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B vitamin intakes modify the association between particulate air pollutants and incidence of all-cause dementia: Findings from the Women's Health Initiative Memory Study

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Abstract

Introduction: Particulate air pollutants may induce neurotoxicity by increasing homocysteine levels, which can be lowered by high B vitamin intakes. Therefore, we examined whether intakes of three B vitamins (folate, B_{12}, and B_6) modified the association between $PM_{2.5}$ exposure and incidence of all-cause dementia.

Methods: This study included 7183 women aged 65 to 80 years at baseline. B vitamin intakes from diet and supplements were estimated by food frequency questionnaires at baseline. The 3-year average $PM_{2.5}$ exposure was estimated using a spatiotemporal model.

Results: During a mean follow-up of 9 years, 342 participants developed all-cause dementia. We found that residing in locations with $PM_{2.5}$ exposure above the regulatory standard (12 $\mu g/m^3$) was associated with a higher risk of dementia only among participants with lower intakes of these B vitamins.

Discussion: This is the first study suggesting that the putative neurotoxicity of $PM_{2.5}$ exposure may be attenuated by high B vitamin intakes.

Keywords

dementia; fine particulate matter; folate; $PM_{2.5}$; vitamin B_{12}; vitamin B_6

1 | NARRATIVE

1.1 | Contextual background

Dementia currently affects nearly 50 million individuals worldwide, and this number may triple by 2050.[1] Although there is no cure for dementia yet, prevention through risk factor modification has the potential to curb the increasing number of people living with dementia.[2] Thus, concrete steps have been taken toward the identification of modifiable risk factors for dementia, such as environmental pollution and diet, during the last few decades.

Exposure to ambient fine particulate matter with diameter <2.5 μm ($PM_{2.5}$) has been increasingly recognized as a novel environmental risk factor for dementia among the elderly.[3] Recent studies have reported associations of $PM_{2.5}$ exposure with brain atrophy, cognitive impairment, and higher risks of Alzheimer's disease and dementia.[4–6] Although the underlying molecular mechanisms of $PM_{2.5}$ neurotoxicity have not been fully understood, previous studies identified a positive association between $PM_{2.5}$ exposure and homocysteine,[7,8] a strong risk factor for dementia independent of sociodemographics, lifestyle, medical history, and apolipoprotein E (*APOE*) genetic susceptibility.[9] It is hypothesized that particulate air pollutants may increase homocysteine levels by disrupting the re-methylation of homocysteine to methionine.[10]

Lifelong nutrition may also have a direct effect on brain function. Previous longitudinal studies have reported associations of certain nutrients, including B vitamins, with brain atrophy and cognitive decline, with some clinical trials confirming these results.[11] Among

the eight B vitamins, three are of particular interest because of their important roles in homocysteine metabolism. Folate and vitamin B_{12} are cofactors required in the re-methylation of homocysteine, while vitamin B_6 is required in a trans-sulfuration pathway that converts homocysteine into cysteine.[12] Thus, physiologic homocysteine levels are determined primarily by dietary intake of folate, vitamin B_{12}, or vitamin B_6. The homocysteine-lowering effects of these three nutrients have been well demonstrated in randomized controlled trials supplemented with single- or multi-B vitamins.[13]

Therefore, we hypothesized that high levels of folate, vitamin B_{12}, and/or vitamin B_6 might counteract the potential neurotoxicity of $PM_{2.5}$ by reducing the level of homocysteine induced by $PM_{2.5}$ exposure. This hypothesis is supported by one previous study, which reported that the associations of exposure to traffic-related particles with total homocysteine level differed comparing individuals with higher and lower concentrations of plasma folate and vitamin B_{12}; the positive association was only observed among those with lower concentrations of these two B vitamins.[10] However, no published studies have examined whether the dietary intakes of B vitamins offer similar protection against the neurotoxic effects of $PM_{2.5}$ exposure.

Here we report the first study that examined the potential effect modification of dietary and supplemental B vitamin intakes on the putative adverse effect of $PM_{2.5}$ exposure related to dementia risk. This study included 7183 community-dwelling women aged 65 to 80 years who were free of all-cause dementia in the Women's Health Initiative (WHI) Memory Study (WHIMS). We first examined the associations between intake of folate, vitamin B_{12}, or vitamin B_6 and incidence of all-cause dementia using multivariable-adjusted cause-specific Cox proportional hazard regression models. Then, we assessed the association between time-varying 3-year average $PM_{2.5}$ exposure and incidence of all-cause dementia using the same models, and categorized the analysis by the intakes of these B vitamins. We showed how the relation between $PM_{2.5}$ exposure and all-cause dementia differed in participants with high versus low B vitamin intakes. Finally, we make suggestions for future research that arise from these insights.

