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Long-Term Exposures to Air Pollution and the Risk of Atrial Fibrillation in the Women's Health Initiative Cohort

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Background: Atrial fibrillation (AF) is associated with substantial morbidity and mortality. Short-term exposures to air pollution have been associated with AF triggering; less is known regarding associations between long-term air pollution exposures and AF incidence.

Objectives: Our objective was to assess the association between long-term exposures to air pollution and distance to road on incidence of AF in a cohort of U.S. women.

Methods: We assessed the association of high resolution spatiotemporal model predictions of long-term exposures to particulate matter (PM_{10} and $PM_{2.5}$), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and distance to major roads with incidence of AF diagnosis, identified through Medicare linkage, among 83,117 women in the prospective Women's Health Initiative cohort, followed from enrollment in Medicare through December 2012, incidence of AF, or death. Using time-varying Cox proportional hazards models adjusted for age, race/ethnicity, study component, body mass index, physical activity, menopausal hormone therapy, smoking, diet quality, alcohol consumption, educational attainment, and neighborhood socioeconomic status, we estimated the relative risk of incident AF in association with each pollutant.

Results: A total of 16,348 incident AF cases were observed over 660,236 person-years of follow-up. Most exposure–response associations were nonlinear. NO_2 was associated with risk of AF in multivariable adjusted models [Hazard Ratio (HR) = 1.18; 95% confidence interval (CI): 1.13, 1.24, comparing the top to bottom quartile, p-for-trend = <0.0001]. Women living closer to roadways were at higher risk of AF (e.g., HR = 1.07; 95% CI: 1.01, 1.13 for living within 50 m of A3 roads, compared with $\geq$1,000 m, p-for-trend = 0.02), but we did not observe adverse associations with exposures to PM_{10}, $PM_{2.5}$, or SO_2. There were adverse associations with PM_{10} (top quartile HR = 1.10; 95% CI: 1.05, 1.16, p-for-trend = <0.0001) and $PM_{2.5}$ (top quartile HR = 1.09; 95% CI: 1.03, 1.14, p-for-trend = 0.002) in sensitivity models adjusting for census region.

Discussion: In this study of postmenopausal women, NO_2 and distance to road were consistently associated with higher risk of AF. https://doi.org/10.1289/EHP7683

Introduction

Atrial fibrillation (AF) is the most common heart rhythm disorder. It was estimated that 7.5 million people in the United States would have developed AF in 2020 and that this number will increase to 12.1 million by 2050 (Chugh et al. 2014; Krijthe et al. 2013; Miyasaka et al. 2006; Morillo et al. 2017). The morbidity and mortality associated with AF are substantial. Despite recent advances in its management (McManus et al. 2012) AF is responsible for more hospitalizations and longer hospital stays than any other arrhythmia and contributes to an increased risk of stroke, congestive heart failure, myocardial infarction (MI), cardiovascular disease (CVD), and total mortality (Odutayo et al. 2016). The challenge posed by the increasing prevalence of AF is further heightened by limited effective targets for its prevention (Huxley et al. 2011; Tedrow et al. 2010). Established AF risk factors explain 50%–60% of AF cases in the population (Huxley et al. 2011; Perez et al. 2013), in comparison with up to 90% for MI (Yusuf et al. 2004). Therefore, a sizeable proportion of the population's attributable risk for AF remains unexplained by current knowledge. Additionally, researchers have found growing evidence that AF is associated with worse outcomes among women than among men (Madan et al. 2019), so population-level approaches could be especially beneficial for women.

Air pollution accounts for an estimated 4.2 million deaths worldwide (Lim et al. 2012; World Health Organization 2018) and has been convincingly associated with overall CVD morbidity and mortality, particularly among women (Brook et al. 2010; Hoek et al. 2013; Newby et al. 2015; Pranata et al. 2020; Rajagopalan

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et al. 2018; Thurston et al. 2017). However, far less evidence is available regarding the possible impact of air pollution on AF. Air pollution has been linked to a number of hypothesized biological pathways underlying both the initiation and maintenance of AF (Watkins et al. 2013), and human exposures to air pollution have been associated with risk of experiencing an episode of AF in the short term (hours to days) (Dahlquist et al. 2020; Link et al. 2013; Shao et al. 2016). Far less evidence exists, however, on the association between long-term exposures to air pollution and incidence of AF. Only a handful of studies have specifically examined associations between long-term exposures and risk of AF, with conflicting results, potentially due at least partly to heterogeneity in both exposure and outcome assessment and limited ability in some studies to adjust for potential confounders (Kim et al. 2018; Kwon et al. 2019; Monrad et al. 2017; Pranata et al. 2020; Shin et al. 2019; Stockfelt et al. 2017). To date, the most consistent associations have been observed with oxides of nitrogen, suggesting that traffic-related exposures may be of greatest interest. However, to the best of our knowledge, no studies have examined the associations between AF risk and distance to roads, a marker of traffic-related exposures.

The availability of information on multiple time-varying measures of air pollution, distance to roads (Bergen et al. 2013; Kirwa et al. 2014; Sampson et al. 2013) and long-term incidence of AF (Azarbal et al. 2014; Perez et al. 2013; Young et al. 2016) in the large, prospective, U.S.-based Women's Health Initiative (WHI) cohort offers a unique opportunity to examine the association of multiple air pollutants and distance to roadways with risk of AF and to identify potentially susceptible subpopulations.

