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Original article

Air Pollution

Ambient air pollution, healthy diet and vegetable intakes, and mortality: a prospective UK Biobank study

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Abstract

Background: Recent studies suggest potential interactions of air pollutants with dietary factors and genetic susceptibility on mortality risk; however, evidence from prospective studies is still lacking. We aimed to assess the association between air pollution and mortality, and investigate the modification effects of a healthy diet and genetic susceptibility.
Methods: A total of 386 937 participants were enrolled from 2006 to 2010 and followed up to 2018 in the UK Biobank study. The annual average air pollutant concentrations of particulate matter (PM) with diameters $\leq$2.5 ($PM_{2.5}$), $\leq$10 (PM_{10}) and between 2.5 and 10 μm ($PM_{2.5–10}$) and nitrogen oxides (NO_2 and NO_x) were calculated and linked to participants' residential addresses. Healthy dietary patterns were evaluated by a healthy diet score (HDS) based on intakes of vegetables, fruit, fish, unprocessed red meat and processed meat. We also calculated genetic risk score (GRS) of the lifespan. We examined potential interactions by setting variable cross-product terms of air pollutants with diets or GRS in the models.
Results: We identified 11 881 deaths [2426 from cardiovascular diseases (CVD), 1211 from coronary heart disease (CHD) and 466 from stroke] during a median follow-up of 8.9 years. We found that $PM_{2.5}$ [hazard ratio (HR), 1.27; 95% CI, 1.05–1.55], PM_{10} (HR, 1.18; 95% CI, 1.04–1.34), NO_2 (HR, 1.05; 95% CI, 1.01–1.08), and NO_x (HR, 1.02; 95% CI, 1.01–1.03) were associated with all-cause mortality. $PM_{2.5}$ was also associated with increased risks of CVD mortality (HR, 1.68; 95% CI, 1.10–2.56) and CHD mortality (HR, 2.08; 95% CI, 1.16–3.75). In addition, we found that adherence to healthy dietary patterns modified associations of $PM_{2.5}$, NO_2 and NO_x with all-cause mortality (P-interaction = 0.006, 0.006 and 0.02, respectively). Among the individual dietary components, vegetable intakes

showed interactions with $PM_{2.5}$, NO_2 and NO_x (*P*-interaction = 0.007, 0.004 and 0.02, respectively). The associations between air pollutants and increased risks of all-cause mortality were attenuated among participants with higher vegetable intakes. We did not observe interactions between air pollutants and HDS on CVD, CHD or stroke mortality (*P*-interaction > 0.05). Besides, we did not find interactions between air pollutants and genetic risk for lifespan on mortality risk.

Conclusion: This study provides evidence linking long-term exposure to various air pollutants to the risk of all-cause, CVD and CHD mortality, and the potential attenuation of a healthy diet, especially high vegetable intakes, on such relations. Our findings highlight the importance of adherence to a healthy diet in lowering ambient air-pollution-related mortality risk.

Key words: air pollution, healthy diet, vegetable intakes, mortality

Key Messages

- Long-term exposure to various ambient air pollutants might be related to the risks of all-cause, cardiovascular diseases and coronary heart disease mortality.
- A healthy diet, especially high vegetable intakes, may attenuate adverse associations between air pollution and mortality risks.
- The importance of adherence to a healthy diet in lowering ambient air-pollution-related mortality risk needs to be addressed.

Introduction

Ambient air pollution is a leading cause of overall disease burden and mortality globally.[1,2] It is estimated that ~4.2 million deaths were attributable to ambient air pollution all over the world in 2016.[3] In particular, ambient air pollution is a major contributor to cardiovascular diseases (CVD) mortality, which accounts for more than half of the total deaths caused by air pollution.[4] Recently, numerous studies have provided compelling evidence that long-term exposure to ambient air pollution is associated with increased risks of all-cause and cause-specific mortality.[5–10] Notably, most of the previous studies only evaluated particulate matter with aerodynamic diameter of $\leq$2.5 μm ($PM_{2.5}$),[5–7,9] nitrogen oxides (NO_2 and NO_x)[11,12] and PM with an aerodynamic diameter of $\leq$10 μm (PM_{10}),[12,13] whereas investigations on other air pollutants such as PM with an aerodynamic diameter of between 2.5 and 10 μm ($PM_{2.5–10}$) were limited.

In addition, recently emerging evidence suggests that the relation between air pollution and human health is likely to be modified by lifestyle factors such as dietary intakes. A recent prospective cohort study (N = 548 845) in the USA showed that a Mediterranean diet modified the association between $PM_{2.5}$, NO_2 and CVD mortality, as participants with a higher alternative Mediterranean Diet Index score exhibited a reduced risk of CVD mortality related to air pollution.[14] Several short-term intervention studies also lent support to the potential modification effects of individual foods or nutrients on the relation between air pollution and cardiopulmonary outcomes.[15–17] However, prospective studies on the interactions between the habitual dietary patterns and comprehensively measured air pollutants are still lacking. Besides, growing evidence shows that human genetic variations may modify individual susceptibility to air pollution[18,19] yet little is known about the interaction between air pollution and genetic variations on mortality risk.

The UK Biobank study is a large-scale prospective cohort study with a wide range of information on air pollutants including $PM_{2.5}$, PM_{10}, $PM_{2.5–10}$, NO_2 and NO_x, as well as dietary intakes and genetic variations. Therefore, we aimed to comprehensively assess the associations of air pollutants with all-cause and CVD mortality, and further investigate the potential modification effects of healthy dietary patterns and genetic variations on these associations.

Methods

Study design and populations

UK Biobank study is a national cohort study of half a million community-dwelling adults aged 40–69 years initiated in the UK from 2006 to 2010. The information on the

baseline questionnaire and anthropometric measures were collected at 22 assessment centres across England, Wales and Scotland. A detailed description of the cohort study and participants was published elsewhere.[20,21] All participants gave written consent.

