RESEARCH ARTICLE

Associations of Sex, Age, and Cardiometabolic Risk Profiles With Brain Structure and Cognition

A UK Biobank Latent Class Analysis

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Abstract

Background and Objectives

It is unknown whether there are sex-related profiles of cardiometabolic health that contribute differently to age-related changes in brain health during midlife. We studied how latent classes of middle-aged individuals clustering by age, sex, menopause, and cardiometabolic health were associated with brain structure and cognitive performance.

Methods

Health, brain, and abdominal MRI data from the UK Biobank cohort (men and women aged >40 years in the United Kingdom) were used. We applied latent class analysis to identify groups of individuals based on age, sex, menopausal status, and cardiometabolic health. We examined associations of class membership with brain volumes (total brain volume [TBV], gray matter volume [GMV], white matter volume [WMV], hippocampal volume, and white matter hyperintensity volume) and cognitive performance.

Results

Data were available for 36,420 individuals (mean age 64.9 years, 48.5% women). Eight latent classes differing in age, sex, and cardiometabolic risk were identified. Class 1 (reference class) included individuals with the lowest probability of older age and cardiometabolic risk, and the healthiest levels of brain volumes and cognition. In those aged >60 years, but not in those aged 50–60 years, the negative associations of age with TBV, GMV, and WMV were greater in the class comprising healthier older women than classes comprising older men of varying cardiometabolic and vascular health. There were no age-class interactions for cognitive test performance.

Discussion

Latent class analysis detected groups of middle-aged individuals clustering by cardiometabolic health. The relationship of age with brain volumes varies by sex, menopausal status, and cardiometabolic health profile.

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Glossary

AD = Alzheimer disease; **AIC** = Akaike information criteria; **BIC** = Bayesian information criteria; **DBP** = diastolic blood pressure; **GMV** = gray matter volume; **HV** = hippocampal volume; ***ICD-10*** = *International Classification of Diseases, 10th revision*; **IDP** = imaging-derived phenotype; **IHD** = ischemic heart disease; **LCA** = latent class analysis; **SBP** = systolic blood pressure; **TBV** = total brain volume; **TDI** = Townsend deprivation index; **WHR** = waist-hip ratio; **WMHV** = white matter hyperintensity volume; **WMV** = white matter volume.

Female sex is associated with an increased incidence of dementia.[1] The increased vulnerability for the development of dementia in women may be due to sex-specific factors such as menopause[2] and sex differences in the effects of age and cardiometabolic disease on brain health.[3] In support of this theory, we have previously demonstrated a stronger relationship of age with lower brain volumes in middle-aged women compared with men and in postmenopausal women compared with premenopausal women.[4]

In addition to increasing dementia risk, aging also increases the risk of developing cardiometabolic disorders.[5] In turn, cardiometabolic disorders increase dementia risk and can work synergistically with aging to further amplify dementia risk.[6] These pathways are likely influenced by sex differences in the timing and pathogenesis of cardiometabolic disease. Although men tend to develop cardiovascular disease earlier in life, their prevalence dramatically increases for women following the menopause transition.[7] Emerging evidence also points to differences in disease pathogenesis, with women more likely to develop microvascular disease than men who tend to develop occlusive macrovascular disease.[8] Studies of sex differences in dementia risk must therefore account for the complex interplay between age, sex, and various patterns of cardiometabolic disorders.

Previous work has generally considered cardiometabolic disorders (e.g., heart disease) as discrete factors independently influencing dementia risk.[9] However, those at risk of dementia often have multiple such disorders, and the pattern or combination of these may be important in determining risk. It is also possible that individuals cluster by cardiometabolic health in an age- and sex-dependent fashion. Understanding how cardiometabolic disorders, sex, and age group together can lead to important insights into potential avenues for risk mitigation. Given the multiplicity of factors at play, it is difficult to use single hypothesis-driven methods to understand the nature of the relationships between exposures, and data-driven techniques may be more useful. Latent class analysis (LCA) is one such method that uses all available data to identify mutually exclusive clusters of individuals, for example, based on clinical patterns of cardiometabolic health, sex, and age,[10] allowing the study of the relationships between these classes with sensitive markers of brain health. The aims of this study were to identify latent classes of middle-aged adults clustering by age, sex, menopause status, and measures of cardiometabolic health and to study the differences in structural brain imaging biomarkers and cognitive test scores between classes.

Methods

Participants

Data used for this analysis were obtained from the UK Biobank. Between 2006 and 2010, a cohort of over 500,000 individuals aged 40–69 years and registered with the National Health Service were recruited.[11] Initial and subsequent assessments collected extensive health and lifestyle information, physical and cognitive measures, and biological samples. From 2014, the UK Biobank began inviting 100,000 of the original participants for brain, heart, and abdominal MRI. Of these individuals, we included participants with complete exposure data: age, sex, menopause status, and measures of cardiometabolic health.

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was obtained from all participants. The UK Biobank approved the study application (Project ID 24954), and we obtained ethics approval from the UK Biobank Research Ethics Committee (reference 11/NW/0382).

Clinical and Demographic Data

These data were collected when participants attended the assessment center for an MRI scan and were downloaded from the UK Biobank Application Management System in April 2018. Age was calculated as age at attendance to the assessment center. Sex was determined by participant response to 2 options from a questionnaire (female or male). An accurate measure of gender as a social construct was not available in the UK Biobank. Therefore, we used the terms female and women to refer to individuals who identified as such and the terms male and men in reference to people who have self-reported as male. Level of education including the attainment of a tertiary degree was determined at first assessment. The Townsend deprivation index (TDI) is a measure of socioeconomic deprivation[12] based on national census data assigned to each participant. Menopause status was defined as the self-reported response to the question, "Have you had your menopause (periods stopped)?" By virtue of the age range of the sample, women who answered "no" to the question were interpreted as comprising both premenopausal and perimenopausal women, and those who answered "yes" were classified as postmenopausal.[13] Participants aged >60 years and/or reporting a history of a bilateral oophorectomy were deemed postmenopausal regardless of survey response, whereas those reporting previous hysterectomy but not oophorectomy were not reclassified. Women with missing menopause data at the imaging visit but who had characterized themselves as postmenopausal at prior visit(s)

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were classified as postmenopausal. The presence of diabetes mellitus, hypertension, and hyperlipidemia was inferred using self-reported or *International Classification of Diseases, 10th revision* (*ICD-10*) codes (eTable 1, links.lww.com/WNL/C250) and/or self-reported or coded use of medication indicated for the condition. Coded medications were classified by a doctor (E.M.L.) as treatments for diabetes, hypertension, or hyperlipidemia. The presence of stroke or ischemic heart disease (IHD) was determined by self-report and/or *ICD-10* codes. Participants who answered "prefer not to answer" or "not sure" to touchscreen questions on cardiometabolic health were coded as having missing data (<5%).

To optimize modeling performance, our data set for LCA excluded individuals without any available touchscreen cardiometabolic data or *ICD-10* codes and pre/perimenopausal women who had characterized themselves as postmenopausal at a prior visit (n = 37). Participants without cardiometabolic questionnaire data but with *ICD-10* codes for other conditions were classified as not having the pertinent cardiometabolic conditions.