Methods

Study Population

Details of enrollment and follow-up in the WHI have been published previously (Anderson et al. 1998, 2003). Women had to be postmenopausal and between the ages of 50 and 79 to be eligible and were recruited through mass mailings and enrolled at 40 clinical centers between 1993 and 1998. Eligibility for enrollment included the intention to reside in the area for at least 3 y, free from any major medical condition which would affect survival within 3 y of study entry, and no reported mental illness, dementia, alcoholism, or drug dependency. Enrolled women ($N=$ 161,808) were included in the observational study (OS, $n=$ 93,676) or one of the randomized control trials (RCT, $n=68{,}132$). Participants filled out baseline questionnaires evaluating their demographics, medical history, and health habits and underwent baseline vital signs measurement, anthropometry, and laboratory testing. After enrollment, each participant was followed through annual questionnaires to update medical history and information on selected risk factors. Changes in residence and the corresponding dates were also collected. For the current analysis, we excluded all women with a history of AF at WHI enrollment ($n=7{,}132$, as reported either on the baseline questionnaire or detected on the baseline electrocardiogram), as well as those women who were never enrolled in Medicare Parts A and B ($n=49{,}688$), or who were missing data on covariates ($n=21{,}871$; Table S1). The women excluded from the analyses were similar to those included for most variables (Table 1; Table S2). However, the excluded women were younger at WHI enrollment (39% vs. 28% <60y), were less likely to be white (78% vs. 87%), and were a little less likely to have never smoked (50% vs. 52%) than the included women. A total of 83,117 women were included in the analyses.

AF Case Ascertainment

Identification of cases of incident AF in WHI has been previously described (Perez et al. 2013). Briefly, AF incidence was defined as having at least a single ICD-9 diagnosis code of 427.31 from inpatient, outpatient, or physician diagnosis codes while the participant was enrolled in Medicare Parts A and B. Participants enrolled in Medicare Parts A and B at WHI enrollment began contributing person-time on the date of enrollment into WHI. However, participants who enrolled in Medicare Parts A and B at a later point in time did not contribute follow-up time until they had been enrolled in Medicare Parts A and B for 2 y to reduce the likelihood that they had developed AF during the interval when they were not insured by Medicare Parts A and B and to avoid falsely misclassifying recurrent AF diagnoses as incident AF. Women who were free of AF during this period entered the risk set at the time of completion of this period (i.e., 2 y after starting to participate in Medicare Parts A and B). Participants who left Medicare and then returned for a subsequent interval were not subjected to a similar 2-y hold-out period, although their person-time during the interval of nonenrollment was not included.

Exposure Assessment

The residential address histories of all WHI participants have been geocoded, and the addresses for women included in these analyses are shown in Figure 1. Participants' time-varying average yearly exposure to ambient particulate matter (PM) less than 2.5 μm ($PM_{2.5}$) or less than 10 μm (PM_{10}), and to gaseous air pollutants including nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) were estimated at each residential address from baseline through the end of 2012 (Bergen et al. 2013; Sampson et al. 2013; Young et al. 2016). These predictions were generated from regionalized national universal kriging models integrating monitoring data from governmental sources, satellite data (for the NO_2 models), and information on hundreds of land-use variables and sources of pollution to generate annual average predictions at each address. The models have been shown to predict concentrations with high cross-validation accuracy for $PM_{2.5}$ ($R^2=0.88$) and NO_2 ($R^2=0.85$), and acceptable accuracy for PM_{10} ($R^2=0.40$–0.63). For participants who changed addresses during follow-up, annual average pollution exposures were calculated by weighting by number of months at each address. Roadway proximity (in meters) for each address was assessed using a Geographic Information System (GIS), including road segments from the three largest U.S. Census Feature Class Codes: A1 (primary roads, typically interstate highways, with limited access, division between the opposing directions of traffic, and defined exits), A2 (primary major, noninterstate highways and major roads without access restrictions), or A3 (smaller, secondary roads, usually with more than two lanes), and only changed if the participant changed addresses. Based on the distribution of distance to road, literature on the decay of exposures from a roadway (Karner et al. 2010) and previous WHI analyses (Kingsley et al. 2015; Kirwa et al. 2014), we categorized exposures as 0–49, 50–199, 200–399, 400–999, and ≥1,000 m.

Potential Confounders, Effect Modifiers, and Mediators

We assessed potential confounding from a number of factors ascertained at WHI enrollment that have been shown to be associated with either AF or the exposures of interest and were not likely to be intermediates of the observed associations, including: study component [OS, hormone replacement therapy (HRT) clinical trial only, dietary modification (DM) trial only, HRT and DM, calcium/Vitamin D trial (CAD) and HRT, or CAD and DM), age (in 5-y intervals), race/ethnicity (American Indian, Asian/Pacific Islander, Black, Hispanic, White, and unknown), BMI (continuous, kilogram per square meter),

Table 1. Demographics and characteristics of 83,117 participants in the Women's Health Initiative (WHI) cohort at enrollment into WHI overall and by upper and lower quartiles[a] of annual average NO_2 and $PM_{2.5}$ exposure.

