Research

Adherence to a MIND-Like Dietary Pattern, Long-Term Exposure to Fine Particulate Matter Air Pollution, and MRI-Based Measures of Brain Volume: The Women's Health Initiative Memory Study-MRI

Cheng Chen,[1,2] Kathleen M. Hayden,[3] Joel D. Kaufman,[4] Mark A. Espeland,[5] Eric A. Whitsel,[6] Marc L. Serre,[7] William Vizuete,[7] Tonya S. Orchard,[8] Xinhui Wang,[9] Helena C. Chui,[9] Mary E. D'Alton,[1] Jiu-Chiuan Chen,[9,10] and Ka Kahe[1,2]

[1]Department of Obstetrics and Gynecology, Vagelos College of Physician and Surgeons, Columbia University, New York, New York, USA
[2]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York, USA
[3]Department of Social Sciences and Health Policy, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA
[4]Department of Environmental and Occupational Health Sciences; Department of Medicine; Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington, USA
[5]Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA
[6]Department of Epidemiology, Gillings School of Global Public Health, Department of Medicine, School of Medicine, University of North Carolina Chapel Hill, Chapel Hill, North Carolina, USA
[7]Department of Environmental Sciences and Engineering, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA
[8]Department of Human Sciences, Human Nutrition Program, Ohio State University, Columbus, Ohio, USA
[9]Department of Neurology, Keck School of Medicine, University of Southern California, Los Angeles, California, USA
[10]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

BACKGROUND: Previous studies suggest that certain dietary patterns and constituents may be beneficial to brain health. Airborne exposures to fine particulate matter [particulate matter with aerodynamic diameter $\leq 2.5\ \mu m$ ($PM_{2.5}$)] are neurotoxic, but the combined effects of dietary patterns and $PM_{2.5}$ have not been investigated.

OBJECTIVES: We examined whether previously reported association between $PM_{2.5}$ exposure and lower white matter volume (WMV) differed between women whose usual diet during the last 3 months before baseline was more or less consistent with a Mediterranean–DASH Intervention for Neurodegenerative Delay (MIND)-like diet, a dietary pattern that may slow neurodegenerative changes.

METHODS: This study included 1,302 U.S. women who were 65–79 y old and free of dementia in the period 1996–1998 (baseline). In the period 2005–2006, structural brain magnetic resonance imaging (MRI) scans were performed to estimate normal-appearing brain volumes (excluding areas with evidence of small vessel ischemic disease). Baseline MIND diet scores were derived from a food frequency questionnaire. Three-year average $PM_{2.5}$ exposure prior to MRI was estimated using geocoded participant addresses and a spatiotemporal model.

RESULTS: Average total and temporal lobe WMVs were $0.74\ cm^3$ [95% confidence interval (CI): 0.001, 1.48] and $0.19\ cm^3$ (95% CI: 0.002, 0.37) higher, respectively, with each 0.5-point increase in the MIND score and were $4.16\ cm^3$ (95% CI: −6.99, −1.33) and $1.46\ cm^3$ (95% CI: −2.16, −0.76) lower, respectively, with each interquartile range (IQR) (IQR = $3.22\ \mu g/m^3$) increase in $PM_{2.5}$. The inverse association between $PM_{2.5}$ per IQR and WMV was stronger (p-interaction <0.001) among women with MIND scores below the median (for total WMV, $-12.47\ cm^3$; 95% CI: −17.17, −7.78), but absent in women with scores above the median ($0.16\ cm^3$; 95% CI: −3.41, 3.72), with similar patterns for WMV in the frontal, parietal, and temporal lobes. For total cerebral and hippocampus brain volumes or WMV in the corpus callosum, the associations with $PM_{2.5}$ were not significantly different for women with high MIND scores and women with low MIND scores.

DISCUSSION: In this cohort of U.S. women, $PM_{2.5}$ exposure was associated with lower MRI-based WMV, an indication of brain aging, only among women whose usual diet was less consistent with the MIND-like dietary pattern at baseline. https://doi.org/10.1289/EHP8036

Introduction

Changes in brain structure that reflect the pathology of dementia are frequently observed before the onset of clinical symptoms (Weiner et al. 2017). Evidence from both epidemiological and laboratory studies supports a role of diet in the prevention of brain atrophy or Alzheimer's disease. For example, higher intakes of B vitamins (Bowman et al. 2012; Cavalieri et al. 2012; de Lau et al. 2009; Hooshmand et al. 2016; Zhong et al. 2017), vitamin E (Gu et al. 2016; Ohshima et al. 2013), carotenoids (den Heijer et al. 2001), flavonoids (Shishtar et al. 2020), and long-chain omega-3 polyunsaturated fatty acids (LCn3PUFAs) (Chen et al. 2020; McNamara et al. 2017) have been associated with more normative brain structure, such as greater cerebral brain volume, greater white matter volume, or less-severe white matter lesions. By contrast, nutrient pattern with high intakes of *trans* fat and saturated fat were associated with greater white matter hyperintensity volumes (Prinelli et al. 2019). High intake of *trans* fat alone was associated with smaller cerebral brain volume (Bowman et al. 2012). Foods that are major sources of nutrients associated with better brain health, such as green leafy vegetables, berries, and fish, have also been associated with better cognitive health, as highlighted in a recent review (Pistollato et al. 2018).

Because foods and nutrients are biologically interactive, dietary patterns may have greater influences on brain health than dietary intakes of individual foods or nutrients have (Tapsell et al. 2016). Recently, Morris et al. (Morris et al. 2015a) developed the Mediterranean–DASH Intervention for Neurodegenerative Delay

(MIND) diet score to measure adherence to a dietary pattern that combines elements of the culturally based Mediterranean diet with the blood pressure–lowering DASH diet. The MIND dietary pattern promotes the intake of dietary components associated with slower cognitive decline (i.e., "brain healthy" foods) while minimizing the intake of foods that have been associated with worse cognitive outcomes (i.e., "brain-unhealthy" foods). Greater adherence to a MIND-like diet (indicated by higher MIND diet scores) has been associated with better cognitive function and lower risks of cognitive impairment and Alzheimer's disease as reviewed by Dominguez et al. and van den Brink et al. (Dominguez et al. 2019; van den Brink et al. 2019). However, the association between MIND-like diet and image-based evidence of brain atrophy, such as brain volume, has not been examined.

In the past decade, studies have increasingly reported associations between exposure to ambient fine particulate matter [particulate matter with aerodynamic diameter $\leq 2.5 \ \mu m$ ($PM_{2.5}$)] and adverse neurological outcomes (Cohen and Gerber 2017; Peters et al. 2015; Xu et al. 2016). Long-term $PM_{2.5}$ exposure was associated with smaller total cerebral brain volume in a cohort of older adults (Wilker et al. 2015) and with smaller white matter volume in a cohort of older women [Women's Health Initiative Memory Study–Magnetic Resonance Imaging (WHIMS-MRI)] (Chen et al. 2015). $PM_{2.5}$ may alter brain structure/networks through multiple pathways, for example, by promoting oxidative stress/neuroinflammation, or by directly inducing myelin loss (Campbell et al. 2005, 2009; Ren et al. 2010; Woodward et al. 2017). Conversely, several of the foods and nutrients promoted by the MIND diet have been associated with a reduced rate of total brain volume loss and a lower risk of white matter lesions (Bowman et al. 2012; Cavalieri et al. 2012; Gopalan et al. 2014; Gu et al. 2016; Shishtar et al. 2020), possibly by reducing oxidative stress or local inflammation, protecting against oligodendrocyte cell death, or facilitating remyelination (Butterfield and Halliwell 2019; Niu et al. 2020; Pu et al. 2013). Thus, greater adherence to a MIND-like dietary pattern might attenuate adverse effects of $PM_{2.5}$ exposure on brain structure. However, to our knowledge, the potential for a MIND-like diet to modify associations between $PM_{2.5}$ exposure and adverse brain outcomes has not been investigated.