1.2 | B vitamins may be neurotrophic by reducing homocysteine level

Diet is a modifiable health behavior. Besides taking supplements, the general population can increase the intakes of folate, vitamin B_{12}, and vitamin B_6 by consuming more green leafy vegetables, grains, nuts, dairy products, seafoods, and organ meat.[11] The neurotrophic effects of folate, vitamin B_{12}, and vitamin B_6 are supported by their essential involvements in the metabolism of homocysteine,[12] which plays a fundamental role in dementia etiology and pathology.[9] High homocysteine levels can cause neurotoxicity through multiple mechanisms, such as by stimulating N-methyl-D-aspartate (NDMA) receptors leading to calcium influx and oxidative damage and downstream cell apoptosis in the brain,[14] and by promoting DNA damage that sensitizes neurons to amyloid beta ($A\beta$) toxicity.[15] In a healthy individual, levels of homocysteine are low due to two rapid metabolism pathways: folate- and vitamin B_{12}-dependent re-methylation of homocysteine to methionine, and a vitamin B_6-dependent trans-sulphuration pathway that converts homocysteine into cysteine.[16] Thus, disruption of the homocysteine cycle due to deficiency of these nutrients can lead to elevated

homocysteine levels and consequently an increased risk of dementia.[17] On the other hand, high intakes of folate, vitamin B_{12}, and vitamin B_6 can lower the level of homocysteine. In randomized controlled trials, supplementation of B vitamins significantly decreased blood homocysteine levels.[18,19] A meta-analysis of 11 large randomized controlled trials with 22,000 participants found that allocation to B vitamins lowered homocysteine concentrations by more than 25%.[18]

Although the homocysteine-lowering effects of the B vitamins have been promising, current epidemiological studies that investigated their neurotrophic effects have yielded inconsistent findings. Some longitudinal studies have suggested a significant inverse association between levels of folate, B_{12}, and B_6 and cognitive impairment or risk of dementia. But, randomized controlled trials generally show no obvious cognitive benefits of B vitamin supplementation.[13,19] For example, in a recent meta-analysis, B vitamin supplementation was not associated with significant improvement of cognitive function measured by Mini-Mental State Examination score.[13] Our study is similar to others that have found no significant benefits of B vitamins on cognition.[20–22] In this population of US elderly women, we found an inverse but not statistically significant association between intake of folate, vitamin B_{12}, or vitamin B_6 with incident all-cause dementia. The intake levels of B vitamins in this study are similar to other US cohorts.[23,24]

The inconsistency of findings in observational studies may be explained by the large variations in study design, population sampled, study quality, type of supplementation, duration of treatment, outcome measurement, and residual confounding. For example, in a previous report of a WHI cohort that investigated the association between B vitamin intakes and the incidence of a combined outcome including both mild cognitive impairment and probable dementia, a significant inverse association was found for folate, but not for vitamins B_{12} and B_6.[25] The null associations observed in this current study within the same cohort suggest that the neurotrophic effects of vitamin B intakes may also vary by the clinically defined neurocognitive endpoints and their associated neuropathological underpinnings. Therefore, evidence should be viewed in the context of the limitations of available data. In addition, the complex interactions between B vitamins and other nutrients as well as demographic, lifestyle, and medical factors make it difficult to conclude any effects of a single nutrient. For example, a greater cognitive benefit of vitamin B supplementation was found among individuals with higher plasma omega-3 fatty acid status in a randomized controlled trial.[26] Similarly, a significant interaction between vitamin B_{12} status and depression was observed; individuals with depression had more significant cognitive improvements associated with higher plasma concentrations of vitamin B_{12}.[27] To test these potential interactions, we performed several sensitivity analyses and found that the associations between B vitamin intakes and all-cause dementia incidence were more marked among individuals with higher dietary intake of long-chain omega-3 polyunsaturated fatty acids (LCn3PUFAs) or with prior depression, although interactions were not statistically significant. Thus, it is possible that interventions with B vitamins are unlikely to be successful in preventing cognitive decline without the consideration of other neurotrophic or neurotoxic factors. These reasons could explain the lack of substantive evidence from this study and trials of vitamin B supplementation designed to prevent dementia.

1.3 | Association of $PM_{2.5}$ exposure with dementia risk was modified by B vitamins possibly through homocysteine metabolism

Air pollution varies geographically because of differences in population density, emissions sources, economic activity, climate, and geophysical conditions,[28] which results in the different exposure levels of $PM_{2.5}$ in the US general population. In contrast to the homocysteine-lowering effect of B vitamins, $PM_{2.5}$ exposure may increase homocysteine levels and consequently result in neurotoxicity. Particle exposure, especially with transition metals bound to particles, may directly inactivate the enzymes involved in homocysteine re-methylation, such as methionine synthase.[29] In addition, reactive oxygen species generated by particle exposures may cause elevated levels of plasma homocysteine.[30] In previous studies, a positive association between $PM_{2.5}$ exposure and homocysteine levels has been observed in adults and infants.[7,8,31] Consequently, we hypothesized that $PM_{2.5}$ exposure might be associated with higher risk of dementia similar to a previous WHI study,[32] and this association might be attenuated by homocysteine-lowering B vitamins.

The median level of 3-year average $PM_{2.5}$ exposure in this study is 11 $\mu g/m^3$, which is similar to other US cohorts during the same years.[33,34] Using cause-specific Cox proportional hazard regression models, we found that women living in locations with ambient $PM_{2.5}$ exposure above the US National Ambient Air Quality Standard (NAAQS; >12 $\mu g/m^3$) had a higher incidence of all-cause dementia, but the point estimate did not reach statistical significance. This observation was generally consistent with previous studies of $PM_{2.5}$ with dementia risk; most studies in other countries reported significant associations while the findings were mixed in the United States.[35] The consistency of evidence regarding $PM_{2.5}$ neurotoxicity also varied by outcome. Most studies of $PM_{2.5}$ and cognitive functions suggested adverse associations, but studies of incident cognitive impairment or dementia were more limited and reported less consistent associations.[36]

However, B vitamin intakes significantly modified the association between $PM_{2.5}$ and dementia risk in this study. Among women with lower intake of folate or B_6 (below the median intake level), the association between $PM_{2.5}$ exposure and all-cause dementia incidence became statistically significant, while it remained non-significant among those with higher intake levels. A similar pattern of modifying effect of $PM_{2.5}$ was observed for vitamin B_{12}, though the interaction was not statistically significant. The pattern of modifying effects and tests of interaction persisted in all sensitivity analyses.