		NO_2 (ppb)		$PM_{2.5}$ ($\mu g/m^3$)	
	Total	Q1: 0.5–7.5	Q4: 15.7–45.6	Q1: 1.7–9.5	Q4: 13.4–25.6
n	83,117	14,417	30,508	12,793	33,876
Age [5-y intervals (%)]					
50–54	7,211 (8.7)	3,066 (21.3)	884 (2.9)	2,992 (23.4)	489 (1.4)
55–59	15,691 (18.9)	4,233 (29.4)	3,185 (10.4)	4,093 (32.0)	3,319 (9.8)
60–64	20,214 (24.3)	3,351 (23.2)	6,729 (22.1)	2,948 (23.0)	7,402 (21.9)
65–69	20,508 (24.7)	2,124 (14.7)	9,636 (31.6)	1,483 (11.6)	11,417 (33.7)
70–74	13,881 (16.7)	1,222 (8.5)	7,034 (23.1)	925 (7.2)	7,939 (23.4)
75–79	5,612 (6.8)	421 (2.9)	3,040 (10.0)	352 (2.8)	3,310 (9.8)
Race/ethnicity (%)					
American Indian	304 (0.4)	87 (0.6)	96 (0.3)	68 (0.5)	102 (0.3)
Asian/Pacific Islander	754 (0.9)	47 (0.3)	405 (1.3)	101 (0.8)	312 (0.9)
Black	6,794 (8.2)	540 (3.7)	4,047 (13.3)	328 (2.6)	4,431 (13.1)
Hispanic	2,227 (2.7)	318 (2.2)	858 (2.8)	520 (4.1)	566 (1.7)
White	72,180 (86.8)	13,321 (92.4)	24,712 (81.0)	11,659 (91.1)	28,100 (82.9)
Unknown	858 (1.0)	104 (0.7)	390 (1.3)	117 (0.9)	365 (1.1)
WHI study component (%)					
Observational study (OS)	48,907 (58.8)	7,996 (55.5)	18,285 (59.9)	7,180 (56.1)	20,621 (60.9)
Hormone replacement therapy (HRT) trial only	6,779 (8.2)	1,344 (9.3)	2,322 (7.6)	1,057 (8.3)	2,591 (7.6)
Dietary modification (DM) trial only	9,939 (12.0)	1,723 (12.0)	3,816 (12.5)	1,621 (12.7)	3,981 (11.8)
HRT and DM	1,433 (1.7)	258 (1.8)	522 (1.7)	218 (1.7)	578 (1.7)
Calcium/Vitamin D (CAD) trial and HRT	5,957 (7.2)	1,284 (8.9)	1,908 (6.3)	981 (7.7)	2,188 (6.5)
CAD and DM	10,102 (12.2)	1,812 (12.6)	3,655 (12.0)	1,736 (13.6)	3,917 (11.6)
Census region of residence (%)					
Northeast	20,104 (24.2)	1,923 (13.3)	9,857 (32.3)	3,255 (25.4)	7,122 (21.0)
Midwest	22,290 (26.8)	3,464 (24.0)	7,975 (26.1)	1,514 (11.8)	11,005 (32.5)
South	24,399 (29.4)	6,446 (44.7)	5,257 (17.2)	2,752 (21.5)	11,041 (32.6)
West	16,324 (19.6)	2,584 (17.9)	7,419 (24.3)	5,272 (41.2)	4,708 (13.9)
Body mass index [kg/m^2 mean (SD)]	27.9 (5.8)	28.0 (5.7)	28.0 (6.0)	27.7 (5.6)	28.0 (5.9)
Hormone therapy use (%)					
Current user	35,511 (42.7)	7,147 (49.6)	10,984 (36.0)	6,643 (51.9)	12,846 (37.9)
Never used	28,214 (33.9)	4,120 (28.6)	12,162 (39.9)	3,357 (26.2)	12,797 (37.8)
Past user	19,392 (23.3)	3,150 (21.8)	7,362 (24.1)	2,793 (21.8)	8,233 (24.3)
Smoking status, (%)					
Current	5,571 (6.7)	1,036 (7.2)	2,102 (6.9)	928 (7.3)	2,232 (6.6)
Never	43,278 (52.1)	7,830 (54.3)	15,387 (50.4)	6,380 (49.9)	17,786 (52.5)
Past	34,268 (41.2)	5,551 (38.5)	13,019 (42.7)	5,485 (42.9)	13,858 (40.9)
Pack-years [mean (SD)]	10.1 (18.7)	9.1 (17.1)	11.2 (20.0)	10.1 (17.9)	10.6 (19.8)
Education (%)					
< = High school diploma/GED	18,344 (22.1)	3,356 (23.3)	6,628 (21.7)	2,430 (19.0)	7,863 (23.2)
School after high school	31,015 (37.3)	5,828 (40.4)	10,808 (35.4)	5,126 (40.1)	12,205 (36.0)
College degree or higher	33,758 (40.6)	5,233 (36.3)	13,072 (42.8)	5,237 (40.9)	13,808 (40.8)
Physical activity, MET-hours [mean (SD)]	12.5 (13.6)	12.3 (13.8)	12.3 (13.4)	13.6 (14.5)	12.0 (13.1)
Diet quality [mean (SD)]	67.5 (10.7)	66.7 (10.6)	67.6 (10.9)	67.0 (10.7)	67.7 (10.8)
Alcohol servings per week [mean (SD)]	2.4 (4.9)	2.3 (4.7)	2.5 (5.0)	2.8 (5.2)	2.3 (10.8)
Systolic blood pressure [mm Hg, mean (SD)]	127.6 (17.7)	125.6 (17.0)	128.9 (17.9)	124.2 (16.7)	129.7 (18.0)
Diastolic blood pressure [mm Hg, mean (SD)]	75.1 (9.2)	75.8 (9.0)	74.8 (9.4)	75.4 (9.0)	75.0 (9.4)
Comorbidities (%)					
Diabetes	3,489 (4.2)	489 (3.4)	1,534 (5.0)	359 (2.8)	1,721 (5.1)
Hyperlipidemia	11,835 (14.2)	1,661 (11.5)	4,856 (15.9)	1,337 (10.5)	5,531 (16.3)
Coronary heart disease (CHD)	2,375 (2.9)	305 (2.1)	1064 (3.5)	212 (1.7)	1,265 (3.7)
Peripheral arterial disease (PAD)	1,590 (1.9)	196 (1.4)	726 (2.4)	158 (1.2)	822 (2.4)
Stroke	1,019 (1.2)	127 (0.9)	454 (1.5)	105 (0.8)	535 (1.6)
Asthma/COPD	9,197 (11.0)	1,553 (10.8)	3,538 (11.6)	1,494 (19.1)	3,856 (11.4)
Congestive heart failure (CHF)	635 (0.8)	88 (0.6)	280 (0.9)	49 (0.4)	345 (1.0)
Neighborhood SES index [mean (SD)][b]	−0.07 (5.3)	−1.32 (4.7)	0.28 (5.8)	0.26 (4.9)	−0.18 (5.7)

