Association of improved air quality with lower dementia risk in older women

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Edited by Douglas Dockery, Department of Environmental Health, Harvard University, Cambridge, MA; received April 25, 2021; accepted November 4, 2021 by Editorial Board Member Kenneth W. Wachter

Late-life ambient air pollution is a risk factor for brain aging, but it remains unknown if improved air quality (AQ) lowers dementia risk. We studied a geographically diverse cohort of older women dementia free at baseline in 2008 to 2012 (n = 2,239, aged 74 to 92). Incident dementia was centrally adjudicated annually. Yearly mean concentrations of fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) were estimated using regionalized national universal kriging models and averaged over the 3-y period before baseline (recent exposure) and 10 y earlier (remote exposure). Reduction from remote to recent exposures was used as the indicator of improved AQ. Cox proportional hazard ratios (HRs) for dementia risk associated with AQ measures were estimated, adjusting for sociodemographic, lifestyle, and clinical characteristics. We identified 398 dementia cases during follow up (median = 6.1 y). $PM_{2.5}$ and NO_2 reduced significantly over the 10 y before baseline. Larger AQ improvement was associated with reduced dementia risks ($HR_{PM2.5}$ 0.80 per 1.78 μg/m^3, 95% CI 0.71–0.91; HR_{NO2} 0.80 per 3.91 parts per billion, 95% CI 0.71–0.90), equivalent to the lower risk observed in women 2.4 y younger at baseline. Higher $PM_{2.5}$ at baseline was associated with higher dementia risk ($HR_{PM2.5}$ 1.16 per 2.90 μg/m^3, 95% CI 0.98–1.38), but the lower dementia risk associated with improved AQ remained after further adjusting for recent exposure. The observed associations did not substantially differ by age, education, geographic region, Apolipoprotein E e4 genotypes, or cardiovascular risk factors. Long-term AQ improvement in late life was associated with lower dementia risk in older women.

air pollution | air quality | dementia | incidence | epidemiology

Consistent evidence from epidemiologic studies and toxicological experiments has shown that ambient air pollution is an important modifiable risk factor of dementia (1). Several studies have shown an increased risk of dementia associated with late-life exposures to regional fine particulate matter ($PM_{2.5}$; with aerodynamic diameter < 2.5 μm) (2–15) and gaseous pollutants (e.g., NO_2; NO_x) (2–4, 11, 12, 15–17) in particular. Over the past 50 y, significant improvements in air quality (AQ) have been observed across the United States because of national policies and strategies aimed at regulating pollution from stationary (power plants; factories) and mobile (vehicles) sources (18). Several US studies have shown that these long-term reductions in air pollution levels are associated with improved lung function (19), decreased bronchitic symptoms (20), lower asthma incidence (21), lengthened life expectancy (22), and reduced mortality (23). However, it remains unclear whether improved AQ also benefits the aging brains.

Therefore, we conducted a multiyear study to examine the association between improved AQ and incidence of dementia, which was based on *Diagnostic and Statistical Manual of Mental Disorders* (Fourth edition) criteria and centrally adjudicated annually (24, 25). We examined data from the Women's Health Initiative (WHI) Memory Study (WHIMS)—Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO) that included a combined 20 y of data on individual-level outdoor air pollution (1998 to 2012) estimated using regionalized national universal kriging models (26–28) and cognitive function assessed annually (2008 to 2018) in a geographically diverse sample of community-dwelling older women in the United States. We hypothesized that improved AQ over the span of 10 y, as indicated by reductions in $PM_{2.5}$ and NO_2 (proxy for traffic pollutants), was associated with lower dementia risk.

Results

Compared to the 257 women excluded because of no follow-up visit (Fig. 1), women with follow-up data (n = 2,541) were more

Significance

Epidemiological studies have demonstrated that improved air quality may improve respiratory health and reduce mortality. Increasing data support late-life exposure to air pollution as a modifiable risk factor for dementia, but whether improved ambient air quality translates to lower dementia risk is unclear. In this study on a geographically diverse cohort of US community-dwelling older women, we found that long-term improvement in ambient air quality in late life was associated with reduced dementia risk. The associations did not significantly differ by age, education, geographic region, Apolipoprotein E e4 genotypes, or cardiovascular risk factors. These findings strengthen the causal association between late-life exposure to air pollution and dementia risk.

Author contributions: X.W., D.Y., and J.-C.C. designed research; X.W., D.Y., and J.-C.C. performed research; X.W., D.P.B., J.D.K., G.A.W., and E.A.W. analyzed data; and X.W., D.Y., J.M., A.J.P., E.G., D.P.B., M.A.E., H.C.C., S.M.R., M.G., J.D.K., G.A.W., E.A.W., J.E.M., S.R.R., and J.-C.C. wrote the paper.

The authors declare no competing interest.

This article is a PNAS Direct Submission. D.D. is a guest editor invited by the Editorial Board.

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This article contains supporting information online at http://www.pnas.org/lookup/suppl/doi:10.1073/pnas.2107833119/-/DCSupplemental.

Published January 4, 2022.

