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Interaction between Long-Term Exposure to Fine Particulate Matter and Physical Activity, and Risk of Cardiovascular Disease and Overall Mortality in U.S. Women

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Background: Increased respiration during physical activity may increase air pollution dose, which may attenuate the benefits of physical activity on cardiovascular disease (CVD) risk and overall mortality.

Objectives: We aimed to examine the multiplicative interaction between long-term ambient residential exposure to fine particulate matter <2.5 microns ($PM_{2.5}$) and physical activity in the association with CVD risk and overall mortality.

Methods: We followed 104,990 female participants of the U.S.-based prospective Nurses' Health Study from 1988 to 2008. We used Cox proportional hazards models to assess the independent associations of 24-months moving average residential $PM_{2.5}$ exposure and physical activity updated every 4 y and the multiplicative interaction of the two on CVD (myocardial infarction and stroke) risk and overall mortality, after adjusting for demographics and CVD risk factors.

Results: During 20 years of follow-up, we documented 6,074 incident CVD cases and 9,827 deaths. In fully adjusted models, $PM_{2.5}$ exposure was associated with modest increased risks of CVD [hazard ratio (HR) for fifth quintile $\geq 16.5\,\mu g/m^3$ compared to first quintile $<10.7\,\mu g/m^3$: 1.09, 95% confidence interval (CI): 0.99, 1.20; $p_{trend} = 0.05$] and overall mortality (HR fifth compared to first quintile: 1.10, 95% CI: 1.02, 1.19; $p_{trend} = 0.07$). Higher overall physical activity was associated with substantially lower risk of CVD [HR fourth quartile, which was ≥24.4 metabolic equivalent of task (MET)-h/wk, compared to first quartile (<3.7 MET-h/wk): 0.61, 95% CI: 0.57, 0.66; $p_{trend} < 0.0001$] and overall mortality (HR fourth compared to first quartile: 0.40, 95% CI: 0.37, 0.42; $p_{trend} < 0.0001$). We observed no statistically significant interactions between $PM_{2.5}$ exposure and physical activity (overall, walking, vigorous activity) in association with CVD risk and overall mortality.

Discussion: In this study of U.S. women, we observed no multiplicative interaction between long-term $PM_{2.5}$ exposure and physical activity; higher physical activity was strongly associated with lower CVD risk and overall mortality at all levels of $PM_{2.5}$ exposure. https://doi.org/10.1289/EHP7402

Introduction

Cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, is the leading cause of death in the United States (Benjamin et al. 2019) and the leading cause of noncommunicable disease-related mortality and morbidity worldwide (Joseph et al. 2017). Two well-established factors associated with incidence of CVD and death are the adverse effects of air pollution exposure and the beneficial effects of physical activity. Air pollution exposure is a major environmental risk factor for overall mortality and CVD risk (Benjamin et al. 2019; Burnett et al. 2018; Laden et al. 2006; Pope et al. 2020, 2015; Yusuf et al. 2020). An estimated 4.2 million premature deaths worldwide (Landrigan et al. 2018) and 5%–10% of annual premature mortality in the contiguous United States (Dedoussi et al. 2020) are associated with ambient air pollution, as well as 29% of incident stroke (Benjamin et al. 2019) and stroke burden, as measured in disability-adjusted life-years (DALY) (Feigin et al. 2016). Physical activity is one of the strongest modifiable factors associated with CVD risk (Benjamin et al. 2019; Joseph et al. 2017), and regular physical activity has been consistently associated with decreased risk of acute myocardial infarction (MI) (Yusuf et al. 2004), decreased risk of coronary heart disease (Chomistek et al. 2016), and decreased risk of stroke (Feigin et al. 2016; O'Donnell et al. 2016). Among women in the Nurses' Health Study (NHS), a prospective cohort of U.S. women, chronic exposure to particulate matter (PM) air pollution has previously been associated with increased risk of MI, coronary heart disease, and overall and cause-specific mortality (DuPré et al. 2019; Hart et al. 2015a, 2015b; Puett et al. 2008, 2009). Also in this cohort, moderate- and moderate-to-vigorous–intensity physical activity have been associated with a decreased risk of CHD (Li et al. 2006; Stampfer et al. 2000) and stroke (Chiuve et al. 2008; Hu et al. 2000).

Although a large body of evidence has observed associations between air pollution exposure and CVD risk and overall mortality and between physical activity and CVD risk and mortality, the interaction between long-term air pollution exposure and physical activity on CVD risk and mortality is not yet fully understood. Physical activity increases deeper respiration and may increase internal air pollution dose at a given concentration, which might attenuate the benefits of physical activity on CVD risk and mortality (Pasqua et al. 2018). Evidence from some, but not all, studies of short-term exposures suggest that air pollution exposure during physical activity may be associated with acute adverse physiological responses in markers of CVD health (Cole-Hunter et al. 2016; Corlin et al. 2018; Giles et al. 2018; Sinharay et al. 2018). Only three studies have investigated the interaction between long-term exposure to air pollutants and physical activity in relation to CVD incidence or mortality. Two studies have examined this interaction for long-term nitrogen dioxide (NO_2) exposure and physical activity in association with mortality and MI risk and did not observe interactions (Andersen et al. 2015;

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Kubesch et al. 2018). One study has examined the interaction between long-term exposure to PM air pollution and physical activity in association with mortality and did not observe interactions (Sun et al. 2020). However, no study has examined the interaction between long-term exposure to PM air pollution and long-term physical activity in association with MI, stroke, and overall mortality risk.

Our objective was to confirm previous associations with physical activity and long-term exposure to PM less than 2.5 microns in diameter ($PM_{2.5}$) and assess the multiplicative interaction between them on CVD risk and overall nonaccidental mortality in the NHS prospective cohort.

Methods

Study Population

The NHS is an ongoing nationwide prospective cohort study of 121,701 U.S. female registered nurses (30–55 y old) enrolled at study inception in 1976. Women were initially enrolled from 11 selected states, though participants now live throughout the contiguous United States. NHS participants complete self-administered questionnaires biennially, providing information on incident disease, medical history, and lifestyle factors. Response rates for most follow-up cycles have been ≥90% (Bao et al. 2016; Morabia 2016). In the current analysis, we followed NHS participants from 1988 to 2008 and included participants if at the beginning of these analyses in 1988 they were alive, had no history of CVD, were still responding to questionnaires, had at least one residential address during follow-up where air pollution predictions were available, and provided information on physical activity on at least one questionnaire. This study protocol was approved by the Institutional Review Board of Brigham and Women's Hospital, Boston, Massachusetts, and consent was implied through the return of the questionnaires.

Outcome Assessment

Methods to confirm incident CVD have been published in detail elsewhere (Hart et al. 2015b; Shan et al. 2020; Yu et al. 2016). Incident CVD was determined as the first occurrence of either fatal and nonfatal acute MI (ICD-9 code 410) or stroke (ICD-9 codes 430 to 437). Participants were asked to report all occurrences of physician-diagnosed incident CVD (MI or stroke) on the baseline, and all subsequent biennial questionnaires and participants (or next-of-kin for fatal cases) provided consent to review all medical records pertaining to their reported diagnosis. Cases of nonfatal CVD were confirmed through medical record review or through interview or a letter confirming hospitalization for the MI or stroke. Cases of fatal CVD were confirmed through hospital record review, autopsy, report of CVD as the underlying cause on the death certificate, a history of CVD and CVD was the most plausible cause of death, or supporting information provided by a family member.