Note: Data for all variables are complete among women included in the study population. COPD, chronic obstructive pulmonary disease; GED, general educational development; MET, metabolic activity of task; ppb, parts per billion; SD, standard deviation; SES, socioeconomic status.
[a]Quartile ranges are based on the full distribution of each pollutant throughout follow-up; women are classified by the annual average exposure at WHI enrollment.
[b]Neighborhood SES index is a composite measure of six census tract-level variables that are each *z*-scored independently for the OS and CT and then summed. Data are from the temporally closest U.S. Census or American Community Survey year, and higher values indicate neighborhoods with more advantage (Diez Roux et al. 2001).

systolic and diastolic blood pressure (continuous), educational attainment (high school diploma/GED or less, some school after high school, and college degree or higher), recreational physical activity (continuous MET-hours per week (Meyer et al. 2009)], and overall diet quality [continuous Alternative Healthy Eating Index (Belin et al. 2011)] and alcohol consumption (continuous, servings per week), assessed via the WHI food frequency questionnaires. Information was also collected on the baseline and follow-up questionnaires on menopausal hormone therapy use (current, never, past user), smoking status (current, former, never), and pack-years of smoking (continuous) and was used to adjust for these time-varying variables. We adjusted for time-varying area-level (neighborhood) socioeconomic status (nSES), calculated from the U.S. Census and American Community Survey (Diez Roux et al. 2001). Specifically, data from the 2000 Census or American Community Survey were extracted on median household income; percent of households receiving dividends, interest, or rent; percent of adults over 25 years of age with a high school degree; percent of adults over 25 with a college degree or greater; percent of the