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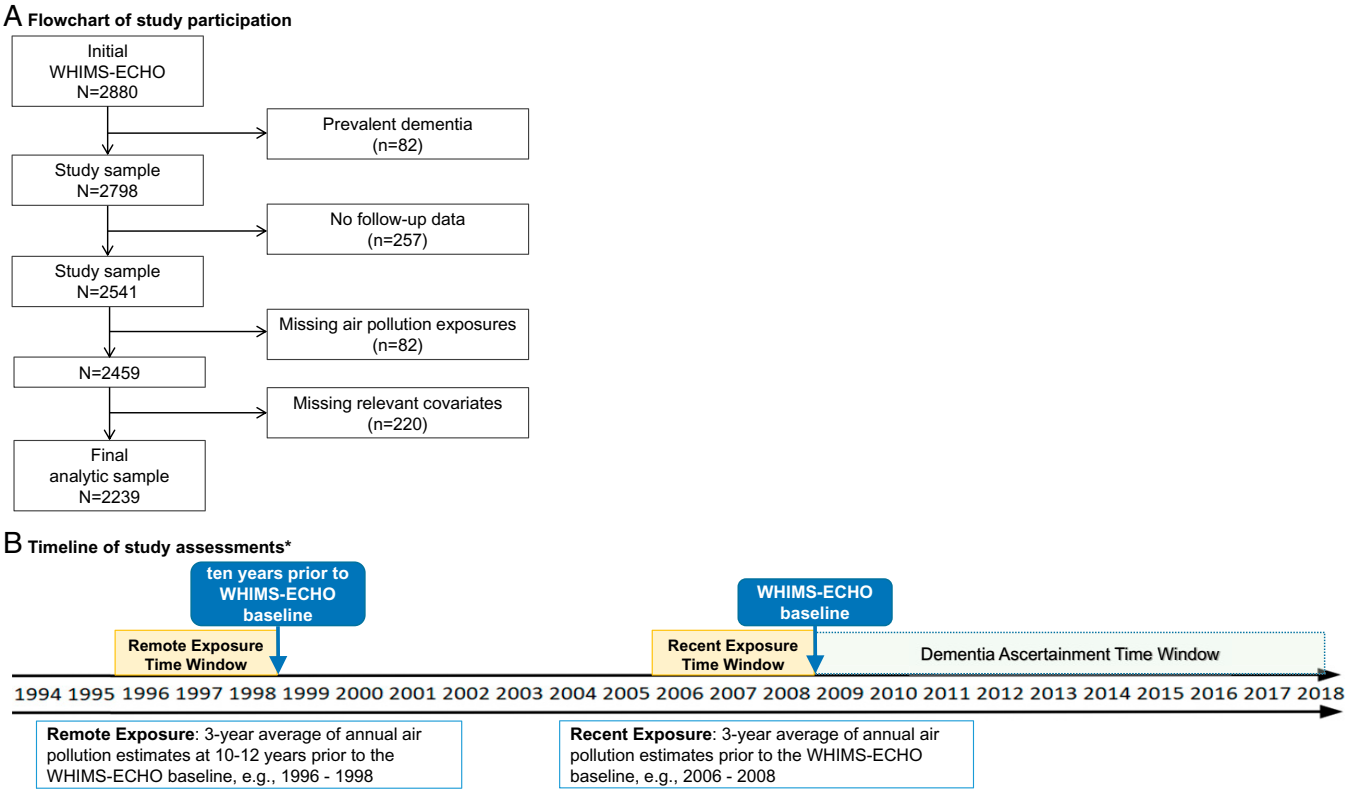

Fig. 1. Flowchart of study population and demonstration of study timeline. The exposure windows may vary depending on each individual's WHIMS-ECHO baseline time.

likely to be younger than 80 y old, self-identify as non-Hispanic White, have four or more years of college education, and have prior postmenopausal hormone treatment but were less likely to have diabetes (*SI Appendix*, Table S1). Compared to those 302 excluded because of missing data (Fig. 1), women included in analyses ($n = 2{,}239$) were more likely to be younger than 80, reside in the Northeast or Midwest, self-identify as non-Hispanic White, have higher educational attainment and household income, and drink more alcohol (*SI Appendix*, Table S2).

Over the 10 y before the WHIMS-ECHO baseline, AQ improved significantly with reduced ambient levels for both $PM_{2.5}$ (13.3 ± 2.7 to 10.5 ± 2.0 μg/m^3; $P < 0.001$) and NO_2 (15.7 ± 7.2 to 10.4 ± 4.9 parts per billion [ppb]; $P < 0.001$; Table 1 and *SI Appendix*, Fig. S1). By the Environmental Protection Agency's (EPA) 1997 standard (29) for $PM_{2.5}$ (15 μg/m^3), non-compliance reduced from 24.0 to 0.2% during the 10-y period, while at the WHIMS-ECHO baseline, 25.6% of $PM_{2.5}$ estimates were still above the 2012 (30) standard (12 μg/m^3). Older women residing in locations with initially high ambient levels of air pollution tended to experience greater AQ improvement for both $PM_{2.5}$ (correlation = 0.67; $P < 0.001$) and NO_2 (correlation = 0.79; $P < 0.001$) (*SI Appendix*, Table S3). Overall, women who were older than 80, residing in the Northeast and West regions, or with higher income experienced larger decreases in ambient levels of both $PM_{2.5}$ and NO_2 (Table 1).