Registered nurses at the assessment center took automated readings of systolic (SBP) and diastolic blood pressure (DBP) measurements using an Omron 705 IT electronic blood pressure monitor. We constructed waist-hip ratios (WHRs) by dividing waist circumference by hip circumference. DNA was extracted from blood samples collected from participants, and genotyping was conducted using 2 similar genotyping arrays (Affymetrix) with quality control by the UK Biobank.[14] Participants carrying at least 1 *APOE*ε4 allele were deemed *APOE*ε4 positive.

Cognitive Test Scores

We used cognitive tests administered by touchscreen at the time of the imaging assessment. These included measures of psychomotor speed, working memory/attention, verbal-numeric reasoning, prospective memory, and visual memory.

Psychomotor Speed

Measured using a timed test of symbol matching, the test was labeled reaction time in the protocol, and the score was the mean response time in milliseconds across trials. Longer times indicate poorer psychomotor speed.

Working Memory/Attention

Participants were shown a 2-digit number to recall after a brief pause. The string of digits presented increased by 1 until the participant made an error or they reached the maximum of 12 digits. The score was the maximum number of digits correctly recalled and labeled numeric memory. Higher scores indicate better performance.

Verbal-Numeric Reasoning

Verbal and numerical problems were presented, and participants were requested to select the correct response from multiple options, labeled fluid intelligence test in the UK Biobank protocol. The score is a total of correct responses, with a maximum possible score of 13. Higher scores indicate better reasoning ability.

Prospective Memory

Participants were advised: "At the end of the games we will show you four coloured symbols and ask you to touch the blue square. However, to test your memory, we want you to actually touch the Orange Circle instead". Later in the assessment, they were presented with the task. Participants were scored dichotomously, depending on whether they correctly completed the task on the first attempt. A positive result indicates better performance.

Visual Memory

Labeled pairs-matching, a random array of symbol cards were presented. Participants were asked to memorize the positions of matching pairs. The cards were then turned over, and participants had to select the matched pairs from memory. From 3- and 6-pair versions of the test, we chose the 6-pair version because there was more scope for score variation. The score was the number of errors made trying to select the pairs. Higher scores reflect poorer visual memory.

Global Cognitive Score

A general cognitive ability score was derived by entering available cognitive test scores into a principal component analysis: reaction time (log transformed) working memory/attention, verbal-numeric memory, prospective memory, and visual memory (log(x + 1) transformed). Scores on the first unrotated principal component were saved and used as a global cognitive score, where higher scores represent superior cognitive function.

Brain MRI Acquisition and Processing

The UK Biobank MRI acquisition protocol and pipeline for generation of imaging-derived phenotypes (IDPs) have been described previously.[15] Brain MRI scans were acquired on a 3T Siemens Skyra using a 32-channel head coil. We used the following IDPs, derived from T1-weighted and T2-weighted fluid-attenuated inversion recovery scans: total brain volume (TBV), gray matter volume (GMV), white matter volume (WMV), total hippocampal volume (HV), and white matter hyperintensity volume (WMHV). TBV is a composite of GMV and WMV. As women have smaller head sizes than men,[16] we used brain volumes normalized for head size. Normalization of brain tissue volumes for head size was performed using a SIENAX-style analysis.[17]

Statistical Analyses

We used simple summary statistics to describe the sample. In initial exploratory analyses, we examined the associations between individual cardiometabolic factors, sex, and outcomes.

LCA was commenced with an estimation of a 2-class model using 16 binary indicators: age >50 years, female sex, no tertiary degree, TDI greater than median, postmenopausal, *APOE*ε4 carrier, current/past smoker, SBP ≥140 mm Hg, DBP ≥90 mm Hg, high WHR, hypertension, hyperlipidemia, diabetes, IHD, and stroke.[18] *APOE*ε4 carrier status was also included due to its interaction with sex and dementia risk.[19] We chose a cut point of 50 years to reflect the mean age of

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menopause.[20] The number of classes was increased, with the estimation algorithm cycling through up to 10,000 iterations, until convergence failed.[21]

We computed Bayesian (BIC) and Akaike information criteria (AIC) for all models. Although the model with the lowest information criteria values generally implies superior fit, it is not uncommon for such values to perpetually decrease with each additional class. These values were therefore plotted to identify the elbow point of diminishing returns,[18] indicating best fit. To strike a balance between achieving goodness of fit without overfitting, and ensuring that the LCA model represents a conceptually useful set of groupings, class enumeration was iterative and exploratory. By examining class sizes and conditional item-response probabilities of each competing model, we avoided expanded versions of models with fewer classes and selected the most parsimonious model. After model selection, latent class membership was fixed for individuals using the item-response probabilities generated.

To examine for the presence of between-class differences in outcome measures, we performed analysis of variance across classes and compared means using the Tukey method. As incorporating a simple dichotomous measure of age in the LCA was unlikely to fully account for the strong correlation of age with brain health outcomes, we also used a continuous measure of age in regression modeling of the associations between class membership and outcomes of interest, with class 1 as the reference. We examined the presence of interaction between age and class membership for all outcomes. In the presence of such interaction, we stratified the sample by age (50–60 and >60 years) to reduce the risk of overextrapolation, given that members of class 1 were younger than all other classes (maximum age 59.8 years; eFigure 1, links.lww.com/WNL/C250). In these subgroup analyses, class 1 was the reference for analysis of people aged 50–60 years, whereas class 2 was the reference for analysis of people aged >60 years. Furthermore, in regression models for cognitive scores, we included TBV, HV, and WMHV as covariables to explore mediation.

p Values were corrected using the false discovery rate method to offset spurious findings through multiple comparisons. We used R version 4.0.1 to perform all analyses and the poLCA package to perform the LCA.

Data Availability

Requests for access to the data used for this study will be considered by the corresponding author.

Table 1 Sample Characteristics

	Total sample (N = 36,420)	Men (n = 18,753)	Women (n = 17,667)	*p* Value
Age, y	64.9 ± 7.7	65.6 ± 7.8	64.2 ± 7.5	<0.001
Postmenopausal	16,574 (45.5)	NA	16,574 (93.8)	NA
Tertiary degree	17,195 (47.2)	8,899 (47.5)	8,296 (47.0)	0.030
Townsend deprivation index[a]	−1.9 ± 2.7	−1.9 ± 2.7	−1.8 ± 2.7	<0.001
White ethnicity	35,222 (96.7)	18,102 (96.9)	17,120 (97.2)	0.150
Hypertension[b]	15,511 (42.6)	9,336 (49.8)	6,175 (35.0)	<0.001
Diabetes[b]	2,278 (6.3)	1,549 (8.3)	729 (4.1)	<0.001
Hyperlipidemia[c]	10,170 (27.9)	7,020 (37.4)	3,150 (17.8)	<0.001
Ischemic heart disease[d]	2,394 (6.6)	1,848 (9.9)	546 (3.1)	<0.001
Stroke[d]	1,667 (4.6)	1,038 (5.5)	629 (3.6)	<0.001
Current or previous smoker	14,101 (38.7)	8,007 (43.1)	6,094 (34.8)	<0.001
Systolic blood pressure, mm Hg	141.0 ± 19.8	144 ± 18.5.	138 ± 20.6	<0.001
Diastolic blood pressure, mm Hg	78.9 ± 10.7	80.5 ± 10.4	77.1 ± 10.6	<0.001
High waist-hip ratio (for sex)[e]	18,434 (52.1)	12,968 (71.0)	5,466 (31.9)	<0.001
***APOE* ε4 carrier**	9,830 (27.0)	4,961 (26.5)	4,869 (27.6)	0.006

Abbreviations: *ICD-10* = *International Classification of Diseases, 10th revision*; NA = not available.
Data are presented as mean ± SD or n (%).
[a] A higher Townsend deprivation index or score implies a greater degree of socioeconomic deprivation.
[b] Self-reported diagnosis or self-reported medication use or coded medication use or *ICD-10* code of condition.
[c] Self-reported medication use or coded medication use or *ICD-10* code of condition.
[d] Self-reported diagnosis or *ICD-10* code of condition.
[e] High waist-hip ratio: women >0.85; men >0.90.