We included deaths from all nonaccidental causes for assessment of overall mortality. Deaths were either reported by next-of-kin or through searches of the National Death Index for nonrespondents. Identification of deaths in the NHS cohort has been validated previously (Rich-Edwards et al. 1994). Primary cause of death was determined through physician review of death certificates and medical records according to the International Classification of Diseases, Ninth Revision (ICD-9).

Exposure Assessment

Assessment of Ambient Residential $PM_{2.5}$ Exposure

Residential addresses were updated every 2 y with each questionnaire cycle and geocoded to obtain latitude and longitude. We calculated exposure to $PM_{2.5}$ at each residential address using spatiotemporal prediction models available in the contiguous United States for each month between January 1988 and December 2007 (Yanosky et al. 2014). The generalized additive mixed models used monthly average $PM_{2.5}$ and/or PM_{10} monitoring data from the U.S. Environmental Protection Agency's Air Quality System and other publicly available networks (Yanosky et al. 2014). Additionally, the models incorporated geospatial predictors (road network data, residential and urban land use, density of $PM_{2.5}$ and PM_{10} point-sources, and elevation data) and monthly average meteorological data (wind speed, temperature, precipitation) (Yanosky et al. 2014). Predictions models were evaluated using 10-fold cross-validation (CV) and predictive accuracy for $PM_{2.5}$ across the contiguous United States was high (CV $R^2 = 0.77$) (Yanosky et al. 2014). Previously, we investigated different lag periods of $PM_{2.5}$ in relation to CVD and mortality in the NHS and found that a longer lag period did not modify associations in comparison with 24-month moving average $PM_{2.5}$ (Hart et al. 2015b). We therefore calculated 24-month moving averages for each questionnaire cycle as a measure of long-term exposures. If 24-month average $PM_{2.5}$ during follow-up was missing, we excluded participants for the corresponding questionnaire cycle in the analyses.

Assessment of Physical Activity

Leisure-time physical activity was assessed using information from the biennial questionnaires. Physical activity was first reported in 1986 and updated every 2 or 4 y (depending on available space on the biennial questionnaire). On each questionnaire assessing physical activity, participants reported the average time per week spent participating in specific leisure-time activities, including walking, jogging, running, bicycling, lap swimming, tennis, squash or racquetball, and calisthenics and other aerobic activities. Over time, activities reported through the questionnaires were expanded to include other low and high intensity activities, such as weight training, yoga, and lawn mowing. Participants reported the average time per week spent participating in each of these leisure-time activities in seven provided categories, ranging from 0 min to ≥11 h/wk. Location (indoors vs. outdoors) of physical activity was not assessed. Time per week spent participating in each activity was multiplied by each activity's metabolic equivalent of task (MET) score to obtain MET-hours per week, which incorporates frequency, duration, and intensity of activity (Ainsworth et al. 2011). We calculated overall physical activity in MET-hours per week by summing the MET-hours per week across all activities. Additionally, we considered MET-hours per week from walking alone, MET-hours per week from vigorous-intensity activities (≥6 METs/hour: jogging, running, biking, swimming, and tennis), MET-hours per week from low- or moderate-intensity activities (<6 METs/hour) (Lee et al. 2019; U.S. Department of Health and Human Services 2019), and MET-hours per week for physical activities likely to be performed outdoors (e.g., walking, running, biking, lawn mowing), created by excluding activities more likely to be performed indoors (squash, racquet ball, arm weight training, leg weight training) from total MET-hours. If physical activity information (MET-hours per week) during follow-up was missing, we excluded participants for the corresponding questionnaire cycle in the analyses.

Potential Confounders and Effect Modifiers

We obtained information on potential confounders and effect modifiers from the biennial questionnaires. Covariates are updated every 2 y, with the exception of diet, which is queried every 4 y, race (assessed in 2004), family history of MI (assessed in 1984),

occupation of the participant's father and mother (assessed in 1976), educational attainment of the participant's husband (assessed in 1992), and participant's educational attainment (assessed in 1992). Additionally, the geocoded addresses were linked to data from the 2000 U.S. Census to obtain information on neighborhood-level socioeconomic status (SES) (www.census.gov). Covariates were selected *a priori* based on previous research in the NHS cohort and wider literature indicating that covariates may be either risk factors for the outcomes or potential confounders of the associations of interest (Anand et al. 2008; Beelen et al. 2014; Cesaroni et al. 2014; Hart et al. 2015b; Hoek et al. 2013; Puett et al. 2008, 2009; Weichenthal et al. 2014). We included age and race in all models. In fully adjusted models, we additionally adjusted for incident cancer, family history of MI, smoking status, pack-years, overall diet quality using the Alternate Healthy Eating Index score (McCullough and Willett 2006), alcohol consumption, multivitamin use, individual-level SES (occupation of the participant's father and mother, educational attainment of the participant's husband, participant's educational attainment, marital status, employment status), and neighborhood-level SES (census tract median income and census tract median home value). If information on time-varying covariates was missing during follow-up, we used information reported on the preceding questionnaire, assuming no changes, to impute missing data. For remaining missing covariate data, we imputed missing data with "0" and accounted for missing covariate data using missing indicators in Cox proportional hazards models.

Statistical Analysis

Person-time was assessed as months of follow-up from the return date of the 1988 questionnaire until incident CVD, death, or the end of follow-up (31 May 31 2008), whichever came first. We used time-varying Cox proportional hazards models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between 24-month average ambient $PM_{2.5}$ exposure [per $10\,\mu g/m^3$ increase (Hart et al. 2015b; Puett et al. 2009) or by quintiles of $PM_{2.5}$ exposure], physical activity [per 9 MET-h/wk for overall physical activity, based on weekly physical activity recommendations (Lee et al. 2019; U.S. Department of Health and Human Services 2019) or by quartiles of overall physical activity, walking, and vigorous activity], and the multiplicative interaction of the two on risk of MI, stroke, MI or stroke combined, and overall mortality. We accounted for missing covariate data using missing indicators. Analyses were stratified by age at follow-up (months) and calendar period to control for age and temporal effects. In categorical analyses, we used the median value of each category to conduct tests for trend. We modeled multiplicative interactions between quintiles of 24-month average $PM_{2.5}$ exposure and quartiles of physical activity using stratified Cox proportional hazards models and tested for statistical significance ($\alpha = 0.05$) using likelihood ratio tests comparing models with and without interaction terms.

We conducted sensitivity analyses to assess the robustness of our findings on physical activity as well as interactions between $PM_{2.5}$ exposure and physical activity in association with CVD and overall mortality. We estimated MET-hours per week for physical activities likely to be performed outdoors (e.g., walking, running, biking, lawn mowing), created by excluding activities more likely to be performed indoors (squash, racquet ball, arm weight training, leg weight training) from total MET-hours. All analyses were conducted in SAS (version 9.4; SAS Institute Inc.).