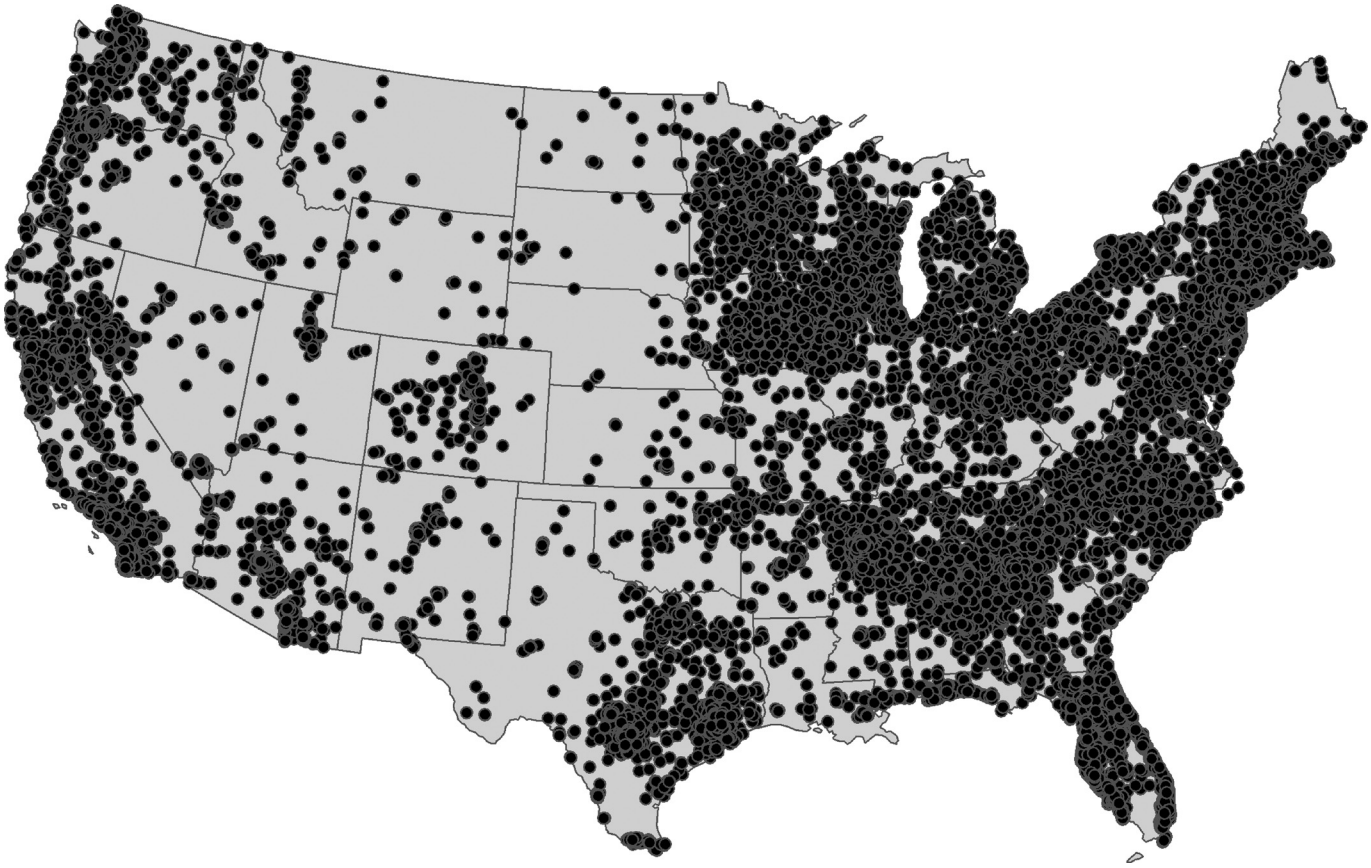

Figure 1. Residential address locations from the Women's Health Initiative (WHI) enrollment visit through December 2012 of the 83,117 WHI participants. Each dot represents a residential address, and women may have contributed multiple dots if they moved throughout follow-up.

population over 16 years of age in professional, managerial, or executive occupations; and median home value. Data for each variable was transformed into a *z*-score (separately for OS and RCT participants), and the *z*-scores were summed to create an nSES score where higher scores indicate neighborhoods of higher advantage. Women with missing covariate data were excluded from analyses (complete case analyses). We assessed effect modification by variables previously examined in the literature as modifiers, including age (above or below the median), smoking status (ever/never), educational attainment, census region of residence (the Northeast, South, Midwest, or West), and self-reported comorbidities [diabetes, asthma, chronic obstructive pulmonary disease (COPD)], hyperlipidemia, coronary heart disease (MI, coronary artery bypass graft, percutaneous transluminal coronary angioplasty), peripheral arterial disease, and stroke yes/no).

Statistical Analyses

We used time-varying Cox proportional hazards regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of incident AF with each pollutant or category of distance to roadway. The time-scale was time, because WHI enrollment and models were stratified by calendar year. Person-time accumulated from the date of enrollment into WHI (or the end of the 2-y hold-out period) through diagnosis of AF, death (ascertained through searches of the National Death Index), or the end of follow-up (December 2012). Penalized splines with three knots were used to determine deviations from linearity in exposure–responses for each pollutant, and if there was statistically significant evidence of nonlinearity via likelihood ratio tests, associations were reported by categories of exposure. For categorical exposures, we calculated *p*-values for linear trends based on the median values within each category. Pollutants were modeled as time-varying annual averages, and distance to road was updated only if participants moved. Basic models were adjusted for age, race/ethnicity, and the WHI study component(s) the woman was in. Multivariable adjusted models included all the potential confounders listed above. In sensitivity analyses to assess the robustness of the models to additional adjustment for potential mediators, we ran models additionally adjusted for systolic and diastolic blood pressure and the following doctor diagnosed comorbidities self-reported at WHI enrollment: diabetes, asthma, COPD, hyperlipidemia, coronary heart disease (MI, coronary artery bypass graft, percutaneous transluminal coronary angioplasty), heart failure, peripheral arterial disease, and stroke.

To assess the potential for effect modification, we calculated stratum-specific effect estimates. We derived *p*-values for effect modification using multiplicative interaction terms for linear exposures or likelihood ratio tests comparing models with and without interactions for categorical exposures.

We conducted sensitivity analyses including frailty terms for clinical enrollment site to adjust for potential spatial autocorrelation and sensitivity analyses adjusted for census region to account for large-scale regional patterns in exposure and outcome assessment. We also conducted sensitivity analyses among the subset of 37,090 women who were already enrolled in Medicare at baseline enrollment into the study to assess whether the use of a hold-out period may have affected results. A *p*-value of 0.05 was used to determine statistical significance.

Results

Baseline characteristics of the 83,117 women included in the analyses are presented in Table 1 overall and by the top and bottom

quartiles of exposure to $PM_{2.5}$ and NO_2. Most women were White (86.8%) and over half had never smoked (52.1%). There were differences across exposures: women with higher levels of exposure were older, hormone therapy use was higher among women with lower levels of exposure, black women were more likely to be exposed to higher levels of pollution, and there were notable differences in exposure by region of the country. Distributions of the annual average exposures throughout follow-up are presented in Table S3. The mean and median levels of annual average $PM_{2.5}$ (11.5 and 11.3 $\mu g/m^3$) and NO_2 (12.3 and 11.3 ppb) throughout follow-up were below the U. S Environmental Protection Agency (U.S. EPA) annual standards in effect in 2021 (12 $\mu g/m^3$ for $PM_{2.5}$, 53 ppb for NO_2; https://www.epa.gov/criteria-air-pollutants/naaqs-table). Most participants lived far from major highways and state routes (A1 and A2 roads, median distance 2,377 m and 2,238 m, respectively) but close to smaller major roads (A3 roads, median 264 m). The exposures of interest were not highly correlated, with the strongest correlations between the measures of PM and NO_2 (0.66 for NO_2 and $PM_{2.5}$ and 0.57 for NO_2 and PM_{10}), and negative correlations between distance to road and each of the pollutants (Table S4).