We analyzed data from the WHIMS-MRI to assess the hypothesis that greater adherence to a MIND-like diet would be associated with larger average normal-appearing brain volumes (excluding areas with evidence of small vessel ischemic disease) as measured by structural MRI. Additionally, we hypothesized that previously reported associations between $PM_{2.5}$ exposure and smaller average white matter volumes in the WHIMS-MRI study population (Chen et al. 2015) would be attenuated among women with higher MIND diet scores relative to women with lower scores indicating less likelihood of consuming a MIND-like diet. We focused on brain areas that have been associated with diet and $PM_{2.5}$ exposure and that are critical to memory, complex cognitive processing, and Alzheimer's disease pathogenesis, including total cerebral brain volume (Ridha et al. 2006), hippocampus volume (Yau et al. 2015), and white matter volume (Alber et al. 2019).

Methods

Study Design and Population

WHIMS is an ancillary study nested in the Women's Health Initiative Hormone Replacement Therapy trial (WHI-HRT). WHI-HRT enrolled 27,500 postmenopausal women 50–79 y old with or without uterus from 40 clinical centers in the period 1996–1998 (henceforth referred to "baseline"). These participants were randomized to either estrogen, estrogen plus progestin, or placebo arms. The detailed exclusion criteria of WHI-HRT are listed in Table S1 and have been published previously (Shumaker et al. 1998). Exclusion criteria related to this study include "has dementia (according to clinical judgement)" and "had stroke or transient ischemic attack in the past 6 mo."

WHI-HRT participants were eligible for enrollment in WHIMS if they were 65–79 y old, they were willing to undergo annual cognitive assessments for 4–6 y, and they were willing to participate in all aspects of WHIMS, possibly including an MRI. A total of 7,427 women who scored over 77 on the baseline modified Mini-Mental State (3MS) test (to indicate normal cognition) proceeded directly to annual follow-up and were eligible for participation in WHIMS-MRI (Jaramillo et al. 2007; Shumaker et al. 1998).

WHIMS-MRI enrolled WHIMS participants older than age 70 y in 2005 in 14 clinical centers, which were selected based on interest, experience in conducting multicenter MRI studies, and availability of MRI equipment. Participants with the following conditions were not recruited in WHIMS-MRI: *a*) the presence of pacemakers, defibrillators, neurostimulators, prohibited medical implants, and foreign bodies that would pose a hazard to the participant during the MRI procedure; or *b*) shortness of breath or inability to lie flat and conditions that could be exacerbated by stress severe enough to preclude an MRI. Thus, a total of 1,403 participants were enrolled in WHIMS-MRI and completed structural brain MRI scans that met quality controls in the period 2005–2006 (Jaramillo et al. 2007).

The present analysis is based on a subset of our previous study of $PM_{2.5}$ exposure and MRI outcomes (Chen et al. 2015). After excluding 32 individuals who reported an implausible total energy intake (< 600 or $> 5,000 \ kcal/d$) or had no information on MIND score, and an additional 69 individuals with missing values of covariates, this analysis includes 1,302 participants. Written informed consents were obtained from all participants. The study design, data collection, and analyses in this study were approved by the institutional review boards of WHI-HRT, WHIMS, and WHIMS-MRI participating institutes.

Assessment of MIND Diet Score

Diet was assessed at baseline (1996–1998) using a semiquantitative food frequency questionnaire (FFQ) that was modified from the National Cancer Institute and Block FFQs (Patterson et al. 1999). This FFQ inquired about the habitual diets over the prior 3 months, including 122 foods or food groups with questions on usual intake frequency and portion size. Food preparation practices and types of added fats were also asked about to obtain data on fat intake. The WHI-FFQ nutrient database was derived from the University of Minnesota Nutrition Coordinating Center food and nutrient database (Schakel et al. 1988) to estimate nutrient intakes.

We calculated MIND scores based on the intakes of 15 dietary components, including 10 brain healthy food groups (leafy greens, other vegetables, beans, whole grains, berries, nuts, nonfried fish, nonfried poultry, olive and canola oil, and wine) and 5 unhealthy food groups (butter or margarine, cheese, red meat, fried foods, and pastries and sweets) (Morris et al. 2015a; Morris et al. 2015b). Because the WHI FFQ is slightly different from the Rush Memory and Aging Project (MAP) FFQ on which the original MIND score was based (Morris et al. 2015a), we adapted the specific foods included in each dietary component group (Table S2). Dietary component groups without detailed descriptions in the MAP study (i.e., whole grains, nuts, wine, butter or margarine, and cheese) were specified in Table S2. WHI dietitians and nutritionists assumed that foods in these food groups were similarly "brain healthy" or "brain unhealthy" based on their expertise. Thus, they selected the appropriate foods reported in the WHI FFQ to be included in these dietary component groups.

Table 1. MIND Diet component serving and scoring.

Categories	Score		
	0	0.5	1
Brain-healthy foods	—	—	—
Leafy greens	≤2 servings/wk	2–6 servings/wk	≥6 servings/wk
Other vegetables	<5 servings/wk	5–7 servings/wk	≥1 serving/d
Beans	<1 serving/wk	1–3 servings/wk	>3 servings/wk
Whole grains	<1 serving/wk	1–2.6 servings/d	≥2.6 servings/d
Berries	<1 serving/wk	1–2 servings/wk	≥2 servings/wk
Nuts	Rarely	<5 servings/wk	≥5 servings/wk
Nonfried fish	Rarely	<1 serving/wk	≥1 serving/wk
Nonfried poultry	<1 serving/wk	1–2 servings/wk	≥2 servings/wk
Olive and canola oils	Not primary oil used	—	Primary oil used
Wine	>1 glass/d or never	<1 glass/d	1 glass/d
Brain-unhealthy foods	—	—	—
Butter or margarine	≥1 serving/d	0.5–1 serving/d	≤0.5 serving/d
Cheese	≥1 serving/d	1–7 servings/wk	<1 serving/wk
Red meat	≥1 serving/d	4–7 servings/wk	<4 servings/wk
Fried foods	≥4 servings/wk	1–4 servings/wk	<1 serving/d
Pastries and sweets	≥1 serving/d	5–7 servings/wk	<5 servings/wk
Total score	—	—	15

Note: The MIND score was retrospectively calculated based on the intakes of 15 dietary components including 10 brain healthy food groups and 5 unhealthy food groups using WHI food frequency questionnaire at baseline (1996–1998). Olive and canola oil consumption was assigned a score of 1 if it was identified as the primary oil used at home, and a score of 0 otherwise. Wine consumption was scored such that women who drank 1 glass/d were assigned a score of 1, and women who occasionally drank wine (<1 glass/d) were assigned a score of 0.5, whereas women were assigned a score of 0 if they never drank wine or if they drank >1 glass/d. For all other dietary components, corresponding component scores were assigned based on the consumption frequency of foods in each group, with scores of 0, 0.5, and 1 assigned for low, medium, and high (respectively) consumption of "brain healthy" foods, and scores of 0, 0.5, and 1 assigned for high, medium, and low (respectively) consumption of brain-unhealthy foods. The total MIND score was computed by summing over the 15 component scores, with a higher value indicating a higher likelihood to consume a MIND dietary pattern. The MIND diet was originally constructed in the Rush Memory and Aging Project (MAP) (Morris et al. 2015a). —, no data; MIND, Mediterranean–DASH Intervention for Neurodegenerative Delay; WHI, Women's Health Initiative.

