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Sex differences in brain aging and predictors of neurodegeneration in cognitively healthy older adults

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ABSTRACT

We evaluated sex differences in MRI-based volume loss and differences in predictors of this neurodegeneration in cognitively healthy older adults. Mixed-effects regression was used to compare regional brain volume trajectories of 295 male and 328 female cognitively healthy Baltimore Longitudinal Study of Aging participants, aged 55–92 years, with up to 20 years of follow-up and to assess sex differences in the associations of age, hypertension, obesity, APOE e4 carrier status, and high-density lipoprotein cholesterol with regional brain volume trajectories. For both sexes, older age was associated with steeper volumetric declines in many brain regions, with sex differences in volume loss observed in frontal, temporal, and parietal regions. In males, hypertension and higher high-density lipoprotein cholesterol were protective against volume loss in the hippocampus, entorhinal cortex, and parahippocampal gyrus. In females, hypertension was associated with steeper volumetric decline in gray matter, and obesity was protective against volume loss in temporal gray matter. Predictors of volume change may affect annual rates of volume change differently between men and women.

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1. Introduction

Evidence from postmortem and in vivo imaging studies shows that advancing age is associated with brain atrophy and ventricular enlargement cross-sectionally and longitudinally (Coffey et al., 1992, 1998; Courchesne et al., 2000; Gur et al., 1991; Murphy et al., 1996; Pfefferbaum et al., 1994; Resnick et al., 2003). It has also been suggested that in vivo imaging studies examining structural regional volumes conducted longitudinally may serve as proxies of brain atrophy (Jack et al., 2017), thus representing a biomarker for neurodegeneration.

Among the factors that may affect age-related brain changes in cognitively normal older adults, sex could play a prominent role. Some cross-sectional studies have found that males have larger brain volumes than females after correcting for body size differences (Allen et al., 2003; Cosgrove et al., 2007; Lüders et al., 2002; Nopoulos et al., 2000; Ritchie et al., 2018), yet others found either null or opposite findings (Fjell et al., 2009; Greenberg et al., 2008; Lemaître et al., 2005; Raz et al., 1997; Salat et al., 2004; Sowell et al., 2007). On the other hand, a number of studies indicate that males have a lower ratio of gray to white matter volume than females (Allen et al., 2003; Goldstein et al., 2001; Gur et al., 1999). In addition, males have lower cortical thickness and smaller frontal lobar volume than females, which may be suggestive of a sex-related vulnerability (Murphy et al., 1996; Xu et al., 2000).

In prior work, our group has reported that males show greater age-related cortical thinning and brain volume changes than females over a follow-up period of up to 10 years (Driscoll et al., 2009; Pacheco et al., 2015; Thambisetty et al., 2010). By contrast, other studies with fewer repeated observations or shorter follow-up intervals, and thus decreased power to detect differences, observed no sex differences in cortical thinning and volumetric change longitudinally (Persson et al., 2014, 2016; Raz et al., 2005, 2010; Yuan et al., 2018). Despite differences in the findings of these studies, it is possible that sex differences in cardiovascular disease (CVD) risk, especially among those who do not develop cognitive impairment, contribute to observations of sex differences in age-related brain volume changes. The effects of hypertension, obesity, and dyslipidemia on cardiovascular-related events are similar between men and women, yet prolonged smoking (Prescott et al., 1998) and diabetes (Huxley et al., 2006; Peters et al., 2014) are more detrimental to women than men. Information on possible

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effects of age-associated comorbidities and cardiovascular risk factors on brain regional volumetric change by sex could elucidate potential preventative and treatment measures that differ between males and females. In our recent report, we identified age, hypertension, obesity, APOE e4 carrier status, and high-density lipoprotein (HDL) cholesterol as predictors of volumetric change in a sample of cognitively normal older adults (Armstrong et al., 2019). Thus, in the present study, we focused on whether there were sex differences in the associations of these predetermined predictors with volume change within a sample of older men and women who did not develop incident cognitive impairment during the follow-up period.

Because sex may play a prominent and independent role in both longitudinal brain volumetric changes and associations of predictors of volumetric change among older adults who remain cognitively normal, we investigated a sample of 617 community-dwelling older adults who remained cognitively healthy over follow-up of up to 20 years. We first investigated whether rates of longitudinal MRI-based tissue loss in the overall sample varied by sex. Based on the prior findings of greater cognitive decline in older men compared with women (McCarrey et al., 2016), we hypothesized that males would show greater age-related volume loss than females. We then stratified the sample by sex to determine whether differential patterns of predictors of volume change emerged in each group separately. We hypothesized that the patterns of these predictors of neurodegeneration would differ between males and females, with males showing greater vulnerability to potential effects of these predictors on volume change.

2. Materials and methods

2.1. Characteristics of the study sample

There were 889 participants from the BLSA neuroimaging substudy who were followed from February 1994 to December 2015 for up to 23 years. The BLSA imaging and visit schedules have varied over time, and enrollment into BLSA has been continuous. Participants in the original imaging study had annual imaging assessments from 1994 to 2004, and they were enrolled based on enrollment procedures described elsewhere (Armstrong et al., 2019). Thereafter, participants aged 60–79 years had biennial BLSA and imaging visits, whereas participants aged ≥80 years had annual visits. Supplemental Fig. 1 illustrates the inclusion and exclusion criteria of the study and defines cognitive status. The analytic sample consisted of 617 participants with 1728 scans over a 20-year period. There were 57 deceased (9.2%) and 38 (6.2%) withdrawn participants. More males (n = 42) than females (n = 15) died during the period, but withdrawnal rates were similar between males and females. The local Institutional Review Board approved the research protocol for this study, and written informed consent was obtained at each visit from all participants.

2.2. Predictors of neurodegeneration

Based on a previous study using BLSA data that examined differences in associations of predictors of volume change by cognitive status (Armstrong et al., 2019), we examined predictors that were related to volume change. These predictors included mean-centered age, sex, race (white vs. nonwhite), APOE e4 carrier status (≥1 vs. 0 e4 alleles), obesity (body mass index ≥30 kg/m^2 vs. <30 kg/m^2), and hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or treatment with antihypertensive medications).

2.3. Image acquisition

Scanning was performed on a General Electric Signa 1.5 T scanner (Milwaukee, WI) or a 3T Philips Achieva. General Electric 1.5-T scans used a high-resolution volumetric spoiled gradient recalled acquisition in a steady state series (axial acquisition, repetition time = 35 ms, echo time = 5 ms, flip angle = 45°, field of view = 24 cm, matrix = 256 × 256, number of excitations = 1, voxel dimensions = 0.94 × 0.94 × 1.5 mm slice thickness). T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) scans were acquired on a 3T Philips Achieva (repetition time = 6.8 ms, echo time = 3.2 ms, flip angle = 8°, image matrix = 256 × 256, 170 slices, pixel size = 1 × 1 mm, slice thickness = 1.2 mm). There were 524 participants (1055 scans) with 3-T MPRAGE images and 99 participants (692 scans) with 1.5-T SPGR images at the baseline. Participants receiving 1.5-T scans comprised enrollees in the original BLSA neuroimaging substudy dating back to 1994 (Resnick et al., 2000).

