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Mediterranean Diet and the Association Between Air Pollution and Cardiovascular Disease Mortality Risk

Chris C. Lim, MS
Richard B. Hayes, DDS, PhD
Jiyoung Ahn, PhD
Yongzhao Shao, PhD
Debra T. Silverman, ScD
Rena R. Jones, PhD
George D. Thurston, ScD

BACKGROUND: Recent experimental evidence suggests that nutritional supplementation can blunt adverse cardiopulmonary effects induced by acute air pollution exposure. However, whether usual individual dietary patterns can modify the association between long-term air pollution exposure and health outcomes has not been previously investigated. We assessed, in a large cohort with detailed diet information at the individual level, whether a Mediterranean diet modifies the association between long-term exposure to ambient air pollution and cardiovascular disease mortality risk.

METHODS: The National Institutes of Health–American Association for Retired Persons Diet and Health Study, a prospective cohort (N=548 845) across 6 states and 2 cities in the United States and with a follow-up period of 17 years (1995–2011), was linked to estimates of annual average exposures to fine particulate matter and nitrogen dioxide at the residential census-tract level. The alternative Mediterranean Diet Index, which uses a 9-point scale to assess conformity with a Mediterranean-style diet, was constructed for each participant from information in cohort baseline dietary questionnaires. We evaluated mortality risks for cardiovascular disease, ischemic heart disease, cerebrovascular disease, or cardiac arrest associated with long-term air pollution exposure. Effect modification of the associations between exposure and the mortality outcomes by alternative Mediterranean Diet Index was examined via interaction terms.

RESULTS: For fine particulate matter, we observed elevated and significant associations with cardiovascular disease (hazard ratio [HR] per 10 μg/m^3, 1.13; 95% CI, 1.08–1.18), ischemic heart disease (HR, 1.16; 95% CI, 1.10–1.23), and cerebrovascular disease (HR, 1.15; 95% CI, 1.03–1.28). For nitrogen dioxide, we found significant associations with cardiovascular disease (HR per 10 ppb, 1.06; 95% CI, 1.04–1.08) and ischemic heart disease (HR, 1.08; 95% CI, 1.05–1.11). Analyses indicated that Mediterranean diet modified these relationships, as those with a higher alternative Mediterranean Diet Index score had significantly lower rates of cardiovascular disease mortality associated with long-term air pollution exposure (*P*-interaction<0.05).

CONCLUSIONS: A Mediterranean diet reduced cardiovascular disease mortality risk related to long-term exposure to air pollutants in a large prospective US cohort. Increased consumption of foods rich in antioxidant compounds may aid in reducing the considerable disease burden associated with ambient air pollution.

Key Words: air pollution ■ diet ■ mortality

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Clinical Perspective

What Is New?

- Whether usual individual dietary patterns can modify the association between long-term air pollution exposure and health outcomes has not been previously examined.
- We linked a large (N=548 845) and well-characterized prospective cohort study with spatiotemporally resolved exposure estimates for annual average fine particulate matter and nitrogen dioxide concentration levels.
- Those reporting more of a Mediterranean diet (higher alternative Mediterranean Diet Index score) had lower rates of death attributable to cardiovascular disease, ischemic heart disease, and cerebrovascular disease associated with long-term exposure to fine particulate matter, and cardiovascular disease and ischemic heart disease associated with long-term exposure to nitrogen dioxide.

What Are the Clinical Implications?

- A Mediterranean diet is indicated to provide protection against adverse cardiovascular effects induced by long-term air pollution exposure.
- These results add to a growing body of literature suggesting that dietary patterns may help reduce cardiovascular events attributable to air pollution exposure, potentially through augmenting antioxidants and reducing oxidative stress.
- Confirmatory independent studies, such as in other prospective cohorts, examinations of clinical outcomes, and long-term randomized interventions, would further strengthen our findings.

Cardiovascular diseases are the most important threat for population health in the 21st century.[1] Ambient air pollution is a major contributor to cardiovascular disease–related mortality globally,[2] with recent analysis estimating that >1.5 million ischemic heart disease deaths annually are attributable to ambient fine particulate matter ($PM_{2.5}$) exposure.[3] Both the American Heart Association and European Society of Cardiology have formally recognized ambient air pollution as a major cardiovascular risk factor.[4]

The overall global disease burden of ambient air pollution has been increasing over the past 25 years because of aging populations, the increasing prevalence of chronic diseases, and rising air pollution levels in developing nations.[3] Despite concerted abatement efforts by government and regulatory agencies across the globe, many locations continue to suffer from major pollution episodes and elevated concentration levels, with 90% of the world's population estimated to currently live in places where air quality levels exceed World Health Organization guidelines.[5] To ameliorate the disease and economic burden imposed by ambient air pollution exposure, policy approaches complementary to air quality improvements and emissions controls may be needed.