Results

Among 104,990 eligible participants, we observed 6,074 incident cases of CVD (MI or stroke), 3,304 incident cases of MI, 2,848 incident cases of stroke, and 9,827 deaths over follow-up. Over the course of follow-up from 1988 to 2008 and standardized to the age-distribution of the study population, participants were on average 63.1 (standard deviation: 8.9) y old (not age-adjusted), had 24-month average $PM_{2.5}$ levels of $13.7\,mg/m^3$ [standard deviation (SD): 3.5], reported overall physical activity participation of 18.3 MET-h/wk (SD: 23.1), were primarily White, never or past smokers, and married (Table 1; Table S1). Those with the highest levels of 24-month average ambient $PM_{2.5}$ exposure were on average younger, slightly less physically active, were less likely to have high cholesterol, had poorer overall diet quality, and were less likely to use multivitamins. Those with highest levels of physical activity on average lived in areas with higher neighborhood SES, were more likely to be of normal weight, were less likely to have hypertension, were less likely to have diabetes, had better overall diet quality, were more likely to use multivitamins, and had husbands with higher levels of education. Over time, average $PM_{2.5}$ levels decreased from $17.0\,\mu g/m^3$ in 1988 to $11.3\,\mu g/m^3$ in 2006, whereas reported participation in overall physical activity increased from 15.4 MET-h/wk in 1988 to 20.9 MET-h/wk in 2006 (Table S1).

Analyses of the associations between 24-month average ambient $PM_{2.5}$ exposure and risk of MI, stroke, and overall mortality showed a modest but consistent increased risk of MI or stroke and overall mortality associated with increasing exposure (Table 2). In fully adjusted models, those in the highest quintile of 24-month average ambient $PM_{2.5}$ exposure ($\geq 16.5\,\mu g/m^3$) had 1.09 times the risk of MI or stroke (95% CI: 0.99, 1.20; $p_{trend} = 0.05$) and 1.10 times the risk of death (95% CI: 1.02, 1.19; $p_{trend} = 0.07$) in comparison with those in the lowest quintile of exposure ($<10.7\,\mu g/m^3$). Continuous analyses per $10\,\mu g/m^3$ greater 24-month average ambient $PM_{2.5}$ exposure were consistent, with 1.09 times the risk of MI or stroke (95% CI: 1.00, 1.19) and 1.07 times the risk of death (95% CI: 1.00, 1.15). Models were robust to adjustment for confounders.

There was a consistent decreased risk of MI and/or stroke and overall mortality associated with higher overall physical activity (Table 3; Figures 1–3). In fully adjusted models, those in the highest quartile of physical activity ($\geq$24.4 MET-h/wk) had 0.61 times the risk of MI or stroke (95% CI: 0.57, 0.66; $p_{trend} < 0.0001$), 0.64 times the risk of MI (95% CI: 0.58, 0.71; $p_{trend} < 0.0001$), 0.58 times the risk of stroke (95% CI: 0.52, 0.65; $p_{trend} < 0.0001$), and 0.40 times the risk of death (95% CI: 0.37, 0.42; $p_{trend} < 0.0001$) in comparison with those in the lowest quartile of overall physical activity (<3.7 MET-h/wk). Continuous analyses based on a 9 MET-h/wk greater overall physical activity were consistent, with 0.98 times the risk of MI or stroke (95% CI: 0.97, 0.98), 0.98 times the risk of MI (95% CI: 0.97, 0.98), 0.97 times the risk of stroke (95% CI: 0.97, 0.98), and 0.95 times the risk of death (95% CI: 0.94, 0.95). Results from analyses for walking and participation in any vigorous physical activity were consistent with those for overall physical activity. Among those who reported participating in any vigorous physical activity (jogging, running, biking, swimming, or tennis) (33% of the study population), higher vigorous physical activity was associated with lower risk for overall CVD, MI, stroke, and overall mortality.

We observed no statistically significant differences in the associations between physical activity and incident MI or stroke, MI, stroke, or overall mortality by 24-month average ambient exposure to $PM_{2.5}$ (Figures 1–3; Tables S2–S4). Analyses for overall physical activity (Figure 1; Table S2), walking (Figure 2; Table S3), and vigorous physical activity (Figure 3; Table S4) were stratified by quintiles of 24-month average ambient exposure to $PM_{2.5}$. For overall physical activity, walking, and vigorous physical activity, there was some suggestion that $PM_{2.5}$ may

Table 1. Age-standardized characteristics of Nurses' Health Study participants throughout follow-up (1988–2008), overall, by quintile of 24-month average ambient $PM_{2.5}$ exposure, and by quartile of total physical activity ($N = 104{,}990$).

	Mean ± SD or %[a]				
		$PM_{2.5}$	$PM_{2.5}$	Physical activity	Physical activity
Characteristic[b]	Overall	Quintile 1	Quintile 5	Quartile 1	Quartile 4
Age (y)[c]	63.1 ± 8.9	66.6 ± 8.3	58.7 ± 8.2	63.7 ± 9.3	63.0 ± 8.4
24-month average ambient $PM_{2.5}$ ($\mu g/m^3$)	13.7 ± 3.5	9.1 ± 1.3	18.8 ± 2.0	13.9 ± 3.5	13.4 ± 3.5
Physical activity (MET-h/wk)					
Overall physical activity	18.3 ± 23.1	20.3 ± 24.8	16.8 ± 21.3	1.5 ± 1.1	47.6 ± 28.9
Walking	7.2 ± 10.6	7.2 ± 9.7	8.0 ± 12.4	1.4 ± 4.3	15.5 ± 14.8
Jogging	0.3 ± 2.7	0.3 ± 2.7	0.2 ± 2.7	0.0 ± 0.6	0.9 ± 5.1
Running	0.2 ± 3.6	0.3 ± 4.0	0.2 ± 3.3	0.0 ± 0.7	0.8 ± 7.0
Biking	1.9 ± 6.4	2.0 ± 6.6	1.9 ± 6.5	0.1 ± 1.3	4.9 ± 11.2
Vigorous activity	3.8 ± 11.6	4.2 ± 12.3	3.6 ± 11.3	0.2 ± 2.8	11.0 ± 20.3
Outdoor physical activity[d]	17.8 ± 22.4	19.5 ± 23.8	16.6 ± 21.1	1.5 ± 1.1	46.1 ± 28.2
Pack-years of smoking	13.1 ± 19.5	12.7 ± 19.0	13.2 ± 19.9	16.1 ± 22.5	11.4 ± 17.3
Census tract median income (per 1,000 USD)	64.0 ± 25.0	60.4 ± 23.9	61.9 ± 24.3	62.2 ± 23.5	66.0 ± 26.9
Census tract median home value (per 1,000 USD)	172.3 ± 128.9	174.8 ± 142.6	169.5 ± 129.7	161.8 ± 114.5	185.2 ± 144.5
Race and ethnicity					
White	94	95	92	93	94
Black	1	1	2	2	1
Other/more than one race	5	4	6	5	5
Hispanic	1	2	1	1	1
24-month average $PM_{2.5}$ quintiles ($\mu g/m^3$)					
Quintile 1: <10.7	20	100	0	18	23
Quintile 2: 10.7 to <12.5	20	0	0	20	20
Quintile 3: 12.5 to <14.4	20	0	0	20	20
Quintile 4: 14.4 to <16.5	20	0	0	21	19
Quintile 5: ≥16.5	20	0	100	21	18
Total physical activity quartiles (MET-h/wk)					
Quartile 1: <3.7	25	23	27	100	0
Quartile 2: 3.7 to <10.9	25	23	26	0	0
Quartile 3: 10.9 to <24.4	25	25	25	0	0
Quartile 4: ≥24.4	25	28	22	0	100
Any vigorous physical activity reported	33	35	33	12	54
Body mass index (kg/m^2)					
<25	47	48	50	38	57
25 to <30	33	32	32	32	30
≥30	20	20	19	30	12
High blood pressure	43	44	41	49	38
High cholesterol	53	55	47	54	50
Diabetes	7	7	7	11	5
Family history of myocardial infarction	37	35	39	38	37
Smoking status					
Never smoker	44	44	47	42	44
Past smoker	43	46	39	41	46
Current smoker	12	10	14	16	9
Alcohol consumption (grams/day)					
0	55	54	58	63	50
0.1 to <5	23	21	23	20	23
5 to <15	14	15	12	11	17
15 to <30	5	6	4	4	6
≥30	3	4	3	3	3
AHEI diet score quartile					
Quartile 1: <42.9	25	22	28	35	18
Quartile 2: 42.9 to <51.8	25	23	25	28	21
Quartile 3: 51.8 to <60.4	25	25	24	22	26
Quartile 4: ≥60.4	25	30	22	15	36
Multivitamin use	47	50	41	42	51
Mother's occupation housewife	64	62	68	64	64
Father's occupation professional/manager	26	28	24	24	28
Husband's highest level of education more than high school	42	44	41	37	48
Registered nursing degree in 1972	86	85	88	85	87
Married - ever	75	76	73	73	76
Retired - ever	44	46	41	42	46