During a median 6.1 (interquartile range [IQR] = 5.2) years of follow up, we identified 398 incident dementia cases. Residing in locations with greater AQ improvement was significantly associated with lower dementia risk (Table 2). In the fully adjusted model (Table 2, Model II) accounting for age, enrollment year, sociodemographic features (geographic region, age, self-reported race/ethnicity, education, family income, and employment status), lifestyles (smoking, alcohol intake, and physical activity), and clinical characteristics (body mass index [BMI], cardiovascular disease [CVD], hypercholesterolemia, hypertension, diabetes mellitus, depressive symptoms, self-reported use of postmenopausal hormone treatment, and WHI hormone treatment assignment) dementia risk decreased by 20% with each IQR increment of improved AQ in $PM_{2.5}$ (hazard ratio [HR], 0.80 per 1.78 μg/m^3; 95% CI: 0.71–0.91) and NO_2 (HR, 0.80 per 3.91 ppb; 95% CI: 0.71–0.90; Table 2, Model II). These putative benefits were equivalent to the lower dementia risk observed in women who were 2.4 y younger at baseline. In the population of older women, to lower dementia risk by slowing the aging process for 1 y (β_{age}, −0.09), the same estimated benefit could be achieved with reduced ambient levels of $PM_{2.5}$ ($\beta_{AQ\ improvement}$, −0.22 per 1.78 μg/m^3) by 0.74 μg/m^3 (calculated as $IQR_{AQ\ improvement} \times \beta_{age}/\beta_{AQ\ improvement}$) or NO_2 ($\beta_{AQ\ improvement}$, −0.22 per 3.91 ppb) by 1.63 ppb over the 10-y period. An elevated dementia risk was found among women exposed to higher $PM_{2.5}$ concentrations at baseline (HR, 1.16 per 2.90 μg/m^3; 95% CI: 0.98–1.38), but the estimated association did not reach statistical significance. For both pollutants, the observed associations between improved AQ and lower dementia risks remained after further adjusting for the corresponding recent or remote exposures (Table 2, Models III and IV).

We found no statistical evidence that the observed association of lower dementia risk with improved AQ substantially differed by age, education, geographic region, common cardiovascular risk factors, or Apolipoprotein E (APOE) e4 genotypes (Fig. 2).

The associations between improved AQ and lower dementia risk remained robust in sensitivity analyses adjusting for potential confounders based on covariates updated prior to the WHIMS-ECHO baseline or temporal changes in relevant covariates from WHI inception (*SI Appendix*, Table S4) to account for any possible residual confounding resulting from temporal misspecification of the confounders. Similar results were found in sensitivity analyses using 1-y average exposure rather than 3-y average

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Table 1. Distribution of air quality measures by population characteristics in the WHIMS-ECHO cohort

		$PM_{2.5}$ ($\mu g/m^3$)*		NO_2 (ppb)*	
	N	Mean ± SD	*P*†	Mean ± SD	*P*†
Air pollution exposure					
Remote exposure	2,239	13.28 ± 2.70	<0.001	15.69 ± 7.15	<0.001
Recent exposure	2,239	10.54 ± 2.00		10.43 ± 4.89	
		AQ improvement in $PM_{2.5}$ ($\mu g/m^3$)*		AQ improvement in NO_2 (ppb)*	
Population characteristics					
Overall	2,239	2.73 ± 1.63		5.26 ± 3.45	
Age					
≤80 y	882	2.62 ± 1.50	0.009	5.00 ± 3.23	0.004
>80 y	1,357	2.81 ± 1.71		5.43 ± 3.58	
Region					
Northeast	723	3.01 ± 0.95	<0.001	5.70 ± 3.25	<0.001
South	444	2.50 ± 1.28		4.93 ± 3.08	
Midwest	549	2.15 ± 1.22		4.36 ± 2.32	
West	523	3.17 ± 2.55		5.88 ± 4.61	
Ethnicity					
Black (not Hispanic)	116	3.28 ± 1.39	<0.001	6.84 ± 2.67	<0.001
White (not Hispanic)	2,049	2.68 ± 1.63		5.13 ± 3.47	
Other	74	3.42 ± 1.84		6.42 ± 3.30	
Education					
High school or GED	566	2.64 ± 1.49	0.04	5.08 ± 3.22	0.09
>High school but <4 y of college	865	2.69 ± 1.77		5.19 ± 3.62	
≥4 y of college	808	2.85 ± 1.57		5.47 ± 3.42	
Employment					
Currently working	348	2.78 ± 1.63	0.79	5.51 ± 3.52	0.31
Not working	212	2.77 ± 1.69		5.11 ± 3.63	
Retired	1,679	2.72 ± 1.62		5.23 ± 3.42	
Income ($)					
<9,999	74	2.73 ± 1.98	0.006	5.02 ± 3.93	0.04
10,000 to 34,999	1,002	2.64 ± 1.66		5.18 ± 3.54	
35,000 to 74,999	827	2.78 ± 1.55		5.22 ± 3.24	
75,000 or more	221	3.07 ± 1.73		5.94 ± 3.87	
Don't know	115	2.55 ± 1.43		5.11 ± 2.87	
Lifestyle					
Smoking status			0.98		0.69
Never smoked	1,241	2.73 ± 1.67		5.27 ± 3.38	
Past smoker	894	2.73 ± 1.59		5.22 ± 3.55	
Current smoker	104	2.76 ± 1.53		5.53 ± 3.52	
Alcohol use					
Nondrinker	261	2.59 ± 1.72	0.48	4.60 ± 3.18	<0.001
Past drinker	372	2.75 ± 1.67		5.37 ± 3.78	
<1 drink per day	1,321	2.76 ± 1.60		5.45 ± 3.41	
≥1 drink per day	285	2.72 ± 1.66		4.84 ± 3.35	
Moderate or strenuous physical activities ≥20 min					
No activity	1,210	2.71 ± 1.63	0.82	5.28 ± 3.41	0.22
Some activity	124	2.76 ± 1.24		5.56 ± 3.18	
2 to 4 episodes/week	482	2.79 ± 1.68		5.38 ± 3.53	
>4 episodes/week	423	2.71 ± 1.69		4.98 ± 3.55	
Physical health					
BMI (kg/m^2)					
<25	623	2.79 ± 1.64	0.44	5.18 ± 3.37	0.45
25 to 29	816	2.74 ± 1.64		5.20 ± 3.25	
≥30	800	2.68 ± 1.61		5.38 ± 3.71	
Hypertension					
No	1,466	2.73 ± 1.65	0.80	5.23 ± 3.52	0.52
Yes	773	2.75 ± 1.59		5.33 ± 3.33	
Hypercholesterolemia					
No	1,860	2.71 ± 1.64	0.14	5.26 ± 3.53	0.96
Yes	379	2.85 ± 1.56		5.25 ± 3.05	
Diabetes					
No	2,149	2.73 ± 1.64	0.27	5.25 ± 3.46	0.46
Yes	90	2.92 ± 1.50		5.52 ± 3.16	
Cardiovascular disease history					
No	1,914	2.73 ± 1.65	0.95	5.26 ± 3.52	0.96
Yes	325	2.73 ± 1.53		5.25 ± 3.04	
Any prior hormone treatment					
No	1,223	2.73 ± 1.44	0.88	5.34 ± 3.30	0.21
Yes	1,016	2.74 ± 1.84		5.16 ± 3.62	
WHI Hormone Therapy Assignment					
CEE-alone placebo	400	2.81 ± 1.74	0.13	5.24 ± 3.33	0.02
CEE-alone	404	2.57 ± 1.65		4.80 ± 3.30	
CEE+MPA placebo	737	2.76 ± 1.55		5.44 ± 3.53	
CEE+MPA	698	2.75 ± 1.64		5.35 ± 3.51	