As air pollution exerts local and systemic responses through inflammatory and oxidative stress pathways,[6] dietary antioxidants could interfere with the mechanisms underlying exposure-related health effects.[7] Recent results from several short-term experimental studies have demonstrated the potential of supplementation with specific foods and nutrients to blunt adverse health effects induced by acute air pollution exposure.[8–10] However, whether usual long-term healthy dietary pattern can modify the association between long-term air pollution exposure and health outcomes is unclear.

A Mediterranean diet emphasizes the consumption of plant-based foods, olive oil, and moderate intake of alcohol, providing a diet highly enriched in antioxidants and anti-inflammatory compounds. In this study, we investigated whether Mediterranean diet reduces the cardiovascular disease mortality risk associated with long-term exposures to $PM_{2.5}$ and nitrogen dioxide (NO_2). Research efforts aimed at evaluating diet as a potential effect modifier could provide insight about cardioprotective mechanisms for air pollution risk reduction.

METHODS

Study Population

Detailed cohort study and participant information has been previously presented.[11] In brief, the National Institutes of Health–American Association for Retired Persons (NIH-AARP) Diet and Health Study was initiated when members of the AARP, 50 to 71 years of age from 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia; Detroit, Michigan), responded to a mailed questionnaire in 1995. The NIH-AARP cohort questionnaires elicited information on demographic and anthropometric characteristics, dietary intake, and numerous health-related factors at enrollment. Contextual environment characteristics for the census tract of each of this cohort's participants have also been compiled, allowing us to also incorporate socioeconomic variables at the census-tract level. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. All participants provided written informed consent before completing the study. This study was approved by the Institutional Review Boards of the National Cancer Institute and New York University School of Medicine.

Cohort Follow-Up and Mortality Ascertainment

Person-years of follow-up were considered for each participant from enrollment to the date of death, the end of follow-up (December 31, 2011), or the date a participant

moved out of the study state or city where s/he lived at enrollment, whichever occurred first. Vital status was ascertained through a periodic linkage of the cohort to the Social Security Administration Death Master File and follow-up searches of the National Death Index Plus for participants who matched to the Social Security Administration Death Master, cancer registry linkage, questionnaire responses, and responses to other mailings. We used the *International Classification of Diseases, 9th Revision* (*ICD-9*) and the *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) to define underlying mortality. Among 566 398 participants enrolled in the NIH-AARP cohort and available for analysis, after excluding those who responded via a proxy (N=15 760), exited the study on the study entry date (N=49), and those with missing $PM_{2.5}$ (N=737) or NO_2 (N=1793) exposure data, the analytic cohort for this work includes 548 845 participants (96.9% of total cohort).

Exposure Assessment

$PM_{2.5}$ exposure estimates at the residential census-tract centroids were obtained from a published spatiotemporal prediction model[12] for the continental United States, available for 1980 to 2010. In brief, geographic predictors and annual average $PM_{2.5}$ data from 1999 through 2010 on a 25-km grid were derived from the US Environmental Protection Agency Federal Reference Method network and the Interagency Monitoring of Protected Visual Environments network. Temporal trends before 1999 were estimated using (1) extrapolation based on $PM_{2.5}$ data in Federal Reference Method/Interagency Monitoring of Protected Visual Environments networks, (2) $PM_{2.5}$ sulfate data in the Clean Air Status and Trends Network, and (3) visibility data across the Weather-Bureau-Army-Navy network. The modeling approach was validated using $PM_{2.5}$ data collected before 1999 from Interagency Monitoring of Protected Visual Environments, California Air Resources Board dichotomous sampler monitoring, the Children's Health Study, and the Inhalable Particulate Network. In the validation using pre-1999 data, the prediction model performed well across 3 trend estimation approaches when validated using Interagency Monitoring of Protected Visual Environments and Children's Health Study data (R^2=0.84–0.91).

The annual NO_2 estimates at the census-tract centroids were derived from a recent model[13] available for years 1990 to 2012, which applied kriging models combining land use regression methods with satellite data to improve model performance on a 25-km grid. The satellite data consist of total tropospheric NO_2 measured via satellite images from the Ozone Monitoring Instrument on the Aurora satellite, whereas the estimation regression covariates were dimension-reduced components of 418 geographic variables. In the kriging models, conventional cross-validated R^2 averaged over all years was 0.85 for the satellite data models and 0.84 for the models without satellite data. Average spatially clustered cross-validated R^2 was 0.74 for the satellite data models and 0.64 for the models without satellite data.