A total of 16,348 incident cases of AF were observed over 660,236 person-years of follow-up. Only the exposure–response relationships for $PM_{2.5}$ and distance to an A3 road did not display statistically significant deviations from linearity (Figure S1); therefore, we present results by quartile or distance category for all exposures for comparability (Table 2). We did not observe evidence of positive associations between $PM_{2.5}$, PM_{10}, or SO_2 with incidence of AF, and in fact, some of the HRs for PM_{10} and $PM_{2.5}$ were slightly below 1. However, higher levels of NO_2 were associated with AF after adjustment for all potential confounders (Table 2). There was little evidence of confounding by the variables included in the multivariable model (Figure S2). In multivariable adjusted models, the HR for women in the highest quartile of NO_2 exposure compared with women in the lowest quartile was 1.18 (95% CI: 1.13, 1.24), and the p-for-trend across quartiles was statistically significant ($p < 0.0001$). We also observed associations with increasing risk of AF with decreasing distance to roads. For example, for the largest roads (A1), women living within 50 m had a multivariable adjusted HR = 1.12 (95% CI: 0.90, 1.39), compared with women living 1,000 or more meters away (p-for-trend = 0.04). Results were generally similar for the smaller major roads (A2 and A3).

Associations were similar in sensitivity models additionally adjusted for blood pressure and self-reported comorbidities [diabetes,

Table 2. Association between annual exposures to PM_{10}, $PM_{2.5}$, SO_2, NO_2, and roadway proximity with incidence of atrial fibrillation in 83,117 participants in the Women's Health Initiative (WHI).

Exposure	Category cutoffs	Cases	Basic HR (95% CI)[a]	Multivariable HR (95% CI)[b]
PM_{10} ($\mu g/m^3$)	Q1: <17.5	4,377	Ref	Ref
	Q2: 17.6–20.3	4,098	0.97 (0.93, 1.01)	0.96 (0.92, 1.01)
	Q3: 20.4–23.4	3,934	0.96 (0.92, 1.00)	0.95 (0.91, 0.99)
	Q4: 23.5–80.7	3,939	1.01 (0.96, 1.06)	1.00 (0.95, 1.04)
	p-for-trend		0.88	0.62
$PM_{2.5}$ ($\mu g/m^3$)	Q1: <9.46	4,326	Ref	Ref
	Q2: 9.47–11.3	4,339	1.00 (0.96, 1.05)	1.00 (0.96, 1.04)
	Q3: 11.4–13.4	4,122	1.00 (0.95, 1.04)	1.00 (0.95, 1.04)
	Q4: 13.5–25.6	3,561	0.98 (0.93, 1.03)	0.98 (0.93, 1.03)
	p-for-trend		0.40	0.45
SO_2 (ppb)	Q1: <1.73	3,800	Ref	Ref
	Q2: 1.74–1.94	4,061	0.97 (0.93, 1.02)	0.97 (0.93, 1.02)
	Q3: 1.95–2.10	4,125	0.92 (0.88, 0.96)	0.91 (0.87, 0.96)
	Q4: 2.11–2.61	4,374	0.98 (0.94, 1.03)	0.99 (0.95, 1.03)
	p-for-trend		0.14	0.26
NO_2 (ppb)	Q1: <7.52	4,004	Ref	Ref
	Q2: 7.53–11.3	3,998	0.98 (0.94, 1.03)	0.99 (0.94, 1.03)
	Q3: 11.4–16.0	4,167	1.06 (1.01, 1.10)	1.06 (1.02, 1.11)
	Q4: 16.1–45.6	4,172	1.18 (1.13, 1.24)	1.18 (1.13, 1.24)
	p-for-trend		<0.0001	<0.0001
Distance to the nearest A1 roadway (m)[c]	≥1,000	12,424	Ref	Ref
	400–999	2,463	1.01 (0.97, 1.06)	1.01 (0.96, 1.05)
	200–399	897	1.08 (1.01, 1.15)	1.05 (0.98, 1.12)
	50–199	504	1.09 (1.00, 1.20)	1.08 (0.98, 1.18)
	0–49	81	1.12 (0.90, 1.39)	1.12 (0.90, 1.39)
	p-for-trend		0.004	0.04
Distance to the nearest A2 roadway (m)[c]	≥1,000	11,547	Ref	Ref
	400–999	2,658	1.04 (1.00, 1.09)	1.04 (0.99, 1.08)
	200–399	1,089	1.08 (1.01, 1.15)	1.07 (1.01, 1.14)
	50–199	655	0.99 (0.92, 1.07)	0.98 (0.90, 1.06)
	0–49	420	1.13 (1.02, 1.24)	1.11 (1.00, 1.22)
	p-for-trend		0.008	0.04
Distance to the nearest A3 roadway (m)[c]	≥1,000	1,872	Ref	Ref
	400–999	3,682	1.02 (0.96, 1.07)	1.02 (0.96, 1.08)
	200–399	3,815	1.03 (0.98, 1.09)	1.03 (0.97, 1.09)
	50–199	4,157	1.04 (0.98, 1.10)	1.03 (0.98, 1.09)
	0–49	2,843	1.08 (1.02, 1.15)	1.07 (1.01, 1.13)
	p-for-trend		0.005	0.02

Note: HRs and 95% CIs are from Cox proportional hazards models; p-for-trends calculated using the median value of each category. CI, confidence interval; HR, hazard ratio; ppb, parts per billion; Ref, reference.