To test whether the observed effect modifications were due to homocysteine as hypothesized, we examined the correlations between plasma homocysteine concentration and B vitamin intakes and 3-year average $PM_{2.5}$ exposure among 274 participants who had plasma homocysteine measurements. We found plasma homocysteine concentration was inversely correlated with B vitamin intakes, and non-significantly positively correlated with 3-year average $PM_{2.5}$ exposure, which, to some extent, supports this hypothesis. This potential effect modification is also supported by studies that found B vitamin levels modified the neurotoxicity of other environmental chemicals in children and adults.[10,37,38] One study found a similar effect modification by B vitamin levels on the association between exposure to traffic-related particles and plasma homocysteine level.[10] The significant positive associations between black carbon and organic carbon exposures

with plasma homocysteine were more pronounced among those with low concentrations of plasma folate and vitamin B_{12}, but were attenuated among individuals with high concentrations. The consistent pattern of effect modification by vitamin B points to the important role of homocysteine involved in the complex pathways linking $PM_{2.5}$ exposure with the accelerated neuropathological processes of dementia.

1.4 | Limitations

First, objective measurements of B vitamins, such as measurements in the erythrocyte cell membrane, were not available. However, the use of a food frequency questionnaire (FFQ) to reflect the intakes of B vitamins is supported in a number of epidemiological studies.[22] Second, data of homocysteine levels were not available in the majority of this study cohort, which limited our ability to explore the potential mechanisms underlying the neurotrophic effects of B vitamins and their effect modification on $PM_{2.5}$ toxicity. Third, similar to other observational studies, the possibility of residual confounding from dietary and non-dietary factors cannot be completely ruled out even after multivariable adjustment. But the consistent results from the main and sensitivity analyses support the internal validity of our findings. Finally, the criteria for inclusion in the WHIMS are as broad as possible so that the results may be generalizable to the larger population of postmenopausal women.[39] However, this study only included elderly women who were predominately non-Hispanic White, thus our findings may not be generalized to men, younger women, or other racial groups/ethnicities. The levels of B vitamin intakes and $PM_{2.5}$ exposure in this study are similar to other US general populations. But, the interaction may not be seen in populations with different distributions and ranges of B vitamin intakes or $PM_{2.5}$ exposure.

1.5 | Conclusions and directions for future research

Findings from this prospective cohort study among elderly women suggest that the potential neurotoxicity of $PM_{2.5}$ exposure on dementia incidence may be more profound among those with lower intake of B vitamins, especially folate and vitamin B_6. Further laboratory studies are warranted to investigate the underlying mechanisms and determine whether homocysteine is driving the observed interaction. Observational studies are also needed to confirm whether B vitamin levels in diet or biomarkers mitigate the neurotoxic effects of $PM_{2.5}$ in other populations.

2 | CONSOLIDATED RESULTS AND STUDY DESIGN

This study used data from the WHIMS, which was an ancillary study to the WHI Clinical Trials (WHI-CT) of postmenopausal hormone therapy. The detailed study design and protocols of the WHI-CT and WHIMS studies are published elsewhere.[39] 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 WHIMS participating centers. In brief, a total of 7427 women, aged 65 to 80 years, free of all-cause dementia and community-dwelling, were recruited from 39 of the WHI clinical centers and 10 satellite sites between 1996 and 1999 (baseline) and were followed through 2010. After excluding 244 participants with incomplete dietary data or who reported an implausible total

energy intake (<600 or >5000 kcal/day), 7183 with data on B vitamin intake (dietary plus supplemental) and $PM_{2.5}$ exposure were included in this analysis.

The study participants in this analysis were predominantly non-Hispanic Whites (87%) with an average age of 70 years at baseline. The median daily intake was 500.1 μg/day (interquartile range [IQR] = 298.0 to 713.8 μg/day) for folate, 10.5 μg/day (IQR = 7.6 to 14.3 μg/day) for vitamin B_{12}, and 2.4 mg/day (IQR = 1.6 to 3.8 mg/day) for vitamin B_6, all above the Recommended Dietary Allowances (RDA; of folic acid = 400 μg, of vitamin B_{12} = 2.4 μg, of vitamin B_6 = 1.3 mg). Only 12% (n = 871) and 1% (n = 90) of the study population had intakes below the RDAs of vitamin B_6 and B_{12}, respectively. For folate, 42% (n = 3014) had intakes below its RDA. Table 1 and Table S1 in supporting information show the baseline characteristics of the study population. Participants with higher intakes of B vitamins were more likely to be supplement users. Those with higher intakes were generally older and more likely to be non-Hispanic Whites. In addition, they were more likely to have higher level of education, family income, and physical activity, but less likely to be current smokers, and obese. Most of the differences remained after the adjustment for multiple comparison using the Benjamini-Hochberg procedure.