Dietary Intake Assessment

At study enrollment, cohort participants completed the AARP 124-item food frequency questionnaire, an early version of the Diet History Questionnaire, to assess dietary intake over the past year. The Diet History Questionnaire has been previously calibrated, and further validation was performed by using two 24-hour recalls within a subset of the NIH-AARP Diet and Health Study.[14] To create components for the scores, guidance-based food group equivalents and nutrient variables from the AARP food frequency questionnaire were used. The MyPyramid Equivalents Database, version 1.0, was merged with the AARP food frequency questionnaire data to derive guidance-based food group equivalents for major food groups,[14] and nutrient estimates for fatty acids by using the US Department of Agriculture Survey Nutrient Database associated with the Continuing Survey for Food Intake by Individuals 1994–1996 and the Nutrition Data System for Research.

We used the alternative Mediterranean diet (aMED) score to assess dietary patterns. The index includes 9 components (total vegetables excluding potatoes, total fruit, nuts, legumes, fish, whole grains, monounsaturated fatty acids:saturated fatty acids ratio, alcohol, and red and processed meat) and takes into account scientific literature on the effect of diet on chronic disease risk.[15] The aMED is adapted for use in an American population, and scores 9 components for a total of 9 points: 1 point is scored for intake at or greater than the sex-specific median for whole grains, vegetables (excluding potatoes), fruit, nuts, legumes, fish, and fatty acids ratio (monounsaturated fatty acids:saturated fatty acids); and 1 point is given for intakes less than the sex-specific median for red and processed meat. Alcohol was based on predetermined cutoffs (1 point is scored for within 10–25 g/d for men and 5–15 g/d for women).

Statistical Methods

We used the extended Cox proportional hazards models to estimate hazard ratios (HRs) of mortality in relation to ambient air pollution levels (per 10 μg/m^3 for $PM_{2.5}$; per 10 ppb for NO_2), assigning long-term exposure for the air pollutants as time-varying covariates with 1-year lagged annual average concentration levels from 1994 to 2010. Fully adjusted multivariable models included the following covariates: age (grouped into 3-year categories), sex, region (6 US states and 2 cities) as strata; race or ethnic group (non-Hispanic white; non-Hispanic black; Hispanic; Asian, Pacific Islander, or American Indian/Alaskan Native; unknown); level of education (less than high school, some high school, high school completed, post–high school or some college, college and postgraduate, unknown); marital status (married, never-married, other, unknown); body mass index (<18.5 kg/m^2, 18.5 to <25.0, 25.0 to <30.0, 30 to <35, 35+, unknown); alcohol (none, <1, 1 to <2, 2 to <3, 3 to <5, and 5+ drinks per day); smoking status (never smoker, former smoker of ≤1 pack/d, former smoker of >1 pack/d, current smoker of ≤1 pack/d, current smoker of >1 pack/d, unknown), in addition to 2 contextual characteristics (median census-tract household income and percent of census-tract population with less than a high school education, based on the 2000 decennial census for the residence at study entry).

We first conducted analyses to test the associations between the air pollutants and cause-specific mortality outcomes. We then assessed potential effect modification by including multiplicative interaction terms between the pollutant and the aMED in the models. Likelihood ratio statistic *P* values (2-sided), comparing model fit with and without

interaction terms, were used to test the statistical significance of each interaction. In addition, we also examined interactions by each individual dietary component of the aMED index.

As a sensitivity analysis, we additionally adjusted for preexisting diseases (heart disease, stroke history, and diabetes mellitus) and evaluated random effects at the metropolitan statistical area level. Given the observable differences across aMED quintile for education and body mass index levels, we also tested for their potentially confounding effects by stratifying the cohort by these covariates and assessing if the effect modification by aMED remained present in the stratified results. In addition, we compared the results after stratifying the population according to population density to test for potential urban/rural differences, and we also performed penalized ridge analyses to simultaneously adjust for both $PM_{2.5}$ and NO_2 in the same model.

To validate our results, we tested whether the Cox proportional hazards assumption was satisfied through examination of the Schoenfeld plots, and we evaluated the degree to which unmeasured confounding potentially influenced our results by calculating the E values.[16] We also assessed whether the linearity assumption of the exposure-response relationship is appropriate by calculating and comparing the Bayesian Information Criterion values for natural spline models with different degrees of freedom.

Packages "survival" and "coxme" in R (version 3.4.4) were used for analysis.