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Results

Sample Characteristics

Complete data were available for 36,420 participants. Table 1 describes the sample characteristics. The mean age was 65.6 years for men and 64.2 years for women. Compared with women, men were more likely to have a greater WHR and a higher prevalence of diabetes, hypertension, hyperlipidemia, current/previous smoking, IHD, and stroke (all $p < 0.05$). Men with diabetes, hypertension, and hyperlipidemia were more likely to be on relevant medications than women (eTable 2, links.lww.com/WNL/C250).

Characteristics of participants who had complete cognitive and brain imaging data are presented in eTable 3 (links.lww.com/WNL/C250). In general, those without cognitive performance data were slightly younger, and those without complete brain imaging data were older and more likely to be male, with a higher prevalence of cardiometabolic comorbidities.

We present associations of individual cardiometabolic factors with cognitive scores and brain volumes stratified by sex in eTables 4–14 (links.lww.com/WNL/C250). As expected, several of these factors were associated with brain volumes and cognitive scores in both men and women, and we observed a few interactions between sex and cardiometabolic factors in predicting brain outcomes.

Latent Class Analysis

Model comparison and fit for the LCA are presented in eTable 15 and eFigure 2 (links.lww.com/WNL/C250). As the maximum log likelihood was reached with a 13-class model, we examined models with 2–12 classes. Statistically, the optimum number of classes appeared to be between 7 and 10. These candidate models were then examined for individual class size, plausibility, and utility. Although the BIC supported a 9-class model, half of the classes supported fewer than 5% of the sample, suggesting overfitting. The 7-class model performed poorly in distinguishing younger and older groups and appeared to

Table 2 Latent Classes and Posterior Probabilities of Age, Sex, Menopause, and Cardiometabolic Risk Factors in an 8-Class Model (n = 36,420)

	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6	Class 7	Class 8
Sample size per class, n	1,293	10,973	3,270	2,112	10,201	2,953	866	4,752
%	3.55	30.13	8.98	0.58	28.01	8.11	2.38	13.05
Age over 50 y	67.09[c]	99.77[c]	99.82[c]	99.91[c]	99.16[c]	97.67[c]	98.74[c]	99.76[c]
Female sex	63.54[c]	81.85[c]	73.19[c]	100.00[c]	25.78	14.92	31.91	3.94
Postmenopausal[a]	12.47	99.88[c]	97.66[c]	99.35[c]	99.64[c]	95.01[c]	95.75[c]	99.63[c]
No tertiary degree	41.04	43.47	49.81	64.01[c]	47.44	53.62	59.60	51.73
Townsend deprivation index greater than median	56.50	50.44	43.96	54.68	51.19	48.68	62.32[c]	49.36
***APOE* ε4 carrier**	26.44	28.91	26.85	31.84	26.40	26.59	18.65	29.56
Current or previous smoker	31.37	32.41	28.55	40.76	42.10	44.84	47.63	52.62
Systolic blood pressure ≥140 mm Hg	10.11	20.31	95.75[c]	58.03	38.45	100.00[c]	51.18	58.98
Diastolic blood pressure ≥90 mm Hg	4.80	1.12	42.72	8.70	4.61	59.89	4.99	10.86
Greater than recommended WHR (for sex)	22.80	11.96	26.54	40.26	82.44[c]	86.44[c]	87.60[c]	80.20[c]
Hypertension	14.73	17.67	36.44	100.00[c]	28.62	51.13	60.30[c]	99.80[c]
Hyperlipidemia	1.19	6.65	9.99	64.49[c]	17.39	31.31	85.01[c]	89.86[c]
Diabetes	0.84	0.81	0.71	12.90	0.73	5.40	100.00[c]	16.30
IHD	0.14	0.06	0.17	22.09[b]	0.06	0.00	0.00	41.77[b]
Stroke	1.37	2.11	1.90	10.99[b]	3.08	5.34	5.63	12.57

Abbreviations: IHD = ischemic heart disease; WHR = waist-hip ratio.
Class 1 members are more likely to be younger, premenopausal if female, and least likely to have hypertension, hyperlipidemia, and stroke. Class 2 members are more likely older, female, postmenopausal, and less likely to have cardiometabolic risk factors. Class 3 members are more likely older, female, postmenopausal, and more likely to have elevated systolic blood pressures. Class 4 members are more likely older, female, postmenopausal, and more likely to have hypertension, hyperlipidemia, and end-organ vascular disease (IHD, stroke). Class 5 members are more likely older, male, with a high WHR, but few other cardiometabolic risk factors. Class 6 members are more likely older, male, with a high WHR, elevated systolic and diastolic blood pressures. Class 7 members are more likely older, male, with a high WHR, diabetes, hyperlipidemia, and hypertension. Class 8 members are more likely older, male, with a high WHR, hyperlipidemia, hypertension, and end-organ vascular disease (IHD and stroke).
[a] In female participants only.
[b] High posterior probabilities relative to low prevalence in the total sample.
[c] Posterior probabilities higher than 0.60 in each class.

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Table 3 Brain Volumes and Cognitive Test Scores by Latent Class Membership

	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6	Class 7	Class 8
Cognitive tests								
Psychomotor speed (milliseconds)	545 ± 96.4	594 ± 106	599 ± 110	636 ± 121	595 ± 110	588 ± 110	620 ± 113	610 ± 116
Working memory/attention (maximum number of digits remembered correctly)	7.0 ± 1.3	6.8 ± 1.3	6.6 ± 1.3	6.3 ± 1.3	6.8 ± 1.3	6.7 ± 1.3	6.6 ± 1.3	6.7 ± 1.3
Verbal-numeric reasoning (fluid intelligence score)	6.8 ± 2.1	6.7 ± 2.0	6.6 ± 2.1	6.1 ± 1.9	6.6 ± 2.1	6.5 ± 2.1	6.2 ± 2.1	6.4 ± 2.1
Prospective memory (% participants correct on the first attempt)	1,123 (86.9)	8,859 (80.7)	2,622 (80.2)	1,446 (68.5)	7,861 (77.1)	2,316 (78.4)	603 (69.6)	3,474 (73.1)
Visual memory (number of incorrect matches)	2.9 ± 2.4	3.5 ± 2.8	3.7 ± 3.0	3.9 ± 3.0	3.7 ± 3.0	3.7 ± 3.0	3.8 ± 3.2	4.1 ± 3.3
Global cognitive score	0.43 ± 1.2	0.08 ± 1.3	−0.09 ± 1.3	−0.61 ± 1.4	−0.01 ± 1.3	−0.05 ± 1.3	−0.04 ± 1.4	−0.26 ± 1.4
Brain volumes, mL								
Total brain	1,568 ± 61.1	1,508 ± 71.0	1,495 ± 70.5	1,478 ± 70.1	1,486 ± 70.1	1,481 ± 70.6	1,467 ± 71.2	1,457 ± 67.35
Gray matter	846 ± 37.2	806 ± 44.2	794 ± 44.4	786 ± 44.7	783 ± 44.8	775 ± 44.2	767 ± 46.1	758 ± 43.5
White matter	722 ± 38.3	702 ± 40.8	702 ± 41.10	693 ± 41.7	703 ± 40.9	706 ± 41.6	699 ± 42.8	699 ± 40.7
Total hippocampal	10.4 ± 1.0	10.2 ± 1.1	10.0 ± 1.1	10.0 ± 1.1	9.7 ± 1.2	9.7 ± 1.2	9.8 ± 1.1	9.3 ± 1.2
White matter hyperintensity	1.6 ± 2.0	3.8 ± 5.0	5.4 ± 6.4	7.8 ± 9.8	5.1 ± 6.5	6.1 ± 7.0	6.3 ± 6.5	7.7 ± 9.0