[a]Basic model adjusted for race/ethnicity, age (5-y intervals), WHI study component.

[b]Multivariable model additionally adjusted for baseline information on body mass index, educational attainment, physical activity, alcohol consumption, and overall diet quality, and time-varying information on hormone replacement therapy use, smoking status and pack-years, and neighborhood socioeconomic status.

[c]U.S. Census Feature Class Codes: A1 (primary roads, typically interstate highways, with limited access, division between the opposing directions of traffic, and defined exits), A2 (primary major, noninterstate highways and major roads without access restrictions), or A3 (smaller, secondary roads, usually with more than two lanes).

asthma, COPD, hyperlipidemia, coronary heart disease (MI, coronary artery bypass graft, and percutaneous transluminal coronary angioplasty), peripheral arterial disease, congestive heart failure, and stroke] that may be potential mediators (Table S5). In sensitivity analyses including a frailty term for enrollment site, the overall patterns were similar to our main multivariable models, although the HR for the top quintile of NO_2 was reduced (1.08; 95% CI: 1.01, 1.14; Table S5). However, in sensitivity analyses additionally adjusting for census region, patterns remained similar for associations with NO_2, SO_2, and distance to road, but not PM_{10} and $PM_{2.5}$. In region-adjusted multivariable models, the HR for the top quartile of PM_{10} (compared to the lowest quartile) was 1.10 (95% CI: 1.05, 1.16, p-for-trend = < 0.0001), and the HR for the top quartile of $PM_{2.5}$ (compared to the lowest quartile) was 1.09 (95% CI: 1.03, 1.14, p-for-trend = 0.002).

Findings were similar to the main multivariable models in sensitivity analyses restricted to the 35,464 women enrolled in Medicare at the time of WHI enrollment (Table S6), suggesting that our results were robust to timing of Medicare enrollment.

There was little consistent evidence of effect modification across the different exposures. Although not statistically significant, there was a suggestion of effect modification by region for all exposures (Figures S3–S9). For PM (p-for-interaction 0.21 and 0.22), associations were consistently positive in the Northeast and West but varied by size fraction in the South and Midwest. For NO_2 (p-for-interaction 0.79), positive associations were observed in all regions, with the largest HRs in the West [Q4 vs. Q1: 1.21 (95% CI: 1.09, 1.35)]. Patterns with distance to A1 (p-for-interaction 0.35) and A3 (p-for-interaction 0.21) roads were similar overall to those for NO_2, with the largest HRs in the West. Associations with distance to A3 roads (p-for-interaction = 0.24) were less clear, with no evidence of a dose response in the West. There was little evidence of effect modification by age, educational attainment, or smoking status. There was no consistent evidence of effect modification by self-report of comorbidities at baseline, although there were some instances of statistically significant p-values for interaction. For example, diabetes appeared to modify the associations with NO_2 (p-for-interaction 0.03) and distance to A1 roads (p-for-interaction 0.02), with larger HRs among women without diabetes at baseline, and women with congestive heart failure had larger HRs for PM_{10} (p-for-interaction 0.045).

Discussion

In the first analysis that we know of in the United States, the incidence of AF was associated with long-term ambient NO_2 and closer residential proximity to major roadways. However, AF was not consistently associated with the other pollutants (PM_{10}, $PM_{2.5}$, SO_2) examined. There was little consistent evidence of effect modification. To our knowledge, this is the first report of an association between distance to road and incident AF, but the results for NO_2 are generally consistent with the limited epidemiological data from other parts of the world (Kim et al. 2018; Kwon et al. 2019; Monrad et al. 2017; Pranata et al. 2020; Stockfelt et al. 2017).

We are aware of only four other studies, all conducted outside the United States, that have specifically examined associations between long-term exposure to air pollution and AF incidence (Kim et al. 2018; Kwon et al. 2019; Monrad et al. 2017; Pranata et al. 2020; Stockfelt et al. 2017). In a Danish cohort, incidence of AF was identified using discharge diagnoses from a hospital, emergency room, or outpatient clinic. Ambient exposures to NO_2 and NO_x from 1984 onward were predicted from a validated model at the residential addresses of each participant. In models adjusted for similar covariates included in our multivariable model, researchers reported an 8% higher risk of AF with each 10-$\mu g/m^3$ increase in 10-y time-weighted mean exposure to NO_2 (they did not observe deviations from linearity when examining splines) (Monrad et al. 2017). They observed similar associations with 1-year time-weighted exposures, similar to what was used in our analyses. In analyses of two Swedish cohorts, cases of AF were identified from the main and secondary diagnoses from the Swedish National Hospital Discharge Register and Death Registry. Exposures to PM_{10}, $PM_{2.5}$, black carbon (a measure of PM from traffic sources), and NO_x were generated from nationwide exposure models based on emission inventories. There was no consistent evidence of an association between AF and any of the air pollution exposures considered, although there were suggestive associations with $PM_{2.5}$ and black carbon in one of the cohorts [the Primary Prevention Study (PPS)] (Stockfelt et al. 2017). In a study based on data from the Korean National Health Insurance Service–National Sample Cohort (covering 96% of the adult population), annual average exposures to $PM_{2.5}$, PM_{10}, SO_2, NO_2, and carbon monoxide were associated with an increased risk of AF, with the strongest relationships for NO_2 (Kim et al. 2018). There was evidence that these associations were stronger among men, those over 60 years of age, individuals with higher BMI, and participants with hypertension or a previous history of MI. No associations were observed in a Korean study of the relationship between long-term air pollution and risk of hospitalization for AF, although multivariable analyses for $PM_{2.5}$ were suggestive (HR = 1.24; 95% CI: 0.75, 2.03 per 10-$\mu g/m^3$ increase) (Kwon et al. 2019). Overall, our findings of an elevated risk of AF with exposures in NO_2, but not PM_{10} or $PM_{2.5}$ are consistent with those from most previous long-term exposure studies. For example, in a recent meta-analysis the pooled HR for AF with $PM_{2.5}$ was 0.93 (95% CI: 0.68, 1.27), with PM_{10} it was HR = 0.91 (95% CI: 0.74, 1.12), and with NO_2 it was HR = 1.01 (95% CI: 1.01, 1.02) all per 10-$\mu g/m^3$ increase (Pranata et al. 2020).