RESULTS

During the follow-up period considered in this study (1995–2011), 126 817 (23.1%) of cohort participants died: 39 532 deaths were attributable to all cardiovascular diseases (CVD; *ICD-9*: 390–459, *ICD-10*: I00–I99); 22 329 were attributable to ischemic heart disease (IHD; *ICD-9*: 410–414, *ICD-10*: I20–I25); 5592 were from cerebrovascular diseases (*ICD-9*: 430–438, *ICD-10*: I60–I69); and 6811 were from dysrhythmias, heart failures, and cardiac arrests (*ICD-9*: 420–429, *ICD-10*: I30–I51). The cohort (N=548 845), with an average age of 62.2 (SD=5.4) at entry, is characterized as mostly white (91.2% of the cohort), male (59.1%), either never (34.8%) or former (49.4%) smokers, with college or postcollege education level (38.3%), overweight (41.3%), and married (68.1%). Summary statistics are provided in Table 1; air pollution concentration levels and covariates were generally consistent across the aMED quintiles, except that those in higher quintiles tended to be never smokers and have higher levels of education. The overall average concentration for $PM_{2.5}$ during the study period was 12.9 (ranging from 3.4 to 23.0) μg/m^3, with a SD of 3.2 μg/m^3; for NO_2, the average was 13.3 (ranging from 2.0 to 37.7) ppb, with SD of 7.6 ppb. The concentration levels for both of the pollutants decreased substantially during the study period across all locations (Figure I in the online-only Data Supplement); the overall annual average levels were 15.3 μg/m^3 and 18.6 ppb in 1994, and 9.2 μg/m^3 and 9.8 ppb in 2010, for $PM_{2.5}$ and NO_2, respectively. The R^2 between $PM_{2.5}$ and NO_2 average annual concentrations was high (0.63), suggesting shared emission sources.

Long-term exposures to the air pollutants were significantly associated with the cause-specific mortality outcomes evaluated (Table 2). For $PM_{2.5}$, we observed elevated and statistically significant associations with CVD (HR, 1.13; 95% CI, 1.08–1.18), IHD (HR, 1.16; 95% CI, 1.10–1.23), and cerebrovascular diseases (HR, 1.15; 95% CI, 1.03–1.28). For NO_2, we found significant associations with CVD (HR, 1.06; 95% CI, 1.04–1.08) and IHD (HR, 1.08; 95% CI, 1.05–1.11). We did not observe significant associations between these air pollutants and cardiac arrest mortality. The aMED variable remained significantly and negatively associated with mortality risks in these models. Adjusting for preexisting diseases and entering a random effects variable at the metropolitan statistical area level did not significantly alter our findings. In the copollutant penalized ridge regression analysis, CVD and IHD mortality risks associated with both $PM_{2.5}$ and NO_2 remained significant, but not cerebrovascular diseases (Table I in the online-only Data Supplement).

Estimates of the modification of the air pollution–mortality associations by aMED scores are shown in Figure (and in Table II in the online-only Data Supplement). We observed decreasing associations between $PM_{2.5}$ and NO_2 with both CVD (*P*-interaction<0.01) and IHD (*P*-interaction<0.01) mortality risks with higher aMED quintiles, with these associations becoming statistically nonsignificant in the highest aMED quintile. Association between $PM_{2.5}$ with cerebrovascular disease mortality (*P*-interaction<0.01) was also significantly reduced among participants with higher aMED scores.

We also evaluated effect modification by the individual dietary components of a Mediterranean diet (Figure II in the online-only Data Supplement). The $PM_{2.5}$-CVD, $PM_{2.5}$-IHD, NO_2-CVD, and NO_2-IHD mortality associations were significantly reduced in subjects who consumed higher amounts of vegetables, and the $PM_{2.5}$-CVD and $PM_{2.5}$-IHD mortality associations were significantly lower among those who consumed higher amounts of whole grains. We also observed that NO_2-IHD association was significantly reduced in subjects who consumed higher amounts of fruits, the NO_2-CVD association was significantly lower among those consuming foods with a higher monounsaturated fatty acids:saturated fatty acids ratio.

The effect modification by aMED of the associations between $PM_{2.5}$ and NO_2 with CVD mortality risk remained statistically significant across different groups of education level (Table III in the online-only Data Supplement), whereas, for IHD mortality, the effect modification was only observed for those with education levels at high school level or less. We also found significant effect modification by aMED among those who have a normal weight or are overweight, but not

Table 1. Descriptive Characteristics of the NIH-AARP Diet and Health Study Based on Quintiles of Alternative Mediterranean Diet Index (aMED) Scores