Abbreviations: IHD = ischemic heart disease; WHR = waist-hip ratio.
Data are presented as mean ± SD or n (%).
Class 1 members are more likely to be younger, premenopausal if female, and least likely to have hypertension, hyperlipidemia, and stroke. Class 2 members are more likely older, female, postmenopausal, and less likely to have cardiometabolic risk factors. Class 3 members are more likely older, female, postmenopausal, and more likely to have elevated systolic blood pressures. Class 4 members are more likely older, female, postmenopausal, and more likely to have hypertension, hyperlipidemia, and end-organ vascular disease (IHD, stroke). Class 5 members are more likely older, male, with a high WHR, but few other cardiometabolic risk factors. Class 6 members are more likely older, male, with a high WHR, elevated systolic and diastolic blood pressures. Class 7 members are more likely older, male, with a high WHR, diabetes, hyperlipidemia, and hypertension. Class 8 members are more likely older, male, with a high WHR, hyperlipidemia, hypertension, and end-organ vascular disease (IHD and stroke).

underfit the data. The 8-class model was slightly more complex in structure, representing a good balance between conceptual and statistical concerns. We therefore chose to implement the 8-class model.

Class sizes and conditional item-response probabilities in the 8-class LCA model are presented in Table 2. Broadly, the classes separated based on age, sex, menopause, and cardiometabolic health. Class 1 members had the lowest probability of being >50 years of age, were more likely to be pre/perimenopausal if female, and were least likely to have hypertension, hyperlipidemia, and stroke. Members of classes 2–4 were more likely older, female, and postmenopausal, with varying degrees of cardiometabolic risk. Specifically, class 2 members were less likely to have cardiometabolic risk factors than those in classes 3 and 4, who in turn were more likely to have elevated SBP and a diagnosis of hypertension, respectively. Among these female-preponderant classes, class 4 members were most likely to have end-organ vascular disease (IHD and stroke). Members of classes 5–8 were more likely to be older men and have a high WHR, and among these male-preponderant classes, members of classes 6–8 were highly likely to have a high SBP and a diagnosis of hypertension. Members of classes 7 and 8 were highly likely to have hyperlipidemia, and everyone in class 7 had diabetes. Class 8 members were the most likely to have end-organ vascular disease.

Cognitive Test Performance Outcomes by Latent Class

Cognitive test performances for each class are presented in Table 3 and illustrated in Figure 1. Unadjusted for age, class 1 exhibited the best performances in psychomotor speed, working memory/attention, reasoning, prospective memory, visual memory, and global cognition ($p < 0.05$). Those in classes 4, 7, and 8 generally had the poorest performances. eTable 16 (links.lww.com/WNL/C250) presents linear regression models examining associations between age, class memberships, and cognitive test performance. Although we did not observe any age-class interactions on cognitive performance, membership in certain classes was associated with cognitive domain scores except for visual memory, independent of age ($p < 0.05$). However, because no individual assigned to the reference group (class 1) was aged over 60 years, these age-adjusted coefficients reflect extrapolation and do not reflect comparisons between individuals in different classes.

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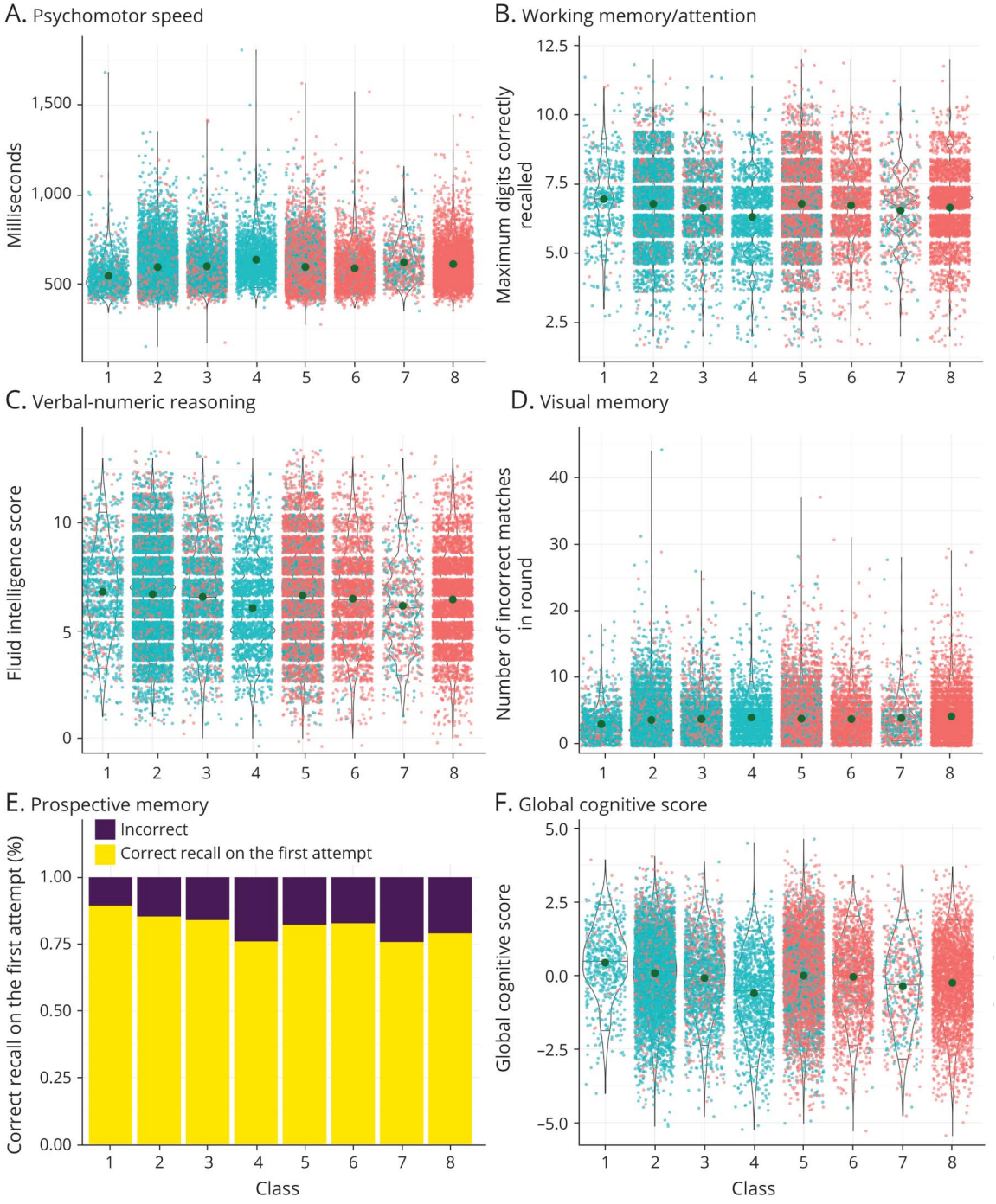
Figure 1 Cognitive Test Performance by Latent Class Membership



(A) Psychomotor speed. (B) Working memory/attention. (C) Verbal-numeric reasoning. (D) Visual memory. (E) Prospective memory. (F) Global cognitive score.