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MRI Scanning and Data Processing

The WHIMS-MRI Quality Control Center at the Department of Radiology, University of Pennsylvania, developed the standardized protocols for MRI scanning (Coker et al. 2009; Resnick et al. 2009). The scanners were standardized by the American College of Radiology (ACR) phantom quality control (QC) protocol (American College of Radiology 1998). Before enrollment of WHIMS-MRI, a set of test scans on the ACR QC phantoms and a volunteer were submitted for review and approved by the Quality Control Center. The ACR phantom tests have been performed on a quarterly basis to assure image quality and calibrate signal-to-noise ratio and spatial distortion.

The 1.5-T scanners at each WHIMS-MRI clinical center are shown in Table S3. Scanning pulse sequences were performed in the following order (Coker et al. 2009; Goveas et al. 2011):
- Series one: three-plane gradient echo localizer for positioning.
- Series two: sagittal T1-weighted spin echo midslice image to demonstrate anatomic location of the anterior commissure–posterior commissure (AC/PC) line for slice angle and slice position.

- Series three: oblique axial spin density/T2-weighted spin echo images (repetition time: 3,200 msec; inversion time: 0 msec; echo time: 30/120 msec; flip angle: 90°; pixel bandwidth: 150.234 Hz/pixel; slice thickness: 3 mm) from the vertex to skull base parallel to the AC/PC plane.
- Series four: oblique axial fast FLAIR T2-weighted spin echo images (repetition time: 8,000 msec; inversion time: 2,000 msec; echo time: 100 msec; flip angle: 90°; pixel bandwidth: 244.141 Hz/pixel; slice thickness: 3 mm) matching slice positions in series three.
- Series five: oblique axial fast spoiled three-dimensional T1-weighted gradient echo images (repetition time: 21 msec; inversion time: 0 msec; echo time: 8 msec; flip angle: 30°; pixel bandwidth: 122.109 Hz/pixel; slice thickness: 1.5 mm) from the vertex to the skull base parallel to the AC/PC plane.

The field of view was 22 cm and the acquisition matrix was 256×256 for series three, four, and five, which were used for analyses of reginal brain volumes. Trained technicians at each center immediately reviewed all scans for protocol compliance and technical problems. Scans were transmitted by an encrypted DICOM image transfer mechanism to the Quality Control Center and analyzed centrally.

To quantify regional brain volumes, T1-weighted volumetric MRI scans were preprocessed for alignment, removal of extracranial material, and segmentation of brain into gray and white parenchyma and cerebrospinal fluid using a standardized protocol (Goldszal et al. 1998). By assigning the tissue type to 92 anatomical regions of interest (ROIs) of the cerebrum and summing the number of respective voxels, volumes of gray matter, white matter, and cerebrospinal fluid at each labeled brain region were obtained using the HAMMER (i.e., the hierarchical attribute matching mechanism for elastic registration) method (Shen and Davatzikos 2002). This technique digitally defined the atlas for each brain lobe and its individual structures. Atlas definitions were then transferred to participants' MRI scans using an image-warping algorithm, which performs pattern matching of anatomically corresponding brain regions. For example, four layers in the hippocampus were identified, including *a*) the high-intensity layer in the cornu

ammonis formed by the pyramidal cell and the stratum oriens layer; *b*) the low-intensity layer in the cornu ammonis formed by the vestigial hippocampal sulcus, the stratum lacunosum-moleculare, and the stratum radiatum; *c*) the stratum moleculare of the dentate gyrus; and *d*) the dentate hilus (Yushkevich et al. 2009). Scans with volume greater than the sample mean of each ROI by more than three standard deviations were flagged as outliers and proceeded to manual inspection. Intracranial volume was defined as the total cerebral hemispheric volumes, including ventricular cerebrospinal fluid and the cerebrospinal fluid within the sulcal spaces (Resnick et al. 2009). Because WHIMS-MRI used standardized protocols for MRI scanning across all participating centers, harmonization to correct site effects was not performed, similar to procedures in previously published WHIMS-MRI studies (Coker et al. 2009; Resnick et al. 2009).

Following additional preprocessing steps, including histogram standardization and coregistration, a brain lesion segmentation algorithm was applied to the multimodal images to segment small vessel ischemic diseases (SVID) (Lao et al. 2008; Zacharaki et al. 2008). The tissue segmentation and lesion segmentation algorithms were combined to classify each voxel as normal (not SVID-affected) or abnormal (SVID-affected) and to calculate the normal-appearing brain volumes at each region excluding areas with evidence of SVID. We focused ROI analyses on hippocampus and white matter that have been associated with diet (Fotuhi et al. 2016; Gardener et al. 2012; Gu et al. 2015; Prinelli et al. 2019; Rodrigues et al. 2020) and $PM_{2.5}$ exposure in a previous analysis of WHIMS-MRI participants (Chen et al. 2015) and that are critical to memory and general cognition (Alber et al. 2019; Yau et al. 2015) and Alzheimer's disease (Alber et al. 2019; Ridha et al. 2006). All data and scans in this analysis passed quality checks.

Estimation of $PM_{2.5}$ Exposure

WHIMS-MRI participants' addresses were collected at each clinic visit, updated at least biannually, and geocoded following a standardized protocol (Whitsel et al. 2004). Spatiotemporal models were constructed using Bayesian Maximum Entropy (BME) to estimate the ambient concentration of $PM_{2.5}$ at all geocoded participant addresses from 1999 to 2005–2006 when the MRI scans were performed (Cacciottolo et al. 2017; Reyes et al. 2017). $PM_{2.5}$ exposure prior to 1999 could not be estimated due to the limited monitoring data. Combining the nationwide monitoring data from the U.S. EPA Air Quality System (AQS) and the output of chemical transport models, this method is able to estimate the average trends and covariance of the air pollution fields over space and time and to show the spatiotemporal interdependence of environmental data. The estimated daily $PM_{2.5}$ exposures were correlated with the monitored levels at AQS (cross-validation Pearson's $r^2 = 0.70$) (Cacciottolo et al. 2017). This BME model was applied to each geocoded location to generate a series of $PM_{2.5}$ exposures that change on a yearly basis, and then were combined with participants' address history, including relocations, to calculate the average $PM_{2.5}$ exposure 3 y preceding the individual-specific MRI scan date. The use of 3-y average $PM_{2.5}$ exposure is consistent with previous study of $PM_{2.5}$ in the WHI (Chen et al. 2015) and should provide a better estimate than commonly used annual average exposure in other population studies.