Characteristics	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* Value
Range of index scores	0–2	3	4	5	6–9	
N	102 099	97 566	112 578	105 761	130 841	
$PM_{2.5}$ (SD)	12.3 (2.8)	12.3 (2.9)	12.4 (2.9)	12.4 (2.9)	12.3 (3.0)	0.88
NO_2 (SD)	12.9 (6.5)	13.0 (6.6)	13.1 (6.6)	13.2 (6.7)	13.3 (6.7)	0.88
Entry age, y (SD)	61.5 (5.5)	61.9 (5.4)	62.2 (5.3)	62.4 (5.3)	62.7 (5.2)	0.54
Sex, n (%)						0.95
Male	61 532 (60.3)	55 776 (57.2)	64 364 (57.2)	61 307 (58)	81 139 (62.0)	
Female	40 567 (39.7)	41 790 (42.8)	48 214 (42.8)	44 454 (42)	49 702 (38.0)	
Race, n (%)						0.99
White	93 825 (91.9)	88 662 (90.9)	101 675 (90.3)	95 904 (90.7)	120 505 (92.1)	
Black	3964 (3.9)	4029 (4.1)	4876 (4.3)	4330 (4.1)	4383 (3.3)	
Hispanic	1695 (1.7)	1933 (2.0)	2307 (2.0)	2088 (2.0)	2174 (1.7)	
Asian/Pacific Islander/Native American	1176 (1.2)	1492 (1.5)	2009 (1.8)	1956 (1.8)	2246 (1.7)	
Education, n (%)						0.60
Less than high school	8981 (8.8)	7112 (7.3)	7130 (6.3)	5356 (5.1)	4676 (3.6)	
Some high school	26 079 (25.5)	21 940 (22.5)	22 704 (20.2)	18 769 (17.7)	17 885 (13.7)	
12 y or high school completed	11 425 (11.2)	10 310 (10.6)	11 265 (10.0)	9903 (9.4)	10 845 (8.3)	
Post–high school or some college	23 437 (23.0)	22 787 (23.4)	26 320 (23.4)	24 706 (23.4)	29 910 (22.9)	
College and postgraduate	28 845 (28.3)	32 197 (33.0)	41 568 (36.9)	43 831 (41.4)	64 304 (49.1)	
BMI, n (%)						0.98
<18.5	1045 (1.0)	811 (0.8)	890 (0.8)	839 (0.8)	1068 (0.8)	
18.5–25	30 068 (29.4)	30 182 (30.9)	36 022 (32.0)	36 347 (34.4)	51 775 (39.6)	
25–30	41 501 (40.6)	39 890 (40.9)	46 961 (41.7)	44 343 (41.9)	54 159 (41.4)	
30–35	18 029 (17.7)	16 463 (16.9)	18 223 (16.2)	15 701 (14.8)	15 874 (12.1)	
>35	8396 (8.2)	7344 (7.5)	7440 (6.6)	5775 (5.5)	4904 (3.7)	
Marital, n (%)						0.99
Married	68 928 (67.5)	65 228 (66.9)	75 627 (67.2)	71 929 (68.0)	91 864 (70.2)	
Never married	27 197 (26.6)	26 565 (27.2)	30 325 (26.9)	27 810 (26.3)	32 166 (24.6)	
Other	5065 (5.0)	4824 (4.9)	5564 (4.9)	5125 (4.8)	5995 (4.6)	
Smoking, (%)						0.33
Never	30 107 (29.5)	32 807 (33.6)	40 077 (35.6)	38 871 (36.8)	49 177 (37.6)	
Former smoker of ≤1 pack/d	21 436 (21.0)	23 880 (24.5)	29 804 (26.5)	30 031 (28.4)	40 750 (31.1)	
Former smoker of >1 pack/d	21 943 (21.5)	20 071 (20.6)	23 409 (20.8)	22 222 (21.0)	27 687 (21.2)	
Current smoker of ≤1 pack/d	13 927 (13.6)	10 729 (11.0)	10 079 (9.0)	7570 (7.2)	6538 (5.0)	
Current smoker of >1 pack/d	10 669 (10.4)	6194 (6.3)	4789 (4.3)	3008 (2.8)	2108 (1.6)	

BMI indicates body mass index.

among those who are obese; however, among the subjects who were obese, the air pollution mortality risks were reduced and, in general, not statistically significant. Across different smoking history groups, we found significant effect modification by aMED among those who are never or ever smokers but not among who are current smokers, although among this group the air pollution mortality risks were also not statistically significant. We also observed that the air pollution–associated mortality risks and modification by aMED were present among participants residing in locations with greater population density, where there were higher air pollution concentration levels (Table IV in the online-only Data Supplement).

