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Article

Exposure–Response Associations of Ambient Heavy Metal and Persistent Organic Pollutant with All-Cause and Cause-Specific Mortality: A Prospective Cohort Study

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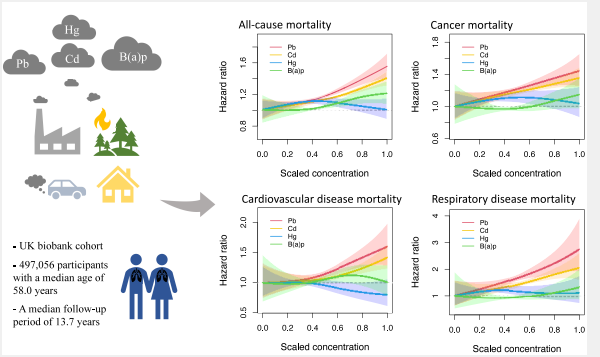
ABSTRACT: The exposure–response associations of ambient heavy metals and persistent organic pollutants (POPs) with mortality in the general population remain unclear. This cohort study aimed to explore the long-term effect of exposure to four air pollutants, including lead (Pb), cadmium (Cd), mercury (Hg), and benzo(a)pyrene [B(a)P] on all-cause and cause-specific mortality. This study involved 497,056 participants from the UK Biobank cohort. We used the Cox proportional hazards model to calculate associations. Effects of joint exposure to heavy metals were estimated using quantile g-computation. Shape of the exposure–response association was examined by fitting penalty splines, in both the total population and subpopulations stratified by age, sex, smoking status, and genetic factors. Modifying effects of age, sex, smoking status, and genetic factors were also examined. Over a median follow-up of 13.7 years, we identified 39,530 (8.0%) deaths. Exposure to mixtures of Pb, Cd, and Hg was associated with 1.040–1.154 times increased risk of all-cause cancer, cardiovascular disease (CVD), stroke, and respiratory disease mortality. Of the specific causes of mortality, Pb and Cd were most strongly associated with respiratory diseases, including chronic obstructive pulmonary disease, followed by ischemic heart disease, CVD, and cancer. Hg and B(a)P seemed to exhibit lower toxicity compared with Pb and Cd. Exposure–response curves demonstrated monotonically increased risk for most mortality outcomes, though Hg was found to be nonlinearly associated with all-cause and stroke mortality. Age, smoking status, and genetic factors were found to modify the susceptibility to heavy metals. Our findings suggested that long-term exposure to heavy metals and B(a)P was monotonically associated with elevated risk of multiple mortality outcomes, indicating there may be no safe threshold for these chemicals. Substantial benefits to public health could be achieved through stringent environmental regulations and clean air initiatives.



KEYWORDS: *heavy metal, persistent organic pollutants, mortality, exposure–response function*

INTRODUCTION

The escalating industrialization and technological globalization have led to a substantial increase in the production and release of a myriad of chemicals into the environment.[1] Among the various chemicals, heavy metals and persistent organic pollutants (POPs) are of greater public health concern given their multiorgan toxicity, carcinogenicity, persistent and nondegradable nature, and the ability of long-range transport and biomagnification in food chains.[2−4] Despite the ban enacted in the Stockholm Convention in 2001, POPs remain a critical concern for global health. For example, it was estimated that 66% of the European population was exposed to benzo(a)pyrene [B(a)P] concentrations exceeding the WHO tolerable risk level (0.12 ng/m^3) in 2020.[5] Heavy metal, as a byproduct of rapid industrialization and increased vehicular traffic, has also proliferated globally, particularly in developing economies.[6]

Many epidemiological studies have linked chronic exposure to heavy metals and POPs, whether intended or unintended, to a wide range of adverse health effects including cancer, cardiovascular disease (CVD), respiratory disease, and mortality,[3,6−8] with possible mechanisms including generation of reactive oxygen species, DNA damage, epigenetic modifications, and activation of receptor pathways (e.g., aryl hydrocarbon receptor).[1,2,9] However, significant gaps in knowledge still remain. First, previous studies have predominantly investigated internal biomarkers in bodily fluids (urinary, blood, and adipose tissue)[7,10,11] or external estimations from diet, water, and soil samples.[12−14] However, the exploration of exposure through inhalation has been less comprehensive.

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Such data insufficiency is especially critical when considering the distinct health risks posed by inhaled heavy metals and POPs, and it complicates the characterization of exposure−response relationships and the refinement of air quality standards. Moreover, some biomarkers are more indicative of recent exposure, potentially obscuring the chronic effects of these substances.[15,16] Second, few studies investigated the modifying effects of other factors, such as lifestyle and genetics, providing little evidence for identifying susceptible populations and design of precision intervention strategies.