Other Covariates

Factors that are associated with diet and brain atrophy based on *a priori* knowledge and those that were adjusted in existing observational studies of diet or $PM_{2.5}$ exposure with brain atrophy were considered as the potential confounders. To reduce the possibility that some factors may be involved in the causal pathways of diet/

$PM_{2.5}$ exposure and brain atrophy (e.g., hypertension, diabetes, hypercholesterolemia, and cardiovascular diseases), we used the data collected at baseline (1996–1998). Baseline characteristics were measured by trained professionals at clinical centers or collected through self-administered questionnaires. These included intracranial volume, demographics (age, race/ethnicity, and U.S. region), socioeconomic status (education and employment status), lifestyle factors [smoking status, alcohol consumption, body mass index (BMI), recreational physical activity, and total energy intake], medical histories (hypertension, diabetes, hypercholesterolemia, and cardiovascular diseases), and WHI-HRT treatment assignment. Intracranial volume has been commonly adjusted in studies of brain atrophy to reduce the bias from difference in brain size. Total energy intake has been commonly considered as a confounder in nutritional studies to reduce the bias from difference in overall diet, and was associated with obesity, which is related to dementia and brain atrophy (Beydoun et al. 2008). Therefore, we adjusted for total energy intake in the main model of the MIND score. Weight and height were measured at baseline to calculate BMI as weight (kilogram) divided by height squared (square meter). Hypertension was defined by self-reported prior diagnosis or use of antihypertensive medications, or measured elevated blood pressure at baseline (systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 mmHg) (Honda et al. 2017). Diabetes was based on self-reported history (when not pregnant) or current treatment (Margolis et al. 2008). Hypercholesterolemia was defined by self-reported use of lipid control medications (Chen et al. 2015). History of cardiovascular diseases was based on self-reported previous coronary heart disease (myocardial infarction, coronary angioplasty, or coronary artery bypass graft), stroke, or transient ischemic attack (Chen et al. 2015). Because this study is ancillary to WHI-HRT, participants were randomly assigned with equal probability to hormone therapy (0.625 mg/d conjugated equine estrogen with/without 2.5 mg/d medroxyprogesterone depending on hysterectomy status) or matching placebo. Those who received hormone therapy might have different diet and brain atrophy compared to controls; thus this assignment was considered as a potential confounder.

Race/ethnicity was self-reported by participants in response to the question "How would you describe your racial or ethnic group? If you are of mixed blood, which group do you identify with most?" They could respond with the options: American Indian or Alaskan Native, Asian or Pacific Islander (ancestry is Chinese, Indo-Chinese, Korean, Japanese, Pacific Islander, Vietnamese), Black or African American (not of Hispanic origin), Hispanic or Latino (ancestry is Mexican, Cuban, Puerto Rican, Central American, or South American), White (not of Hispanic origin), and Other. Participants were asked to indicate the single group that they most identified with. Only 109 of the 1,302 participants included in this analysis self-reported that their race/ethnicity was something other than non-Hispanic White, including 4 American Indians or Alaskan Natives, 20 Asians or Pacific Islanders, 57 non-Hispanic Black people or African Americans, 18 Hispanics or Latinos, and 10 others. Because of the small numbers within more specific subgroups, we grouped all other race/ethnicity categories together for analyses. Although we were only able to use a dichotomous race/ethnicity variable, it was found to be related to MIND score quartiles (Table 2). In addition, dichotomous race/ethnicity has been collected and adjusted in other cohorts investigating diet (McEvoy et al. 2019; Pearson et al. 2016) and $PM_{2.5}$ exposure (Loop et al. 2013; Wang et al. 2014) with brain aging or cognitive outcomes. Thus, we believe that race/ethnicity is a demographic factor and a marker of socioeconomic status that is very likely to be a confounder in our analyses, and the dichotomous variable should be sufficient to control for its confounding.

Table 2. Baseline (1996–1998) characteristics of the study population by quartiles (Q) of baseline MIND score ($n = 1,302$).

Categories	Total	Quartiles of MIND scores (points)				p-Value
		Q1 (≤5.5)	Q2 (5.6–6.5)	Q3 (6.6–7.5)	Q4 (>7.5)	
n	1,302	364	298	298	342	—
Median points	6.5	5.0	6.3	7.0	8.5	—
Age (y)	69.7 ± 3.6	69.3 ± 3.6	69.5 ± 3.5	69.7 ± 3.5	70.2 ± 3.7	0.0074
Race/ethnicity	—	—	—	—	—	0.0051
Non-Hispanic White	1,193 (91.6)	345 (28.9)	274 (23.0)	275 (23.0)	299 (25.1)	—
Other[a]	109 (8.4)	19 (17.4)	24 (22.0)	23 (21.1)	43 (39.5)	—
U.S. region	—	—	—	—	—	<0.001
Northeast	304 (23.3)	72 (23.7)	58 (19.1)	80 (26.3)	94 (30.9)	—
South	186 (14.3)	46 (24.7)	41 (22.1)	53 (28.5)	46 (24.7)	—
Midwest	465 (35.7)	171 (36.8)	130 (27.9)	83 (17.9)	81 (17.4)	—
West	347 (26.7)	75 (21.6)	69 (19.9)	82 (23.6)	121 (34.9)	—
Education	—	—	—	—	—	<0.001
Less than high school	54 (4.1)	25 (46.3)	8 (14.8)	10 (18.5)	11 (20.4)	—
High school graduate or equivalents	298 (22.9)	118 (39.6)	75 (25.2)	51 (17.1)	54 (18.1)	—
College graduate or higher degree	950 (73.0)	221 (23.2)	215 (22.6)	237 (25.0)	277 (29.2)	—
Employment	—	—	—	—	—	0.21
Currently employed	236 (18.1)	77 (32.6)	49 (20.8)	51 (21.6)	59 (25.0)	—
Currently not employed	139 (10.7)	40 (28.8)	27 (19.4)	26 (18.7)	46 (33.1)	—
Retired	927 (71.2)	247 (26.6)	222 (24.0)	221 (23.8)	237 (25.6)	—
Smoking status	—	—	—	—	—	0.034
Never	751 (57.7)	232 (30.9)	174 (23.2)	167 (22.2)	178 (23.7)	—
Former	494 (37.9)	114 (23.1)	110 (22.2)	118 (23.9)	152 (30.8)	—
Current	57 (4.4)	18 (31.6)	14 (24.6)	13 (22.8)	12 (21.0)	—
Alcohol consumption	—	—	—	—	—	<0.001
Never	163 (12.5)	60 (36.8)	39 (23.9)	29 (17.8)	35 (21.5)	—
Former	213 (16.4)	75 (35.2)	49 (23.0)	44 (20.7)	45 (21.1)	—
Current <1 drink/d	777 (59.7)	205 (26.4)	179 (23.0)	194 (25.0)	199 (25.6)	—
Current ≥1 drink/d	149 (11.4)	24 (16.1)	31 (20.8)	31 (20.8)	63 (42.3)	—
BMI	—	—	—	—	—	<0.001
<25.0 kg/m²	391 (30.0)	80 (20.5)	82 (21.0)	92 (23.5)	137 (35.0)	—
25.0–29.9 kg/m²	491 (37.7)	129 (26.2)	124 (25.3)	114 (23.2)	124 (25.3)	—
≥30.0 kg/m²	420 (32.3)	155 (36.9)	92 (21.9)	92 (21.9)	81 (19.3)	—
Moderate or strenuous activities ≥20 min	—	—	—	—	—	<0.001
No activity	733 (56.3)	253 (34.5)	183 (25.0)	147 (20.0)	150 (20.5)	—
Some activity	76 (5.8)	19 (25.0)	17 (22.4)	16 (21.0)	24 (31.6)	—
2–4 episodes/wk	261 (20.1)	64 (24.5)	51 (19.5)	66 (25.3)	80 (30.7)	—
≥4 episodes/wk	232 (17.8)	28 (12.1)	47 (20.3)	69 (29.7)	88 (37.9)	—
Total energy intake (kcal/d)	1,536 (1,160–1,939)	1,669 (1,257–2,081)	1,565 (1,159–1,919)	1,454 (1,092–1,868)	1,454 (1,117–1,803)	<0.001
Baseline 3MS score (points)	97 (95–99)	97 (95–98)	97 (95–99)	97 (95–99)	97 (94–99)	0.18
Hypertension (self-report, medications, or measured elevated BP)	—	—	—	—	—	>0.99
No	634 (48.7)	177 (27.9)	144 (22.7)	145 (22.9)	168 (26.5)	—
Yes	668 (51.3)	187 (28.0)	154 (23.1)	153 (22.9)	174 (26.0)	—