Many of the hypothesized biological mechanisms underlying AF have also been associated with exposure to air pollution and roadway traffic (Chin 2015), implying that air pollution generally may act on AF incidence through a number of pathways (Brook et al. 2004, 2010; Watkins et al. 2013). Two of the most commonly explored mechanisms are systemic inflammation and oxidative stress, both of which have been positively associated with increases in both short- and long-term exposures to air pollution (Brook et al. 2010; Liu et al. 2019) and with incidence of AF (Aviles et al. 2003; Conen et al. 2010; Yang and Dudley 2013). Hypertension is also a potential mechanism because it is a key risk factor for AF (Huxley et al. 2011; Perez et al. 2013). Short- and long-term air pollution exposures have been associated with hypertension in numerous studies (Brook et al. 2009, 2011; Chan et al. 2015; Coogan et al. 2012, 2015; Dai et al. 2016; Delfino et al. 2010; Dong et al. 2013; Dvonch et al. 2009; Giorgini et al. 2015, 2016; Liang et al. 2014; Zanobetti et al. 2004), and higher levels of long-term traffic exposure have been associated with higher left and right ventricular mass (Leary et al. 2014; Van Hee et al. 2009, 2010). The available evidence also suggests that short-term air pollution exposure is associated with higher heart rate, reductions in most indices of heart rate variability, and changes in electrophysiology, particularly among older or susceptible individuals, such as those with obesity (Brook et al. 2010; Ishida et al. 2010; Koide et al. 2008; Link and Dockery 2010; Magnani et al. 2011; Schnabel et al. 2009). Therefore, there is substantial evidence from animal and human studies to suggest that air pollution may work through multiple biological pathways to increase incidence of AF, although these mechanisms do not explain why we observed more consistent findings with NO_2 and distance to road than with the other pollutants.

Our study has some important limitations. Exposures were estimated at the home of each participant, as opposed to being weighted by individual time–activity patterns, likely leading to exposure misclassification, even among these women with a median age of 63 y during follow-up. Most of our potential confounders

were available only from the baseline visit, which may have resulted in increased residual confounding over time. However, the results from our models with different levels of confounding adjustment were quite similar. The results of our frailty models, adjusted for clinical site, were attenuated relative to our main models. This may be due to reduced exposure variability within participants from the same site or may imply that there are additional spatial exposures that may confound our results. It is also possible that we failed to identify some cases of AF that may have occurred between the baseline questionnaire and enrollment in Medicare. We expect that this source of outcome misclassification would decrease our statistical power and thus lessen the likelihood of detecting statistically significant associations because, if bias was absent, the associations (non-null HRs) should still be evident. Indeed, results were similar in sensitivity analyses restricted to women who were enrolled in Medicare continuously throughout follow-up. We also will have missed asymptomatic individuals who did not receive treatment, again reducing statistical power and making it harder to detect associations, as well as those women who may have had limited access to health care to obtain a diagnosis. Last, WHI solely comprises postmenopausal women who are mostly White; therefore our results may not be generalizable to premenopausal women, men, or more diverse populations, if there are differences in the underlying mechanisms or exposure distributions in those populations. Our results may also not be generalizable to the full WHI cohort, because women who were excluded from this study tended to be younger at enrollment into WHI and were less likely to be White than women we included.

On the other hand, this study has notable strengths. We had data from a large, prospective cohort study with a long follow-up period, a large number of cases, and rigorous baseline assessment of lifestyle and behavioral factors, increasing our power to detect associations with adjustment for numerous potential confounders, including lifestyle factors (e.g., diet, physical activity), that have not been available in previous studies. We were also able to estimate annual exposures to a large number of potential pollutants at the home of each participant from models with high validity and were able to account for residential mobility. The geographic distribution of the cohort also allowed us to explore these associations across a wide distribution of exposure levels, including more than 50% of the cohort with estimated exposures below current U.S. EPA standards.

In conclusion, in this large study of postmenopausal women, exposures to NO_2 and distance to roadway, but not other pollutants, were associated with an increased risk of AF. This finding suggests that long-term exposures to traffic-related air pollutants may be an emerging population level risk factor for AF.

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