Abbreviations: CEE, conjugated equine estrogens; GED, general educational development; MPA, medroxyprogesterone acetate.

*Recent exposures were 3-y average exposures estimated at the WHIMS-ECHO baseline. Remote exposures were 3-y average exposures estimated 10 y before the WHIMS-ECHO baseline. AQ improvement was defined as the reduction from remote to recent exposures.

†*P* values were calculated using ANOVA *F* tests for mean exposures.

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Table 2. Estimated HRs for the risk of all-cause dementia associated with AQ measures

A. Exposure to $PM_{2.5}$*

Models	AQ improvement in $PM_{2.5}$			Recent $PM_{2.5}$			Remote $PM_{2.5}$		
	HR[†]	95% CI	*P* Value[‡]	HR[†]	95% CI	*P* Value[‡]	HR[†]	95% CI	*P* Value[‡]
Model I[§]	0.85	0.77, 0.94	0.006	1.19	1.04, 1.37	0.02	1.00	0.89, 1.12	0.99
Model II[¶]	0.80	0.71, 0.91	0.002	1.16	0.98, 1.38	0.14	0.93	0.82, 1.07	0.40
Model III[#]	0.80	0.70, 0.90	<0.001	1.08	0.91, 1.29	0.39			
Model IV[||]	0.76	0.64, 0.90	0.002				1.09	0.90, 1.33	0.39

B. Exposure to NO_2*

	AQ improvement in NO_2			Recent NO_2			Remote NO_2		
Model I[§]	0.83	0.74, 0.93	0.006	1.02	0.90, 1.15	0.89	0.92	0.80, 1.04	0.29
Model II[¶]	0.80	0.71, 0.90	0.002	1.01	0.87, 1.17	0.91	0.87	0.74, 1.01	0.14
Model III[#]	0.78	0.69, 0.89	<0.001	1.07	0.92, 1.25	0.37			
Model IV[||]	0.75	0.62, 0.90	0.002				1.12	0.88, 1.41	0.37

*Recent exposures were 3-y average exposures estimated at the WHIMS-ECHO baseline. Remote exposures were 3-y average exposures estimated 10 y before the WHIMS-ECHO baseline. AQ improvement was defined as reduction from remote to recent exposures. AQ improvement in $PM_{2.5}$: IQR = 1.78 μg/m^3. Recent $PM_{2.5}$: IQR = 2.90 μg/m^3. Remote $PM_{2.5}$: IQR = 3.25 μg/m^3. AQ improvement in NO_2: IQR = 3.91 ppb. Recent NO_2: IQR = 6.19 ppb. Remote NO_2: IQR = 9.42 ppb.

[†]HR for all-cause dementia per each IQR increase of AQ measures.

[‡]*P* values from Model I and II were corrected using Benjamini–Hochberg false discovery rate method across $PM_{2.5}$ and NO_2 exposures.

[§]Incorporated inverse-probability weighting approach and adjusted for enrollment year.

[¶]Model I + demographic variables (age, geographic region/spatial random effect, and race/ethnicity), socioeconomic factors (education, income, and employment status) and neighborhood characteristics, lifestyle factors (smoking, drinking, and physical activities), hormone use, hormone therapy assignment, cardiovascular risk factors (hypertension, diabetes, and hypercholesterolemia), depression, BMI, and CVD histories.