Table 2. (*Continued.*)

Categories	Total	Quartiles of MIND scores (points)				p-Value
		Q1 (≤5.5)	Q2 (5.6–6.5)	Q3 (6.6–7.5)	Q4 (>7.5)	
Diabetes (self-report or medications)	—	—	—	—	—	0.80
No	1,257 (96.5)	352 (28.0)	285 (22.7)	289 (23.0)	331 (26.3)	—
Yes	45 (3.5)	12 (26.7)	13 (28.9)	9 (20.0)	11 (24.4)	—
Hypercholesterolemia (self-report or medications)	—	—	—	—	—	0.0057
No	1,094 (84.0)	321 (29.3)	258 (23.6)	237 (21.7)	278 (25.4)	—
Yes	208 (16.0)	43 (20.7)	40 (19.2)	61 (29.3)	64 (30.8)	—
Cardiovascular disease (self-report)	—	—	—	—	—	0.34
No	1,121 (86.1)	316 (28.2)	249 (22.2)	254 (22.7)	302 (26.9)	—
Yes	181 (13.9)	48 (26.5)	49 (27.1)	44 (24.3)	40 (22.1)	—
WHI-HRT treatment assignment	—	—	—	—	—	0.62
Estrogen-alone intervention	242 (18.6)	75 (31.0)	58 (24.0)	55 (22.7)	54 (22.3)	—
Estrogen+progesterone intervention	405 (31.1)	112 (27.7)	84 (20.7)	98 (24.2)	111 (27.4)	—
Placebo	655 (50.3)	177 (27.1)	156 (23.8)	145 (22.1)	177 (27.0)	—
3-y moving average $PM_{2.5}$ ($\mu g/m^3$)	11.8 ± 2.5	11.8 ± 2.3	11.7 ± 2.3	11.7 ± 2.4	12.2 ± 2.7	0.050

Note: Results are presented as means ± standard deviations and medians [interquartile ranges (IQRs)] for continuous variables and counts (percent across quartiles of MIND score) for categorical variables. *p*-Values are for any difference across quartiles of MIND score (Kruskal-Wallis test or chi-square test, as appropriate). —, no data; BMI, body mass index; BP, blood pressure; min, minutes; MIND, Mediterranean–DASH Intervention for Neurodegenerative Delay; WHI-HRT, Women's Health Initiative Hormone Replacement Therapy trial; 3MS, the modified Mini-Mental State.
[a] Disaggregated data for participants in the "Other" race/ethnicity group is provided in Table S5.

Statistical Analyses

Participants' baseline characteristics were summarized with means ± standard deviations, medians [interquartile ranges (IQRs)] or numbers of participants (proportions). Kruskal-Wallis tests and chi-square tests were used to assess the overall differences across quartiles of MIND score.

Multivariable linear regression models were used to examine the associations between MIND score and brain volumes with adjustment for intracranial volume, age, race/ethnicity (non-Hispanic White or others), U.S. regions (Northeast, South, Midwest, or West), education levels (less than high school, high school graduate or equivalents, or college graduate or higher degree), employment (currently employed, currently not employed, or retired), smoking status (never, former, or current smokers), alcohol consumption (never, former, current drinkers <1 drink/d, or current drinkers ≥1 drink/d), BMI (<25.0, 25.0–29.9, or ≥30.0 kg/m²), moderate or strenuous recreational physical activity ≥20 min (none, some activity, 2–4 episodes/wk, or >4 episodes/wk), medical histories (hypertension, diabetes, hypercholesterolemia, and cardiovascular diseases; yes or no), WHI-HRT treatment assignment (estrogen-alone, estrogen+progesterone intervention, or placebo), and total energy intake.

We estimated associations between $PM_{2.5}$ exposure and brain volumes using multivariable linear regression adjusted for all covariates except total energy intake. Separate models were used to estimate the associations between $PM_{2.5}$ and brain volumes for women with low MIND diet scores (< the median score of 6.5 points) and women with high MIND diet scores (≥6.5 points), respectively. We used additional covariate-adjusted models that included multiplicative product terms for $PM_{2.5}$ exposure (continuous) and the dichotomous MIND diet score to derive interaction *p*-values.

Several sensitivity analyses were performed to gauge the robustness of the results. First, diet or $PM_{2.5}$ exposure might have increased the risk of stroke after baseline, and stroke might have led to changes in brain volumes, thus making it a potential causal intermediate. Women with a history of stroke during the 6 months before enrollment were excluded from the WHI-HRT study, but 126 participants experienced a stroke after baseline but before the WHIMS MRI was performed. Therefore, we performed a sensitivity analysis after excluding these women to assess whether stroke events after baseline might have been involved in the associations between diet or $PM_{2.5}$ and MRI outcomes. Second, although all participants had normal cognition based on the 3MS score (Teng and Chui 1987) and they were free from clinically diagnosed dementia at baseline, those with better cognitive health (indicated by a higher 3MS score) might have larger brain volumes. A healthy diet is also related to better cognition. Thus, we additionally adjusted for the baseline 3MS score to further reduce the potential bias resulting from the differences in brain health at baseline (Chen et al. 2015). Third, SVID volume was negatively correlated with normal-appearing white matter volume according to our previous study of $PM_{2.5}$ exposure and MRI outcomes (Chen et al. 2015), and it might be affected by diet or $PM_{2.5}$ exposure. Thus, we additionally adjusted for SVID volume in each region to explore whether SVID could affect the observed associations. Fourth, we estimated associations between 15 individual MIND diet components and brain volumes using multivariable linear regression models adjusted for the covariates included in the primary models. For each MIND diet component, participants with the highest component score (i.e., 1) were compared with those with the lowest component score (i.e., 0). Fifth, because the overall benefits of adherence to a MIND-like diet may be driven by dietary intakes of individual nutrients and dietary constituents, we used available data and separate models to estimate associations of MRI outcomes with IQR increases in estimated intakes of folate, vitamin B_6, vitamin B_{12}, vitamin C, vitamin E, α-carotene, β-carotene, LCn3PUFAs,

saturated fat, and *trans* fat, respectively, adjusted for the primary model covariates. In a previous subset of WHIMS-MRI, we found that higher levels of LCn3PUFAs in red blood cells and in diet were associated with larger white matter volumes and appeared to modify the association between $PM_{2.5}$ exposure and white matter volumes (Chen et al. 2020), which supports this sensitivity analysis.