A total of 342 participants developed all-cause dementia during the mean follow-up of 9 years (standard deivation = 4 years). The incidence rate in our study is 5.31/1000 person-years, which is comparable to other US cohorts of women with similar ages and followed up during similar years.[40,41] Because competing risk of death is possible (165 deaths compared to 342 all-cause dementia cases), we used cause-specific Cox proportional hazard regression models.[42] These models were applied to examine the associations between B vitamin intakes and incidence of all-cause dementia. The models were adjusted for age, race/ethnicity, US regions, educational attainment, family income, smoking status, alcohol consumption, body mass index (BMI), moderate or strenuous physical activity ≥20 minutes, randomization assignment in WHI trials, log-transformed Center for Epidemiologic Studies Depression (CES-D) score (to indicate prior depressive disorders), medical histories (hypertension, diabetes, hypercholesterolemia, and cardiovascular diseases), and corresponding B vitamin supplemental use.

After adjustment for potential confounders, we found an inverse but not statistically significant association between intake of folate, vitamin B_{12}, or vitamin B_6 with incident all-cause dementia (Table 2). The associations were not appreciably altered in any sensitivity analysis. The inverse associations between B vitamin intakes and all-cause dementia incidence were more marked while still non-significant among individuals with higher intake of LCn3PUFAs or with prior depression, although the interactions were not statistically significant. *APOE* genotype did not appreciably modify the associations among those with genetic data (n = 4372).

We compared the high to low level of time-varying 3-year average $PM_{2.5}$ exposure defined based on the US NAAQS (12 $\mu g/m^3$) in relation to all-cause dementia incidence using cause-specific Cox proportional hazard regression models. We found that women living in locations with ambient $PM_{2.5}$ exposure above the US NAAQS had a higher incidence of all-cause dementia (high vs. low level of $PM_{2.5}$ exposure: hazard ratio [HR] = 1.15 [0.88,

1.51]), but the point estimate did not reach statistical significance. The Kaplan Meier curves are presented in Figure S1 in supporting information. We further categorized the analysis by intake of folate, vitamin B_{12}, or vitamin B_6 (< median vs. ≥ median intake levels). Interactions between $PM_{2.5}$ exposure and B vitamin intakes were tested.

We found that B vitamin intakes significantly modified the association between $PM_{2.5}$ and dementia risk (Table 3). Among women with lower intake of folate (below the median level 500.09 μg/day), the association between $PM_{2.5}$ exposure and all-cause dementia incidence became statistically significant (HR = 1.53 [1.07, 2.21], *P* for interaction = 0.02). In contrast, there was no statistical evidence for increased dementia risk associated with high $PM_{2.5}$ among women with higher intake of folate (HR = 0.86 [0.59, 1.24]). A similar pattern of modifying effect of $PM_{2.5}$ was observed for vitamin B_6 (vitamin B_6 below the median level 2.41 mg/day: HR = 1.50 [1.03, 2.19]; above the median level: HR = 0.91 [0.64, 1.30]; *P* for interaction = 0.046). Although the interaction by vitamin B_{12} was not statistically significant (*P* for interaction = 0.051), the potential adverse effect of $PM_{2.5}$ exposure on all-cause dementia incidence became stronger among those with lower intake of B_{12} (vitamin B_{12} below the median level 10.46 μg/day: HR = 1.47 [1.02, 2.11]; above the median level: HR = 0.90 [0.62, 1.30]). The pattern of modifying effects and tests of interaction for folate and vitamin B_6 remained statistically significant in all sensitivity analyses. The interaction for vitamin B_{12} was stronger with further adjustment for baseline Modified Mini-Mental State Examination (3MS) score (to measure baseline cognition; *P* for interaction = 0.03).

To test whether the observed effect modification might be explained by homocysteine as hypothesized, we examined the correlations between plasma homocysteine concentration and B vitamin intakes and 3-year average $PM_{2.5}$ exposure among 274 participants who had plasma homocysteine measurements. We found that plasma homocysteine concentration was inversely correlated with B vitamin intakes (Spearman correlation coefficient was –0.27 [P <0.01] with folate, – 0.30 [P <0.01] with vitamin B_{12}, and –0.39 [P <0.01] with vitamin B_6), and non-significantly positively correlated with 3-year average $PM_{2.5}$ exposure (Spearman correlation coefficient was 0.06 [P = 0.68]). Compared to the total study population, these participants tend to be older and have lower education level and alcohol consumption. But, we did not find this population to have significantly different B vitamin intakes or $PM_{2.5}$ exposure.