In our main analysis ($N = 502\,506$) we excluded participants who had a history of cancer or CVD on the basis of self-report or medical records (27 885 males and 33 174 females) as well as an additional 19 514 participants with missing dietary information. After excluding participants with missing air pollution measurements, a total of 386 937 participants were included in the final analysis.

Air pollution measurements

The Land Use Regression (LUR)-based model developed by the ESCAPE study group was adopted to estimate the annual average concentration of $PM_{2.5}$, PM_{10}, $PM_{2.5–10}$, NO_2 and NO_x.[22,23] The annual average air pollutant concentrations were calculated through pollutant-specific LUR models using the predictor variables obtained from the Geographic Information System and linked to participants' residential addresses given at the UK Biobank baseline visit.[24,25] Air pollution estimates for $PM_{2.5}$, $PM_{2.5–10}$ and NO_x were only available for the year 2010, whereas NO_2 and PM_{10} had the exposure data for several years (2005, 2006, 2007 and 2010 for NO_2, and 2007 and 2010 for PM_{10}), thus the means of the values of the two air pollutants were included in the analysis.

Ascertainment of death

Death dates were obtained by reviewing the death certificates held by the National Health Service Information Centre for participants in England and Wales and the National Health Service Central Register Scotland for participants from Scotland. The cause of death was coded according to the International Classification of Disease, 10th revised edition (ICD-10) assigned to the primary cause of death. We used ICD-10 code of I00–I99 to define deaths due to CVD, where coronary heart diseases (CHD) and stroke were identified as code of I20–I25 and I60–I64, respectively.

Dietary intake and covariates assessment

At baseline, all participants completed a touchscreen questionnaire to collect information about socio-demographic characteristics, lifestyles, dietary intakes and medical history of prevalent diseases.

We assessed diet based on a touchscreen food frequency questionnaire (FFQ). Participants reported their daily intake of dietary consumption including poultry, beef, lamb/mutton, processed meat, oily fish, non-oily fish, fresh fruit, dried fruit, raw vegetables and cooked vegetables by answering touchscreen multiple-choice questions. Frequency categories of meat and fish were recoded: 'never' = 0, 'less than once a week' = 0.5, 'once a week' = 1, '2–4 times a week' = 3, '5–6 times a week' = 5.5 and 'once or more daily' = 7. Servings for beef, lamb/mutton and pork were summed to create the frequency of consumption of unprocessed red meat. For vegetables and fruit, participants were asked about how many heaped tablespoons of cooked/salad or raw vegetables or pieces of fresh/dried fruit they consumed per day. Tablespoons of cooked/salad and raw vegetables were added to create the consumption of vegetables and pieces of fresh and dried fruit were added to create the consumption of fruit. The validity and repeatability of the touchscreen FFQ have been described in a previous study.[26] We defined healthy diets according to the healthy diet score (HDS) calculated on the basis of the following factors: vegetable intake of at least four tablespoons each day (median); fruit intake of at least three pieces each day (median); fish intake of at least twice each week (median); unprocessed red meat intake of no more than twice each week (median); and processed meat intake of no more than twice each week (median). One point was given for each favourable dietary factor and the total diet score ranged from 0 to 5.[27] Participants were classified into three groups of poor dietary pattern (score of 0 or 1), medium dietary pattern (score of 2 or 3) or ideal dietary pattern (score of 4 or 5).[28]

Data on several potential confounders including age, sex, race, average household income, Townsend deprivation index, smoking status, alcohol consumption status, body mass index (BMI) and physical activity were collected. The Townsend deprivation index is a composite measurement of deprivation based on unemployment, overcrowded household, non-car ownership and non-home ownership, with higher Townsend index scores indicating greater levels of deprivation.[29] The index was calculated using the preceding national census data prior to participants joining the UK Biobank. Physical activity was measured using the metabolic equivalent task (MET)-minutes based on items from the short International Physical Activity Questionnaire. In addition, height and weight were measured by trained nurses during the baseline assessment centre visit and BMI was calculated through dividing the weight in kilograms by the square of the height in metres. The history of hypertension, diabetes and respiratory diseases [chronic obstructive pulmonary disease (COPD) and emphysema] was based on self-report or medical records, or both. Information on medications use (cholesterol-lowering medication, blood

pressure medication, and insulin) was collected through a touchscreen question 'Do you regularly take any of the following medications?'.

Genotyping and genetic risk score

The genotyping process and arrays used in the UK Biobank study have been published elsewhere.[30] We calculated the genetic risk score (GRS) for lifespan based on previously reported genetic variants,[31] where 12 single-nucleotide polymorphisms (SNPs) were included. Details regarding the selected SNPs are provided in Supplementary Table S1 (available as Supplementary data at *IJE* online). In the analytical sample, we only included unrelated participants of European descent.[32] Finally, a total of 294 443 individuals were included to calculate lifespan GRS using a weighted method.[33] The number of risk alleles (0, 1 or 2) for each individual was summed after multiplication with the risk estimate (years of life) between the SNP and lifespan: weighted GRS = $(\beta_1 \times SNP_1 + \beta_2 \times SNP_2 + \ldots + \beta_n \times SNP_n) \times (N/\text{sum of the } \beta \text{ coefficients})$. The GRS for lifespan ranged from 4.5 to 22.7, with a higher GRS indicating increased years of life. Participants were classified into three groups of low (score of 16.0–22.7), intermediate (score of 14.2–15.9) and high (score of 4.5–14.1) genetic risk for lifespan.

Statistical analysis

Descriptive statistics for continuous variables are presented as mean [standard deviation (SD)], whereas categorical variables are presented as percentages. We coded missing data as a missing indicator category for categorical variables such as smoking status and with mean values for continuous variables.