2.4. Harmonization of MUSE anatomical labels across 1.5-T SPGR and 3-T MPRAGE

A new automated labeling method specifically designed to achieve a consistent parcellation of brain anatomy in longitudinal MRI studies with scanner and imaging protocol differences was used to harmonize BLSA MRI data. This method combines the MUSE anatomical labeling approach (Doshi et al., 2016) with harmonized acquisition-specific atlases (Erus et al., 2018). The approach is described in more detail in the study by Erus et al. (2018). Briefly, using 35 labeled 3-T MPRAGE brain MRIs from the OASIS data set as atlases, we first performed the MUSE labeling method on 3-T MPRAGE images for 32 BLSA participants with 1.5-T SPGR at an earlier time point. Then, for each participant, we deformably registered their 1.5-T SPGR image to their 3-T MPRAGE image using a robust registration strategy that combines an ensemble of registrations obtained using 2 different algorithms and multiple smoothness parameters. From these steps, we obtained 32 pairs of 1.5-T SPGR and 3-T MPRAGE images in the same space with common anatomical labels, which served as atlases in the MUSE approach to obtain labels on the entire BLSA collection of 1.5-T SPGR and 3-T MPRAGE images. This workflow for anatomical labeling has been extensively validated on the BLSA MRI data set (Erus et al., 2018). Stability measures for longitudinal volumes were consistent over time, with intraclass correlations of volumes ranging from 0.89 to 0.99 within 1.5 T and 3T scanners and 0.84 to 0.97 between 1.5-T and 3-T among the sample that remained cognitively normal.

2.5. Volumes of regions of interest

We examined volumes for whole brain, total gray matter (GM), total white matter (WM), ventricles, and lobar GM and WM (frontal, temporal, parietal, and occipital). Sex differences in volumetric change were reported as widespread in a previous analysis using BLSA data (Driscoll et al., 2009). We also examined the volume of the corpus callosum (Luders et al., 2014), as sex differences have been shown in this region. Finally, we included volumes of the amygdala, hippocampus, entorhinal cortex, and parahippocampal gyrus, areas implicated in Alzheimer's disease pathology.

2.6. Statistical analysis

We characterized the sample using means and percentages, and we evaluated differences in baseline sample characteristics by sex, using 2-sample t-tests for continuous variables and χ^2 tests for

categorical variables. Type I error level was set to 0.05 for ROI analyses, and we applied Bonferroni correction of $p \leq 0.003$ for multiple comparisons adjustment for 17 brain ROIs. Stata SE 15.0 (StataCorp, 2017) was used for all analyses.

2.6.1. Baseline and longitudinal brain volumetric change as a function of sex

Linear mixed-effects models were used to compare baseline and longitudinal changes in global and lobar regions in the overall sample. They account for the variability in visits, follow-up time, unequal number of measurements, and age because BLSA participants enter in the study at different ages, have been in the study for various lengths of time, have unequally spaced follow-up visits, and have unequal numbers of measurements. The models use all available data (a snapshot in time) and do not rely on listwise deletion.

Our base model consisted of fixed effects, that is, baseline intracranial volume (ICV), image type (1.5-T SPGR vs. 3-T MPRAGE), age, sex, race, time since first MRI, and 2-way interactions of image type, age, sex, and race with time, and random effects (intercept and slope) with unstructured covariance. We used baseline rather than time-varying ICV to account for head size variation, as previously recommended for longitudinal studies (Barnes et al., 2010; Pengas et al., 2009). Random effects allowed individual-specific baseline brain volumes and rates of volumetric change to vary. Effect sizes for the difference in baseline ROI volumes were calculated by dividing the estimated difference in the baseline volumes between males and females by the estimated standard deviation at the baseline. In addition, effect sizes for difference in rates of ROI volumetric changes by sex were calculated by dividing the estimated difference in annual rates of change by the estimated standard deviation of the between-subject rates of change. Given that this analysis was exploratory, all results are reported in tables to help guide future research.

As a secondary analysis, we examined the association of sex with global and lobar volumetric change in a sample without baseline vascular burden. Vascular burden was a cumulative score of current smoking status, hypertension diagnosis, diabetes (fasting glucose >125 mg/dL, a pathologic oral glucose tolerance test, or a positive history of a diagnosis plus treatment with oral antidiabetic drugs or insulin), obesity, and elevated total cholesterol (≥200 mg/dL vs. <200 mg/dL) (Gottesman et al., 2017).

2.6.2. Predictors of volumetric change as a function of sex

To evaluate the association of predictors of volumetric change among cognitively normal participants, we added the following fixed effects to our base model: hypertension, obesity, APOE e4 carrier status, HDL cholesterol, and 2-way interactions of hypertension, obesity, APOE e4 carrier status, and HDL cholesterol with time. Individual 3-way interactions (predictor*sex*time) were significant when evaluating the volume changes in certain, not all, regions of interest as a function of each predictor, sex, and time in

Table 1
Sample characteristics from the Baltimore Longitudinal Study of Aging (N = 617)