Results from the addition of structural brain measure to the models of associations between class membership and cognitive performance are presented in eTable 17 (links.lww.com/WNL/C250). Brain volume measures attenuated the associations between class membership and cognitive performance by greater than 20% in only 4 models: HV attenuated the associations between class 4 membership and psychomotor speed (39%) and attention/working memory (28%). TBV and WMHV attenuated the associations between class 4 membership and psychomotor speed (41% and 48%, respectively).

Structural Brain Imaging Outcomes and Latent Classes

Mean brain volumes for each class are presented in Table 3 and illustrated in Figure 2. Class 1 individuals had the largest TBV, GMV, WMV, and HV and the smallest WMHV, whereas members of class 8 had the smallest TBV, GMV, and HV

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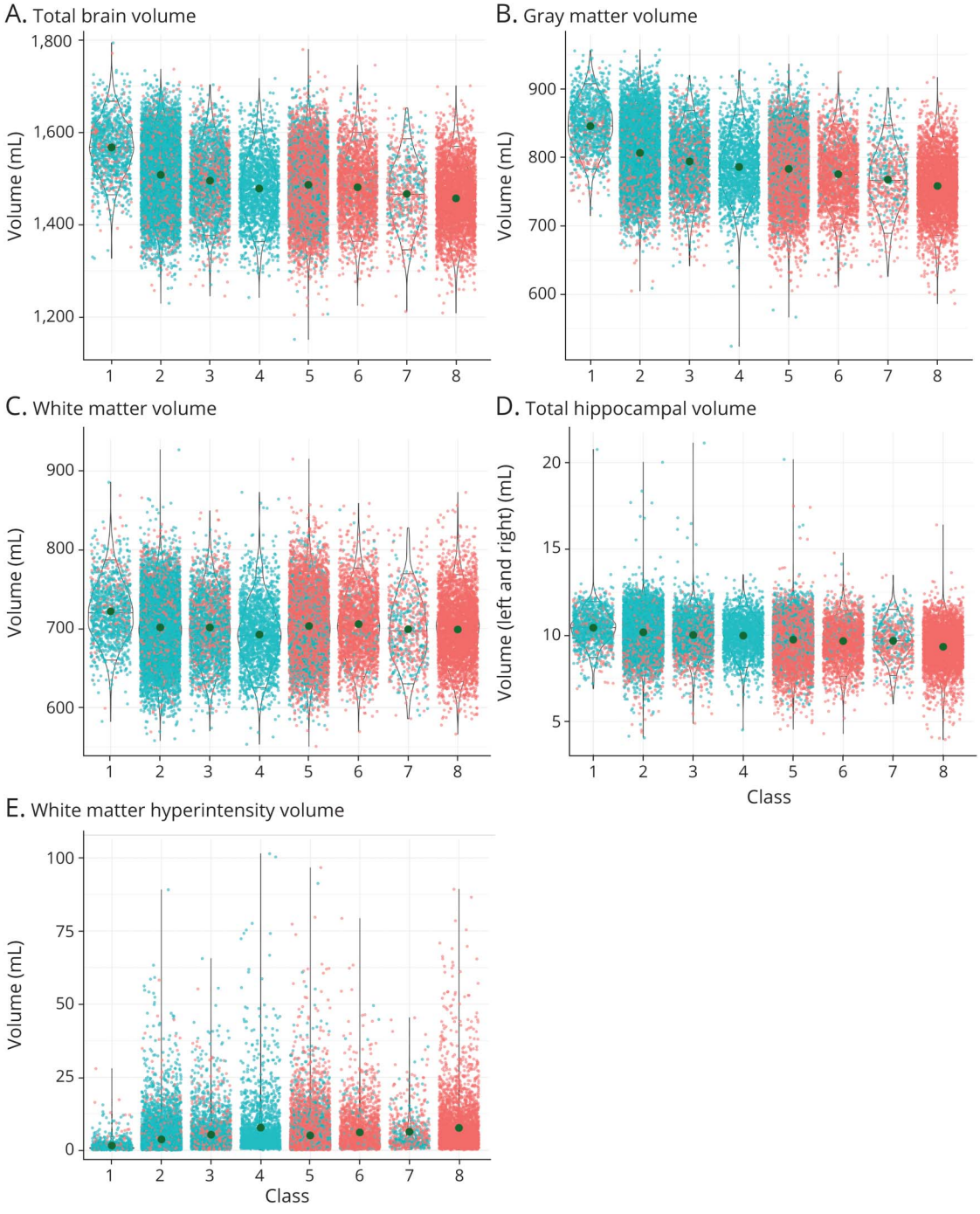
Figure 2 Mean Brain Volumes (mL) by Latent Class Membership



(A) Total brain volume. (B) Gray matter volume. (C) White matter volume. (D) Total hippocampal volume. (E) White matter hyperintensity volume.

compared with members of other classes ($p < 0.05$). Members of classes 4 and 8 tended to have the highest WMHV.

In linear regression analysis of the whole sample, we found statistically significant interactions between age and classes 2–8 for TBV, GMV, HV, and WMHV (all adjusted $p < 0.05$) such that each additional year of age was associated with lower TBV, GMV, and HV and higher WMHV in classes 2–8 relative to class 1 (eTable 18, links.lww.com/WNL/C250). Predicted volumes and graphed interactions are presented in eFigure 3. The main driver for these interactions appeared to be the weak association between age and brain volumes in class 1 (younger participants with a low likelihood of cardiometabolic risk) relative to other classes. No interaction was detected for WMV for which the associations of age (negative, $p < 0.05$) and class membership (positive, $p < 0.05$) were independent. In analysis restricted to participants aged 50–60 years, far fewer age-class interactions were detected, with each