Survival time for each participant was calculated as the duration from the response date of the baseline survey through to the death date or date of censoring, whichever came first. The Cox proportional hazard regression model was adopted to assess the association between air pollution and all-cause and cause-specific mortality. Hazard ratios (HRs) and 95% CIs were calculated for each 10 $\mu g/m^3$ increase in $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, NO_2 and NO_x. The multivariable models were adjusted for the potential confounding factors, namely, age, sex, race (White European, mixed, South Asian, Black, others), UK Biobank assessment centre, Townsend deprivation index, alcohol consumption status (current, former, never, missing), smoking status (current, former, never, missing), BMI (kg/m^2), physical activity (MET-minutes/week), HDS (0, 1, 2, 3, 4, 5), diabetes (yes/no) and hypertension (yes/no). In the genetic analysis, we further adjusted for genotyping batch and the first 10 genetic principal components.

We first conducted analyses to assess associations between air pollutants and mortality. To evaluate whether genetic predisposition to lifespan may modify the associations, we conducted a stratified analysis according to genetic susceptibility for lifespan and explored the potential gene–air pollution interactions on mortality risk. Then we tested the air pollution–healthy diet interaction by setting variable cross-product terms of air pollutants with the HDS in the models. When testing the interaction between the air pollution and individual dietary components, the models included other dietary components simultaneously.

We also conducted several sensitivity analyses to determine the robustness of our findings. First, we additionally adjusted for average total household income (<£18 000, £18 000–£30 999, £31 000–£51 999, £52 000–£100 000, >£100 000 and 'do not know' or missing) and education years of the participants. Second, we further adjusted for the history of medications use including antihypertensive medications (yes/no), insulin (yes/no) and cholesterol-lowering medications (yes/no) as well as respiratory diseases (yes/no) at baseline. In addition, we restricted the sample to participants with complete data. Furthermore, in order to evaluate the effect of red wine consumption in testing the effect modification of the healthy diet, we conducted a sensitivity analysis to additionally adjust for red wine consumption among current alcohol drinkers. Finally, since participants with a history of CVD might be more susceptible to air pollution exposures, we conducted a sensitivity analysis including participants with a history of CVD.

All analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA). All *P*-values for the tests were two-sided and P-values < 0.05 were considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of the participants are shown in Table 1. The mean age of participants eligible for the analysis was 56.1 ± 8.1 years. The proportion of males and females was 45.4% and 54.6%, respectively. Participants were mainly of White descent and current drinkers. In addition, the mean Townsend deprivation index of the participants was -1.4 ± 3.0. Only 10.1% of the participants were current smokers and the mean BMI and MET-minutes/week were 27.3 kg/m^2 and 2664.3 min. In total, 39.3 % of the participants had an ideal dietary pattern. The self-reported prevalence of hypertension, diabetes and emphysema/COPD was 25.9%, 4.7% and 1.6%,

respectively. In addition, mean ± SD estimates of $PM_{2.5}$, PM_{10}, $PM_{2.5–10}$, NO_2 and NO_x were 10.0 ± 1.1, 19.3 ± 1.9, 6.4 ± 0.9, 29.2 ± 9.2 and 43.8 ± 15.5 μg/m^3, respectively. $PM_{2.5}$, NO_2, NO_x and PM_{10} were positively correlated with each other (correlation coefficient = 0.64–0.85, $P<0.001$), as the highest correlation was observed between $PM_{2.5}$ and NO_x (correlation coefficient = 0.85) (Supplementary Table S2, available as Supplementary data at *IJE* online).

Table 1 Baseline characteristics of participants in the UK Biobank study

	Entire cohort ($N = 386\,937$)
Characteristics	
Age (years)	56.1 (8.1)
Sex, male (%)	45.4
Race, White (%)	94.4
Body mass index (kg/m^2)	27.3 (4.7)
Townsend deprivation index	−1.4 (3.0)
Current drinkers (%)	92.5
Current smokers (%)	10.1
MET (min/week)	2664.3 (2460.4)
Healthy diet score (%)	
0–1	11.9
2–3	48.8
4–5	39.3
Prevalent hypertension (%)	25.9
Prevalent diabetes (%)	4.7
Prevalent emphysema/COPD (%)	1.6
$PM_{2.5}$ (μg/m^3)	10.0 (1.1)
PM_{10} (μg/m^3)	19.3 (1.9)
$PM_{2.5–10}$ (μg/m^3)	6.4 (0.9)
NO_2 (μg/m^3)	29.2 (9.2)
NO_x (μg/m^3)	43.8 (15.5)

MET, metabolic equivalent task; COPD, chronic obstructive pulmonary disease; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm; $PM_{2.5–10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides.

Association between various air pollutants and mortality

During a median follow-up of 8.9 years (3 432 547 person-years), we identified 11 881 deaths among cohort participants, where 2426 deaths were attributed to CVD, 1211 deaths were attributed to CHD and 466 deaths were from stroke. The associations between each 10-μg/m^3 increase in various air pollutants and all-cause and cause-specific mortality are presented in Table 2. In the multivariable model adjusted for age, sex, race, UK Biobank assessment centre, Townsend deprivation index, alcohol consumption, smoking status, BMI, MET-minutes/week, HDS, diabetes and hypertension, we found that $PM_{2.5}$ (HR, 1.27; 95% CI, 1.05–1.55), PM_{10} (HR, 1.18; 95% CI, 1.04–1.34), NO_2 (HR, 1.05; 95% CI, 1.01–1.08) and NO_x (HR, 1.02; 95% CI, 1.01–1.03) were associated with all-cause mortality. In addition, we observed that exposure to $PM_{2.5}$ was associated with higher risks of CVD mortality (HR, 1.68; 95% CI, 1.10–2.56) and CHD mortality (HR, 2.08; 95% CI, 1.16–3.75). However, we did not find an association between air pollution and stroke mortality.