Baseline characteristics	Overall	Females	Males	*p*-value for difference by sex
	N = 617	N = 326	N = 291	
Age, in y, mean (SD)	71.2 (8.7)	70.3 (8.7)	72.2 (8.5)	0.008
White, n (%)	450 (72.9)	214 (65.6)	236 (81.1)	<0.001
Education, in y, mean (SD)	16.9 (2.5)	16.6 (2.5)	17.2 (2.5)	0.005
APOE e4 carrier status, n (%)	127 (20.6)	77 (23.6)	50 (17.2)	0.072
Vascular burden, n (%)				0.055
0 conditions	221 (35.5)	105 (32.2)	116 (39.3)	
1 condition	259 (42.0)	151 (46.3)	108 (37.1)	
2+ conditions	137 (22.2)	70 (21.5)	67 (23.0)	
Components of vascular burden, n (%)				
Diabetes	26 (4.2)	5 (1.5)	21 (7.2)	<0.001
Elevated total cholesterol	231 (37.4)	157 (48.1)	74 (25.4)	<0.001
Hypertension	129 (20.9)	51 (15.6)	78 (26.8)	0.001
Obesity	154 (25.0)	85 (26.1)	69 (23.7)	0.643
Current smoker	20 (3.2)	4 (1.2)	16 (5.5)	0.003
Systolic blood pressure, in mm Hg, mean (SD)	119.0 (17.8)	116.0 (16.4)	122.3 (18.7)	<0.001
Diastolic blood pressure, in mm Hg, mean (SD)	67.6 (11.2)	66.5 (10.7)	68.8 (11.6)	0.010
Antihypertensive medications, n (%)	265 (43.2)	128 (39.3)	137 (47.1)	0.067
HDL cholesterol, in mg/dL, mean (SD)	59.9 (17.5)	67.1 (16.8)	51.8 (14.5)	<0.001
Baseline 3-T scan, n (%)	519 (84.1)	285 (87.4)	234 (80.4)	0.017
Number of 3-T scans, n (%)	1045 (60.5)	580 (65.8)	465 (54.9)	<0.001
Intracranial volume, mean (SD)	1397.8 (143.2)	1305.7 (106.4)	1488.3 (114.9)	<0.001
Follow-up time, mean (SD)	3.5 (4.7)	3.6 (5.0)	3.4 (4.5)	0.409
Follow-up time for those with ≥2 visits, mean (SD)	4.1 (1.9)	4.3 (5.2)	3.9 (4.6)	0.192
Number of follow-up visits, n (%)				0.786
1	617 (100.0)	326 (100.0)	291 (100.0)	
2	368 (59.6)	189 (58.0)	179 (61.5)	
3	172 (27.9)	89 (27.3)	83 (28.5)	
4	101 (16.4)	45 (13.8)	56 (19.2)	
5	83 (13.5)	36 (11.0)	47 (16.2)	
6	73 (11.8)	33 (10.1)	40 (13.7)	
7	67 (10.9)	31 (9.5)	36 (12.4)	
8	59 (9.6)	28 (8.6)	31 (10.7)	
9	49 (7.9)	24 (7.4)	25 (8.6)	
10	42 (6.8)	22 (6.7)	20 (6.9)	
11	34 (5.5)	19 (5.8)	15 (5.2)	
12+	63 (10.2)	39 (12.0)	24 (8.2)	

We used t-tests for continuous variables and chi-squared tests for categorical variables. There were 142 (23.0%) missing for APOE e4 genotype, 3 (0.5%) missing for baseline elevated cholesterol, 4 (0.7%) missing for antihypertensive medications, and 3 (0.5%) missing for baseline obesity status.
Key: APOE, apolipoprotein; HDL, high-density lipoprotein; ICV, intracranial volume; LDL, low-density lipoprotein; SD, standard deviation.

Table 2
Annual rates of change in regional brain volumes (in cm^3) in the overall sample and between males and females in the Baltimore Longitudinal Study of Aging (N = 617)

Brain regions of interest	Annual rate of change in regional brain volumes in overall sample			Unstandardized volumes								Standardized volumes							
				Annual rate of change in regional brain volumes in males		Annual rate of change in regional brain volumes in females		Difference in annual rate of change in regional brain volumes between men and women				Annual rate of change in regional brain volumes in males		Annual rate of change in regional brain volumes in females		Difference in annual rate of change in regional brain volumes between men and women			
	β	SE	*p*-value	β	SE	β	SE	β	SE	*p*-value	Effect size	β	SE	β	SE	β	SE	*p*-value	Effect size
Total brain	**−4.375**	**0.423**	**<0.001**	**−5.213**	**0.480**	**−3.536**	**0.438**	**−1.677**	**0.357**	**<0.001**	**−0.891**	**−0.042**	**0.004**	**−0.029**	**0.004**	**−0.014**	**0.003**	**<0.001**	**−0.891**
GM	**−3.728**	**0.335**	**<0.001**	**−4.547**	**0.379**	**−2.909**	**0.347**	**−1.638**	**0.281**	**<0.001**	**−1.001**	**−0.068**	**0.006**	**−0.043**	**0.005**	**−0.024**	**0.004**	**<0.001**	**−1.001**
Frontal GM	**−1.337**	**0.119**	**<0.001**	**−1.561**	**0.136**	**−1.114**	**0.124**	**−0.447**	**0.102**	**<0.001**	**−0.772**	**−0.075**	**0.006**	**−0.053**	**0.006**	**−0.021**	**0.005**	**<0.001**	**−0.772**
Temporal GM	**−0.653**	**0.062**	**<0.001**	**−0.786**	**0.070**	**−0.520**	**0.064**	**−0.266**	**0.050**	**<0.001**	**−0.908**	**−0.062**	**0.006**	**−0.041**	**0.005**	**−0.021**	**0.004**	**<0.001**	**−0.908**
Parietal GM	**−0.597**	**0.065**	**<0.001**	**−0.723**	**0.074**	**−0.470**	**0.067**	**−0.253**	**0.055**	**<0.001**	**−0.895**	**−0.067**	**0.007**	**−0.044**	**0.006**	**−0.024**	**0.005**	**<0.001**	**−0.895**
Occipital GM	**−0.425**	**0.063**	**<0.001**	**−0.515**	**0.072**	**−0.335**	**0.066**	**−0.180**	**0.054**	**0.001**	**−0.579**	**−0.051**	**0.007**	**−0.033**	**0.007**	**−0.018**	**0.005**	**0.001**	**−0.579**
WM	**−1.693**	**0.183**	**<0.001**	**−1.936**	**0.206**	**−1.450**	**0.189**	**−0.486**	**0.151**	**0.001**	**−0.583**	**−0.036**	**0.004**	**−0.027**	**0.004**	**−0.009**	**0.003**	**0.001**	**−0.583**
Frontal WM	**−0.724**	**0.076**	**<0.001**	**−0.821**	**0.085**	**−0.628**	**0.078**	**−0.193**	**0.060**	**0.001**	**−0.542**	**-0.039**	**0.004**	**−0.030**	**0.004**	**−0.009**	**0.003**	**0.001**	**−0.542**
Temporal WM	**−0.298**	**0.050**	**<0.001**	−0.334	0.056	−0.261	0.051	−0.073	0.042	0.079	−0.371	−0.027	0.005	−0.021	0.004	−0.006	0.003	0.079	−0.371
Parietal WM	**−0.309**	**0.047**	**<0.001**	**−0.360**	**0.053**	**−0.258**	**0.048**	**−0.102**	**0.040**	**0.010**	**−0.442**	**−0.033**	**0.005**	**−0.024**	**0.004**	**−0.009**	**0.004**	**0.010**	**−0.442**
Occipital WM	**−0.109**	**0.030**	**<0.001**	−0.111	0.035	−0.106	0.032	−0.005	0.026	0.855	−0.030	−0.019	0.006	−0.018	0.005	−0.001	0.004	0.855	−0.030
Ventricles	**1.199**	**0.110**	**<0.001**	**1.425**	**0.130**	**0.973**	**0.114**	**0.452**	**0.107**	**<0.001**	**0.465**	**0.068**	**0.006**	**0.047**	**0.005**	**0.022**	**0.005**	**<0.001**	**0.465**
Corpus callosum	**−0.062**	**0.006**	**<0.001**	**−0.074**	**0.007**	**−0.050**	**0.006**	**−0.024**	**0.005**	**<0.001**	**−0.704**	**−0.042**	**0.004**	**-0.028**	**0.004**	**−0.014**	**0.003**	**<0.001**	**−0.704**
Amygdala	**−0.014**	**0.002**	**<0.001**	−0.015	0.003	−0.014	0.002	−0.001	0.002	0.577	−0.098	−0.053	0.009	−0.049	0.008	−0.004	0.007	0.577	−0.098
Hippocampus	**−0.046**	**0.005**	**<0.001**	**−0.053**	**0.006**	**−0.040**	**0.005**	**−0.012**	**0.004**	**0.004**	**−0.435**	**−0.062**	**0.007**	**−0.047**	**0.006**	**−0.015**	**0.005**	**0.004**	**−0.435**
Entorhinal cortex	**−0.019**	**0.006**	**0.001**	−0.018	0.006	−0.020	0.006	0.001	0.005	0.752	0.060	−0.028	0.010	−0.030	0.009	0.002	0.007	0.752	0.060
Parahippocampal gyrus	**−0.026**	**0.006**	**<0.001**	−0.030	0.007	−0.021	0.007	−0.009	0.005	0.093	−0.283	−0.034	0.008	−0.024	0.008	−0.010	0.006	0.093	−0.283