Note: AHEI, Alternate Healthy Eating Index; MET, metabolic equivalent of task; $PM_{2.5}$, particulate matter <2.5 microns; SD, standard deviation.

[a]Values are means ± SD or percentages and are standardized to the age distribution of the study population and represent the average values over the course of follow-up from 1988 to 2008, accounting for changes in time-varying characteristics.

[b]Characteristics are updated every 2 y, with the exception of diet, which is queried every 4 y, race (assessed in 2004), family history of MI (assessed in 1984), occupation of the participant's father and mother (assessed in 1976), educational attainment of the participant's husband (assessed in 1992), and participant's educational attainment (assessed in 1992).

[c]Not age standardized.

[d]Outdoor physical activity excludes types of assessed physical activity that are more likely to be engaged in indoors for some or all of the time (squash, racquet ball, arm weight training, leg weight training).

Table 2. Associations between 24-month average $PM_{2.5}$ exposure and incident myocardial infarction, stroke, and overall mortality among Nurses' Health Study participants 1988–2008 ($N = 104{,}990$)

Outcome	Cases (n)	Person-years (n)	Basic[a] HR (95% CI)	Fully adjusted[b] HR (95% CI)
$PM_{2.5}$ ($\mu g/m^3$)				
MI or stroke				
Q1: <10.7	1,324	323,283	Ref	Ref
Q2: 10.7–12.4	1,324	326,570	1.08 (1.00, 1.17)	1.07 (0.99, 1.16)
Q3: 12.5–14.3	1,277	326,727	1.11 (1.02, 1.20)	1.10 (1.02, 1.19)
Q4: 14.4–16.4	1,188	328,381	1.12 (1.03, 1.21)	1.09 (1.01, 1.19)
Q5: ≥16.5	961	327,052	1.11 (1.02, 1.22)	1.09 (0.99, 1.20)
p for trend[c]			0.01	0.05
Continuous ($10\,\mu g/m^3$)	6,074	1,632,012	1.12 (1.03, 1.21)	1.09 (1.00, 1.19)
MI				
Q1: <10.7	697	323,763	Ref	Ref
Q2: 10.7–12.4	693	327,058	1.06 (0.95, 1.18)	1.05 (0.95, 1.17)
Q3: 12.5–14.3	686	327,178	1.11 (0.99, 1.23)	1.10 (0.99, 1.22)
Q4: 14.4–16.4	674	328,816	1.16 (1.04, 1.30)	1.13 (1.01, 1.26)
Q5: ≥16.5	554	327,400	1.13 (0.99, 1.27)	1.09 (0.96, 1.24)
p for trend[c]			0.02	0.07
Continuous ($10\,\mu g/m^3$)	3,304	1,634,215	1.16 (1.03, 1.30)	1.13 (1.01, 1.26)
Stroke				
Q1: <10.7	645	323,721	Ref	Ref
Q2: 10.7–12.4	648	327,009	1.10 (0.98, 1.23)	1.09 (0.98, 1.22)
Q3: 12.5–14.3	609	327,186	1.10 (0.98, 1.23)	1.10 (0.98, 1.23)
Q4: 14.4–16.4	527	328,817	1.06 (0.94, 1.19)	1.04 (0.92, 1.17)
Q5: ≥16.5	419	327,435	1.08 (0.94, 1.24)	1.07 (0.93, 1.23)
p for trend[c]			0.34	0.49
Continuous ($10\,\mu g/m^3$)	2,848	1,634,168	1.05 (0.93, 1.19)	1.04 (0.92, 1.18)
Overall mortality				
Q1: <10.7	2,553	324,401	Ref	Ref
Q2: 10.7–12.4	2,352	327,652	1.11 (1.04, 1.17)	1.08 (1.02, 1.15)
Q3: 12.5–14.3	2,111	327,781	1.08 (1.01, 1.14)	1.07 (1.01, 1.13)
Q4: 14.4–16.4	1,670	329,360	1.05 (0.99, 1.12)	1.03 (0.97, 1.10)
Q5: ≥16.5	1,141	327,839	1.12 (1.04, 1.21)	1.10 (1.02, 1.19)
p for trend[c]			0.02	0.07
Continuous ($10\,\mu g/m^3$)	9,827	1,637,033	1.09 (1.02, 1.17)	1.07 (1.00, 1.15)

Note: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; $PM_{2.5}$, particulate matter <2.5 microns; Q, quintile; Ref, referent.
[a]Basic model: adjusted for age and race (White yes/no).
[b]Fully adjusted model: additionally adjusted for incident cancer (yes/no), family history of myocardial infarction (yes/no), smoking status (never, past, current), pack-years, Alternate Healthy Eating Index score quartiles, alcohol consumption (0.0, <5.0, 5.0–9.9, 10.0–19.9, or ≥20.0 g/d), multivitamin use (yes/no), census tract median income (USD), census tract median home value (USD), occupation father (professional or other), occupation mother (housewife or other), husband's level of education more than high school (yes/no), registered nursing degree in 1992 (yes/no), marital status (married or not married), retirement status (retired or not retired).
[c]p for trend based on median quintile values.

have attenuated the beneficial effects of physical activity on risk of MI among the most exposed groups (14.4–16.4 $\mu g/m^3$ and ≥16.5 $\mu g/m^3$). However, there was no statistical evidence of a difference in associations between physical activity and MI across quintiles of $PM_{2.5}$ exposure ($p_{interaction} = 0.18$–0.35). We observed less precise relationships between quartiles of vigorous physical activity and incident MI or stroke, MI, stroke, or overall mortality, because vigorous physical activity was reported by just 33% of the study participants.

The results for sensitivity analyses estimating activities that are likely to be performed outdoors (e.g., walking, running, biking, lawn mowing) were consistent with overall physical activity, walking, and vigorous physical activity analyses (Tables S5–S6). We observed a consistent decreased risk of MI and/or stroke and overall mortality associated with higher physical activity (Table S5) and no statistically significant differences in the associations between physical activity and incident MI or stroke, MI, stroke, or overall mortality by 24-month average ambient exposure to $PM_{2.5}$ (Table S6).