3 | DETAILED METHODS

3.1 | Assessment of B vitamin and other nutrient intakes

A semi-quantitative FFQ was used to assess the intakes of foods at baseline.[43] Nutrient intakes including B vitamins and LCn3PUFAs were estimated using a database derived from the University of Minnesota's Nutrition Coordinating Center (Minnesota Nutrition Data System for Research).[44]

Because 30% of the participants returned their baseline dietary assessments after the mandatory folate fortification in foods in 1998, a dietary folate equivalent was calculated to account for the changes in folate content in foods and the differences in bioavailability of natural folate and synthetic folic acid from fortification among these participants.[25]

Supplemental intakes of B vitamins were assessed using the information from single supplements, supplement mixtures (e.g., B-complex mixtures), and multivitamins provided by participants.[45] In this study, the intake of B vitamins was the sum of dietary and supplemental sources. To account for the potential confounding by energy density and to reduce measurement errors, B vitamin intake was adjusted for total energy intake with the residual method in all analyses.[25]

3.2 | Estimation of $PM_{2.5}$ exposure

Because $PM_{2.5}$ exposure is geographically diverse across the United States and changes over time, we incorporated changes of residential histories to calculate cumulative $PM_{2.5}$ exposure. Participantss addresses, collected at each clinic visit and updated at least biannually, were geocoded following a standardized protocol.[46] Using the Bayesian maximum entropy (BME)-based spatiotemporal modeling method,[32,47] the daily ambient concentration of $PM_{2.5}$ across the nation was modeled from 1999 to 2010. $PM_{2.5}$ exposure prior to 1999 could not be estimated due to the limited monitoring data. By integrating nationwide monitoring data from the US Environmental Protection Agency Air Quality System (AQS) and the output of chemical transport models, this BME method characterizes spatiotemporal interdependence of environmental data to estimate mean trends and covariance of the air pollution fields over space and time. Empirical data showed that the resulting BME estimates of daily $PM_{2.5}$ exposures correlated well with the AQS recorded concentrations.[32] This statistically validated BME model was applied to each geocoded participant address to generate a yearly time-series of $PM_{2.5}$ exposure, and then combined with participant address histories, including relocations, to calculate the 3-year moving average $PM_{2.5}$, as an indicator of long-term exposure.

3.3 | Ascertainment of all-cause dementia

All-cause dementia cases were ascertained and centrally adjudicated using annual screening of global cognitive function, neuropsychological and functional assessment, and clinical data following the standardized WHIMS protocol that had four phases. The details have been described and published elsewhere.[39,48] In brief, in phase 1, centrally trained/certified and masked interviewers administered the 3MS examination during annual screenings. Women who scored below an education-adjusted cutoff point on the 3MS (≤72 points for women with ≤8 years of formal education and ≤76 points for the rest; to increase sensitivity, new cutoff points were implemented after 16 months: ≤80 points for women with ≤8 years of education and ≤88 points for the rest) were considered to have possible cognitive impairment and underwent phase 2 of the WHIMS. Phase 2 included the administrations of the Modified Telephone Interview for Cognitive Status (TICSm), East Boston Memory Test (immediate and delayed recall), Verbal Fluency-Animals, Digit Span, oral Trail Making Test, the Geriatric Depression Scale-Short Form, and WHI Insomnia Rating Scale questionnaires. Centrally trained and certified technicians administered these tests and conducted a telephone interview about the participant's functioning with a pre-identified friend or family member whom the participant had named. In phase 3, a local board-certified physician with expertise in dementia reviewed all available cognitive test results and evaluated the participant neurologically. The physician then classified the participant as having no dementia, mild cognitive impairment, or probable dementia, based on the

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria.[49] Phases 2 and 3 allow presumptive diagnosis of cognitive functioning. Women suspected to have probable dementia underwent phase 4. A non-contrast computed tomography brain scan and laboratory blood tests were conducted to rule out possible reversible causes of cognitive decline. If dementia was still suspected, all clinical and test data were then transmitted to the WHIMS Clinical Coordinating Center at Wake Forest University School of Medicine for review and central adjudication. The central adjudication committee consisted of three board-certified specialists (two neurologists and one geriatric psychiatrist) with extensive experience in dementia. Two neurologists independently evaluated the data and assigned a classification. When consensus was not achieved between the neurologists, the geriatric psychiatrist joined the discussion until a consensus was reached.

3.4 | Measurements and definitions of other variables

Information on age, race/ethnicity, US region, education attainment; family income; employment status; smoking status; alcohol consumption; BMI; physical activity; prior depression; randomization assignment in WHI trials; and medical histories of hypertension, diabetes, hypercholesterolemia, and cardiovascular diseases were collected through self-administered questionnaires at baseline. BMI (kg/m^2) was calculated as weight in kilograms divided by height (meters) squared. The presence of prior depressive disorders was examined through a short form of the CES-D scale.[50] Hypertension was defined by any self-reported use of antihypertensive medication or elevated blood pressure (systolic blood pressure ≥140 or diastolic blood pressure ≥90 mmHg).[51] Diabetes was defined by a physician's diagnosis and oral medications or insulin therapy via self-report.[52] Hypercholesterolemia was defined by any self-reported use of anti-hypercholesterolemic medication.[53] History of cardiovascular diseases included self-reported previous coronary heart disease, stroke, or transient ischemic attack.[53] Among 274 participants in this study, total plasma homocysteine was determined by high performance liquid chromatography with post-column fluorescence detection.[54] *APOE* genotype was available for 4372 participants based on genome-wide association study (GWAS) results.[55] To measure neighborhood socioeconomic status (NSES) at baseline, WHI calculated the NSES score.[56]

3.5 | Detailed statistical analyses

Baseline characteristics of the participants were summarized and compared across quartiles of B vitamin intakes using analysis of variance for continuous variables or Chi-squared test for categorical variables. The Benjamini-Hochberg procedure was used to control type 1 error across the multiple tests.[57] In addition, the average intakes of B vitamins were reported across subgroups of baseline characteristics.