All bolded values mean $p \leq 0.05$. Linear mixed-effects models that included baseline ICV, scanner type, age, sex, race, time, and 2-way interactions of scanner type, age, sex, and race with time were used to determine annual rates of change. Continuous variables were mean-centered, and sex was effect-coded to obtain estimates for both males and females.
Key: GM, gray matter; SE, standard error; WM, white matter.

the overall sample (Supplemental Table 2). However, when all 3-way interactions were added to the base model, the 3-way interactions were no longer significant, which could be due to the analysis being underpowered. For consistency and ease of interpretation across regions of interest, we then stratified the linear mixed effects models by sex to determine if there are differences in patterns of associations of predictors of volume change between males and females. We performed sensitivity analyses to examine the associations if we excluded 1.5-T scans from the sex-stratified models.

3. Results

3.1. Characteristics of study sample

Table 1 shows the baseline sample characteristics for the overall sample and by sex. On average, males (n = 291) were older and had more years of education, lower HDL cholesterol, higher systolic and diastolic blood pressure, and greater ICV than females (n = 326) (Table 1). In addition, males were more likely to be white and current smokers as well as have diabetes and hypertension than females. Distributions of obesity, APOE e4 carrier status, vascular burden, use of any antihypertensive medication, and follow-up time were similar between males and females.

3.2. Baseline and longitudinal brain volumetric change as function of sex

At the baseline, males had larger ventricles, amygdala, entorhinal cortex, parahippocampal gyrus than females, while females had larger frontal GM and WM and parietal GM (Supplemental Table 1).

Table 2 contains the annual rates of change in unstandardized and standardized regional brain volumes in the overall sample, in males and females, and the difference in the annual rate of change in these volumes between males and females. Longitudinally, males had steeper volumetric declines in total brain ($\beta = -1.677$, SE = 0.357, $p < 0.001$), GM ($\beta = -1.638$, SE = 0.281, $p < 0.001$), and WM ($\beta = -0.486$, SE = 0.151, $p = 0.001$) and increased ventricular enlargement ($\beta = 0.452$, SE = 0.107, $p < 0.001$) than females (Table 2). In terms of lobar GM and WM regions, males had steeper volumetric declines in frontal ($\beta = -0.447$, SE = 0.102, $p < 0.001$), temporal ($\beta = -0.266$, SE = 0.050, $p < 0.001$), parietal ($\beta = -0.253$, SE = 0.055, $p < 0.001$), and occipital ($\beta = -0.180$, SE = 0.054, $p = 0.001$) GM as well as frontal ($\beta = -0.193$, SE = 0.060, $p = 0.001$) and parietal ($\beta = -0.102$, SE = 0.040, $p = 0.010$) WM than females. In addition, males had steeper volumetric declines in the corpus callosum ($\beta = -0.024$, SE = 0.005, $p < 0.001$) and hippocampus ($\beta = -0.012$, SE = 0.004, $p = 0.004$) than females. However, there were no significant sex differences in rates of change in volumes of temporal WM, occipital WM, amygdala, entorhinal cortex, and parahippocampal gyrus (Table 2). Fig. 1 depicts sex differences in volumetric change to highlight the finding that males had more volume loss across many ROIs than females. The unadjusted baseline volumes and annual rates of volume change are available in Supplemental Table 2. Fig. 2 shows the adjusted trajectories of brain volume change by five-year age intervals for males and females in several key regions: total brain, GM, ventricles, and hippocampus, while Supplemental Fig. 2 shows the unadjusted trajectories of brain volume change as a function of age between males and females in the same regions.

As a secondary analysis, we examined longitudinal volume change in global and lobar regions as a function of sex in a sample without vascular burden (Supplemental Table 3). Although most associations were in the same direction and similar in magnitude to those from main analysis (Table 2), sex was not associated with greater ventricular enlargement or with volumetric change in the corpus callosum, frontal GM, and occipital GM in the sample without vascular burden.

3.3. Predictors of volumetric change as a function of sex

In these analyses, we first evaluated whether each predictor modified the association of sex with annual volume change. There were some 3-way interactions at $p < 0.10$ when we added each predictor, predictor*time, and predictor*time*sex to the base model (Supplemental Table 3). Males with increased baseline HDL cholesterol had less steep volume declines in the hippocampus ($\beta = 0.001$, SE = 0.000, $p = 0.078$), entorhinal cortex ($\beta = 0.001$, SE = 0.000, $p = 0.049$), and parahippocampal gyrus ($\beta = 0.001$, SE = 0.000, $p = 0.082$) than females with mean baseline HDL cholesterol. Male APOE e4 carriers had steeper volume declines in parietal GM ($\beta = -0.599$, SE = 0.360, $p = 0.096$) and frontal WM ($\beta = -0.310$, SE = 0.121, $p = 0.011$) as well as greater ventricular enlargement ($\beta = 0.255$, SE = 0.122, $p = 0.037$) than female APOE e4 noncarriers. Hypertensive males had less steep volume declines in parahippocampal gyrus ($\beta = 0.028$, SE = 0.013, $p = 0.026$) than females with low/normal BMI. Older males had less steep volume decline in the corpus callosum ($\beta = 0.001$, SE = 0.001, $p = 0.042$) than younger females. White males had steeper volumetric declines in temporal ($\beta = -0.249$, SE = 0.130, $p = 0.094$), parietal ($\beta = -0.265$, SE = 0.098, $p = 0.007$), occipital ($\beta = -0.131$, SE = 0.065, $p = 0.044$) WM, and temporal GM ($\beta = -0.249$, SE = 0.130, $p = 0.055$) than nonwhite females. Based on observed trends toward 3-way interactions, we performed analyses stratified by sex.