Discussion

As expected, in this nationwide cohort of women, higher long-term exposures to ambient $PM_{2.5}$ and lower physical activity were associated with higher risks of incident MI, stroke, and overall mortality. These findings were robust to time-varying adjustment for demographics, CVD risk factors, and individual-level and neighborhood-level SES. Although we hypothesized, based on studies of short-term PM exposures, that long-term ambient $PM_{2.5}$ exposure might attenuate the benefits of physical activity, we observed that higher physical activity was strongly associated with lower CVD risk and overall mortality at all levels of air pollution exposure. However, there was a suggestion of an attenuation of the association of physical activity on MI risk among those with higher levels of $PM_{2.5}$ exposure, regardless of the metric of physical activity examined.

The findings from this study are consistent with previous studies investigating the interaction between long-term exposure to air pollutants and physical activity in association with mortality and MI. In the only previous study investigating long-term exposure to $PM_{2.5}$ and physical activity in relation to overall and cause-specific mortality, there was no evidence of interaction between long-term $PM_{2.5}$ exposure and physical activity among 58,643 participants 65 years of age or older from the Hong Kong Elderly Health Service Cohort (Sun et al. 2020). Two studies have examined the interactions of physical activity with another pollutant, NO_2. In a study of 52,061 participants from the Danish Diet, Cancer, and Health Cohort living in urban centers, no interaction was observed between long-term NO_2 exposure and physical activity in association with overall and cause-specific mortality (Andersen et al. 2015). In a second study of 57,053 participants in the same cohort, no interaction was observed between long-term NO_2 exposure and

Table 3. Associations between physical activity and incident myocardial infarction, stroke, and overall mortality among Nurses' Health Study participants 1988–2008 ($N = 104{,}990$).

Outcome	Cases (n)	Person-years (n)	Basic[a] HR (95% CI)	Fully adjusted[b] HR (95% CI)
Overall physical activity (MET h/wk)				
MI or stroke				
Q1: <3.7	2,248	405,352	Ref	Ref
Q2: 3.7–10.8	1,451	408,458	0.69 (0.64, 0.74)	0.74 (0.70, 0.80)
Q3: 10.9–24.3	1,281	409,422	0.61 (0.57, 0.65)	0.69 (0.64, 0.74)
Q4: ≥24.4	1,094	408,780	0.53 (0.49, 0.57)	0.61 (0.57, 0.66)
p for trend[c]			<0.0001	<0.0001
Continuous (9 MET h/wk)	6,074	1,632,012	0.97 (0.96, 0.97)	0.98 (0.97, 0.98)
MI				
Q1: <3.7	1,223	406,151	Ref	Ref
Q2: 3.7–10.8	803	408,970	0.69 (0.63, 0.76)	0.76 (0.70, 0.83)
Q3: 10.9–24.3	673	409,907	0.58 (0.53, 0.64)	0.68 (0.61, 0.74)
Q4: ≥24.44	605	409,187	0.53 (0.48, 0.59)	0.64 (0.58, 0.71)
p for trend[c]			<0.0001	<0.0001
Continuous (9 MET h/wk)	3,304	1,634,215	0.97 (0.96, 0.97)	0.98 (0.97, 0.98)
Stroke				
Q1: <3.7	1,053	406,070	Ref	Ref
Q2: 3.7–10.8	668	408,996	0.68 (0.62, 0.75)	0.73 (0.66, 0.80)
Q3: 10.9–4.3	626	409,895	0.65 (0.59, 0.72)	0.71 (0.64, 0.78)
Q4: ≥24.4	501	409,208	0.52 (0.47, 0.58)	0.58 (0.52, 0.65)
p for trend[c]			<0.0001	<0.0001
Continuous (9 MET h/wk)	2,848	1,634,168	0.97 (0.96, 0.97)	0.97 (0.97, 0.98)
Overall mortality				
Q1: <3.7	4,671	407,148	Ref	Ref
Q2: 3.7–10.8	2,193	409,645	0.51 (0.48, 0.54)	0.58 (0.55, 0.61)
Q3: 10.9–24.3	1,613	410,500	0.37 (0.35, 0.39)	0.45 (0.43, 0.48)
Q4: ≥24.4	1,350	409,740	0.32 (0.30, 0.34)	0.40 (0.37, 0.42)
p for trend[c]			<0.0001	<0.0001
Continuous (9 MET h/wk)	9,827	1,637,033	0.93 (0.93, 0.94)	0.95 (0.94, 0.95)
Walking (MET-hours/week)				
MI or stroke				
Q1: <0.6	2,094	338,605	Ref	Ref
Q2: 0.6–3.0	1,742	477,879	0.67 (0.63, 0.72)	0.72 (0.68, 0.77)
Q3: 3.1–9.9	1,166	386,251	0.55 (0.51, 0.59)	0.63 (0.58, 0.67)
Q4: ≥10.0	1,072	429,278	0.49 (0.46, 0.53)	0.58 (0.54, 0.63)
p for trend[c]			<0.0001	<0.0001
Continuous (9 MET h/wk)	6,074	1,632,012	0.82 (0.80, 0.85)	0.87 (0.84, 0.90)
MI				
Q1: <0.6	1,156	339,316	Ref	Ref
Q2: 0.6–3.0	934	478,540	0.64 (0.58, 0.69)	0.69 (0.63, 0.76)
Q3: 3.1–9.9	615	386,693	0.51 (0.46, 0.57)	0.60 (0.54, 0.66)
Q4: ≥10.0	599	429,666	0.48 (0.43, 0.53)	0.58 (0.53, 0.65)
p for trend[c]			<0.0001	<0.0001
Continuous (9 MET h/wk)	3,304	1,634,215	0.82 (0.79, 0.86)	0.88 (0.84, 0.92)
Stroke				
Q1: <0.6	968	339,270	Ref	Ref
Q2: 0.6–3.0	826	478,504	0.71 (0.65, 0.78)	0.76 (0.69, 0.83)
Q3: 3.1–9.9	564	386,678	0.60 (0.54, 0.67)	0.66 (0.59, 0.73)
Q4: ≥10.0	490	429,716	0.51 (0.45, 0.57)	0.58 (0.51, 0.65)
p for trend[c]			<0.0001	<0.0001
Continuous (9 MET h/wk)	2,848	1,634,168	0.83 (0.79, 0.87)	0.86 (0.82, 0.90)
Overall mortality				
Q1: <0.6	4,679	340,313	Ref	Ref
Q2: 0.6–3.0	2,534	479,320	0.48 (0.46, 0.50)	0.54 (0.51, 0.57)
Q3: 3.1–9.9	1,511	387,203	0.35 (0.33, 0.37)	0.42 (0.39, 0.44)
Q4: ≥10.0	1,103	430,197	0.27 (0.25, 0.29)	0.34 (0.32, 0.37)
p for trend[c]			<0.0001	<0.0001
Continuous (9 MET h/wk)	9,827	1,637,033	0.62 (0.59, 0.64)	0.69 (0.67, 0.71)
Vigorous physical activity (MET-hours/week)				
MI or stroke				
No vigorous activity	4,383	1,085,426	Ref	Ref
Any vigorous activity	1,691	546,586	0.83 (0.79, 0.88)	0.91 (0.86, 0.96)
Q1: <1.4	187	62,281	Ref	Ref
Q2: 1.4–6.2	739	210,781	1.01 (0.86, 1.19)	1.04 (0.88, 1.22)
Q3: 6.3–13.4	417	136,132	0.91 (0.76, 1.08)	0.96 (0.80, 1.14)
Q4: ≥13.5	348	137,393	0.74 (0.62, 0.88)	0.80 (0.67, 0.96)
p for trend[c]			<0.0001	0.0001
Continuous (9 MET h/wk)	6,074	1,632,012	0.93 (0.89, 0.96)	0.94 (0.91, 0.97)