Because competing risk of death is possible (165 deaths compared to 342 all-cause dementia cases), we used cause-specific Cox proportional hazard regression models, which treated participants who died as being censored at the time of death.[42] These models were applied to examine the associations between B vitamin intake quartiles and incidence of all-cause dementia using the lowest quartile as the referent. We reported the hazard ratios with corresponding 95% confidence intervals. The models were adjusted for abovementioned covariates, including age (65–69, 70–74, or ≥75 years), race/ethnicity (non-Hispanic White,

Black, Hispanic White, or "others or missing"), US regions (Northeast, South, Midwest, or West), educational attainment (less than high school, high school graduate or equivalent, or college graduate and higher degree), family income (<$10,000, $10,000–$34,999, $35,000–$74,999, $75,000 or more, or "Don't know"), smoking status (never, former, or current smokers), alcohol consumption (never, former, current <1 drink/day, or current ≥1 drink/day), BMI (<25.0 kg/m^2, 25.0 to <30.0 kg/m^2, or ≥30.0 kg/m^2), moderate or strenuous physical activity ≥20 minutes (none, some activity, 2 to 4 episodes/week, or ≥4 episodes/week), randomization assignment in WHI trials (intervention or control groups in the Hormone Therapy trial, Diet Modification trial, and Calcium/Vitamin D trial), log-transformed CES-D score, medical histories (hypertension, diabetes, hypercholesterolemia, and cardiovascular diseases), and corresponding B vitamin supplemental use. The possible linear trend in the main effect of B vitamin was examined by using the median value of each quartile of dietary intake and the *P* value was reported.

The association between time-varying 3-year average $PM_{2.5}$ exposure and incidence of all-cause dementia was assessed using the same cause-specific Cox proportional hazard regression models, and categorized by intake of folate, vitamin B_{12}, or vitamin B_6. The multivariable-adjusted hazard ratios comparing the high to low level of $PM_{2.5}$ exposure defined based on the US NAAQS (12 $\mu g/m^3$) were reported. Interactions were tested using the indicator variable of high $PM_{2.5}$ exposure and the dichotomous variables of pre-specified nutritional factors (<median vs. ≥median), and the *P* values for interactions were reported.

To test the robustness of the findings, several sensitivity analyses were performed. First, the models were additionally adjusted for the intake of the two other B vitamins. For example, when examining folate, vitamin B_{12} and B_6 intakes were additionally included in models. Second, the 3MS score at baseline was additionally included in models to evaluate potential biases resulting from self-selection among participants with better brain health at baseline. Third, because previous studies have shown some dietary and non-dietary factors may modify the association between B vitamin intake and all-cause dementia incidence,[26,27] additional variables were considered as potential effect modifiers when examining the main effects of B vitamins. These factors included *APOE* carrier status (ε4-positive vs. ε4-negative), dietary intake of LCn3PUFAs (below vs. above median intake 0.10 g/day), and prior depression indicated by log-transformed CES-D score (below vs. above median value −6.36). Fourth, because $PM_{2.5}$ exposure was estimated using participants' addresses, we additionally adjusted for WHI clinical center ($n = 39$) to further reduce the possible residual spatial confounding. Fifth, because socioeconomic status may be an important confounder for the association between air pollution and brain aging, we further adjusted for NSES score when examining the interactions of interest. Finally, to explore whether the effect modifications might be due to homocysteine as hypothesized, we examined the Spearman correlations between plasma homocysteine concentration and B vitamin intakes or 3-year average $PM_{2.5}$ exposure among 274 participants who had homocysteine measurements. All analyses were performed using SAS version 9.4 (SAS Institute). A two-sided *P*-value <0.05 was considered statistically significant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

1. Systematic review: Based on a comprehensive review, fine particulate matter ($PM_{2.5}$) has neurotoxicity possibly by increasing homocysteine level, which is a strong risk factor for dementia. In addition, three B vitamins (i.e., folate, vitamin B_{12}, and B_6) have homocysteine-lowering effects that have been well demonstrated in randomized controlled trials. Therefore, high levels of these B vitamins may reduce the homocysteine level induced by $PM_{2.5}$ exposure and thus counteract its neurotoxicity. However, no published study has examined this potential interaction.
2. Interpretation: This study shows that the association between $PM_{2.5}$ exposure and all-cause dementia risk was significantly more profound among elderly women with lower intakes of these B vitamins. The findings offer a modifiable behavioral approach to counter potential $PM_{2.5}$ neurotoxicity.
3. Future directions: Future studies are warranted to elucidate the underlying mechanisms and to confirm whether B vitamin levels in diet or biomarkers mitigate the neurotoxic effects of $PM_{2.5}$ in other populations.