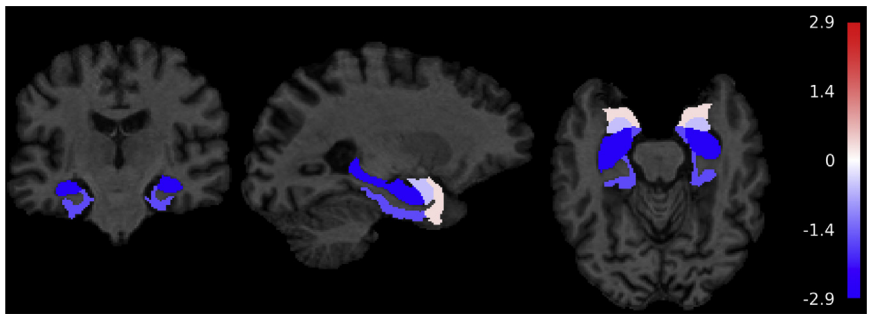

Fig. 1. Sex differences in volumetric change (in cm^3) in cognitively normal participants in Baltimore Longitudinal Study of Aging (N = 617). The color bar represents t-values from the results of the linear mixed-effects models. These models consisted of fixed effects (baseline intracranial volume, image type [1.5-T SPGR vs. 3-T MPRAGE], age, sex, race, time since first MRI, and 2-way interactions of image type, age, sex, and race with time) and random effects (intercept and time) with unstructured covariance. Note that the colors are uniform within regional labels because the figures depict ROI rather than voxel-based analyses. Abbreviation: MPRAGE, magnetization-prepared rapid gradient echo. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

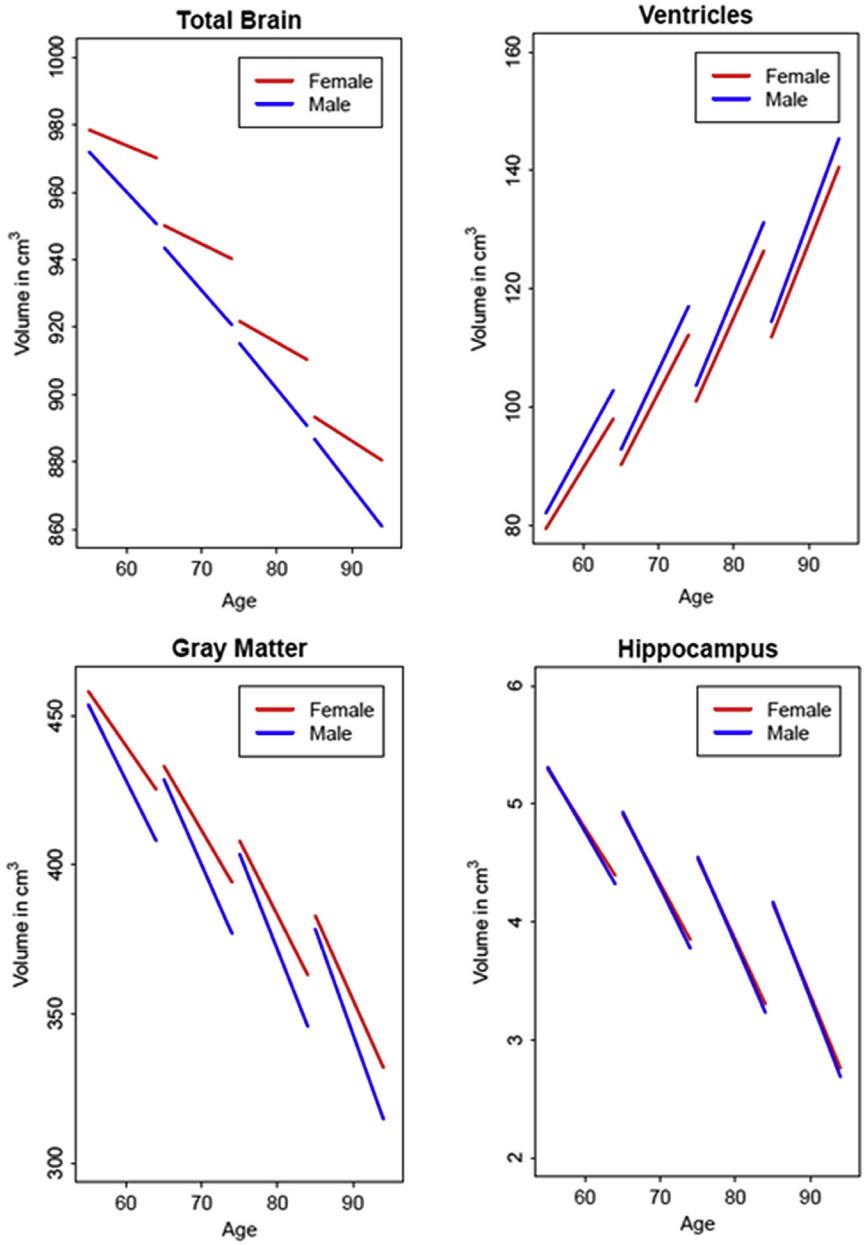

Fig. 2. Volumetric changes (in cm^3) in the total brain, ventricles, gray matter, and hippocampus between males and females in the overall sample (N = 617). Predicted values for volumes come from linear mixed-effects models consisting of fixed effects, that is, baseline intracranial volume, image type (1.5-T SPGR vs. 3-T MPRAGE), age, sex, race, hypertension, obesity, APOE e4 carrier status, HDL cholesterol, time since first MRI, and 2-way interactions of image type, age, sex, race, hypertension, obesity, APOE e4 carrier status, HDL cholesterol with time, and random effects (intercept and time) with unstructured covariance. Abbreviations: HDL, high-density lipoprotein; MPRAGE, magnetization-prepared rapid gradient echo.