Effect modification by healthy dietary patterns and genetic susceptibility

We found effect modification of the air pollution–mortality associations by HDS, the indicator for adherence to healthy dietary patterns (Table 3). The associations of $PM_{2.5}$, NO_2 and NO_x with all-cause mortality were weaker among participants with higher HDS than those with lower HDS (P-interaction = 0.006, 0.006 and 0.02, respectively). However, no significant interaction of healthy dietary patterns with PM_{10} or $PM_{2.5–10}$ on all-cause mortality was observed (Supplementary Table S3, available as Supplementary data at *IJE* online). We further assessed the interaction between air pollutants and each dietary component separately on all-cause mortality. We found that vegetable intakes showed an interaction with $PM_{2.5}$ (P-interaction = 0.007), NO_2 (P-interaction = 0.004)

Table 2 Adjusted HRs and 95% CIs for a 10-μg/m^3 increase in air pollution concentrations with risk of all-cause and cause-specific mortality in the UK Biobank study

Cause of death	Deaths	$PM_{2.5}$	PM_{10}	$PM_{2.5–10}$	NO_2	NO_x
All-cause	11 881	1.27 (1.05–1.55)	1.18 (1.04–1.34)	1.02 (0.83–1.25)	1.05 (1.01–1.08)	1.02 (1.01–1.03)
Cardiovascular disease	2426	1.68 (1.10–2.56)	1.13 (0.85–1.50)	1.16 (0.74–1.81)	1.04 (0.97–1.11)	1.03 (1.00–1.05)
Coronary heart disease	1211	2.08 (1.16–3.75)	1.35 (0.90–2.03)	1.41 (0.75–2.62)	1.08 (0.99–1.19)	1.04 (1.00–1.08)
Stroke	466	0.66 (0.25–1.78)	0.79 (0.42–1.51)	0.67 (0.23–1.93)	0.97 (0.83–1.12)	0.96 (0.89–1.03)

Adjusted for age, sex, race (White European, mixed, South Asian, Black, others), UK Biobank assessment centre, Townsend deprivation index, alcohol consumption status (current, former, never, missing), smoking status (current, former, never, missing), body mass index (kg/m^2), physical activity (metabolic equivalent task-minutes/week), healthy diet score (0, 1, 2, 3, 4, 5), diabetes (yes/no) and hypertension (yes/no). HR, hazard ratio; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm, PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm; $PM_{2.5–10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides.

Table 3 The HRs and 95% CIs of $PM_{2.5}$, NO_2 and NO_x with all-cause mortality, stratified by healthy dietary patterns in the UK Biobank study

	Air pollution concentrations (quintiles)					
	Q1	Q2	Q3	Q4	Q5	*P*-interaction
$PM_{2.5}$						0.006
Poor dietary pattern	1.00	1.00 (0.85–1.17)	1.02 (0.87–1.21)	1.00 (0.85–1.18)	1.12 (0.95–1.33)	
Medium dietary pattern	1.00	1.06 (0.98–1.16)	1.04 (0.96–1.13)	1.11 (1.02–1.20)	1.09 (1.00–1.20)	
Ideal dietary pattern	1.00	1.05 (0.95–1.16)	1.04 (0.94–1.15)	1.04 (0.94–1.15)	1.07 (0.96–1.19)	
NO_2						0.006
Poor dietary pattern	1.00	1.00 (0.85–1.18)	1.06 (0.90–1.24)	1.13 (0.96–1.34)	1.15 (0.94–1.40)	
Medium dietary pattern	1.00	1.03 (0.94–1.12)	1.07 (0.99–1.17)	1.12 (1.02–1.22)	1.18 (1.06–1.31)	
Ideal dietary pattern	1.00	1.06 (0.96–1.17)	1.06 (0.96–1.17)	1.07 (0.96–1.19)	1.13 (0.99–1.29)	
NO_x						0.02
Poor dietary pattern	1.00	1.02 (0.87–1.20)	1.03 (0.87–1.21)	1.00 (0.84–1.18)	1.10 (0.93–1.31)	
Medium dietary pattern	1.00	1.03 (0.94–1.12)	1.08 (0.99–1.18)	1.05 (0.97–1.15)	1.13 (1.03–1.24)	
Ideal dietary pattern	1.00	1.01 (0.92–1.12)	1.09 (0.99–1.21)	1.07 (0.97–1.19)	1.08 (0.96–1.20)	

Adjusted for age, sex, race (White European, mixed, South Asian, Black, others), UK Biobank assessment centre, Townsend deprivation index, alcohol consumption status (current, former, never, missing), smoking status (current, former, never, missing), body mass index (kg/m^2), physical activity (metabolic equivalent task-minutes/week), diabetes (yes/no) and hypertension (yes/no). HR, hazard ratio; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides.