[#]Model II with both AQ improvement measure and corresponding recent exposure in model.

[||]Model II with both AQ improvement measure and corresponding remote exposure in model.

(*SI Appendix*, Table S5). Similar results were found in the sensitivity analyses with multiple imputation to include those women who were excluded from our analyses for missing air pollution and covariate data (*SI Appendix*, Table S6).

Discussion

In a geographically diverse cohort of community-dwelling older women followed for 20 y, utilizing individual-level estimates of ambient air pollution concentrations to assess improved AQ over the span of 10 y, we found that decreasing long-term ambient levels of $PM_{2.5}$ and NO_2 in late life were associated with lower dementia risk. This association remained after adjusting for sociodemographics (age, geographic region, race/ethnicity, education, income, and employment status), lifestyle factors (smoking, alcohol, and physical activity), or clinical characteristics (BMI, depressive symptoms, diabetes, hypercholesterolemia, hypertension, CVD, and hormone treatment). The putative benefit of $PM_{2.5}$ reduction remained after further adjusting for the adverse effect of recent $PM_{2.5}$. There was no strong evidence that the lower dementia risk associated with improved AQ differed by age, education, geographic region, cardiovascular risk factors, or APOE e4 genotypes.

The observed lower dementia risk associated with improved AQ strengthens the hypothesized causal role of late-life exposure to ambient air pollution and its contribution to pathological brain aging. We observed an elevated risk of dementia among older women living in locations with higher recent $PM_{2.5}$ exposure (Table 2*A*, Model II), although the estimated association did not reach statistical significance. For both $PM_{2.5}$ and NO_2, statistically nonsignificant positive associations between remote exposures and dementia risk were also found in models further adjusting for AQ improvements (Table 2, Model IV). Although our models had adjusted for inverse probability weights, it is unclear whether these imprecise estimates might have reflected the selective attrition of more sensitive participants before the WHIMS-ECHO baseline. Despite the compelling epidemiological evidence supporting the association between ambient air pollution and dementia risk, uncertainties regarding their causal relationship have been raised (31). Scientists have advocated for quasi-experimental studies that take advantage of the decreasing air pollution levels to strengthen the causal associations in the reported adverse health effects of air pollution exposures (32). If increased dementia risk is observed with higher exposures—and these relations are truly causal—then, in the environmental context with improved AQ, the observed dementia risk should decrease as suggested by our study. Furthermore, our study findings raise an important question regarding the reversibility of exposure-induced damage to the aging brain, which will be better addressed by an experimental paradigm of improved AQ in animal models, although neurotoxicological studies of this kind are currently limited.

Our study adds important data to the literature on the putative health benefits of improved AQ in US populations. While many studies have examined the impact of short-term changes in air pollution, only a few population-based cohort studies have examined the long-term trends in air pollution. For instance, reduced $PM_{2.5}$ concentrations across two time periods (1974 to 1989 and 1990 to 1998) were associated with reduced mortality in the follow up of the Harvard Six-Cities Study (23). The Children's Health Study showed that the benefits of AQ improvement continuing after the 2000s was linked with positive lung growth (19), decreased bronchitic symptoms (20), and lower asthma incidence (21, 33). Our study examined the 1998 to 2012 exposure periods and showed that the putative health benefit of continued improvement in long-term AQ may extend to the brain health of older women by lowering their risk of dementia. Moreover, our findings provide the impetus for EPA's future cost–benefit analyses to include the assessment of brain health. The overall benefits of the Clean Air Act are likely far greater than previously estimated (34) since dementia is among the most expensive chronic diseases in the United States, with a total monetary cost estimated between 159 to $215 billion in 2010 alone (35). Additionally, $PM_{2.5}$ and NO_2 are both produced from combustion processes, with NO_2 likely representing the gaseous surrogate of the traffic-related air pollutants mixture. Therefore, our finding of lower dementia risk associated with decreasing