TABLE 1

Baseline characteristics of the study population by quartiles (Q) of B vitamin intakes (n = 7183)[a,b,c]

		Folate (μg/d)			B_{12} (μg/d)			B_6 (mg/d)		
	Total	**Q1**	**Q4**	***P* value**	**Q1**	**Q4**	***P* value**	**Q1**	**Q4**	***P* value**
Median level (IQR)	-	251.6(219.8–276.2)	834.1 (760.0–989.2)	-	6.2 (5.1–7.0)	17.3(15.3–29.1)	-	1.3 (1.2–1.4)	4.6 (4.010.2)	-
Supplemental use (yes, %)	-	0.6	52.6	<0.05[d]	1.5	50.9	<0.05[d]	0.3	53.0	<0.05[d]
Age (%)				<0.05[d]			<0.05			<0.05[d]
65–69y	45.9	27.4	23.2		26.8	23.7		27.2	23.7	
70–74y	36.0	23.9	26.3		23.7	26.0		23.6	26.3	
≥75 y	18.1	21.0	27.1		23.0	26.2		22.2	25.9	
Race/ethnicity (%)				<0.05[d]			<0.05[d]			<0.05[d]
Non-Hispanic White	87.4	24.8	25.7		24.7	25.3		23.0	26.0	
Black	6.7	25.3	17.6		24.2	24.0		38.3	15.7	
Hispanic White	2.3	33.1	17.8		42.3	18.4		45.4	14.7	
Other or missing	3.6	24.1	27.6		23.7	24.9		35.8	25.7	
US region (%)				<0.05[d]			<0.05			<0.05[d]
Northeast	27.0	24.6	26.0		25.7	25.2		25.1	25.8	
South	21.0	22.2	27.9		24.4	27.0		26.0	24.1	
Midwest	24.2	28.3	21.8		24.8	22.3		21.9	23.7	
West	27.8	24.5	24.7		24.9	25.6		26.8	26.0	
Education (%)				<0.05[d]			<0.05			<0.05[d]
Less than high school	7.4	32.0	17.2		27.2	22.7		32.7	18.7	
High school graduate or equivalents	22.0	31.2	21.2		27.3	22.3		29.3	20.7	
College graduate or higher degree	70.7	22.4	27.0		24.0	26.1		22.8	27.0	
Family income (%)				<0.05[d]			0.38			<0.05[d]
<$10,000	5.4	31.4	17.6		25.7	23.6		33.2	18.7	
$10,000–$34,999	48.6	27.1	23.2		25.6	24.8		25.8	24.1	
$35000–$74,999	32.6	22.7	26.8		24.6	24.8		23.4	27.4	
$75000 or more	10.0	20.0	31.2		23.0	27.7		22.4	25.0	

		Folate (μg/d)			B_{12} (μg/d)			B_6 (mg/d)		
	Total	**Q1**	**Q4**	***P* value**	**Q1**	**Q4**	***P* value**	**Q1**	**Q4**	***P* value**
Don't know	3.4	22.2	26.6		25.0	24.6		23.8	25.4	
Smoking status (%)				<0.05			0.14			<0.05[d]
Never	52.7	25.2	24.7		24.8	24.6		24.2	24.7	
Former	40.2	24.1	26.4		25.0	25.7		24.3	26.8	
Current	7.1	29.4	19.1		27.6	23.9		34.8	17.7	
Alcohol consumption (%)				<0.05			<0.05[d]			0.39
Never	12.9	25.7	23.0		25.5	26.7		26.4	23.5	
Former	19.4	25.6	24.3		23.9	27.4		24.1	25.2	
Current <1 drink/d	55.3	24.0	25.7		23.7	24.9		25.3	24.9	
Current ≥1 drink/d	12.4	27.3	25.6		31.2	20.7		22.6	27.4	
BMI (%)				<0.05[d]			<0.05			<0.05
<25.0 kg/m^2	29.2	21.3	28.5		24.0	25.8		23.4	27.5	
25.0−<30.0 kg/m^2	26.6	24.7	24.4		23.4	24.3		25.1	24.1	
≥30.0 kg/m^2	34.2	28.4	22.8		27.5	25.2		26.0	24.0	
Moderate or strenuous activities ≥20 min (%)			<0.05[d]			<0.05			<0.05[d]	
None	58.2	27.6	21.7		26.6	23.7		28.2	22.1	
Some activity	4.9	27.8	26.1		23.3	26.1		23.0	23.6	
2–4 episodes/week	19.6	23.5	27.3		22.3	26.8		22.2	29.2	
≥4 episodes/week	17.4	17.1	33.3		22.8	27.3		17.9	30.5	
Hormone therapy trial (%)				<0.05			0.39			<0.05
Estrogen-alone intervention	19.5	28.3	21.7		27.2	24.8		27.5	23.0	
Estrogen-alone control	19.6	25.4	24.7		25.5	24.9		26.6	24.5	
Estrogen + progesterone intervention	29.8	23.7	25.7		23.7	24.3		23.7	25.6	
Estrogen + progesterone control	31.1	24.0	26.6		24.5	25.8		23.7	26.0	
Diet modification trial (%)				<0.05[d]			<0.05			<0.05[d]
Not randomized	76.5	22.4	27.1		24.1	25.8		23.7	26.2	
Intervention	9.5	34.7	18.1		27.9	23.8		30.4	21.6	
Control	14.0	32.4	18.5		27.9	21.5		28.4	21.0	
Calcium/vitamin D trial (%)				0.29			0.19			0.07