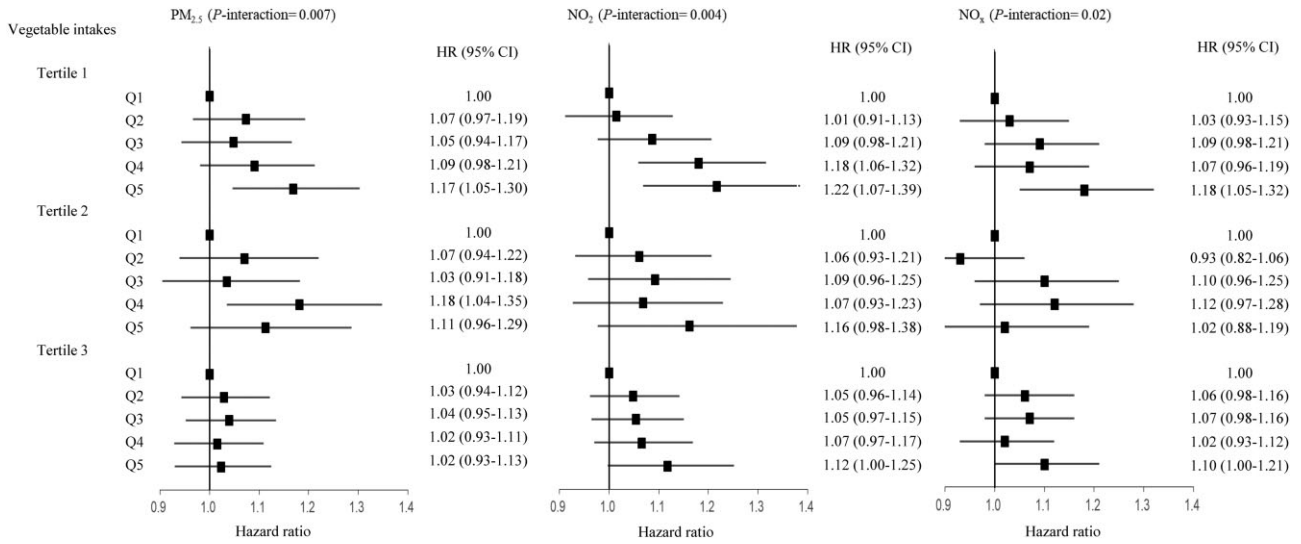

Figure 1 The associations of particulate matter with diameters of ≤2.5 μm, nitrogen dioxide and nitrogen oxides (in quintiles) with all-cause mortality stratified by vegetable intakes (tertiles). Multivariable model was adjusted for age, sex, race (White European, mixed, South Asian, Black, others), UK Biobank assessment centre, Townsend deprivation index, alcohol consumption (current, former, never, missing), smoking status (current, former, never, missing), body mass index (kg/m^2), physical activity (metabolic equivalent task-minutes/week), diabetes (yes/no), hypertension (yes/no) and intakes of fruits, unprocessed red meat, fish and processed meat

and NO_x (*P*-interaction = 0.02) (Figure 1). The HR of the highest quintile vs the lowest quintile of $PM_{2.5}$ for all-cause mortality was 1.17 (1.05–1.30) among participants with low vegetable intakes, 1.11 (0.96–1.29) for participants with medium vegetable intakes and 1.02 (0.93–1.13) for participants with high vegetable intakes. The corresponding HRs were 1.22 (1.07–1.39), 1.16 (0.98–1.38) and 1.12 (1.00–1.25) for NO_2; and 1.18 (1.05–1.32), 1.02 (0.88–1.19) and 1.10 (1.00–1.21) for NO_x. The interactions between air pollutants and other dietary components were not statistically significant. Besides, we did not observe interactions between air pollutants and HDS with CVD, CHD or stroke mortality (Supplementary Table S4, available as Supplementary data at *IJE* online).

In order to evaluate the effect modification of genetic susceptibility, we first assessed the association between

lifespan GRS and mortality risk. In the models adjusting for sex, age, assessment centre, genotyping batch and the first 10 genetic principal components, we observed associations of lifespan GRS with all-cause mortality (HR, 0.96; 95% CI, 0.93–0.98; $P < 0.001$), CVD mortality (HR, 0.91; 95% CI, 0.87–0.96; $P < 0.001$) and CHD mortality (HR, 0.86; 95% CI, 0.80–0.93; $P < 0.001$) but not with stroke mortality (HR, 0.99; 95% CI, 0.87–1.12; $P = 0.83$). In addition, the associations between air pollution and mortality stratified by genetic risk of lifespan are shown in Supplementary Table S5 (available as Supplementary data at *IJE* online). We did not find statistically significant interactions between air pollutants and genetic susceptibility of lifespan on mortality risk (all P for interaction > 0.05).

Sensitivity analyses

The results were robust after further adjustment for average total household income and education levels (Supplementary Table S6, available as Supplementary data at *IJE* online) or additional adjustment for antihypertensive medications use, insulin use, cholesterol-lowering medications use and history of respiratory diseases at baseline (Supplementary Table S7, available as Supplementary data at *IJE* online). Also, the sensitivity analysis only including participants with complete data did not change the results appreciably (Supplementary Table S8, available as Supplementary data at *IJE* online). In addition, the results did not alter appreciably when including participants with a history of CVD (Supplementary Table S9, available as Supplementary data at *IJE* online) or additionally adjusting for red wine consumption among current alcohol drinkers (Supplementary Table S10, available as Supplementary data at *IJE* online). In order to explore the role of potential confounders in the interaction between air pollution and healthy dietary patterns, we first described the baseline characteristics of participants according to the HDS in Supplementary Table S11 (available as Supplementary data at *IJE* online). To minimize the potential influence of the correlated variables on the associations, we had carefully adjusted for these variables (educational years, BMI, etc.) in the analyses. We also assessed the interaction between air pollution and the HDS in subgroups stratified by BMI (<30 vs $\geq 30\,kg/m^2$) or years of education (<15 vs ≥ 15 years). The results showed that the interaction between air pollution and the HDS was more evident among participants with lower BMI or higher educational years (Supplementary Table S12, available as Supplementary data at *IJE* online).

Discussion

In this prospective cohort study, we observed associations of $PM_{2.5}$, PM_{10}, NO_2 and NO_x with all-cause mortality. Exposure to $PM_{2.5}$ might be also associated with elevations in risk for CVD and CHD mortality. Such associations were not modified by the lifespan GRS based on 12 SNPs. In addition, we found that healthy dietary patterns might modify the associations of $PM_{2.5}$, NO_2 and NO_x with all-cause mortality, as lower HRs were found among participants with higher HDS. Among the individual dietary components, vegetable intakes showed the strongest modification effect. The associations between air pollutants and increased risks of all-cause mortality appeared be attenuated among participants with higher vegetable intakes.