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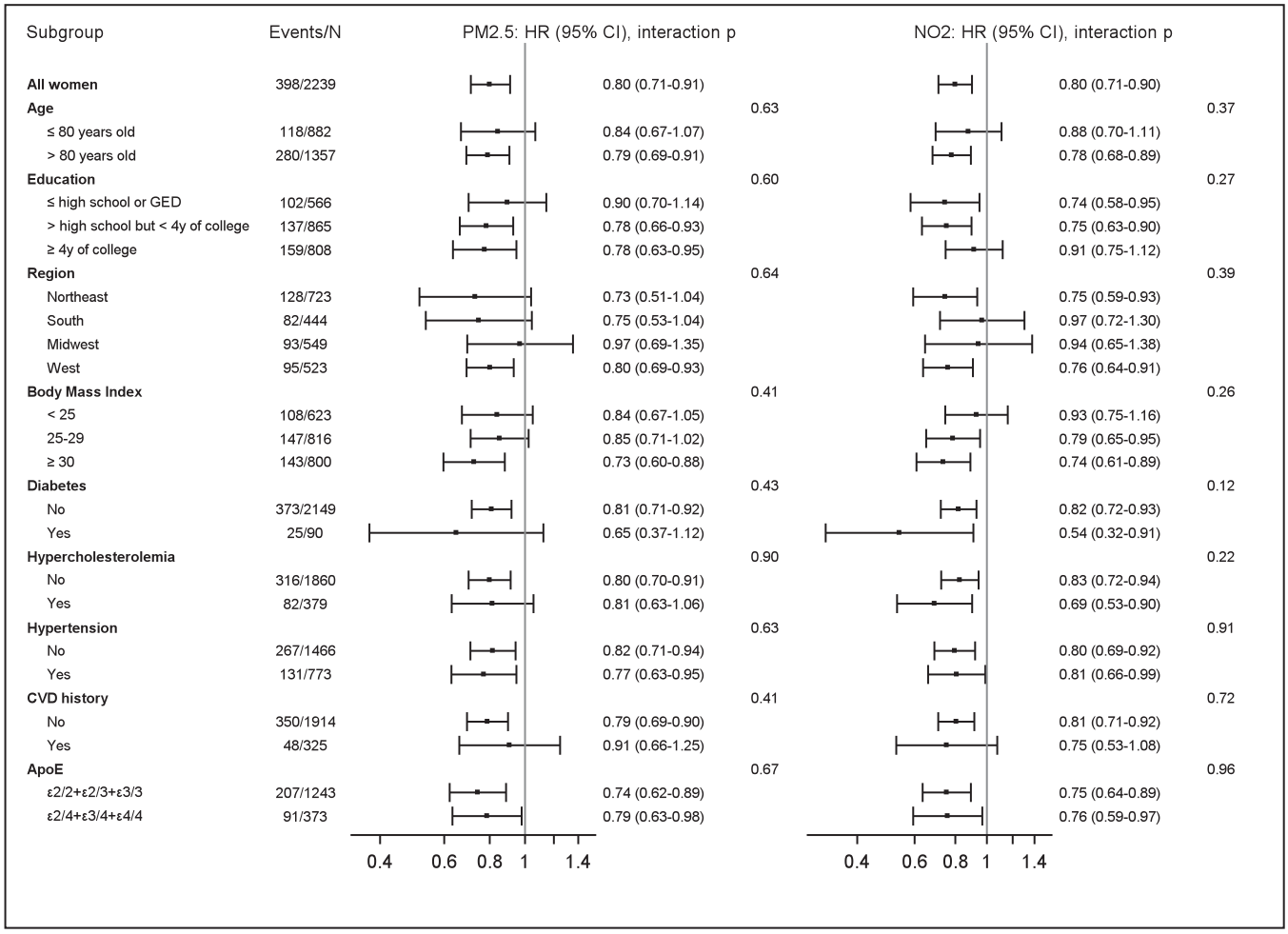

Fig. 2. Estimated HRs for the risk of all-cause dementia associated with AQ improvement, stratified by population characteristics. HR (95% CI) for all-cause dementia per each IQR of improvement in $PM_{2.5}$ and NO_2, incorporating inverse-probability weighting approach and adjusting for enrollment year, demographic variables (age, geographic region/spatial random effect, and race/ethnicity), socioeconomic factors (education, income, and employment status) and neighborhood characteristics, lifestyle factors (smoking, drinking, and physical activities), hormone use, hormone therapy assignment, cardiovascular risk factors (hypertension, diabetes, and hypercholesterolemia), depression, BMI, and CVD histories. Recent exposures were 3-y average exposures estimated at the WHIMS-ECHO baseline. Remote exposures were 3-y average exposures estimated 10 y before the WHIMS-ECHO baseline. AQ improvement was defined by reduction from remote to recent exposures. AQ improvement in $PM_{2.5}$: IQR = 1.78 $\mu g/m^3$. AQ improvement in NO_2: IQR = 3.91 ppb. *P* values were for the test of interaction between AQ improvement and each subgroup unadjusted for multiplicity. No *P* values were statistically significant after Benjamini–Hochberg false discovery rate adjustment.

ambient levels of both $PM_{2.5}$ and NO_2 may imply that the observed health benefits of AQ improvement are due to the overall reduction in ambient air pollution levels rather than driven by specific control programs to mitigate either $PM_{2.5}$ or NO_2 in the United States. To put our findings into context, we compared our effect size to the dementia risk in smokers as documented in the literature. Based on a 2020 report of the Lancet Commission, later-life smoking was associated with a 60% increased risk of dementia among individuals >65 y of age (relative risk, 1.6; 95% CI: 1.2–2.2) (1). Previous research studying the benefit of smoking cessation on dementia risk among men ≥60 y of age found that compared to continual smokers, cessation of smoking for more than 4 y was associated with a significantly lower risk of dementia (HR, 0.86; 95% CI: 0.75–0.99) (36). The observed risk reduction associated with improved AQ in late life found in our study may be comparable to smoking cessation, but its magnitude was smaller than the increased risk associated with late-life smoking.

We make the following recommendations for future research to advance the environmental neurosciences of air pollution neurotoxicity on brain aging. According to Jack et al. (37), changes in biomarkers (e.g., amyloid β; Tau-mediated neuronal injury and dysfunction) and brain structure first emerge during the preclinical stage followed by memory decline and subsequent dementia. We previously reported that ambient levels of late-life $PM_{2.5}$ were associated with progressive gray matter atrophy in brain areas vulnerable to Alzheimer's disease neuropathologies (38), which resulted in subsequent decline in episodic memory at preclinical stages (39). Therefore, future studies need to examine if improved AQ may help preserve brain volume, maintain function of neural networks, or slow cognitive decline at preclinical stages. Experimental studies have demonstrated that particle pollutants may promote early biomarkers of neurodegenerative disease (accumulation of amyloid-β; phosphorylation of Tau) (40). Future studies with high-quality longitudinal data on positron emission tomography scans and fluid-based biomarkers can help us better understand the underlying neuropathological processes amendable to improved AQ in late life.