Examination of the Schoenfeld plots revealed that the Cox proportional hazards assumption was satisfied (results not shown), and the E values ranged from 1.51 to 1.57 for mortality outcomes associated with $PM_{2.5}$ and 1.24 to 1.37 for mortality outcomes associated with NO_2 (Table V in the online-only Data Supplement), suggesting

Table 2. Cause-Specific Mortality Hazard Ratios With 95% CIs in Relation to Air Pollution Concentrations (per 10 μg/m³ for $PM_{2.5}$; per 10 ppb for NO_2)

Cause of Death	Deaths, n	*ICD-9* & *ICD-10* Codes	Base Model		Base Model + Adjustment for Preexisting Diseases		Base Model + Adjustment for MSA-Level Random Effects	
			$PM_{2.5}$	NO_2	$PM_{2.5}$	NO_2	$PM_{2.5}$	NO_2
			HR (95% CI)*	HR (95% CI)*	HR (95% CI)*	HR (95% CI)*	HR (95% CI)*	HR (95% CI)*
Cardiovascular disease	39 532	390–459; I00–I99	1.13 (1.08–1.18)	1.06 (1.04–1.08)	1.13 (1.09–1.18)	1.08 (1.05–1.09)	1.11 (1.05–1.16)	1.06 (1.04–1.09)
Ischemic heart disease	22 329	410–414; I20–I25	1.16 (1.10–1.23)	1.08 (1.05–1.11)	1.17 (1.10–1.23)	1.08 (1.05–1.11)	1.17 (1.10–1.23)	1.06 (1.03–1.09)
Cerebrovascular disease	5592	430–438; I60–I69	1.15 (1.03–1.28)	1.04 (0.99–1.09)	1.16 (1.04–1.30)	1.05 (0.99–1.10)	1.16 (1.04–1.30)	1.05 (0.99–1.10)
Cardiac arrest	6811	420–429; I30–I51	0.98 (0.88–1.09)	1.02 (0.97–1.07)	1.00 (0.91–1.12)	1.03 (0.98–1.08)	1.04 (0.92–1.18)	1.04 (0.98–1.10)

aMED indicates alternative Mediterranean Diet Index; HR, hazard ratio; *ICD-9*, *International Classification of Diseases, 9th Revision*; *ICD-10*, *International Statistical Classification of Diseases, 10th Revision*; MSA, metropolitan statistical level; NO_2, nitrogen dioxide; and $PM_{2.5}$, fine particulate matter.

*Adjusted for sex and location as strata; and age (time-varying), race, BMI, education, smoking, diet (aMED), and marriage at individual level; and median income and % with high school education at census-tract level.

that the level of unmeasured confounding needed to explain away the effect estimates is likely to be large. Assessment of natural spline models with different degrees of freedom (df) suggested that assumption of linearity of the exposure-response relationship was appropriate, with df=1 having the lowest Bayesian Information Criterion.

DISCUSSION

In this large, well-characterized prospective US cohort, long-term exposures to $PM_{2.5}$ and NO_2 were significantly associated with CVD and IHD mortality, and exposure to $PM_{2.5}$ was also significantly associated with cerebrovascular disease mortality. Results showed that a Mediterranean diet significantly modified these relationships, because those with a higher aMED score had significantly lower rates of CVD mortality adjusting for the usual CVD contributors.

A Mediterranean diet has shown beneficial effects on cardiovascular health, improving blood pressure, endothelial function, and lipid profiles while reducing inflammatory responses and oxidative stress.[17,18] These