As the main air pollutant contributing to the global public health burden, $PM_{2.5}$, has been associated with life-threatening risk in numerous epidemiologic studies.[34,35] In the current analysis, we observed a robust association between $PM_{2.5}$ and mortality after controlling for smoking and other covariates. We found that a per $\mu g/m^3$ elevation in $PM_{2.5}$ was associated with a 2% higher all-cause mortality risk, which was generally comparable with the estimates from previous investigations.[5,10,34] We further observed that the associations of $PM_{2.5}$ with CVD and CHD mortality were more marked compared with all-cause mortality, in concordance with several previous studies.[36,37] However, we did not find an association between long-term exposure to $PM_{2.5}$ and stroke mortality. The observed associations between $PM_{2.5}$ and stroke mortality are inconsistent across different studies.[38–40] Such discrepancy may be partly due to different stroke subtypes or sex differences.[40,41] The number of stroke deaths was far lower than CHD deaths in the current analysis, somewhat limiting the power to detect the association, if any, between $PM_{2.5}$ and risk of stroke mortality.

In addition, we observed that PM_{10}, NO_2 and NO_x were associated with all-cause mortality. Such observations are in line with several prospective studies.[42,43] The association between $PM_{2.5–10}$ and mortality is inconsistent across previous investigations[44] and we found a non-significant association in the current analysis. Besides, findings from previous studies on PM_{10}, $PM_{2.5–10}$, NO_2 and NO_x with CVD mortality have been heterogeneous,[45–47] possibly because of variations in confounding factors and the spatial resolution of air pollution concentrations across different studies. Furthermore, the previous studies were generally in support of high risks of CVD mortality associated with these air pollutants and we also observed elevated risks of CVD and CHD mortality with higher

exposures to PM_{10}, $PM_{2.5–10}$, NO_2 and NO_x even though the associations were not statistically significant.

Intriguingly, we observed that healthy dietary patterns modified the associations of $PM_{2.5}$, NO_2 and NO_x with all-cause mortality, as mortality risks attributable to these air pollutants were mitigated among those with healthier dietary patterns, characterized by higher HDS. In addition, among individual dietary components, we found that vegetable intakes showed interactions with $PM_{2.5}$, NO_2 and NO_x on all-cause mortality. Alleviated associations of these air pollutants with all-cause mortality were observed among participants with higher vegetable intakes compared with lower vegetable intakes. Our findings add novel data to the growing evidence of the modification effects of dietary factors on the relations of air pollutants and human health.[14,48,49] Notably, we found that the interactions between air pollutants and the HDS were more pronounced among participants with lower BMI or higher educational years, which could be partially explained by the fact that individuals with lower BMI or higher years of education were more likely to have a higher HDS. Despite being carefully adjusted for in the analyses, the role of these confounders in the interaction between air pollution and the HDS on mortality risk should be explored further. However, we did not find an interaction between air pollution and HDS with CVD, CHD or stroke mortality. The negative results might be partly due to limited CVD, CHD or stroke deaths in the study.

Our findings on the interactions of healthy dietary patterns, especially high vegetable intakes, with air pollution are biologically plausible. The healthy dietary pattern is rich in foods and nutrients that promote antioxidative and anti-inflammatory activities. Antioxidants such as vitamins and carotenoids in vegetables and fruit as well as omega-3 polyunsaturated fatty acids from fish oil play an important role in limiting oxidative and inflammatory damage.[15,50] Long-term exposure to air pollution may adversely affect human health mainly through activating pathways mediating oxidative stress and inflammation, which lead to a variety of life-threatening impairments including systemic endothelial dysfunction, thrombosis pathways, autonomic imbalance and atherosclerosis progression.[4,51] Thus, we assumed that the attenuated associations of $PM_{2.5}$, NO_2 and NO_x with all-cause mortality among participants with healthy dietary patterns might be partly through antioxidant and anti-inflammatory components in healthy diets. Such a postulation is supported by multiple intervention studies that illustrated the attenuated risk of the adverse health effects of air pollution from intakes of specific dietary supplements with antioxidant and anti-inflammatory effects.[15–17,52,53] For example, an intervention study showed supplementation of olive oil could ameliorate the short-term adverse vascular effect of concentrated PM while altering blood markers associated with vasoconstriction and fibrinolysis.[17] Of note, vegetable intakes are well known for being rich in antioxidants including vitamin C and vitamin E. A previous study showed that a 6-month vitamin C and E supplementation decreased several biomarkers of oxidative stress and protected against the oxidative insult associated with PM exposure derived from a coal electric-power plant.[53] In addition, the airway hyper-responsiveness induced by NO_2 may be prevented by supplementation with vitamin C in healthy patients.[54]

Previous studies have suggested that genetic susceptibility may modify the relations between environmental factors and human health outcomes;[18,19] however, we did not observe an interaction between air pollution and genetic variations for lifespan on mortality risk. The GRS of the lifespan was calculated based on genetic variants that constituted only a small proportion of the variation seen in the human lifespan; this may partly explain the null interaction between the genetic score and air pollution on mortality risk.

Strengths and limitations

The strengths of this study include a large sample size, measurements of air pollutants using reliable prediction models and uniform information on detailed individual-level dietary intakes and other risk factors, which increased the precision of the effect estimates. Furthermore, the information on a wide range of air pollutants is available in the UK Biobank study, which enabled us to assess the association between air pollution and mortality risk comprehensively. However, there are also several potential limitations to be addressed. First, the number of deaths, especially for the mortality of stroke, was relatively low for stratified analyses. Second, air pollution levels were linked to participants' home addresses, whereas individual activities such as time spent at home or in traffic were not considered, which might lead to exposure measurement errors. Third, since air pollution data were not available during follow-up in UK Biobank, the association between long-term exposure to air pollution and mortality risk would be interpreted with caution. Further studies with long-term repeated measurements are needed to validate the findings. Fourth, the dietary information in the UK Biobank study was self-reported and relatively simple, so the HDS might not exactly reflect overall healthy dietary behaviours. Furthermore, only a single dietary assessment was available at baseline and the changes in diet over the follow-up period were not evaluated. Future studies with expanded and repeated information on dietary intakes would be warranted to confirm the modification effect. Fifth, although

multiple covariates were controlled, we could not exclude the possibility of residual confounding existing. In addition, we could not determine the causality of our findings due to the observational design of the study. Further clinical trials are needed to assess whether the observed associations are causal. Furthermore, only 12 SNPs were included in calculating the lifespan GRS, which might not reflect the variation in the human lifespan. Therefore, our findings should be confirmed in future studies. In addition, only 294 443 individuals of European descent were included for assessing the effect modification by genetic susceptibility of the air pollution–mortality associations; further studies are needed to investigate the genetic modification in other ethnic/racial groups. Finally, most of the participants were of European descent in the present study, thus the generalization of the results to other populations should be interpreted with caution.