We recognize several limitations of our study. First, our air pollution estimates were based on ambient levels modeled at the participants' addresses and did not incorporate personal exposure assessment. However, the use of individual-level estimates of

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ambient air pollution is highly relevant to studying the health benefits of reduced ambient levels of pollutants, which are regulated by the EPA. Second, the use of modeled air pollution estimates may contribute uncertainty to the analyses, and the exposure measurement errors may have varied between the two time points, which may have biased our results. Third, we could not completely rule out the possibility of unmeasured confounding by other environmental factors (e.g., noise and green space) or their longitudinal changes concurrent with improved AQ. However, it is unlikely that these environmental factors could contribute to health benefits of AQ improvement because noise levels have been increasing (41) over time, while green space has been decreasing (42), because of increasing urbanization. Fourth, we only examined if improved AQ in late life translated to the benefit in lowering dementia risk and were unable to estimate ambient levels during the midlife period. Air pollution in later life (age >65 y) was recently recognized as a potentially modifiable risk factor for dementia (1); however, the literature on midlife exposure to air pollution and brain aging is scant. Fifth, we only looked at the absolute change in ambient levels of pollutants from remote to recent periods; therefore, any variability in the pattern of change between exposure periods may not have been captured in our measure of AQ improvement. In addition, although the WHIMS participants had high residential stability, we did not have access to the exact location data to better protect this confidential information. Therefore, we were unable to tell how much of the improved air quality was due to moving to locations with lower exposures or driven by the overall declining trend over 10 y. Lastly, our findings may not be generalizable to older men.

Our study has several unique methodological strengths in studying the long-term health benefit of AQ improvement. First, the observed benefit of lowered dementia risk associated with improved AQ was based on within-cohort comparisons, greatly reducing the possible confounding by between-cohort differences that might be present in previous studies on respiratory health benefits based on cross-cohort comparisons (43). Second, we used individual-level estimates of improved AQ defined prior to the assessment of dementia, and this approach not only ensures the temporality between AQ improvement and health benefit but also minimizes the spatial confounding in previous studies with improved AQ defined at the county/city/community level. Lastly, our analyses accounted for different sources of spatiotemporal confounding, including the adjustment of temporal changes in CVD risks, lifestyle factors, neighborhood socioeconomic characteristics, and clinical characteristics that may occur concurrently with AQ improvement.

In conclusion, we found that long-term AQ improvement was robustly associated with lower dementia risk among older women. The association did not vary by geographic region, age, education, underlying genetic risk, or cardiovascular risk factors. These findings strengthen the hypothesized causal association between late-life exposure to air pollution and dementia risk. Future studies are needed to further explore whether this long-term benefit in late life is measurable at preclinical stages and to understand the underlying neuropathological processes modifiable by reducing air pollution exposures.

Materials and Methods

Study Sample. We conducted a longitudinal study on older women (n = 2,880; aged 74 to 92) of the WHIMS-ECHO study, which followed WHIMS participants annually since 2008. WHIMS was an ancillary study to the WHI hormone therapy (WHI-HT) trials initiated in 1993 and followed participants with in-person visits through 2008 (44). We excluded WHIMS-ECHO participants with prevalent dementia (n = 82), without follow-up data (n = 257), or missing data on AQ measures or relevant covariates (n = 302), resulting in the current study on 2,239 women (Fig. 1). The Institutional Review Board at the University of Southern California reviewed and approved all study protocols. Written informed consent was obtained from all participants as part of WHI-HT, WHIMS, and the extension studies. Access to all data elements used in this study may be made available following the established WHI policies.

Ascertainment of Incident Dementia. WHIMS-ECHO participants underwent an annual telephone interview that included the modified Telephone Interview for Cognitive Status (TICSm) (45), a validated cognitive screening tool (46). For women with TICSm below 31, informant interviews were conducted by phone with previously identified proxies (friends or family members) using the standardized Dementia Questionnaire to assess histories of dementia-related cognitive and behavioral changes, functional impairment, and relevant medical histories. The Dementia Questionnaire interview of proxies has been validated against the criterion standard of full clinical assessment with acceptable sensitivity and specificity (>90%) and interrater agreement (98%) (47, 48). All data from the longitudinal assessments were then submitted to the central adjudication committee, consisting of experts in the diagnosis of dementia, to ascertain dementia cases based on the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) (24).

Air Pollution Estimation. Participants' residential addresses, prospectively collected since 1993 and updated at least biannually, were geocoded (49). We used validated regionalized national universal kriging models to estimate ambient concentrations of $PM_{2.5}$ and NO_2. These models utilized US EPA monitoring data and incorporated partial least squares regression of geographic covariates. Over 300 geographic covariates (e.g., emissions, land use, vegetation index, traffic, and proximity to features) were used in the historical models for pre-1999 $PM_{2.5}$ estimation and in the national models for post-1999 $PM_{2.5}$ estimation (27, 28). Over 400 geographic covariates covering proximity and buffer measures as well as satellite-derived NO_2 data were used to estimate NO_2 (26). The average cross-validation R^2 nationwide was 0.84 to 0.91 for pre-1999 $PM_{2.5}$, 0.88 for post-1999 $PM_{2.5}$, and 0.85 for NO_2 (26–28). Annual estimates were aggregated to the 3-y average prior to the WHIMS-ECHO baseline (recent exposure) and the corresponding 3-y average ~10 y earlier (remote exposure), accounting for residential mobility that took place within each 3-y time window (Fig. 1). Reduction from remote to recent exposures was used as the individual-level measure of improved long-term AQ across 10 y. We focused on reduction in the 3-y average, which was the primary standard for long-term $PM_{2.5}$ exposure regulated by the EPA.