We evaluated the relationship of baseline age, hypertension, obesity, APOE e4 carrier status, and HDL cholesterol with volumetric change in global and lobar regions when stratifying by sex to determine the relationships in males and females separately. The results for these analyses are listed in Table 3. Some relationships between older baseline age and volume change were similar between males and females. In both males and females, older age was associated with volumetric declines in GM (males: $\beta = -0.0786$, SE = 0.0342, $p = 0.021$; females: $\beta = -0.0488$, SE = 0.0210, $p = 0.020$), temporal GM (males: $\beta = -0.0189$, SE = 0.0060, $p = 0.002$; females: $\beta = -0.0104$, SE = 0.0039, $p = 0.008$), amygdala (males: $\beta = -0.0005$, SE = 0.0002, $p = 0.024$; females: $\beta = -0.0005$, SE = 0.0002, $p = 0.002$), and hippocampus (males: $\beta = -0.0021$, SE = 0.0005, $p < 0.001$; females: $\beta = -0.0017$, SE = 0.0004, $p < 0.001$), as well as greater ventricular enlargement over time (males: $\beta = 0.0399$, SE = 0.0130, $p = 0.002$; females: $\beta = 0.0378$, SE = 0.0070, $p < 0.001$). After Bonferroni correction, age-related relationships with the ventricles and hippocampus remained for both men and women. In addition, APOE e4 carrier status was not associated with change in brain volumes by sex (Table 3).

There were also differences in the patterns of associations between baseline age and volume change between males and females. Among males only, older age was associated with steeper declines in entorhinal cortex ($\beta = -0.0013$, SE = 0.0005, $p = 0.012$), as well as less steep volume declines in WM ($\beta = 0.0390$, SE = 0.0180, $p = 0.030$), especially in parietal WM ($\beta = 0.0116$, SE =

Table 3
Predictors of neurodegeneration between cognitively normal male and female older adults in the Baltimore Longitudinal Study of Aging

Brain regions of interest	Age * time			Hypertension * time			Obesity * time			APOE e4 status * time			HDL * time		
	β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Males only (N = 291, number of observations = 847)															
Total brain	0.0017	0.0409	0.966	−0.2943	0.5748	0.609	−0.0981	0.4332	0.821	−0.2514	0.6908	0.716	−0.0436	0.0250	0.081
GM	**−0.0786**	**0.0342**	**0.021**	0.0649	0.4815	0.893	−0.1560	0.3559	0.661	0.1607	0.5788	0.781	−0.0150	0.0209	0.471
Frontal GM	−0.0065	0.0127	0.608	0.1057	0.1820	0.561	−0.1507	0.1220	0.217	0.1807	0.2182	0.408	−0.0065	0.0076	0.395
Temporal GM	**−0.0189**	**0.0060**	**0.002**[a]	0.0456	0.0835	0.585	0.0546	0.0668	0.414	0.0530	0.1009	0.599	−0.0039	0.0037	0.304
Parietal GM	−0.0056	0.0064	0.386	−0.0214	0.0909	0.814	−0.0183	0.0698	0.793	−0.0097	0.1091	0.929	−0.0053	0.0039	0.180
Occipital GM	−0.0103	0.0063	0.103	−0.0982	0.0896	0.273	0.0250	0.0709	0.725	−0.0174	0.1074	0.871	−0.0041	0.0039	0.292
WM	**0.0390**	**0.0180**	**0.030**	−0.2015	0.2537	0.427	0.0892	0.1974	0.651	−0.0963	0.3042	0.751	−0.0099	0.0110	0.372
Frontal WM	0.0136	0.0077	0.077	−0.0295	0.1083	0.786	−0.0177	0.0865	0.838	0.0801	0.1302	0.538	−0.0022	0.0048	0.640
Temporal WM	0.0079	0.0047	0.094	−0.1112	0.0661	0.093	0.0223	0.0526	0.672	−0.1480	0.0795	0.063	−0.0046	0.0029	0.116
Parietal WM	**0.0116**	**0.0046**	**0.012**	0.0135	0.0656	0.836	0.0459	0.0500	0.358	−0.0179	0.0786	0.819	−0.0032	0.0028	0.260
Occipital WM	0.0047	0.0030	0.121	−0.0597	0.0432	0.166	**0.0644**	**0.0328**	**0.049**	0.0076	0.0517	0.884	0.0003	0.0019	0.877
Ventricles	**0.0399**	**0.0130**	**0.002**[a]	−0.1322	0.2012	0.511	0.0053	0.0750	0.943	−0.0886	0.2410	0.713	−0.0105	0.0075	0.161
Corpus callosum	0.0001	0.0006	0.831	−0.0073	0.0080	0.362	−0.0032	0.0062	0.604	−0.0066	0.0096	0.492	−0.0001	0.0004	0.734
Amygdala	**−0.0005**	**0.0002**	**0.024**	0.0003	0.0032	0.930	0.0013	0.0022	0.557	−0.0014	0.0038	0.721	0.0001	0.0001	0.488
Hippocampus	**−0.0021**	**0.0005**	**<0.001**[a]	**0.0128**	**0.0064**	**0.046**	−0.0024	0.0050	0.627	−0.0054	0.0077	0.482	0.0005	0.0003	0.072
Entorhinal cortex	**−0.0013**	**0.0005**	**0.012**	−0.0057	0.0074	0.444	0.0068	0.0063	0.281	0.0031	0.0090	0.729	**0.0009**	**0.0003**	**0.008**
Parahippocampal gyrus	−0.0012	0.0006	0.057	0.0145	0.0086	0.091	0.0044	0.0070	0.527	0.0100	0.0103	0.334	**0.0008**	**0.0004**	**0.030**
Females only (N = 326, number of observations = 881)															
Total brain	−0.0286	0.0275	0.297	−0.8579	0.5740	0.135	0.4631	0.3455	0.180	−0.4046	0.4320	0.349	0.0074	0.0139	0.594
GM	**−0.0488**	**0.0210**	**0.020**	**−0.9437**	**0.4418**	**0.033**	0.4643	0.2735	0.090	−0.2805	0.3289	0.394	0.0027	0.0106	0.802
Frontal GM	**−0.0180**	**0.0078**	**0.021**	−0.2318	0.1635	0.156	0.1835	0.0961	0.056	0.0236	0.1248	0.850	−0.0019	0.0040	0.632
Temporal GM	**−0.0104**	**0.0039**	**0.008**	**−0.2437**	**0.0817**	**0.003**[a]	0.1000	0.0527	0.058	0.0024	0.0598	0.967	0.0025	0.0020	0.205
Parietal GM	**−0.0097**	**0.0043**	**0.023**	−0.1224	0.0893	0.171	0.0480	0.0546	0.379	−0.0355	0.0668	0.596	0.0017	0.0022	0.423
Occipital GM	−0.0070	0.0040	0.081	−0.0756	0.0845	0.371	0.0732	0.0508	0.149	−0.0450	0.0641	0.482	0.0007	0.0020	0.718
WM	−0.0159	0.0099	0.109	−0.1273	0.2036	0.532	0.0538	0.1393	0.699	0.0265	0.1405	0.850	0.0018	0.0049	0.719
Frontal WM	−0.0036	0.0042	0.396	−0.0346	0.0857	0.687	−0.0439	0.0623	0.480	0.0196	0.0574	0.733	0.0005	0.0020	0.819
Temporal WM	0.0009	0.0031	0.777	−0.0501	0.0655	0.444	0.0667	0.0400	0.096	−0.0440	0.0486	0.365	−0.0007	0.0016	0.651
Parietal WM	−0.0011	0.0027	0.688	0.0076	0.0555	0.891	0.0485	0.0346	0.160	0.0267	0.0404	0.509	0.0021	0.0013	0.123
Occipital WM	**−0.0037**	**0.0018**	**0.045**	−0.0191	0.0382	0.617	0.0130	0.0240	0.587	−0.0103	0.0281	0.714	0.0013	0.0009	0.175
Ventricles	**0.0378**	**0.0070**	**<0.001**[a]	−0.1728	0.1442	0.231	**−0.1504**	**0.0575**	**0.009**	−0.0074	0.1171	0.950	−0.0063	0.0034	0.065
Corpus callosum	**−0.0015**	**0.0004**	**0.001**[a]	−0.0076	0.0093	0.412	−0.0050	0.0053	0.341	−0.0102	0.0073	0.166	0.0001	0.0002	0.616
Amygdala	**−0.0005**	**0.0002**	**0.002**[a]	0.0018	0.0035	0.620	0.0018	0.0018	0.318	−0.0017	0.0029	0.554	0.0001	0.0001	0.149
Hippocampus	**−0.0017**	**0.0004**	**<0.001**[a]	0.0046	0.0078	0.553	**0.0088**	**0.0044**	**0.047**	−0.0083	0.0061	0.174	0.0001	0.0002	0.565
Entorhinal cortex	−0.0007	0.0004	0.091	0.0072	0.0081	0.372	−0.0018	0.0048	0.702	−0.0020	0.0061	0.736	0.0002	0.0002	0.298
Parahippocampal gyrus	**−0.0011**	**0.0005**	**0.022**	−0.0118	0.0102	0.246	−0.0006	0.0057	0.917	−0.0059	0.0080	0.463	0.0004	0.0002	0.082