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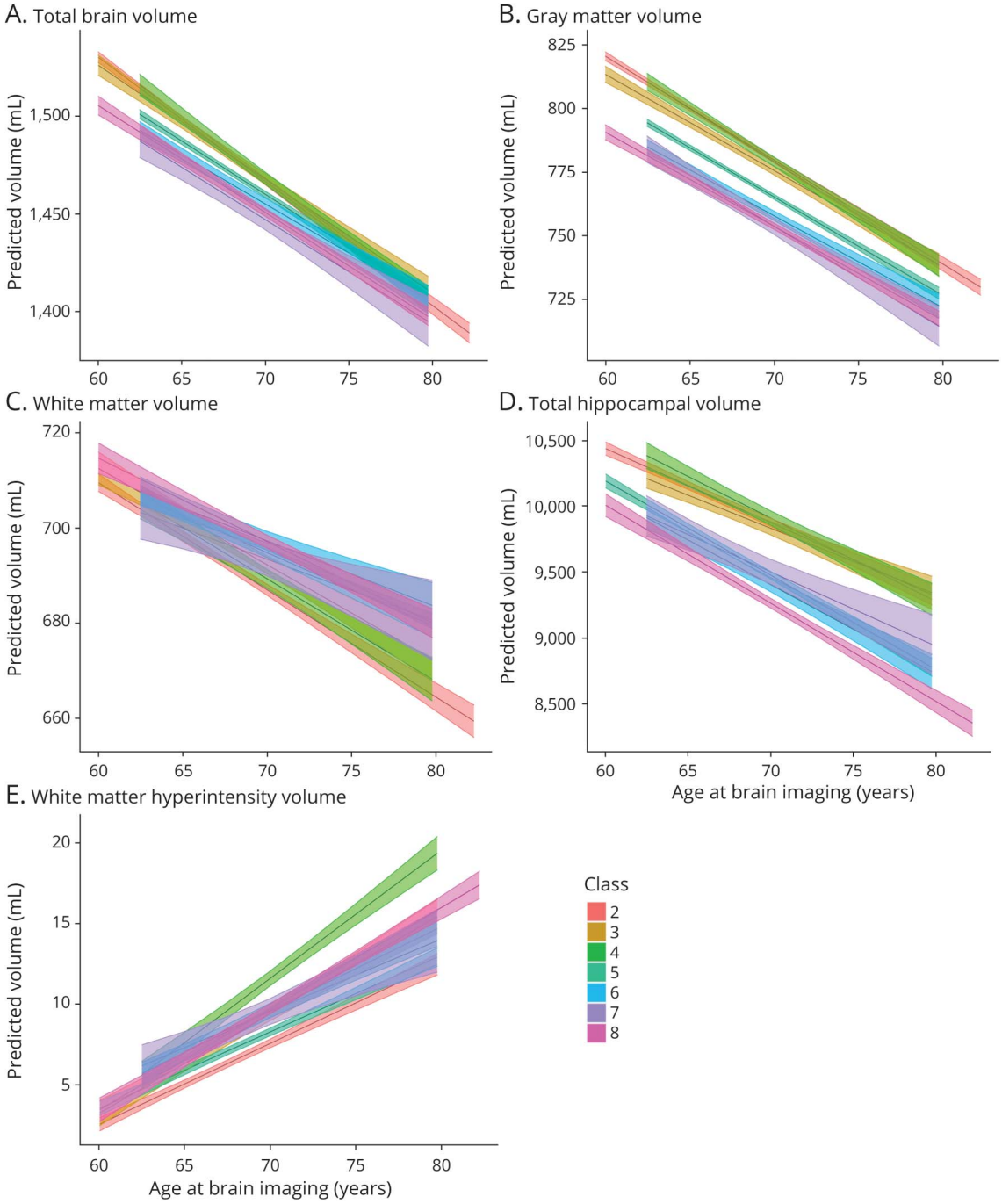
Figure 3 Age-Class Interactions for Brain Volumes (mL) in >60-Year-Old Subsample



(A) Total brain volume. (B) Gray matter volume. (C) White matter volume. (D) Total hippocampal volume. (E) White matter hyperintensity volume.

additional year of age associated with a larger decrease of WMV in classes 2 and 5, and HV in class 6, relative to class 1 (eTable 19, links.lww.com/WNL/C250).

In analyses restricted to people aged >60 years, there were age-class interactions for TBV, GMV, WMV, HV, and WMHV (all adjusted $p < 0.05$). Predicted volumes and graphed interactions are presented in Figure 3. Generally, a stronger negative relationship was observed in class 2 (comprising mainly post-menopausal women with low likelihood of excess adiposity and cardiovascular risk) between age and TBV, GMV, and WMV than in classes 5, 6, and 8. Conversely, the negative association between age and HV was weaker for those in class 2 than individuals in classes 5, 6, and 8. We also found a stronger positive association between age and WMHV in class 2 than in classes 3, 4, and 8 (eTable 20, links.lww.com/WNL/C250).

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Discussion

In this large population-based sample, middle-aged individuals appeared to cluster by sex, age, and varying degrees of cardiometabolic and vascular health. Members of the youngest, healthiest class (class 1) performed best cognitively and had the healthiest brain volumes, and those in classes with most cardiometabolic factors of interest generally had poorer brain health outcomes, particularly when they already had established end-organ vascular disease (classes 4 and 8). We found interactions between class membership and age for brain volumes, but not for cognitive scores, which confirmed that the effect of age on brain volumes was least evident in the younger class 1. However, on excluding those under 60 years, we found that the negative effect of age on total, gray, and white matter volumes was stronger in the class consisting of healthier, older, postmenopausal women than in classes comprising mainly older men of varying cardiometabolic health, suggesting a sex-dependent effect of cardiometabolic health on the age–brain atrophy relationship. These data, taken as a whole, suggest that there may be particular groups of people at a greater risk of accelerated brain aging as a result of sex-dependent clustering of cardiometabolic factors.

This interplay between sex, age, and cardiometabolic health is reflected in the classes generated by the LCA, which were striking for several reasons. First, there was a distinctly healthy and younger class of both sexes—pre/perimenopausal women and men—suggesting that some men are comparable to pre/perimenopausal women with respect to their cardiometabolic and brain health, contrary to the general belief that men develop cardiometabolic risk factors at earlier ages than women.[22] Second is the clear separation of the data set by sex in the older classes (age >50 years), where we observed 4 predominantly male and 3 predominantly female classes, with each class diverging by gradations of cardiometabolic burden. Not only do these results support findings from previous studies reporting between-sex differences in individual cardiovascular factors[23,24] but also extend these findings by clearly illustrating clusters and patterns of cardiometabolic risk that are age and sex specific. Moreover, the process by which the latent classes were formed was independent of brain outcomes, which reinforces the validity of the relationships with brain outcomes that we observed.

We found that class membership modified the association between age and brain volumes, and these relationships differed depending on the age category examined. The age-class interactions on brain structure became particularly pronounced from 60 years of age. In this older sample, each additional year was associated with lower total (gray and white) brain volumes for postmenopausal women with better cardiometabolic health compared with classes of predominantly male subjects who were less healthy. This extends results from our prior work, which demonstrated that the negative effects of age on brain structure appear to be greater in women than men, particularly after menopause.[4] This may also reflect subtle menopause-related sex differences in how the brain responds to cardiometabolic factors. For example, although a diagnosis of hypertension, hyperlipidemia, and diabetes in midlife is associated with a higher risk of dementia in both sexes, the risk may be greater for women.[23] Similarly, a meta-analysis has found that for every 10 mm Hg increase in SBP, there was a 25% and 15% increase in cardiovascular disease risk for women and men, respectively.[25] Treatments for cardiovascular disorders may also not be as effective for women than for men. Some studies have observed that statins are less successful at lowering cholesterol in women compared with men,[26] and angiotensin receptor blockers may improve survival rates for men, but not women with hypertension or cardiovascular disease.[27] Although such biological differences in therapeutic responses may exist, it is also possible that prescription of treatments also differs between sexes, as we found in our data, and consistent with prior work.[28] Women with diabetes are also more susceptible to cardiovascular disease and Alzheimer disease (AD), especially after menopause,[29] possibly due to greater changes in body fat distribution and insulin resistance. The absence of age-class interactions with cognition in our study is congruent with the temporal relationship of brain atrophy preceding clinically perceptible declines in cognition.[30] The observed attenuation of associations between class membership and cognitive scores by brain volume measures indicates that follow-up of these individuals over a sufficient length of time may be required to unmask these interactions if present.