Table 3. (*Continued.*)

Outcome	Cases (*n*)	Person-years (*n*)	Basic[a] HR (95% CI)	Fully adjusted[b] HR (95% CI)
MI				
No vigorous activity	2,401	1,086,969	Ref	Ref
Any vigorous activity	903	547,246	0.80 (0.74, 0.87)	0.89 (0.82, 0.96)
Q1: <1.4	106	62,344	Ref	Ref
Q2: 1.4–6.2	395	211,060	0.97 (0.78, 1.21)	0.99 (0.80, 1.23)
Q3: 6.3–13.4	220	136,302	0.86 (0.68, 1.08)	0.90 (0.71, 1.14)
Q4: ≥13.5	182	137,540	0.69 (0.54, 0.88)	0.76 (0.59, 0.97)
p for trend[c]			<0.0001	0.002
Continuous (9 MET h/wk)	3,304	1,634,215	0.92 (0.87, 0.96)	0.94 (0.89, 0.98)
Stroke				
No vigorous activity	2,038	1,086,970	Ref	Ref
Any vigorous activity	810	547,198	0.87 (0.80, 0.95)	0.93 (0.86, 1.01)
Q1: <1.4	82	62,358	Ref	Ref
Q2: 1.4–6.2	357	211,035	1.09 (0.86, 1.39)	1.11 (0.87, 1.42)
Q3: 6.3–13.4	201	136,278	0.99 (0.76, 1.28)	1.03 (0.79, 1.34)
Q4: ≥13.5	170	137,527	0.81 (0.62, 1.06)	0.86 (0.66, 1.13)
p for trend[c]			0.003	0.01
Continuous (9 MET h/wk)	2,848	1,634,168	0.94 (0.89, 0.98)	0.95 (0.90, 0.99)
Overall mortality				
No vigorous activity	7,467	1,088,968	Ref	Ref
Any vigorous activity	2,360	548,065	0.69 (0.66, 0.72)	0.77 (0.73, 0.81)
Q1: <1.4	303	62,453	Ref	Ref
Q2: 1.4–6.2	1,010	211,396	0.81 (0.71, 0.93)	0.83 (0.73, 0.94)
Q3: 6.3–13.4	566	136,492	0.75 (0.65, 0.86)	0.80 (0.69, 0.92)
Q4: ≥13.5	481	137,723	0.61 (0.53, 0.70)	0.66 (0.57, 0.77)
p for trend[c]			<0.0001	<0.0001
Continuous (9 MET h/wk)	9,827	1,637,033	0.92 (0.90, 0.95)	0.94 (0.91, 0.97)

Note: CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; MI, myocardial infarction; Q, quartile; Ref, referent.
[a]Basic model: adjusted for age and race (White yes/no).
[b]Fully adjusted model: additionally adjusted for incident cancer (yes/no), family history of myocardial infarction (yes/no), smoking status (never, past, current), pack-years, Alternate Healthy Eating Index score quartiles, alcohol consumption (0.0, <5.0, 5.0–9.9, 10.0–19.9, or ≥20.0 g/d), multivitamin use (yes/no), census tract median income (USD), census tract median home value (USD), occupation father (professional or other), occupation mother (housewife or other), husband's level of education more than high school (yes/no), registered nursing degree in 1992 (yes/no), marital status (married or not married), retirement status (retired or not retired).
[c]*p* for trend based on median quartile values.

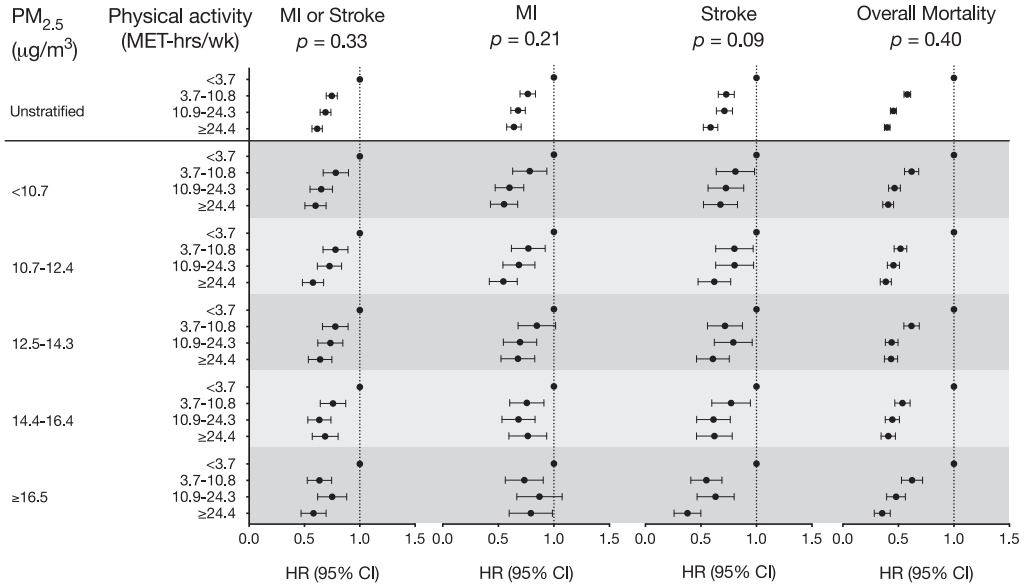

Figure 1. Associations between quartiles of overall physical activity and incident CVD and overall mortality, overall and stratified by quintiles of 24-month average ambient $PM_{2.5}$ exposure among Nurses' Health Study participants 1988–2008 ($N = 104{,}990$) (See Table S2). Fully adjusted model: adjusted for age and race (White yes/no), incident cancer (yes/no), family history of myocardial infarction (yes/no), smoking status (never, past, current), pack-years, Alternate Healthy Eating Index score quartiles, alcohol consumption (0.0, <5.0, 5.0–9.9, 10.0–19.9, or ≥20.0 g/d), multivitamin use (yes/no), census tract median income (USD), census tract median home value (USD), occupation father (professional or other), occupation mother (housewife or other), husband's level of education more than high school (yes/no), registered nursing degree in 1992 (yes/no), marital status (married or not married), retirement status (retired or not retired). Note: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task; MI, myocardial infarction; *p*, *p*-value for interaction for stratified Cox proportional hazards models using likelihood ratio tests; $PM_{2.5}$, particulate matter <2.5 microns.