Linear mixed-effects models consisted of fixed effects, that is, baseline intracranial volume (ICV), image type (1.5-T SPGR vs. 3-T MPRAGE), age, race, hypertension, obesity, APOE e4 carrier status, high-density lipoprotein cholesterol, time since first MRI, and 2-way interactions of image type, age, race, hypertension, obesity, APOE e4 carrier status, and HDL cholesterol with time, and random effects (intercept and time) with unstructured covariance. The analyses were stratified by sex. All bolded values indicate $p < 0.05$.

Key: GM, gray matter; SE, standard error; WM, white matter.

[a] Indicates significance at Bonferroni correction of $p \leq 0.003$. Predictor × Time indicates the association of predictor with annual rate of change in brain volume.

0.0046, $p = 0.012$) (Table 3). Among females only, older age was associated with volumetric declines in the corpus callosum ($\beta = -0.0015$, SE = 0.0004, $p = 0.001$), frontal GM ($\beta = -0.0180$, SE = 0.0078, $p = 0.021$), and parietal GM ($\beta = -0.0097$, SE = 0.0043, $p = 0.023$). After Bonferroni correction, age-related association with temporal GM remained for men, while age-related associations with the corpus callosum and amygdala remained for women (Table 3).

Differences in patterns of associations for the other predictors, that is, hypertension, obesity, and HDL cholesterol, also emerged between males and females (Table 3). Males with, compared to those without, hypertension had less steep volume decline in the hippocampus ($\beta = 0.0128$, SE = 0.0064, $p = 0.046$), while hypertension was associated with steeper volumetric declines in GM ($\beta = -0.9437$, SE = 0.4418, $p = 0.033$), especially in temporal GM ($\beta = -0.2437$, SE = 0.0817, $p = 0.003$), where it survived Bonferroni correction, among females. Although there were no significant associations of obesity with volume change among males, obesity was associated with less increase in ventricular volume ($\beta = -0.1504$, SE = 0.0575, $p = 0.009$) and less steep declines in hippocampal volumes ($\beta = -0.0088$, SE = 0.0044, $p = 0.047$). Among males, higher HDL cholesterol was associated with less steep volume decline in the entorhinal cortex ($\beta = 0.0009$, SE = 0.0003, $p = 0.008$) and parahippocampal gyrus ($\beta = 0.0008$, SE = 0.0004, $p = 0.030$), yet there were no associations of HDL cholesterol with volume change among females (Table 3).

3.4. Sensitivity analyses

When we restricted the scans to 3-T images, the number of observations dropped by half for both men and women (Supplemental Table 4). Although the magnitudes of associations for some effects were diminished (perhaps due in part to shorter longitudinal follow-up), directions of effects remained the same.

4. Discussion

In this study, we found sex differences in regional volumetric change, with males having steeper volumetric declines than females, even in the absence of cardiovascular risk factors. When comparing patterns of predictors of volumetric change between males and females, distinct patterns emerged for males and females separately. While older age was associated with widespread volumetric declines in both males and females, the associations of hypertension, obesity, and HDL cholesterol with volume change differed between the groups. Hypertensive females had steeper volumetric declines in GM, especially in the temporal lobe, but this was not present in hypertensive males. Although there were no associations between obesity and volume change among males, obesity was associated with decreased ventricular enlargement among females. Higher HDL cholesterol was associated with less steep volume declines in both the entorhinal cortex and parahippocampal gyrus among males, but not in females. APOE e4 carrier status was not associated with volume change in older men and women who maintained cognitive health over extended follow-up, suggesting that APOE e4 risk has a greater effect in those with greater vulnerability to cognitive decline (Armstrong et al., 2019). The lack of an APOE e4 effect in cognitively normal individuals is consistent with some prior studies (Persson et al., 2014; Raz et al., 2010) but differs from an earlier BLSA report (Moffat et al., 2000) over a shorter follow-up that would not have considered long-term cognitive status.

We found that sex differences in volume loss were widespread across the brain, with males having greater volume loss over time than females. Males had steeper rates of annual decline than females in most global and lobar regions, excluding temporal and occipital WM. Males also experienced greater ventricular enlargement than females. These results are consistent with our previous studies of the effects of sex on volume change (Driscoll et al., 2009; Pacheco et al., 2015; Thambisetty et al., 2010) and suggest that females may be less vulnerable to age-related atrophy. Similarly, Ritchie et al. (2015) reported that men had more volumetric decline in total brain and GM than females. Our findings are also consistent with cross-sectional observations of lower age-adjusted volumes of the medial temporal lobe in men compared with women in the Mayo Clinic Study of Aging (Jack et al., 1997).