Our finding of lower brain volumes with each additional year of aging for classes of postmenopausal women compared with their less healthy male counterparts indicates that there are mechanisms other than cardiometabolic factors at play. The menopausal transition marks an abrupt decline in estrogen production and is responsible for numerous physical and cognitive symptoms experienced during midlife for women.[13] Estrogens, especially 17β-estradiol, promote neuron viability, regulate β-amyloid accumulation, lower tau hyperphosphorylation, improve cerebral blood flow, and exert anti-inflammatory benefits in the brain.[2] Estrogens also impart cardioprotective effects,[31] and its loss following menopause is linked to the emergence of a constellation of cardiovascular risk factors known as the metabolic syndrome,[32] which is in itself associated with an increased dementia risk.[9] The transition to menopause may therefore represent a window of accelerated brain aging, with hormonal shifts triggering the emergence of cardiometabolic disease and consequent brain changes.

In contrast to our findings with TBV, GMV, and WMV, the negative association of age with HV was greater in predominantly male classes than classes comprising older women. This is consistent with studies indicating that brain aging patterns vary by sex, and the direction of interaction may depend on whether cortical or subcortical brain matter is involved.[33-36] Our previous work found steeper inverse associations between male sex and subcortical GMV,[4] and similar inverse associations have been reported between male

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sex and HV of younger adults.[33-36] Nonetheless, men consistently have larger hippocampi,[37] so the clinical implications for a more rapid volumetric decline are yet uncertain, particularly when AD and related dementias are more prevalent in women.[1] This sex-specific disparity may be partly explained by the brain reserve model, which emphasizes quantitative measures of structural integrity and volume that support cognitive performance.[38] According to this model, individuals with high brain and/or cognitive reserve, compared with those with low reserve, demonstrate better cognitive performance and later cognitive decline despite equal amounts of pathology.[38] Male brains may therefore be better protected even before the dual insults of menopause and accelerated cardiovascular risk for women at midlife. More studies investigating sex and gender contributions to reserve are required to better understand the mechanisms for sex-specific effects on regional brain structures over time, particularly in later midlife.

Our study has the strength of using a large, well-characterized sample with detailed volumetric brain imaging data. Where possible, self-reported data were validated by coded medication and hospital diagnoses. We also used a data-driven approach (LCA) to account for multidimensionality and cluster middle-aged individuals on the basis of sex, age, and cardiometabolic profiles, to compare them for measures of brain health. An advantage of using LCA is that the groupings originate from the data and are not limited by our current understandings of disease pathways. Previous studies have used latent class or cluster analysis to define subgroups of neurocognitive syndromes in people with and without dementia,[39-44] as well as the patterns of cardiometabolic risk factors,[45-48] but none have explored for an underlying relationship between the 2. However, this study has some limitations. The participants in this study were volunteers rather than randomly selected. Similarly, those who had missing brain imaging data were generally less healthy than those who did. As such, our results may not be fully generalizable, although we speculate that the inclusion of such people in the analysis may strengthen our reported relationships. Menopause status was determined by self-report, and the cross-sectional nature of our study limits the ability to draw conclusions about declines in brain health. In addition, our analyses considered sex as binary, as measured in the UK Biobank, assuming homogeneity of gender representation within the self-reported categories of sex. We were therefore unable to partition out the potential effects of sex (a biological construct) and gender (a social construct) on the associations we found. Future studies would benefit from defining these constructs better in their analyses.[49] Finally, longitudinal studies are required to explore whether the kinds of classes identified behave differently over time with respect to brain health and how this relates to sex- and/or gender-related factors.

In conclusion, groups of middle-aged individuals cluster by sex, age, menopause status, and cardiometabolic health, and these groups differ by cognitive and imaging measures of brain aging. Data-driven approaches such as those used in this study can help understand whether these groups are at a greater or lower risk of progression to dementia, thus enabling better targeting of prevention efforts in the future. Further work is needed to refine our understanding of the relationship between menopause, cardiometabolic health, and brain health in women as they age and also uncover relevant menopause-related factors unrelated to cardiometabolic health. Such studies have the potential to inform ways to reduce the risk of brain aging and dementia for both men and women.

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Taya A. Collyer, PhD	Peninsula Clinical School, Monash University; National Centre for Healthy Ageing, Melbourne, Australia	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Richard J. Beare, PhD	Peninsula Clinical School, Monash University; National Centre for Healthy Ageing; Murdoch Children's Research Institute, Melbourne, Victoria, Australia	Analysis or interpretation of data
Emma M. Lane, MD	Peninsula Clinical School, Monash University, Melbourne, Victoria, Australia	Analysis or interpretation of data
Amanda J. Vincent, MD, PhD	Monash Centre for Health Research and Implementation, Monash University; Department of Endocrinology, Monash Health, Melbourne, Victoria, Australia	Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design

Continued

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Appendix *(continued)*

Name	Location	Contribution
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Russell Thomson, PhD	Centre for Research in Mathematics, Western Sydney University, New South Wales, Australia	Major role in the acquisition of data
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Alex Fornito, PhD	The Turner Institute for Brain and Mental Health, Monash University, Melbourne, Victoria, Australia	Major role in the acquisition of data
Velandai K. Srikanth, MD, PhD	Peninsula Clinical School, Monash University; National Centre for Healthy Ageing; Department of Geriatric Medicine, Peninsula Health, Melbourne, Victoria; Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