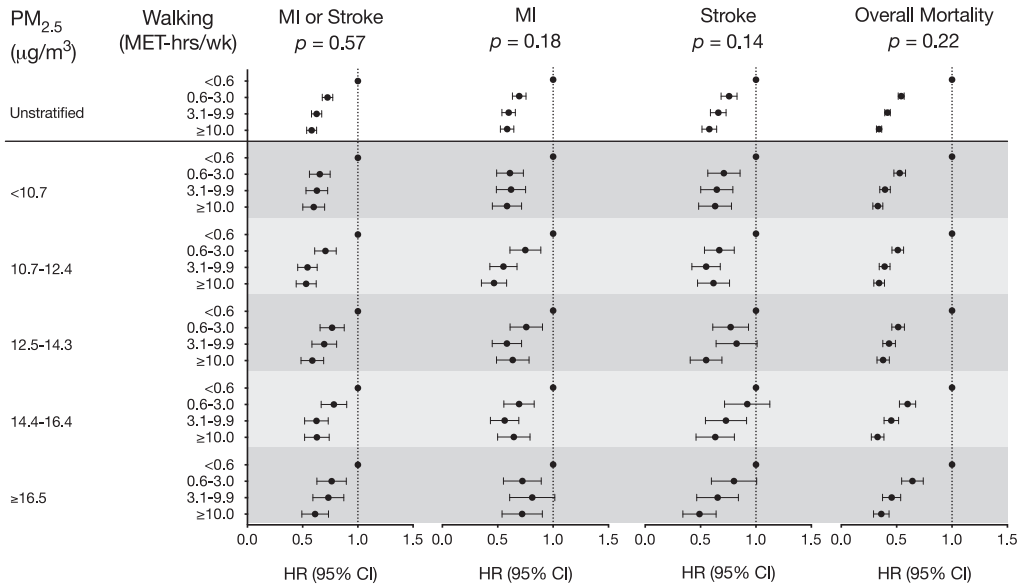

Figure 2. Associations between quartiles of leisure-time walking, and incident CVD and overall mortality, overall and stratified by quintiles of 24-month average ambient $PM_{2.5}$ exposure among Nurses' Health Study participants 1988–2008 ($N = 104{,}990$) (See Table S3). Fully adjusted model: adjusted for age and race (White yes/no), incident cancer (yes/no), family history of myocardial infarction (yes/no), smoking status (never, past, current), pack-years, Alternate Healthy Eating Index score quartiles, alcohol consumption (0.0, <5.0, 5.0–9.9, 10.0–19.9, or ≥20.0 g/d), multivitamin use (yes/no), census tract median income (USD), census tract median home value (USD), occupation father (professional or other), occupation mother (housewife or other), husband's level of education more than high school (yes/no), registered nursing degree in 1992 (yes/no), marital status (married or not married), retirement status (retired or not retired). Note: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task; MI, myocardial infarction; *p*, *p*-value for interaction for stratified Cox proportional hazards models using likelihood ratio tests; $PM_{2.5}$, particulate matter <2.5 microns.

physical activity in association with incident and recurrent MI (Kubesch et al. 2018). Among 359,067 Taiwanese adults, no interaction was observed between long-term $PM_{2.5}$ exposure and physical activity in relation to systemic inflammation, a biomarker of CVD risk (Zhang et al. 2018). Similarly, among 39,259 Chinese participants of the Henan Rural Cohort Study, no statistically significant interactions were observed between PM air pollution and physical activity in relation to metabolic syndrome prevalence (Hou et al. 2020b). However, in other cross-sectional studies of the same cohort, interactions were observed between long-term exposure to air pollution and physical activity in relation to CVD risk factors: Physical activity was found to attenuate associations between long-term exposure to air pollutants and increased platelet size, a biomarker of CVD and CVD-related mortality risk (Hou et al. 2020a), whereas PM air pollution exposure was more strongly associated with increased prevalence of hypertension among those with higher levels of physical activity (Li et al. 2020).

A much larger body of literature exists on the interaction between short-term exposure to air pollutants and physical activity. Interactions between air pollution exposure and physical activity have been observed in relation to acute cardiopulmonary responses. Among 20 nonsmoking men 18–26 years of age in Beijing, China, participants with higher levels of physical activity frequency had higher acute cardiopulmonary responses to $PM_{2.5}$ (Chen et al. 2018). In a cross-over study among 28 healthy adults assigned to settings with high- and low-traffic exposures and rest or intermittent exercise, the association between traffic-related air pollution (TRAP) and heart rate variability was modified by physical activity in high-traffic but not low-traffic exposure settings (Cole-Hunter et al. 2016). Among 2,078 patients enrolled in a cardiac rehabilitation program, short-term elevation in $PM_{2.5}$ exposure was associated with decreased cardiopulmonary responses measured during cardiopulmonary exercise tests conducted between 2003 and 2011 (Giorgini et al. 2015). In a study of 122 adults across three European cities, physical activity was measured using a wearable activity tracker over the course of 3 separate weeks spread across 3 seasons. Concurrently, participants carried an active air pollution sampler to assess black carbon exposure. The inverse association between black carbon exposure and subclinical lung function was weaker among those with higher levels of physical activity (Laeremans et al. 2018). However, in this same study, no interactions were observed between black carbon exposure and physical activity in relation to blood pressure (Avila-Palencia et al. 2019). In a cross-over study among 119 participants 60 years of age and older, TRAP exposure attenuated the protective effects of walking for 2 h on cardiovascular parameters among both healthy participants and participants with chronic cardiopulmonary diseases (Sinharay et al. 2018). However, in a study of 18 recreationally active men with mean age of 25, no evidence of interaction between air pollution exposure and physical activity in association with acute pulmonary inflammation was observed in low- and high-intensity cycling experiments (Giles et al. 2018). The differences between the long-term and short-term studies could be due to a number of factors. It is possible that the acute pulmonary responses observed in short-term studies do not ultimately manifest as clinical CVD outcomes or mortality. It might also be possible that short-term high exposure scenarios are not reflective of long-term exposure. Future studies may investigate possible biological mechanisms, include physical activity locations using, for instance, smartphone global positioning system data (Fore et al. 2020) and assess air pollution exposure during physical activity to better understand the discrepancy between the findings from studies investigating short- and long-term exposures to air pollutants.

The findings from this study are consistent with previous single-exposure studies on long-term $PM_{2.5}$ exposure and physical activity in relation to stroke, MI, and overall mortality. A recent meta-analysis of >25 y of cohort studies on $PM_{2.5}$ exposure and mortality found a meta-estimated mortality HR of 1.08 (95% CI: 1.06, 1.11) per 10 $\mu g/m^3$ greater $PM_{2.5}$ exposure (Pope et al. 2020). Results from continuous analyses in this study are consistent, with an HR of 1.07 (95% CI: 1.00, 1.15) for overall mortality per 10 $\mu g/m^3$ greater 24-month average $PM_{2.5}$