All analyses were performed using SAS (version 9.4; SAS Institute). Two-sided $p \leq 0.05$ were considered statistically significant for all analyses, including interactions. In addition we reported *p*-values that were adjusted for multiple comparisons using the Benjamini-Hochberg procedure (Hochberg and Benjamini 1990).

Results

In the study cohort (Table 2), the average age at baseline was 70 y (± 3.6 y). The participants were predominately non-Hispanic White individuals (92% of the population), but women in the "Other" race/ethnicity category were more likely to have MIND scores in the highest quartile in comparison with non-Hispanic White participants. On average, women with higher (vs. lower) MIND diet scores were older and were more likely to have had some college education, have been former smokers, consume ≥ 1 alcoholic drink per day, have a normal BMI ($<25.0 \text{ kg/m}^2$), engage in moderate or strenuous physical activity, consume less total energy intake, and have had a history of hypercholesterolemia when enrolled in the WHI-HRT (in the period 1996–1998). In addition, 3-y average $PM_{2.5}$ exposures prior to MRI were higher among those with MIND diet scores in the top quartile ($12.2 \pm 2.7 \text{ µg/m}^3$) compared with the lowest quartile ($11.8 \pm 2.5 \text{ µg/m}^3$). There were no significant differences in the total intracranial volume or in intracranial-volume-adjusted SVID-affected brain volumes (measured in 2005–2006) according to MIND diet score quartiles (Table S4). The baseline (1996–1998) characteristics of participants in WHI-HRT and WHIMS, in comparison with those in this study, are shown in Table S5. At baseline in the period 1996–1998, women in the present study were older than those not recruited from the WHI-HRT per enrollment criteria (69 y, IQR 67–72 vs. 63 y, IQR 58–69 for WHI-HRT). In this analysis and WHI-HRT, non-Hispanic Black people/African Americans accounted for the largest proportion of women in the categories excluding Non-Hispanic Whites. Non-Hispanic Black people/African Americans (4% vs. 10% for WHI-HRT) and Hispanics/Latinos (1% vs. 6% for WHI-HRT) were more likely to be excluded from the present analysis in comparison with WHI-HRT; thus women in the present analysis were more likely to be non-Hispanic White (92% vs. 81% for WHI-HRT). In addition, compared with those not recruited from the WHI-HRT, women in the present analysis were less likely to live in the South (14% vs. 26% for WHI-HRT), more likely to live in the Midwest (36% vs. 25% for WHI-HRT), more likely to have college or above degree (73% vs. 70% for WHI-HRT), more likely to be never-smokers (58% vs. 50% for WHI-HRT), more likely to have current

alcohol consumption <1 drink/d (60% vs. 55% for WHI-HRT), less likely to be obese (BMI $\geq 30 \text{ kg/m}^2$, 32% vs. 38% for WHI-HRT), more likely to have hypertension (51% vs. 45% for WHI-HRT) and hypercholesterolemia (16% vs. 14% for WHI-HRT), and less likely to have diabetes (4% vs. 6% for WHI-HRT). Median MIND diet scores were the same for all three groups (7 points, IQR 6–8).

A 0.5-point increase in the MIND diet score was associated with a 0.74 cm^3 [95% confidence interval (CI): 0.001, 1.48] higher average total white matter volume (WMV) when adjusted for covariates (Table 3). A 0.5-point increase in MIND diet score was also associated with a nominally significant higher average WMV in the temporal lobe (0.19 cm^3, 95% CI: 0.002, 0.37), whereas associations were positive but not significant for WMV in the frontal lobe (0.33 cm^3, 95% CI: –0.01, 0.67) and parietal lobe (0.18 cm^3, 95% CI: –0.03, 0.39). Associations between MIND diet scores and WMV in the corpus callosum, and associations with total brain, normal brain, and hippocampus volumes, were null or close to the null. The *p*-values were larger and all >0.05 with the adjustment for multiple comparisons.

Associations between 0.5-point increases in MIND diet scores and brain volumes were similar but slightly attenuated when 126 women who had a stroke during follow-up were excluded, and after adjustment for SVID volume (e.g., estimated mean differences in total WMV were 0.64 cm^3; 95% CI: –0.12, 1.40 and 0.57 cm^3; 95% CI: –0.11, 1.26, respectively) (Table S6). Adjusting for the 3MS score at baseline had little influence on model estimates (Table S6). Estimated associations with individual food groups that contribute to the MIND diet score indicated that high (*vs.* low) consumption of several brain-healthy foods (leafy greens, other vegetables, beans, nonfried fish, and nonfried poultry) and low (vs. high) consumption of two brain-unhealthy foods (red meat and fried foods), was positively associated with brain volumes and WMV (Table S7). However, model estimates also suggested lower volumes in association with high consumption of some brain healthy foods (whole grains and nuts) and low consumption of some brain-unhealthy foods (butter or margarine and cheese), whereas both positive and inverse associations with individual outcomes were estimated for other dietary components. IQR increases in several individual nutrients were associated with higher brain volumes and WMV in most locations, specifically, folate (significant for hippocampus), vitamin C (significant for normal brain and hippocampus), α-carotene (significant for frontal lobe WMV), β-carotene (significant for total and frontal lobe WMVs), and LCn3PUFAs (significant for all WMVs, consistent with a previous WHIMS-MRI analysis by Chen et al. 2020) (Table S8). IQR increases in saturated fat and trans-fat intakes were associated with lower volumes in most locations (nonsignificant) (Table S8). However, associations with intakes of vitamins B_6, B_{12}, and E were null or inverse (nonsignificant) (Table S8).

Consistent with a prior report (Chen et al. 2015), an IQR (3.22 µg/m^3) increase in 3-y $PM_{2.5}$ prior to MRI was associated

Table 3. Multivariable linear regression of normal-appearing brain volumes (measured by MRI in 2005–2006) with baseline MIND score ($n = 1,302$).

Categories	Adjusted β (95% CI)	Unadjusted *p*-Value	Benjamini-Hochberg *p*-Value
Total brain	0.10 (−0.17, 0.38)	0.47	0.90
Normal brain	0.23 (−0.15, 0.61)	0.23	0.90
Total white matter	0.74 (0.001, 1.48)	0.050	0.33
Frontal lobe	0.33 (−0.01, 0.67)	0.055	0.33
Parietal lobe	0.18 (−0.03, 0.39)	0.087	0.43
Temporal lobe	0.19 (0.002, 0.37)	0.047	0.33
Corpus callosum	0.001 (−0.02, 0.02)	0.90	0.90
Hippocampus	0.0007 (−0.02, 0.02)	0.59	0.90

Note: The associations are expressed as the linear regression coefficients (95% CI, cubic centimeters) per 0.5-point increment in the continuous variable of MIND score using linear regression models. All models were adjusted for intracranial volume, age, race/ethnicity, U.S. regions, education levels, employment, smoking status, alcohol consumption, BMI, physical activity, medical histories of hypertension, diabetes, hypercholesterolemia, and cardiovascular diseases, WHI-HRT treatment assignment, and total energy intake. The *p*-values were adjusted for multiple comparisons with the Benjamini-Hochberg procedure. BMI, body mass index; CI, confidence interval; MIND, Mediterranean–DASH Intervention for Neurodegenerative Delay; MRI, magnetic resonance imaging; WHI-HRT, Women's Health Initiative Hormone Replacement Therapy trial.