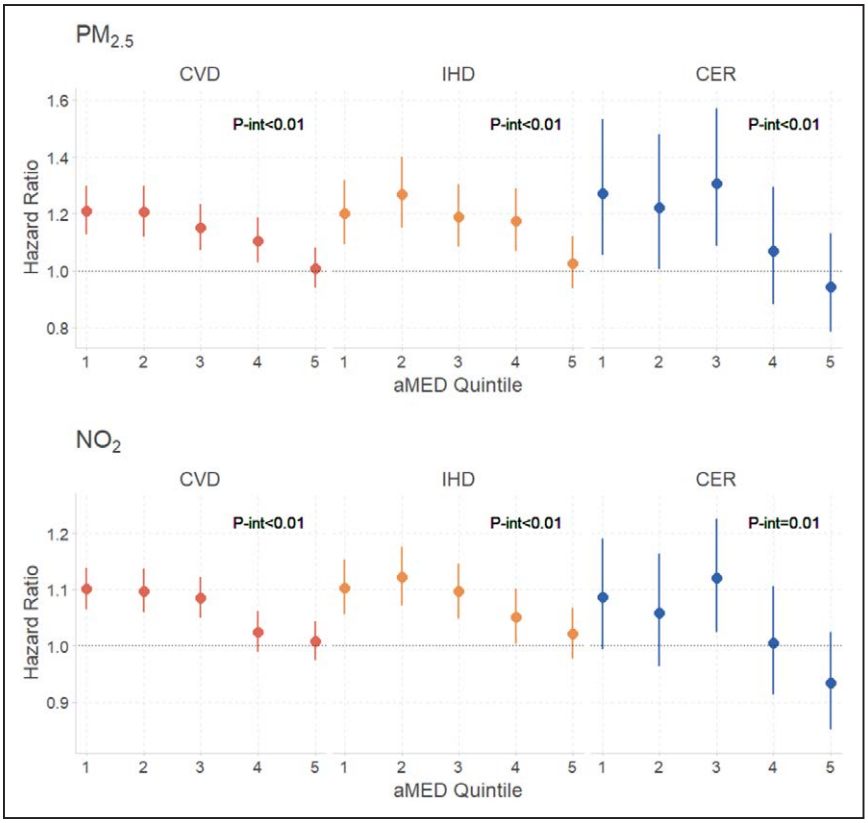

Figure. Hazard ratios and 95% CIs associated with air pollutants by quintiles of aMED (alternative Mediterranean Diet Index) score.
CAR indicates cardiac arrests; CER, cerebrovascular disease; CVD, cardiovascular disease; IHD, ischemic heart disease; and p-int, *P* interaction.

benefits have been consistently observed in meta-analyses, cohort studies, and randomized controlled trials.[19–21] Previous investigations within the NIH-AARP cohort also reported reduction in all-cause and cause-specific mortality risk with conformity to a Mediterranean diet.[14,22] Attenuation of the CVD mortality risk associated with air pollution exposure by dietary patterns, as observed here, is therefore consistent with past evidence of oxidative stress as an underlying mechanism for air pollution–induced health effects, and suggests that a healthful dietary pattern enriched in antioxidant and anti-inflammatory compounds could interact with mechanisms underlying air pollution–induced health effects. For example, dietary antioxidants may scavenge the reactive oxygen species and free radicals generated from exposure to air pollution before they can activate pathways in pathogenesis of air pollution–induced cardiovascular health effects.[23] Attenuation of air pollution–CVD and IHD mortality associations by unsaturated fats, fruits, vegetables, and whole grains, as observed in our analysis, supports this hypothesis.

Multiple intervention studies to date have demonstrated the beneficial capacity of dietary supplementation to mitigate adverse cardiopulmonary effects of air pollution exposure. In a randomized, controlled trial in Mexico City, supplementation with fish oil reduced the negative impact of $PM_{2.5}$ on heart rate variability and biomarkers of response to oxidative stimuli among the elderly.[24,25] Supplementation with vitamins C and E for 6 months decreased several biomarkers of oxidative stress among electric power plant workers and provided protection against the oxidative insult associated with air pollutants derived from coal burning.[26] In an experimental study of healthy middle-aged adults exposed to concentrated air pollution, dietary supplementation with olive oil attenuated concentrated air pollution–induced impaired vascular endothelial function while altering blood markers associated with fibrinolysis and vasoconstriction.[27] In a 12-week randomized intervention trial in Chinese adults, broccoli sprouts also facilitated the urinary excretion of mercapturic acids of air pollutants, the glutathione-derived conjugates of benzene and acrolein, suggesting that supplementation with broccoli sprouts enhanced detoxification of traffic-related pollutants.[28] Broccoli sprout extracts also suppressed the nasal inflammatory response, measured by total white blood cell counts in nasal lavage fluid induced by diesel exhaust particles.[29]

Recent mechanistic studies have also identified several potential biological pathways by which diet could modulate the association between air pollution exposure and health responses. In a single-blind placebo-controlled crossover study of 10 adults, $PM_{2.5}$ exposure induced methylation changes in genes involved in mitochondrial oxidative energy metabolism, whereas B vitamin supplementation prevented these changes.[7] Increased blood levels of fish-based omega-3 fatty acids attenuated increases in fibrinogen associated with short-term increases in ambient PM among 135 patients.[30] Vitamin E and omega-3 fatty acids mitigated $PM_{2.5}$-induced inflammation and oxidative stress, decreasing inflammatory cytokines interleukin 6 and tumor necrosis factor α levels in human umbilical vein vascular endothelial cells.[31] In animal studies, vitamin E and omega-3 fatty acids also protected against cardiac tissue injury,[32] whereas blueberry anthocyanin–enriched extracts improved ECG abnormalities, decreased cytokine levels, and inhibited cardiomyocyte apoptosis in $PM_{2.5}$-exposed rats.[33]

Although such past studies have sought to identify specific foods or nutrients capable of mitigating acute responses to air pollution exposures, whether a healthful dietary pattern can modify the association between long-term air pollution exposure and health outcomes has not yet been assessed. Similar epidemiological evidence supporting our findings is very limited, mainly because of a lack of available detailed dietary information in comparable cohort studies on the long-term effects of air pollution. Our results here, however, are consistent with findings from the Danish Cancer and Diet cohort (N=52 061), which found that participants with higher total consumption of fruits and vegetables had significantly lowered risks of CVD and IHD mortality associated with long-term NO_2 exposure.[23] In an earlier analysis of this current cohort with a limited analysis of 3 dietary variables (fruit, vegetables, and total fat), we found that higher fruit and vegetable consumption lowered diabetes mellitus mortality associated with $PM_{2.5}$ and NO_2 exposures.[34] Evaluation of the $PM_{2.5}$-CVD associations in the comparable American Cancer Society Cancer Prevention Study II Cohort (N=669 046), on the other hand, did not find that fat, fruit, vegetable, and fiber consumptions modified these relationships.[35]