References

1. Alzheimer's Association. 2019 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2019;15(3):321-387.
2. Pike CJ, Carroll JC, Rosario ER, Barron AM. Protective actions of sex steroid hormones in Alzheimer's disease. *Front Neuroendocrinol*. 2009;30(2):239-258.
3. Regitz-Zagrosek V, Lehmkuhl E, Mahmoodzadeh S. Gender aspects of the role of the metabolic syndrome as a risk factor for cardiovascular disease. *Gend Med*. 2007;4: S162-S177.
4. Than S, Moran C, Beare R, et al. Interactions between age, sex, menopause, and brain structure at midlife: a UK Biobank study. *J Clin Endocrinol Metab*. 2021; 106(2):410-420.
5. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. *Circulation*. 2021;143(8):e254-e743.
6. Stampfer M. Cardiovascular disease and Alzheimer's disease: common links. *J Intern Med*. 2006;260(3):211-223.
7. Mikkola TS, Gissler M, Merikukka M, Tuomikoski P, Ylikorkala O. Sex differences in age-related cardiovascular mortality. *PLoS One*. 2013;8(5):e63347.
8. Nebel RA, Aggarwal NT, Barnes LL, et al. Understanding the impact of sex and gender in Alzheimer's disease: a call to action. *Alzheimers Dement*. 2018;14(9):1171-1183.
9. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology*. 2005;64(2):277-281.
10. Lanza ST, Tan X, Bray BC. Latent class analysis with distal outcomes: a flexible model-based approach. *Struct Equat Modeling*. 2013;20(1):1-26.
11. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779.
12. Townsend P, Phillimore P, Beattie A. *Health and Deprivation: Inequality and the North*. Routledge, 1988.
13. Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E. Perimenopause as a neurological transition state. *Nat Rev Endocrinol*. 2015;11(7):393-405.
14. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018;562(7726):203-209.
15. Alfaro-Almagro F, Jenkinson M, Bangerter NK, et al. Image processing and quality control for the first 10,000 brain imaging datasets from UK Biobank. *Neuroimage*. 2018;166:400-424.
16. Barnes J, Ridgway GR, Bartlett J, et al. Head size, age and gender adjustment in MRI studies: a necessary nuisance? *Neuroimage*. 2010;53(4):1244-1255.
17. Smith SM, Zhang Y, Jenkinson M, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage*. 2002;17(1):479-489.
18. Nylund-Gibson K, Choi AY. Ten frequently asked questions about latent class analysis. *Transl Issues Psychol Sci*. 2018;4(4):440.
19. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA*. 1997; 278(16):1349-1356.
20. Gold EB. The timing of the age at which natural menopause occurs. *Obstet Gynecol Clin*. 2011;38(3):425-440.
21. Linzer DA, Lewis JB. poLCA: an R package for polytomous variable latent class analysis. *J Stat Softw*. 2011;42(10):1-29.
22. Maas AH, Appelman YE. Gender differences in coronary heart disease. *Neth Heart J*. 2010;18(12):598-603.
23. Azad NA, Al Bugami M, Loy-English I. Gender differences in dementia risk factors. *Gend Med*. 2007;4(2):120-129.
24. Huo N, Vemuri P, Graff-Radford J, et al. Sex differences in the association between midlife cardiovascular conditions or risk factors with midlife cognitive decline. *Neurology*. 2021;98(6):e623-e632.
25. Wei YC, George NI, Chang CW, Hicks KA. Assessing sex differences in the risk of cardiovascular disease and mortality per increment in systolic blood pressure: a systematic review and meta-analysis of follow-up studies in the United States. *PLoS One*. 2017;12(1):e0170218.
26. Santos RD, Waters DD, Tarasenko L, et al. Low- and high-density lipoprotein cholesterol goal attainment in dyslipidemic women: the Lipid Treatment Assessment Project (L-TAP) 2. *Am Heart J*. 2009;158(5):860-866.
27. Rabi DM, Khan N, Vallee M, Hladunewich MA, Tobe SW, Pilote L. Reporting on sex-based analysis in clinical trials of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker efficacy. *Can J Cardiol*. 2008;24(6):491-496.
28. Zhao M, Woodward M, Vaartjes I, et al. Sex differences in cardiovascular medication prescription in primary care: a systematic review and meta-analysis. *J Am Heart Assoc*. 2020;9(11):e014742.
29. Juutilainen A, Kortelainen S, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Gender difference in the impact of type 2 diabetes on coronary heart disease risk. *Diabetes Care*. 2004;27(12):2898-2904.
30. Rusinek H, De Santi S, Frid D, et al. Regional brain atrophy rate predicts future cognitive decline: 6-year longitudinal MR imaging study of normal aging. *Radiology*. 2003;229(3):691-696.
31. Iorga A, Cunningham CM, Moazeni S, Ruffenach G, Umar S, Eghbali M. The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. *Biol Sex Differ*. 2017;8(1):33.
32. Carr MC. The emergence of the metabolic syndrome with menopause. *J Clin Endocrinol Metab*. 2003;88(6):2404-2411.
33. Gunning-Dixon FM, Head D, McQuain J, Acker JD, Raz N. Differential aging of the human striatum: a prospective MR imaging study. *AJNR Am J Neuroradiol*. 1998; 19(8):1501-1507.
34. Pruessner JC, Collins DL, Pruessner M, Evans AC. Age and gender predict volume decline in the anterior and posterior hippocampus in early adulthood. *J Neurosci*. 2001;21(1):194-200.
35. Raz N, Gunning-Dixon F, Head D, Rodrigue KM, Williamson A, Acker JD. Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume. *Neurobiol Aging*. 2004;25(3):377-396.
36. Wang Y, Xu Q, Luo J, Hu M, Zuo C. Effects of age and sex on subcortical volumes. *Front Aging Neurosci*. 2019;11:259.
37. Tan A, Ma W, Vira A, Marwha D, Eliot L. The human hippocampus is not sexually-dimorphic: meta-analysis of structural MRI volumes. *Neuroimage*. 2016;124: 350-366.
38. Barulli D, Stern Y. Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends Cogn Sci*. 2013;17(10):502-509.
39. Davidson JE, Irizarry MC, Bray BC, et al. An exploration of cognitive subgroups in Alzheimer's disease. *J Int Neuropsychol Soc*. 2010;16(2):233.
40. Libon DJ, Drabick DA, Giovannetti T, et al. Neuropsychological syndromes associated with Alzheimer's/vascular dementia: a latent class analysis. *J Alzheimers Dis*. 2014;42(3):999-1014.
41. Scheltens NM, Galindo-Garre F, Pijnenburg YA, et al. The identification of cognitive subtypes in Alzheimer's disease dementia using latent class analysis. *J Neurol Neurosurg Psychiatry*. 2016;87(3):235-243.
42. Eppig JS, Edmonds EC, Campbell L, et al. Statistically-derived subtypes and associations with cerebrospinal fluid and genetic biomarkers in mild cognitive impairment: a latent profile analysis. *J Int Neuropsychol Soc*. 2017;23(7):564.
43. Zammit AR, Hall CB, Katz MJ, et al. Class-specific incidence of all-cause dementia and Alzheimer's disease: a latent class approach. *J Alzheimers Dis*. 2018;66(1):347-357.
44. Roberto N, Portella MJ, Marquié M, et al. Neuropsychiatric profiles and conversion to dementia in mild cognitive impairment, a latent class analysis. *Scientific Rep*. 2021; 11(1):1-9.
45. Södergren M, Wang WC, Salmon J, Ball K, Crawford D, McNaughton SA. Predicting healthy lifestyle patterns among retirement age older adults in the WELL study: a latent class analysis of sex differences. *Maturitas*. 2014;77(1):41-46.

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46. Dhana K, van Rosmalen J, Vistisen D, et al. Trajectories of body mass index before the diagnosis of cardiovascular disease: a latent class trajectory analysis. *Eur J Epidemiol*. 2016;31(6):583-592.
47. Ahanchi NS, Hadaegh F, Alipour A, Ghanbarian A, Azizi F, Khalili D. Application of latent class analysis to identify metabolic syndrome components patterns in adults: Tehran Lipid and Glucose study. *Sci Rep*. 2019;9(1):1-8.
48. Hendryx M, Dinh P, Chow A, et al. Lifestyle and psychosocial patterns and diabetes incidence among women with and without obesity: a prospective latent class analysis. *Prev Sci*. 2020;21:850-860.
49. Mielke MM, Aggarwal NT, Vila-Castelar C, et al. Consideration of sex and gender in Alzheimer's disease and related disorders from a global perspective. *Alzheimers Dement*. Epub 2022 Apr 8.

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