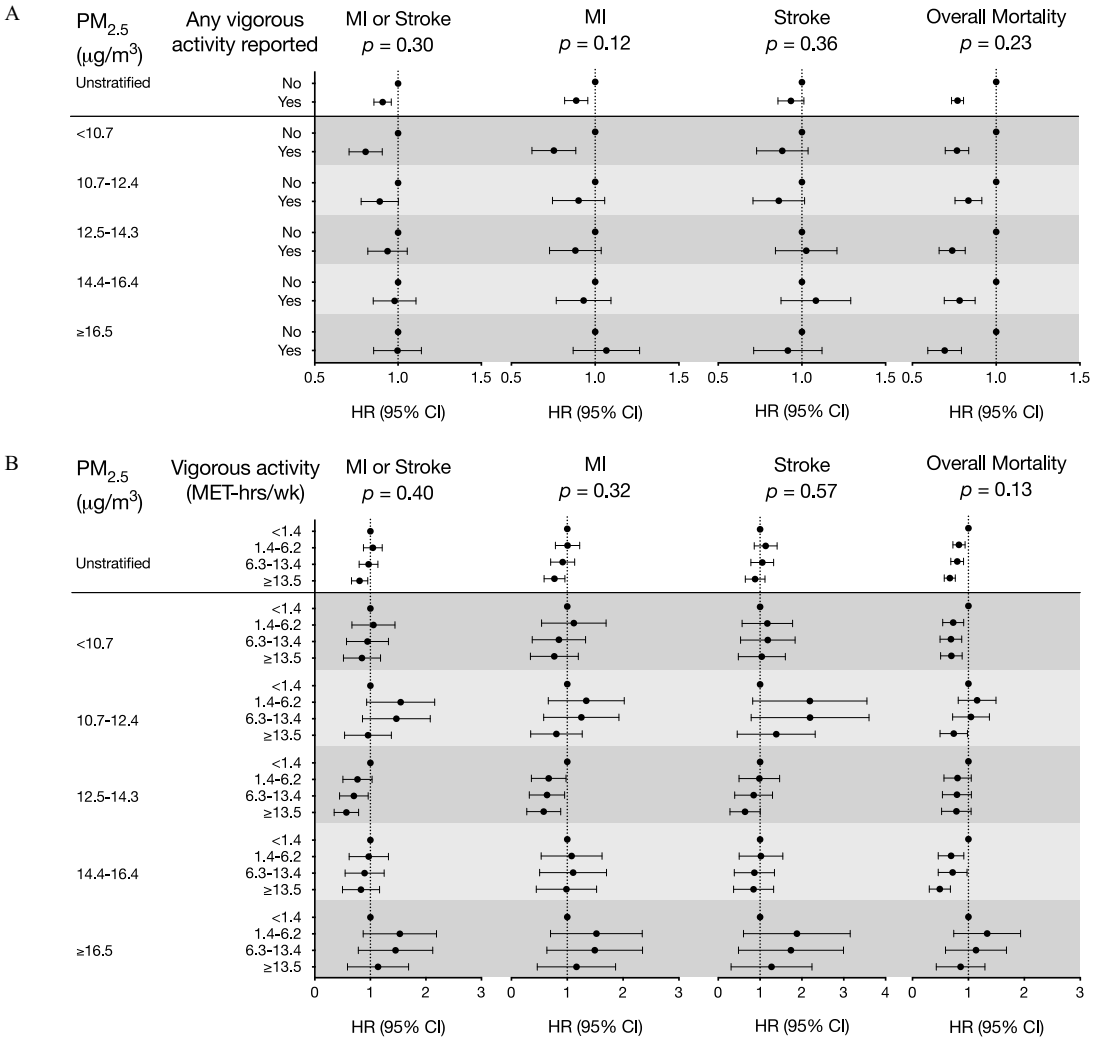

Figure 3. Associations between vigorous physical activity, and incident CVD and overall mortality, overall and stratified by quintiles of 24-month average ambient $PM_{2.5}$ exposure among Nurses' Health Study participants 1988–2008 ($N = 104{,}990$) for (A) any amount of vigorous physical activity reported, and (B) quartiles of vigorous physical activity, among those who reported participation in any vigorous physical activity (See Table S4). Fully adjusted model: adjusted for age and race (White yes/no), incident cancer (yes/no), family history of myocardial infarction (yes/no), smoking status (never, past, current), pack-years, Alternate Healthy Eating Index score quartiles, alcohol consumption (0.0, <5.0, 5.0–9.9, 10.0–19.9, or ≥20.0 g/d), multivitamin use (yes/no), census tract median income (USD), census tract median home value (USD), occupation father (professional or other), occupation mother (housewife or other), husband's level of education more than high school (yes/no), registered nursing degree in 1992 (yes/no), marital status (married or not married), retirement status (retired or not retired). Note: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task; MI, myocardial infarction; *p*, *p*-value for interaction for stratified Cox proportional hazards models using likelihood ratio tests; $PM_{2.5}$, particulate matter <2.5 microns.

exposure. A meta-analysis of physical activity and mortality in adults ≥60 y old observed a relative risk (RR) of death of 0.88 (95% CI: 0.71, 0.87) for each 150 min of moderate-to-vigorous-intensity physical activity per week (Hupin et al. 2015). Another meta-analysis of physical activity and CVD risk observed a RR of MI of 0.84 (95% CI: 0.70, 1.00) and RR of stroke of 0.85 (95% CI: 0.77, 0.94) per 11.25 MET-h/wk (Wahid et al. 2016). Findings from this study are consistent, with our observed HR of 0.95 (95% CI: 0.94, 0.95) for overall mortality, HR of 0.98 (95% CI: 0.97, 0.98) for MI, and HR of 0.97 (95% CI: 0.97, 0.98) for stroke, per 9 MET-h/wk, comparable to 90 min of moderate-to-vigorous-intensity physical activity per week.

This study has some limitations. The NHS comprises women who are predominantly white, non-Hispanic, and middle-age and who at one time were nurses. These findings may not be generalizable to men or populations that are more racially and socioeconomically diverse. In this study, we observed stronger associations between long-term $PM_{2.5}$ exposure and MI and overall mortality, compared with stroke. Although associations with long-term $PM_{2.5}$ exposure may differ by stroke subtype (Amini et al. 2020), we were unable to examine specific subtype of stroke due to small stroke subtype case numbers. Combining stroke subtypes may have contributed to the observed weaker associations for stroke. The $PM_{2.5}$ levels observed in this study reflect average ambient exposure levels observed in the contiguous United States between 1988 and 2008, whereas other geographic regions may experience higher average ambient $PM_{2.5}$ levels (Hystad et al. 2020; Lee et al. 2018). These findings may not be generalizable to populations exposed to higher levels of long-term ambient $PM_{2.5}$ exposure. We used a sophisticated spatiotemporal exposure model to estimate residential ambient $PM_{2.5}$ levels biennially throughout follow-up. However, we do not have information on time-activity patterns or personal $PM_{2.5}$ exposures. Furthermore, although participants reported average duration and intensity of weekly physical activity, we do not have information on the time, location, variability, or duration of each activity and do not have information on $PM_{2.5}$ exposures specifically during physical activity. This would increase the measurement error in our $PM_{2.5}$ estimates and would make it more

challenging to detect interactions between $PM_{2.5}$ exposures and physical activity. However, results from sensitivity analyses that estimate time spent engaging in physical activities that are likely to be performed outdoors were consistent with the results from the main analyses investigating overall physical activity, walking, and vigorous physical activity.

This study also has notable strengths. Through the extensive follow-up procedures in the NHS, we were able to capture not only fatal events, but also the incidence of all CVD outcomes. All outcomes have also undergone medical record confirmation, increasing our confidence in the reporting of outcomes. We were able to follow NHS participants over several decades and were able to include time-varying information on residential $PM_{2.5}$ exposure and physical activity. Additionally, we have extensive time-varying information on confounders, including diet and other CVD risk factors, allowing us to control for these factors in our models.

In conclusion, we observed that those exposed to higher levels of long-term ambient residential $PM_{2.5}$ exposure had a modest increased risk of overall CVD and mortality in this nationwide cohort of adult women. Across measures and intensity of physical activity, we observed that those with higher levels of physical activity had decreased risks of overall CVD, MI, stroke, and mortality. Moreover, we observed no multiplicative interactions between long-term $PM_{2.5}$ exposure and any measure of physical activity: Physical activity was protective for overall CVD, MI, stroke, and mortality at all levels of long-term $PM_{2.5}$ exposure. Although this is the first study to investigate the interaction between long-term $PM_{2.5}$ exposure and physical activity in relation to CVD, results are consistent with previous studies investigating mortality and interactions between long-term NO_2 exposure and physical activity. These findings suggest that physical activity is beneficial to risk of incident overall CVD, MI, stroke, and overall mortality at ambient levels of $PM_{2.5}$ experienced in the contiguous United States.

Acknowledgments

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