Table 4. The associations [adjusted β(95% CI)] between PM$_{2.5}$ exposure before MRI and normal-appearing brain volumes (measured by MRI in 2005–2006) stratified by baseline MIND score ($n = 1,302$).

Categories	MIND diet score <6.5 (median)	MIND diet score ≥6.5 (median)	Unadjusted p for interaction	Benjamini-Hochberg adjusted p for interaction
Total brain	−0.51 (−2.28, 1.25)	−0.17 (−1.50, 1.16)	0.69	0.78
Normal brain	−0.41 (−2.81, 1.99)	1.04 (−0.79, 2.87)	0.78	0.78
Total white matter	−12.47 (−17.17, −7.78)	0.16 (−3.41, 3.72)	<0.001	<0.001
Frontal lobe	−4.56 (−6.61, −2.51)	0.70 (−0.99, 2.39)	<0.001	0.0011
Parietal lobe	−1.97 (−3.35, −0.59)	0.90 (−0.10, 1.90)	<0.001	0.0021
Temporal lobe	−3.27 (−4.44, −2.10)	−0.48 (−1.35, 0.40)	<0.001	0.0021
Corpus callosum	−0.16 (−0.29, −0.02)	−0.09 (−0.19, 0.01)	0.45	0.78
Hippocampus	−0.01 (−0.12, 0.11)	−0.02 (−0.11, 0.07)	0.48	0.78

Note: The associations are expressed as the linear regression coefficients (95% confidence interval, cubic centimeters) per interquartile (3.22 µg/m^3) increment in the continuous variable of PM$_{2.5}$ exposure prior to the MRI examination. All models were constructed using linear regression models with the adjustment for intracranial volume, age, race/ethnicity, U.S. regions, education levels, employment, smoking status, alcohol consumption, BMI, physical activity, medical histories of hypertension, diabetes, hypercholesterolemia, and cardiovascular diseases, and WHI-HRT treatment assignment. The multiplicative product of the continuous PM$_{2.5}$ exposure and the dichotomous variable of MIND score levels was included in the models to test for significant interactions. The p-values of the interaction terms were adjusted for multiple comparisons with the Benjamini-Hochberg procedure. BMI, body mass index; CI, confidence interval; MIND, Mediterranean–DASH Intervention for Neurodegenerative Delay; MRI, magnetic resonance imaging; WHI-HRT, Women's Health Initiative Hormone Replacement Therapy trial.

with significantly lower average total, temporal lobe, and corpus callosum WMVs (e.g., for total WMV, –4.16 cm^3; 95% CI: –6.99, –1.33) (Table S9). Among women with MIND diet scores below the median, an IQR increase in 3-y PM$_{2.5}$ was associated with lower average total, frontal lobe, parietal lobe, and temporal lobe WMVs, while associations with the same outcomes were positive or negative but closer to the null for women with MIND diet scores above the median (all nominal interaction $p < 0.001$) (Table 4). For example, an IQR increase in PM$_{2.5}$ was associated with a –12.47 cm^3 average difference in total WMV (95% CI: –17.17, –7.78) among women with lower MIND diet scores, compared with an average difference of 0.16 cm^3 (95% CI: –3.41, 3.72) among women with higher MIND diet scores. In contrast, there were no clear differences in associations between PM$_{2.5}$ and total brain volume, normal brain volume, hippocampus volume, or corpus callosum WMV between women with high vs. low MIND diet scores (interaction p-values 0.45–0.78). In the sensitivity analyses when women who experienced stroke during follow-up were excluded, and with additional adjustment for baseline 3MS scores or for SVID volume, differences in associations between PM$_{2.5}$ and the outcomes between women with low and high MIND diet scores were consistent with the primary analysis (Table S10).

Discussion

In this prospective cohort of older women, a higher MIND diet score at baseline, consistent with greater adherence to a MIND-like diet, was associated with larger WMVs 7–10 y later. In addition, associations between PM$_{2.5}$ exposure and lower WMVs were stronger among women with MIND diet scores below the median but close to the null for women with scores above the median. White matter tracts interconnect widely distributed cognitive networks; thus white matter abnormalities, particularly those due to impaired myelin and oligodendrocytes (the cells responsible for the production and maintenance of myelin), could exacerbate the clinical manifestations of underlying cortical-based neurodegenerative diseases such as Alzheimer's disease (Nasrabady et al. 2018).

Although this study is one of a few studies to examine the association between MIND diet and brain structure, our findings are in concordance with evidence relating the Mediterranean diet to more normative white matter brain structure (Gardener et al. 2012; Gu et al. 2015; Pelletier et al. 2015; Rodrigues et al. 2020). Evidence of higher average white matter volumes in women with greater adherence to a MIND-like diet was further supported by findings for intakes of individual MIND diet components and specific nutrients.

Vegetables are major sources of B vitamins, vitamin C, vitamin E, carotenoids, and flavonoids. These nutrients have been related to reduction in white matter lesions (Bowman et al. 2012; Cavalieri et al. 2012; den Heijer et al. 2001; Gopalan et al. 2014; Gu et al. 2016; Ohshima et al. 2013; Prinelli et al. 2019; Shishtar et al. 2020). In our sensitivity analysis of single nutrients, α-carotene and β-carotene intakes were associated with greater WMVs, particularly in the frontal lobe. Insufficient intakes of B vitamins, particularly folate, vitamin B$_{12}$, and vitamin B$_6$, may cause hyperhomocysteinemia, which is an established risk factor for white matter damage and Alzheimer's disease (Hooshmand et al. 2013; Smith and Refsum 2016). In a clinical trial of patients with severe cerebral small vessel disease, B vitamin supplementation was associated with a significant reduction in white matter hyperintensity volume (Cavalieri et al. 2012). In addition, antioxidants, such as vitamin C, vitamin E, carotenoids, and flavonoids, have been associated with less severe white matter damage. In several cross-sectional analyses comparing the differences in middle-age and older adults, higher serum carotenoid levels were associated with less-severe periventricular white matter lesions (den Heijer et al. 2001), lower serum vitamin C and vitamin E levels were associated with worse deep white matter lesions (Ohshima et al. 2013), and higher dietary flavonoid intakes were associated with smaller white matter hyperintensity volume (Shishtar et al. 2020). A 2-y randomized clinical trial found that supplementation with vitamin E attenuated the progression of white matter lesions possibly by reducing glutamate-induced excitotoxicity (Gopalan et al. 2014), which may cause increased vulnerability and death of oligodendrocytes (Pak et al. 2003). In a rat model, Epimedium flavonoids significantly alleviated white matter nerve fiber injuries and demyelination, and increased the number of mature oligodendrocytes in the white matter (Niu et al. 2020). Thus, nutrients with antioxidative properties may alleviate white matter loss by protecting mature oligodendrocytes and facilitating remyelination, though intakes of vitamins B$_6$, B$_{12}$, and E were not associated with higher average WMV in this study population.

