 years of age. This high susceptibility for microvascular brain damage in midlife women may be associated with perimenopausal hormonal changes (Leeuw et al., 2001). Reductions in estrogen levels, which play an important role in brain maintenance via promoting cerebral blood flow, protecting against oxidative stress, and stimulating synaptogenesis, may render the brain especially vulnerable to ischemic damage (Leeuw et al., 2001; Toffoletto et al., 2014; Zárate et al., 2017; Russell et al., 2019). In line with these pathophysiological hypotheses, it is well established that female-specific risk factors such as menopause contribute to cognitive impairment and dementia in women (Gannon et al., 2019). Interactions of varying levels of sex hormones with vascular risk factors in brain aging, however, have not been studied in population cohorts so far.

## Sex-Differences in the Association of White Matter Damage With Cognitive Functions

We found no significant association of any of the cognitive test results with WMH. Higher FA values, however, were associated with better motor functions (Pegboard Test) in both men and women as well as with better working memory, and psychomotor speed, respectively (TMT A and B) in men only.

Some of the above discussed studies, that showed associations of arterial hypertension with white matter damage, also reported declines in executive functions associated with the extent of white matter pathology (Sachdev et al., 2009; Debette et al., 2011; Veldsman et al., 2020). However, only one of these studies evaluated sex-differences in this association. In line with our findings, Sachdev et al. found WMH to be associated with reduced processing speed in men only (Sachdev et al., 2009). One potential explanation why men are cognitively more affected by the same extent of white matter damage, might be sex-differences in cognitive reserve or brain reserve, respectively (O'Dwyer et al., 2012; Stern et al., 2020; Subramaniapillai et al., 2021). Especially in premenopausal women, protective effects of estrogen are supposed to play a role in the maintenance of prefrontal cortex function and consecutively in the preservation of executive functions (Keenan et al., 2001; Shanmugan and Epperson, 2014).

The association of Pegboard Test with white matter damage in both sexes is an interesting finding and supports a recent report of fine motor skills to show a strong association with age-related decline and markers of brain aging (Yao et al., 2021). Further studies are warranted to evaluate whether fine motor skills or motor speed can serve as a particularly sensitive test of cognitive and brain aging.

## Strengths and Limitations

Our study is looking at sex-differences in white matter damage from various angles. Based on the hypothesis that white matter pathology does not simply act as a mediator in the association between vascular risk factors and cognitive decline, we differentiated between sex-differences in the impact of risk factors on white matter pathology on the one side and the impact of white matter pathology on cognition on the other side. Also of note is the age spectrum of 35–65 years, as most cohort studies on aging are settled in later life. It must be noted that we did not adjust for multiple testing. Our results are of explorative nature and thus need to be validated in an independent sample before drawing any conclusions (Bender and Lange, 2001). We might also have missed some effects due to lack of power. For example, the sex-differences in the prevalence of white matter pathology were not

significant on their own, but the pattern clearly showed more pathology in women compared to men.

### Summary

The present study extends available evidence on sex-differences in the causes, patterns, and consequences of white matter damage. While we found men to have a slightly worse cardiovascular risk profile, women had a larger volume of WMH. Women's white matter also showed a higher susceptibility to some risk factors, particularly smoking and arterial hypertension. Nevertheless, associations between microstructural white matter integrity and psychomotor speed were only observed in men, suggesting a higher cognitive reserve in women. Future studies with follow-up, multimodal MRI as well as genetic and hormonal data are warranted to evaluate vulnerable age periods and pathophysiological mechanisms that underlie the observed sex-differences and that can support the proposed mechanisms of brain as well as cognitive reserve. Based on these investigations, studies are needed, that evaluate whether a sex-specific modification of the observed risk factors can slow down white matter damage and cognitive aging.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the University of Münster and Westphalian Chamber of Physicians in Münster, North Rhine-Westphalia, Germany. The participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

NB, NW, and HM drafted the manuscript. NB conducted and programmed all statistical analysis. NW applied the MRI data workflow. MD-N applied the MRI data workflow and revised the manuscript for intellectual content. HM came up with the research idea and supervised all analyses. KB (principal investigator of the BiDirect Study) helped substantially in writing and editing of the manuscript. All authors contributed to the article and approved the submitted version.

## FUNDING

This work was supported by the German Federal Ministry of Education and Research (BMBF grants 01ER1205, 01ER0816, and 01ER1506). The funding source was not involved in the writing of the manuscript or in the decision to submit it for publication.

## ACKNOWLEDGMENTS

We thank everybody involved in the BiDirect study, particularly the study nurses and data managers. Most importantly, we thank the BiDirect participants who made this research possible.

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