Covariate Data. At the WHI study inception, information on demographics (geographic region, age, and self-reported race/ethnicity), socioeconomic factors (education, family income, and employment status), and lifestyle factors (smoking, alcohol intake, and physical activity) were collected using a structured questionnaire. Clinical covariates included BMI (calculated from measured height and weight), depressive symptoms (assessed by the Center for Epidemiological Studies—depression scale, short form), self-reported use of postmenopausal hormone treatment, WHI hormone treatment assignment, and prior histories of CVD, hypercholesterolemia, hypertension, and diabetes mellitus. Good reliability and validity of both the self-reported medical histories and the physical measures have been previously documented (50–52). Socioeconomic characteristics of residential neighborhoods were characterized using US Census tract-level residential data (53). Lifestyle and clinical covariates (BMI, blood pressure, and CVD events) were also updated before the WHIMS-ECHO baseline. APOE e4 genotype data were obtained for a subset of women (n = 1,616). Details on covariates are available in *SI Appendix*.

Statistical Approaches. We used ANOVA F tests to compare the mean exposure differences across population characteristics and χ^2 tests to evaluate the difference in population characteristics for women included in the analytic sample compared to those excluded. Cox proportional hazard models were used to estimate HRs and 95% CIs for dementia risk associated with improved AQ as well as with recent and remote exposures. We incorporated inverse-probability weighting (54) to account for differential attrition over follow up (details in *SI Appendix*). Follow-up time was defined as days since WHIMS-ECHO enrollment to the first occurrence of the cognitive assessment leading to the classification of dementia, death, or the last date of cognitive assessment (through June 2018), whichever came first. Proportional hazard assumptions were evaluated by testing the significance of the additional interaction of the predictor and log-transformed survival time. Linearity in associations was evaluated by testing the significance of the additional quadratic term. Potential confounders included demographics, geographic region, socioeconomic status, neighborhood socioeconomic characteristics, lifestyle factors, and clinical characteristics at the WHI inception. To control for temporal trends and spatial confounding, all models included an indicator for WHIMS-ECHO enrollment year and a random effect for 39 WHI clinic sites.

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As the Clean Air Act mandates that the EPA sets AQ standards to provide a safe margin for susceptible populations (55), we explored whether the putatively lower dementia risk associated with improved AQ might differ by age, education, geographical region, cardiovascular risk factors, and APOE e4 genotype using a product term of the AQ improvement and each potential effect modifier.

To examine if our findings could be explained by regression to the mean in AQ improvement measures, we further adjusted for recent or remote exposures. To address possible residual confounding resulting from temporal misspecification of potential confounders including lifestyle factors, neighborhood socioeconomic characteristics, and clinical characteristics, the Cox models were refitted with an adjustment of either the updated measures before WHIMS-ECHO baseline or the changes in these relevant covariates since WHI inception. To evaluate if the associations were sensitive to the use of 3-y averages, we also conducted the analyses using 1-y average exposure. We also refitted the Cox models after applying multiple imputation (56) to address missing data (details in *SI Appendix*). *P* values for statistical testing were corrected for multiple comparison using the Benjamini–Hochberg (57) method to control the false discovery rate.

All statistical analyses were performed using R software, version 3.6.2 (R Project for Statistical Computer) and SAS software, version 9.4 (SAS Institute). All tests were interpreted at the 0.05 significance level using a two-sided alternative hypothesis.

Data Availability. Data, codebook, and analytic code used in this report are held by the NIH-funded Coordinating Center of the Women's Health Initiative at the Fred Hutchinson Cancer Research Center and may be accessed as described on the Women's Health Initiative website: https://www.whi.org/page/working-with-whi-data.

ACKNOWLEDGMENTS. This study is supported by Grants R01AG033078 (principal investigator [PI]: J.-C.C.), RF1AG054068 (PI: J.-C.C.), R01ES025888 (PI: J.-C.C. and J.D.K.), the National Institutes of Environmental Health Sciences (5P30ES007048), and the Alzheimer's Disease Research Center at the University of Southern California (P50AG005142 and P30AG066530). D.Y. and J.-C.C. are also supported by P01AG055367. D.Y. is supported by a grant from the Alzheimer's Association (AARF-19-591356). The air pollution models were developed under the Science to Achieve Results Research Assistance Agreements RD831697 (Multi-Ethnic Study of Atherosclerosis and Air Pollution [MESA Air]) and RD-83830001 (MESA Air Next Stage), awarded by the US EPA. M.A.E. receives funding from the Wake Forest Alzheimer's Disease Core Center (P30AG049638-01A1). S.M.R. is supported by the Intramural Research Program, National Institute on Aging, NIH. The WHI program is funded by the National Heart, Lung, and Blood Institute, NIH, US Department of Health and Human Services through Contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. A list of contributors to WHI is available at https://www-whi-org.s3.us-west-2.amazonaws.com/wp-content/uploads/WHI-Investigator-Long-List.pdf.

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