The volumetric differences observed between males and females suggest that sex hormones may play a role in brain atrophy over time. It has been proposed that estrogen and progesterone may have a protective effect against brain volume loss in women (Green and Simpkins, 2000), although the WHIMS randomized trials with conjugated equine estrogens in older postmenopausal women do not support this hypothesis (Resnick et al., 2009). Conversely, greater WM volume decline in men may be related to the role that androgen, a sex hormone more predominant in males, plays in myelinogenesis. As age increases, levels of androgen decrease, thus reducing recruitment of astrocytes in the remyelination process (Bielecki et al., 2016).

Another possible explanation for the sex differences in rates of volume change relates to differential health risks and possible selection biases. There are well-known sex differences in CVD risk, with males having higher age-adjusted CVD mortality and morbidity rates than females (Mosca et al., 2011). Sex is associated with differential risk for age-related diseases, but males who remained cognitively normal were more likely to have fewer cardiovascular risk factors (elevated total cholesterol and obesity, in particular) overall as well as higher mean baseline HDL cholesterol than females. As noted by Raz et al. (1997), this type of selection bias may hide sex differences in secular trends. To address this possible bias, we evaluated rates of volumetric change in males and females without baseline vascular burden. Sex differences in rates and patterns of longitudinal volumetric change remained in the absence of CVD risk.

We performed sex-stratified analysis to determine whether associations of predictors of neurodegeneration showed similar associations with volumetric brain changes in males and females. Stratified analyses of prespecified predictors of neurodegeneration revealed some sex differences in the patterns of these associations. Hypertensive males had less steep volume declines in the hippocampus, whereas hypertensive females had greater declines in temporal GM. In prior work, we found that hypertension was associated with slower rates of hippocampal volume loss among those who remained cognitively normal, whereas hypertension was associated with steeper hippocampal volumetric declines in the subsequently impaired sample (Armstrong et al., 2019). Our current analyses suggest the association in cognitively normal individuals could be driven by the males. The findings in males differ from other studies reporting that hypertensive men have lower hippocampal volumes (Chen et al., 2006; Gianaros et al., 2006; Taki et al., 2004) or that there are no sex differences in the influence of hypertension on declines in hippocampal volume (Raz et al., 2005). In females, the association between hypertension and greater overall and temporal lobe GM may be associated with postmenopausal estrogen loss. In midlife to late midlife, premenopausal females generally have lower blood pressure than age-matched men likely due to the estrogen modulating effects on the renin-angiotensin-aldosterone system, which can result in beneficial effects on the cardiovascular and central nervous system (Fischer et al., 2002; Yang and Reckelhoff, 2011). The loss of estrogen after menopause, however, can lead to higher blood pressure (Burt et al., 1995;

Calhoun and Oparil, 1998), and cognitively normal women could be more sensitive to hypertension-associated GM volume loss.

Regarding obesity, we found differences in the association with volume change among females only. Obesity in females was associated with slower rate of ventricular enlargement and less steep volume declines in the hippocampus. The apparent protective effect of obesity in older females in these brain regions is consistent with findings from the Women's Health Initiative Memory Study in that lower, rather than higher, BMI was associated with reduced brain volumes in older females over time (Driscoll et al., 2016). Consistent with the interpretation in the WHIMS study, it is likely that weight loss, rather than weight gain, in older women is a marker of future disease. We did not find any associations of obesity with GM and ventricular volume change among older males, although the proportions of males and females with obesity were similar.

We found that HDL cholesterol was associated with less steep volume loss in temporal lobe cortical regions only among males. Previous findings suggest that high levels of HDL cholesterol may be protective against hippocampal atrophy (Wolf et al., 2004). Although we failed to see an association between HDL cholesterol and hippocampal volume change, we did see associations between higher HDL cholesterol levels and reduced volume loss in the parahippocampal gyrus and entorhinal cortex, areas that show early atrophic changes in the AD neurodegenerative process (de Leon et al., 2004). Men with lower HDL levels may be more at risk for volume change because reduced HDL may contribute to the onset of the inflammatory response that occurs in the pathogenesis of atherosclerosis (Barter et al., 2007; Patel et al., 2009; Sampietro et al., 2006) or inflammaging, a state of increasing age-associated low-grade inflammatory state (Chung et al., 2009; Ferrucci et al., 2005). Greater HDL cholesterol has been inversely associated with lower levels of adiponectin and IL-6, markers of age-related inflammation, among healthy adult males (Miles et al., 2008).

There are many strengths of this study. First, this study consists of an extensively characterized large sample of older adults who remained cognitively healthy over lengthy follow-up. This limits generalizability to less selected cohorts but provides important information on sex differences in people who maintain cognitive health. Second, our image processing pipeline uses state-of-the-art and validated multi-atlas approaches for regional definition, yielding high measurement stability over time. There were also several limitations to our study. First, our sample is highly educated, mostly Caucasian, and has a higher socioeconomic status, thus limiting generalizability. Nevertheless, prior BLSA studies have shown similar rates of brain changes over time, relative to other studies (Resnick et al., 2003). Second, most participants were recruited in later life, so there is information missing on midlife risk factors. Third, as this is an ongoing study, 14.4% of the sample had only a single assessment at the time of this analysis but are included in the analysis, as they contribute to stability of cross-sectional associations. Fourth, we did not detect any significant predictor*sex*time interactions after adding these to the base model. It is likely that larger sample sizes are necessary to determine higher order associations. Fifth, nonrandom missingness is always an issue in prospective studies. BLSA home visits minimize the impact of this concern with respect to long-term cognitive status, as participants continued to be followed with cognitive testing when they stop returning to the BLSA for clinic visits. Finally, the study of specific indicators rather than a global construct of vascular burden is a limitation, yet we did not find any significant associations between a composite of cardiovascular risk factors, defined as vascular burden, and change in brain volumes among cognitively normal older adults (Armstrong et al., 2019).

In summary, we found widespread sex differences in the rates of regional volume loss, with men showing faster rates of neurodegeneration. We also found sex differences in the factors related to brain volume decline in men and women. Certain predictors were associated with less tissue loss in the hippocampus, entorhinal cortex, and parahippocampal gyrus, as men with hypertension or high HDL cholesterol, and women with obesity were less susceptible to tissue volume decline in the temporal lobe over time. Future investigations with longer follow-ups should include examination of sex differences in possible synergistic effects of risk factors on change in brain volumes. For instance, previous studies have found that APOE e4 carrier status and hypertension may have a synergistic effect on brain aging (Rast et al., 2017; Raz et al., 2009; Rodrigue et al., 2013), but it is unclear whether sex affects these associations. These findings highlight the importance of examining the differences in patterns of neurodegeneration among men and women in relation to risk factors, as these factors could differentially affect rates of tissue volume change over time.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2019.05.020.

Disclosure

The authors report no conflicts of interest.

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