Besides vegetables, nonfried fish intake is a source of LCn3PUFAs and is another important component of MIND diet that may be responsible for the observed associations of MIND-like diet with WMV, as reported by a previous analysis of a subset of the same women included in the present analysis (Chen et al. 2020). In some cross-sectional studies of human, higher nonfried fish intake (Virtanen et al. 2008) and blood omega–3 fatty acid levels (Bowman et al. 2012; Bowman et al. 2013; Nagai et al. 2015; Suwa et al. 2015; Tan et al. 2012) have been associated with lower white matter hyperintensity volume. In *in vitro* studies, LCn3PUFAs have been reported to protect oligodendrocytes against excitatory cell death (Pu et al. 2013) and induce M2 polarization in cultured microglia (Chen et al. 2014), which supports the hypothesis that LCn3PUFAs can promote the

remyelination of white matter by resolving local inflammation (Miron et al. 2013).

The "brain-unhealthy" components of the MIND diet are high in saturated and/or *trans* fats. Higher intakes of saturated and *trans* fats were associated with lower average WMVs in our study, though the associations were not statistically significant. In previous cross-sectional analyses of older adults, nutrient patterns with high intakes of *trans* and/or saturated fats were associated with greater white matter hyperintensities volume (Prinelli et al. 2019) and smaller total cerebral brain volume (Bowman et al. 2012).

In the population as a whole, higher MIND diet scores, indicating greater adherence to a MIND-like diet, were associated with higher average WMV, whereas higher 3-y average $PM_{2.5}$ exposure was associated with lower WMV. However, the association between $PM_{2.5}$ and lower WMV appeared to be stronger among women with MIND diet scores below the median and absent among women with higher MIND diet scores. Although underlying molecular mechanisms of $PM_{2.5}$ neurotoxicity are uncertain, several interconnected mechanisms might explain why greater adherence to a MIND-like diet appeared to be protective in our study population. First, short-term (24-h or 7-d moving average) $PM_{2.5}$ exposure has been associated with higher plasma total homocysteine (Baccarelli et al. 2007; Ren et al. 2010), which, in turn, has been associated with lower cerebral WMV (Feng et al. 2013) and greater white matter hyperintensities (Vermeer et al. 2002). Particulate air pollutants may increase homocysteine levels by disrupting the remethylation of homocysteine to methionine (Park et al. 2008). A previous study of short-term ambient air pollution and plasma homocysteine concentrations in older men reported positive associations with black carbon and organic carbon among men with plasma folate and vitamin B_{12} concentrations below the study population median and reported null associations among men with higher plasma folate and vitamin B_{12} levels (Park et al. 2008). These findings suggest that high levels of homocysteine-lowering B vitamins might protect against white matter damage by mitigating PM-mediated increases in homocysteine. However, the authors did not find significant differences in associations between $PM_{2.5}$ and homocysteine in relation to plasma folate or B_{12} levels. In addition, although estimated folate intakes were positively associated with hippocampus volume in our study population, estimated B_{12} intakes did not appear to be beneficial. Second, the organic fraction coated at the surface of particles and the transition metals of the particles' core can generate reactive oxygen species able to induce systematic oxidative DNA damage (Fougère et al. 2015). Myelinating oligodendrocytes in the brain are highly sensitive to oxidative stress (Kim et al. 2020), which impairs the differentiation of oligodendrocyte precursor cells (French et al. 2009) and may result in myelin loss and white matter abnormalities. Natural antioxidants including vitamins, carotenoids, and flavonoids have been proposed to ameliorate oxidative damage in humans and nonhuman models of Alzheimer's disease (Butterfield and Halliwell 2019), and thus they may protect oligodendrocytes and white matter from the oxidative damages induced by $PM_{2.5}$ exposure. Third, $PM_{2.5}$ exposure also might have a direct influence on myelin loss and/or chronic microglial activation, as suggested by experimental evidence that ambient fine particle matter induced decreased myelin basic protein and increased Iba1 immunostaining, a marker for microglial activation, in a mouse model (Woodward et al. 2017). On the other hand, as suggested in an *in vivo* and *in vitro* study of mice fed with LCn3PUFAs-enriched diet, LCn3PUFAs prevented the loss of myelin basic protein, attenuated the myelin sheath damage, and maintained the nerve fiber conduction velocity following a controlled cortical impact (Pu et al. 2013). LCn3PUFAs also inhibited the degeneration of oligodendrocytes directly and prevented the demise of oligodendrocytes

indirectly by mitigating microglial activation in microglia/oligodendrocyte cocultures (Pu et al. 2013). We recently reported that the association between $PM_{2.5}$ and lower WMV was attenuated or absent among WHIMS-MRI participants with high levels of RBC LCn3PUFAs and high estimated dietary intakes of LCn3PUFAs (Chen et al. 2020). Overall, existing evidence supports the potential for high dietary intake of LCn3PUFAs to counteract possible neurotoxic effects of $PM_{2.5}$ on white matter.

A limitation of our study is that MIND diet score was calculated based on the existing dietary information derived from the WHI FFQ, which is slightly different from the original Rush MAP FFQ (Morris et al. 2015a) on which the MIND score was based. WHI FFQ also has a limitation that is similar to that of MAP FFQ, which is that only limited foods were queried for some food groups. For example, WHI FFQ only asked about the consumption of strawberries and kiwi for berry consumption in one question, whereas MAP FFQ only asked about strawberries. Second, diet was self-reported based on participants' recalls of "usual" intakes in the prior 3 months and was measured only once at baseline, which limited our ability to assess variation in diet over time. Third, brain volumes were measured only once; thus we were not able to assess changes in brain structure over time. Fourth, WHIMS-MRI study used standardized protocols for MRI scanning across all participating centers and has been well known for its solid brain image data, but there may be instrument-related variability in the brain volumetric data, which is common in multisite MRI studies. A new method has been recently developed to harmonize structural brain MRI data across diverse studies (Pomponio et al. 2020), which may be used in future WHIMS-MRI studies. Fifth, as with other observational studies, residual confounding by unobserved or unmeasured factors, such as factors related to overall healthy lifestyle and baseline intelligence, might bias our results. We adjusted for baseline status of other diseases to reduce the likelihood that these medical history variables were intermediates of the associations of interest, but this possibility was not zero. Sixth, this study included only older women who were predominately non-Hispanic White; thus our findings may not be generalized to men, younger women, or other specific racial groups/ethnicities. In addition, we were not able to separate those with other races/ethnicities to more specific subgroups. Therefore, residual confounding may be possible. Seventh, the present study focused on $PM_{2.5}$ as a regional pollutant, but other unmeasured pollutant mixtures might have similar influences on brain structure and confounded our results. Finally, estimates of $PM_{2.5}$ exposure were only available after 1999 by using the spatiotemporal model. Because air pollution levels have declined over the past 20 y, exposure to $PM_{2.5}$ during mid- or earlier life may exert a greater risk for accelerated aging of white matter, which should be investigated in future studies.

In conclusion, older women whose baseline diets were more consistent with the MIND-like dietary pattern had higher WMV than women with lower MIND diet scores. In addition, the association between 3-y average $PM_{2.5}$ exposure and lower WMV was strengthened among women with MIND diet scores below the median and became null among women with scores above the median. Overall, these findings provide further support for the benefits of a dietary pattern characterized by higher intakes of vegetables and nonfried fish and lower intakes of animal-based and high saturated fat foods to brain health.

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