Conclusions

In this prospective study, our results suggest that long-term exposure to ambient air pollution might be associated with the risk of all-cause, CVD and CHD mortality. Our study provides evidence to support the potential modification effects of dietary intakes, with vegetable intakes being the main contributor, in lowering the risk of premature deaths related to ambient air pollution. Our findings highlight the importance of adherence to a healthy diet in lowering ambient air-pollution-related mortality risk. Further intervention studies are warranted to validate our findings.

Ethics approval

Ethical approval was obtained from National Health Service National Research Ethics Service (Ref: 11/NW/0382).

Data availability

This research has been conducted using the public UK Biobank resource.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

M.W. and L.Q. conceived of and designed the study, interpreted the data and drafted and critically revised the manuscript. M.W. and T.Z. performed the statistical analysis. All authors contributed to the interpretation of the results and critical revision of the manuscript. All authors approved the final manuscript.

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Conflict of interest

None declared.

References

1. Cohen AJ, Brauer M, Burnett R *et al.* Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017;**389**:1907–18.
2. Landrigan PJ, Fuller R, Acosta NJR *et al.* The Lancet Commission on pollution and health. *Lancet* 2018;**391**: 462–512.
3. World Health Organization. 9 Out of 10 People Worldwide Breathe Polluted Air, But More Countries Are Taking Action. Geneva, 2018. https://www.who.int/news-room/detail/02-05-2018-9-out-of-10-people-worldwide-breathe-polluted-air-but-more-countries-are-taking-action. (9 March 2021, date last accessed).
4. Rajagopalan S, Al-Kindi SG, Brook RD. Air pollution and cardiovascular disease: JACC state-of-the-art review. *J Am Coll Cardiol* 2018;**72**:2054–70.
5. Li T, Zhang Y, Wang J *et al.* All-cause mortality risk associated with long-term exposure to ambient PM2.5 in China: a cohort study. *Lancet Public Health* 2018;**3**:e470–77.
6. Yin P, Brauer M, Cohen A *et al.* Long-term fine particulate matter exposure and nonaccidental and cause-specific mortality in a large national cohort of Chinese men. *Environ Health Perspect* 2017;**125**:117002.
7. Pope CA 3rd, Lefler JS, Ezzati M *et al.* Mortality risk and fine particulate air pollution in a large, representative cohort of U.S. adults. *Environ Health Perspect* 2019;**127**:77007.
8. Di Q, Dominici F, Schwartz JD. Air pollution and mortality in the Medicare population. *N Engl J Med* 2017;**377**:1498–99.
9. Pinault L, Tjepkema M, Crouse DL *et al.* Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian community health survey cohort. *Environ Health* 2016;**15**:18.
10. Beelen R, Raaschou-Nielsen O, Stafoggia M *et al.* Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. *Lancet* 2014;**383**:785–95.