The high spatial correlation between $PM_{2.5}$ and NO_2 and similar findings of effect modification of cardiovascular mortality outcomes by diet suggest that these pollutants likely originate from fossil fuel combustion from a similar source, most likely traffic. NO_2 is an indicator of vehicle engine exhaust emissions, a complex mixture including transition metals and polycyclic aromatic hydrocarbons.[36] Recent results[37] implicate fossil fuel combustion–derived air pollution as most responsible for the associations that have been observed between long-term air pollution exposure and CVD mortality. Exposures to $PM_{2.5}$ and NO_2 (and correlated substances) can activate pathways mediating oxidative stress and inflammation, thereby potentially promoting CVD mechanisms including systemic endothelial dysfunction, thrombosis, autonomic imbalance, atherosclerosis progression, insulin resistance, and dyslipidemia.[38]

This study has the major advantage of drawing on a large prospective cohort specifically designed to assess participant diet and its relationship to chronic diseases. This study also has the strength of utilizing the latest air

pollution prediction models to provide spatiotemporally detailed exposure estimates for the air pollutants for the entire follow-up period. We used a commonly used index score to measure diet quality, which allows for findings to be more readily translated to public health guidelines. However, several potential weaknesses also exist in this study. With measures of diet collected only at baseline, we could not account for possible changes in intake and trends in patterns over time. Similarly, this analysis only included personal covariates recorded at baseline, so that any follow-up changes in these factors could not be accounted for. Other than knowing if and when participants leave the NIH-AARP cohort study areas, we presently lack information on residence location after those participants moved out of the study region, which may result in potential exposure misclassification. Moreover, a Mediterranean dietary pattern may also reflect other overall healthy behaviors that were not fully adjusted for in this analysis. Another limitation is that the NIH-AARP cohort has a limited number of participants in races other than white and black non-Hispanic, and therefore our findings may not be generalizable to others in the US general population, although a reason that this would not be so is not obvious.

The global public health and associated economic burden of ambient air pollution is immense. According to the World Health Organization, exposure to ambient air pollution is the fifth leading mortality risk factor in the world, estimated to cause >4.2 million deaths annually.[5] The findings here suggest that a healthful dietary pattern can modify air pollution–induced adverse cardiovascular health effects, and thereby reduce mortality risk associated with long-term air pollution exposures. Because it is unknown whether aMED has similar associations with attenuating other adverse effects of air pollution, such as respiratory events or lung cancer, or whether the attenuation of CVD events would extend to higher levels of long-term air pollution exposure, additional studies are needed to address these gaps of knowledge. Overall, our results have the potential to inform affected individuals exposed to high ambient air pollution levels, and both policy makers and those developing dietary guidelines, as to the potential role of dietary patterns in protecting public health from adverse effects of air pollution. Thus, in concert with air quality standards and emissions control policies to protect health against the most harmful effects of air pollution, individual-level prevention strategies and population-wide policy efforts to promote healthier diets, aimed at countering the oxidative stress induced by air pollution exposure, may provide complementary approaches.

Conclusion

In this prospective cohort of older US adults, long-term ambient air pollution exposure was significantly associated with an increase in cardiovascular mortality. Those reporting eating a Mediterranean diet had significantly lower rates of CVD mortality associated with long-term air pollution exposure, suggesting that dietary patterns enriched in antioxidant foods and compounds could potentially provide protection against the adverse health effects induced by long-term exposure to ambient air pollution. These findings are also consistent with past evidence of oxidative stress as underlying mechanism for air pollution–induced health effects. Confirmatory studies exploring other health outcomes, combinations of certain foods and nutrients, and randomized clinical trials would further strengthen our findings.

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Correspondence

Chris C. Lim, MS, Department of Environmental Medicine, NYU School of Medicine, 341 East 25th St, New York, NY 10010. Email cchaeha@gmail.com

Affiliations

Departments of Environmental Medicine (C.C.L., R.B.H., J.A., Y.S., G.D.T.) and Population Health (R.B.H., J.A., Y.S., G.D.T.), New York University School of Medicine. Division of Cancer Epidemiology & Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD (D.T.S., R.R.J.).

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C.C. Lim designed the study, analyzed the data, and wrote the manuscript. Drs Silverman, Jones, Ahn, and Shao edited the manuscript and contributed to discussion. Drs Hayes and Thurston were the main investigators for the study and edited the manuscript.

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Disclosures

None.

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