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		Folate (μg/d)			B_{12} (μg/d)			B_6 (mg/d)		
	Total	**Q1**	**Q4**	***P* value**	**Q1**	**Q4**	***P* value**	**Q1**	**Q4**	***P* value**
Not randomized	44.1	24.6	24.7		24.6	24.8		24.9	25.2	
Intervention	27.5	25.5	24.4		25.5	23.8		26.2	23.8	
Control	28.4	25.2	26.1		25.1	26.4		23.9	25.9	
Log-transformed CES-D score[c]	−5.62 ±1.77	−5.55 ±1.86	−5.68 ±1.69	<0.05	−5.54 ±1.89	−5.60 ±1.80	0.35	−5.54 ±1.90	−5.65 ±1.72	0.07
Hypertension (yes, %)	39.2	25.2	25.4	0.92	25.1	24.4	0.82	24.8	24.6	0.66
Diabetes (yes, %)	6.5	25.1	27.0	0.74	17.3	31.1	<0.05[d]	23.8	26.6	0.63
Hypercholesterolemia (yes, %)	18.0	21.8	27.9	<0.05	24.5	23.7	0.43	22.6	25.9	0.18
Cardiovascular disease (yes, %)	17.4	24.1	26.4	0.19	23.0	27.5	0.06	21.8	26.9	<0.05

Abbreviations: BMI, body mass index; CES-D, Shortened Center for Epidemiologic Studies Depression; IQR, interquartile range.

[a]B vitamin intakes were adjusted for total energy intake with the residual method.

[b]Results are presented by medians (IQR), means ± standard deviations or proportions (row proportions across quartiles of B vitamin intakes and column proportions for the total sample). The column proportions were used to show the distributions of baseline characteristics in the total population. The row proportions in Q1 and Q4 of B vitamins were presented to show the differences in the lowest and highest quartile. *P* values are for any differences across quartiles of B vitamin intakes using analysis of variance or Chi-squared test as appropriate.

[c]The presence of prior depressive disorders was examined through CES-D scale.

[d]The *P*-values remained <0.05 after the adjustment for multiple comparisons using the Benjamini-Hochberg procedure.

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TABLE 2

Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) of incident all-cause dementia by quartiles of B vitamin intakes[a,b,c]

	Quartiles of B vitamin intakes				*P* for trend
	Q1 (lowest)	**Q2**	**Q3**	**Q4 (highest)**	
Folate (μg/d)					
Range	<297.97	297.97-<500.01	500.01-<713.78	≥713.78	-
Cases	83	91	87	81	-
Person-years	16,382.18	16,057.95	16,275.41	15,702.91	-
HR (95% CI)	1 (Ref.)	0.90 (0.64,1.27)	0.82 (0.51,1.33)	0.82 (0.48, 1.41)	0.50
B_{12} (μg/d)					
Range	<7.59	7.59−<10.45	10.45−<14.27	≥14.27	-
Cases	88	85	80	89	-
Person-years	16,301.65	16,256.46	15,962.45	15,897.89	-
HR (95% CI)	1 (Ref.)	0.86 (0.61,1.20)	0.74 (0.47,1.16)	0.73 (0.44,1.21)	0.28
B_6 (mg/d)					
Range	<1.58	1.58−<2.41	2.41−<3.75	≥3.75	-
Cases	80	86	87	89	-
Person-years	15,751.79	16,467.32	16,006.03	16,193.32	-
HR (95% CI)	1 (Ref.)	0.94 (0.66,1.33)	1.04 (0.62,1.75)	0.94 (0.52, 1.72)	0.78

[a] B vitamin intakes were adjusted for total energy intake with the residual method.

[b] All models were constructed using Cox proportional hazards regression model. *P* for trend was examined by using the medians of each B vitamin intake quartiles.

[c] All models were adjusted for age; race; US region; education; family income; smoking status; alcohol consumption; body mass index; physical activity; randomization assignment in Women's Health Initiative trials; prior depression; histories of hypercholesterolemia, diabetes, hypertension, and cardiovascular diseases; and corresponding B vitamin supplemental use.

TABLE 3

Associations (HRs [95% CIs]) between $PM_{2.5}$ exposure levels and incident all-cause dementia categorized by intakes of B vitamins[a,b,c]

	All-cause dementia	
	Cases/person-years	**$PM_{2.5}$ exposure high (>12 $\mu g/m^3$) versus low (≤12 $\mu g/m^3$)**
All participants	342/64,418.45	1.15 (0.88,1.51)
Folate (μg/d)		
<500.09 (median)	174/32,440.13	1.53(1.07, 2.21)
≥500.09 (median)	168/31,978.32	0.86 (0.59,1.24)
P for interaction	0.02	
B_{12} (μg/d)		
<10.46 (median)	173/32,558.12	1.47(1.02, 2.11)
≥10.46 (median)	169/31,860.33	0.90 (0.62,1.30)
P for interaction	0.051	
B_6 (mg/d)		
<2.41 (median)	166/32,219.11	1.50(1.03, 2.19)
≥2.41 (median)	176/32,199.34	0.91 (0.64,1.30)
P for interaction	0.046	

[a] B vitamin intakes were adjusted for total energy intake with the residual method. The high and low level of $PM_{2.5}$ exposure was defined based on the US National Ambient Air Quality Standard.

[b] All models were constructed using cox proportional hazards regression model with the adjustment for age; race; US region; education; employment; family income; BMI; smoking status; alcohol consumption; physical activity; prior depression; randomization assignment in WHI trials; and histories of hypercholesterolemia, diabetes, hypertension, and cardiovascular diseases.

[c] In categorized analyses, models were additionally adjusted for vitamin B supplemental use (yes or no).

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; WHI, Women's Health Initiative.