11. Klompmaker JO, Janssen NAH, Bloemsma LD *et al.* Effects of exposure to surrounding green, air pollution and traffic noise with non-accidental and cause-specific mortality in the Dutch national cohort. *Environ Health* 2021;**20**:82.
12. Hvidtfeldt UA, Sorensen M, Geels C *et al.* Long-term residential exposure to PM2.5, PM10, black carbon, NO2, and ozone and mortality in a Danish cohort. *Environ Int* 2019;**123**:265–72.
13. Kim H, Byun G, Choi Y, Kim S, Kim SY, Lee JT. Effects of long-term exposure to air pollution on all-cause mortality and cause-specific mortality in seven major cities of South Korea: Korean national health and nutritional examination surveys with mortality follow-up. *Environ Res* 2021;**192**:110290.
14. Lim CC, Hayes RB, Ahn J *et al.* Mediterranean diet and the association between air pollution and cardiovascular disease mortality risk. *Circulation* 2019;**139**:1766–75.
15. Peter S, Holguin F, Wood LG *et al.* Nutritional solutions to reduce risks of negative health impacts of air pollution. *Nutrients* 2015;**7**:10398–416.
16. Tong H. Dietary and pharmacological intervention to mitigate the cardiopulmonary effects of air pollution toxicity. *Biochim Biophys Acta* 2016;**1860**:2891–98.
17. Tong H, Rappold AG, Caughey M *et al.* Dietary supplementation with olive oil or fish oil and vascular effects of concentrated ambient particulate matter exposure in human volunteers. *Environ Health Perspect* 2015;**123**:1173–79.
18. Ward-Caviness CK. A review of gene-by-air pollution interactions for cardiovascular disease, risk factors, and biomarkers. *Hum Genet* 2019;**138**:547–61.
19. Fave MJ, Lamaze FC, Soave D *et al.* Gene-by-environment interactions in urban populations modulate risk phenotypes. *Nat Commun* 2018;**9**:827.
20. Sudlow C, Gallacher J, Allen N *et al.* UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015;**12**:e1001779.
21. Fry A, Littlejohns TJ, Sudlow C *et al.* Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. *Am J Epidemiol* 2017;**186**:1026–34.
22. Eeftens M, Beelen R, de Hoogh K *et al.* Development of land use regression models for PM(2.5), PM(2.5) absorbance, PM(10) and PM(coarse) in 20 European study areas: results of the ESCAPE project. *Environ Sci Technol* 2012;**46**:11195–205.
23. Beelen R, Hoek G, Vienneau D *et al.* Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in Europe—the ESCAPE project. *Atmos Environ* 2013;**72**:10–23.
24. Aung N, Sanghvi MM, Zemrak F *et al.* Association between ambient air pollution and cardiac morpho-functional phenotypes insights from the UK biobank population imaging study. *Circulation* 2018;**138**:2175–86.
25. Doiron D, de Hoogh K, Probst-Hensch N *et al.* Air pollution, lung function and COPD: results from the population-based UK Biobank study. *Eur Respir J* 2019;**54**:1802140.
26. Bradbury KE, Young HJ, Guo W, Key TJ. Dietary assessment in UK Biobank: an evaluation of the performance of the touchscreen dietary questionnaire. *J Nutr Sci* 2018;**7**:e6.
27. Pazoki R, Dehghan A, Evangelou E *et al.* Genetic predisposition to high blood pressure and lifestyle factors: associations with midlife blood pressure levels and cardiovascular events. *Circulation* 2018;**137**:653–61.
28. Lloyd-Jones DM, Hong Y, Labarthe D *et al.* Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation* 2010;**121**:586–613.
29. Adams J, Ryan V, White M. How accurate are Townsend Deprivation Scores as predictors of self-reported health? A comparison with individual level data. *J Public Health (Oxf)* 2005;**27**:101–06.
30. Bycroft C, Freeman C, Petkova D, *et al.* Genome-wide genetic data on ~500,000 UK Biobank participants. bioRxiv; doi:10.1101/166298, 20 July 2017, preprint: not peer reviewed.
31. Timmers PR, Mounier N, Lall K *et al.*; eQTLGen Consortium. Genomics of 1 million parent lifespans implicates novel pathways and common diseases and distinguishes survival chances. *Elife* 2019;**8**:e39856.
32. Said MA, Verweij N, van der Harst P. Associations of combined genetic and lifestyle risks with incident cardiovascular disease and diabetes in the UK biobank study. *JAMA Cardiol* 2018;**3**:693–702.
33. Ripatti S, Tikkanen E, Orho-Melander M *et al.* A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. *Lancet* 2010;**376**:1393–400.
34. Dockery DW, Pope CA 3rd, Xu X *et al.* An association between air pollution and mortality in six U.S. cities. *N Engl J Med* 1993;**329**:1753–59.
35. Vodonos A, Awad YA, Schwartz J. The concentration-response between long-term PM2.5 exposure and mortality; a meta-regression approach. *Environ Res* 2018;**166**:677–89.
36. Pinault LL, Weichenthal S, Crouse DL *et al.* Associations between fine particulate matter and mortality in the 2001 Canadian Census Health and Environment Cohort. *Environ Res* 2017;**159**:406–15.
37. Lepeule J, Laden F, Dockery D, Schwartz J. Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. *Environ Health Perspect* 2012;**120**:965–70.
38. Cesaroni G, Badaloni C, Gariazzo C *et al.* Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. *Environ Health Perspect* 2013;**121**:324–31.
39. Pope CA 3rd, Burnett RT, Thurston GD *et al.* Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004;**109**:71–77.
40. Hoek G, Krishnan RM, Beelen R *et al.* Long-term air pollution exposure and cardio- respiratory mortality: a review. *Environ Health* 2013;**12**:43.
41. Yuan S, Wang J, Jiang Q *et al.* Long-term exposure to PM2.5 and stroke: a systematic review and meta-analysis of cohort studies. *Environ Res* 2019;**177**:108587.
42. Fischer PH, Marra M, Ameling CB *et al.* Air pollution and mortality in seven million adults: the Dutch Environmental Longitudinal Study (DUELS). *Environ Health Perspect* 2015;**123**:697–704.
43. Heinrich J, Thiering E, Rzehak P *et al.* Long-term exposure to NO2 and PM10 and all-cause and cause-specific mortality in a

prospective cohort of women. *Occup Environ Med* 2013;**70**: 179–86.

44. Adar SD, Filigrana PA, Clements N, Peel JL. Ambient coarse particulate matter and human health: a systematic review and meta-analysis. *Curr Environ Health Rep* 2014;**1**:258–74.
45. Atkinson RW, Butland BK, Anderson HR, Maynard RL. Long-term concentrations of nitrogen dioxide and mortality: a meta-analysis of cohort studies. *Epidemiology* 2018;**29**:460–72.
46. Dehbi HM, Blangiardo M, Gulliver J *et al.* Air pollution and cardiovascular mortality with over 25 years follow-up: a combined analysis of two British cohorts. *Environ Int* 2017;**99**: 275–81.
47. Beelen R, Stafoggia M, Raaschou-Nielsen O *et al.* Long-term exposure to air pollution and cardiovascular mortality: an analysis of 22 European cohorts. *Epidemiology* 2014;**25**:368–78.
48. Lim CC, Hayes RB, Ahn J *et al.* Association between long-term exposure to ambient air pollution and diabetes mortality in the US. *Environ Res* 2018;**165**:330–36.
49. Raaschou-Nielsen O, Andersen ZJ, Jensen SS *et al.* Traffic air pollution and mortality from cardiovascular disease and all causes: a Danish cohort study. *Environ Health* 2012;**11**:60.
50. Galland L. Diet and inflammation. *Nutr Clin Pract* 2010;**25**:634–40.
51. Brook RD, Rajagopalan S, Pope CA 3rd *et al.* Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation* 2010;**121**:2331–78.
52. Romieu I, Tellez-Rojo MM, Lazo M *et al.* Omega-3 fatty acid prevents heart rate variability reductions associated with particulate matter. *Am J Respir Crit Care Med* 2005;**172**:1534–40.
53. Possamai FP, Junior SA, Parisotto EB *et al.* Antioxidant intervention compensates oxidative stress in blood of subjects exposed to emissions from a coal electric-power plant in South Brazil. *Environ Toxicol Pharmacol* 2010;**30**:175–80.
54. Mohsenin V. Effect of vitamin C on NO2-induced airway hyperresponsiveness in normal subjects: a randomized double-blind experiment. *Am Rev Respir Dis* 1987;**136**:1408–11.