In this article, we aimed to address current gaps by directly linking ambient heavy metals and POPs to all-cause and cause-specific mortality within a large-scale British cohort. We also examined the exposure−response relationships in both the total and subpopulations stratified by demographic, lifestyle, and genetic factors.

MATERIALS AND METHODS

Study Population

A subset of 497,056 participants from the UK biobank was included in the study (see Supplementary methods for detailed description of the UK biobank in Supporting Information). Exclusions were made for 2578 participants who died of external causes (ICD-codes: S00-Z99), 2511 with a follow-up period ≤2 years, and 224 with missing data on home location or air pollutants (Supporting Information: Figure S1). The follow-up period was defined from the date the participants attended the assessment center to the date of death or loss of follow-up, or on the censor dates for mortality data defined by the UK biobank (30 November 2022), whichever came earlier.

Ambient Air Pollution

Annual average concentration data on Pb, Cd, Hg, and B(a)P in 2004−2010 were obtained from the co-operative program for monitoring and evaluation of the long-range transmission of air pollutants in Europe (also known as "European Monitoring and Evaluation Programme", EMEP, https://emep.int/, Figures S2−S5 in Supporting Information). We selected these four chemicals primarily due to data availability. Meanwhile, Pb, Cd, and Hg were among the three particularly harmful metals according to the United Nations Economic Commission for Europe (UNECE) Convention;[5] B(a)P is an important marker of polycyclic aromatic hydrocarbons (PAHs) mixtures and has been commonly found in the air.[2,17] EMEP is a scientifically based and policy-driven program under the Convention on Long-range Transboundary Air Pollution (CLRTAP) for international cooperation to solve transboundary air pollution problems. By incorporating emission (both regional and global), meteorological, and geophysical (e.g., land cover) data, concentrations on heavy metals and B(a)Ps were modeled using the Global EMEP Multi-Media Modeling System model by the Meteorological Synthesizing Centre-East.[5] In contrast to other heavy metals (Pb and Cd) that are bound to aerosol particles, Hg is present in the atmosphere mainly in the gaseous elemental form (Hg^0).[5] We therefore focused on Hg^0 in the surface layer in this study. For B(a)P, it was in both the gaseous and particulate phase, with the particulate phase being the dominant one.[5]

Outcome Assessment

Mortality information including dates and primary underlying causes of death was extracted from the death registry data (under Category 100093 in the UK biobank). The underlying causes of death were determined by the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). In this study, mortality outcomes included all nonaccidental causes [later referred to as all-cause] (A00-R99), cancer (C00−C97), lung cancer (C34), colorectal cancer (CRC, C18−C20), CVD (I00−I99), ischemic heart disease (IHD, I20−I25), stroke (I60−I64), respiratory disease (J00-J99), chronic obstructive pulmonary disease (COPD, J41-J44), nervous system disease (G00-G99), and Alzheimer's disease (AD, G30). Cancer, CVD, and respiratory and nervous system diseases were the four leading causes of deaths among the cohort (http://www.ukbiobank.ac.uk/), with lung cancer, CRC, IHD, stroke, COPD, and AD as the leading causes within each category.

Covariates

Potential confounding covariates included age, sex, annual household income, region, current employment status, qualifications, ethnicity, activity intensity, smoking, drinking, body mass index, and diet quality (see details in Supplementary methods of Supporting Information). Beyond the 12 covariates, we additionally adjusted for genetic risks associated with five mortality outcomes—CVD, IHD, stroke, CRC, and AD—by utilizing the standard polygenic risk scores (PRS) for CVD, coronary artery disease, ischemic stroke, bowel cancer, and AD provided by the UK biobank (see detailed description of PRS calculation in **Supplementary methods** of Supporting Information).[18]

Statistical model

The Cox proportional hazards model was used to estimate associations. The assessment center entered the model as a strata variable. We used a 3-year average air pollution level in the baseline year and two prior years as the main exposure. For example, if a participant was enrolled in 2006, then long-term exposure was defined as the average concentrations of 2004−2006. Air pollution data were aligned with participants' health records by the geographical coordinates of their residential addresses at enrollment. Participants' residential places have a resolution of 1 km, and we used the air pollution concentration in the nearest grid to represent their exposure. We acknowledge that using residential address-based concentrations to estimate individual exposure may introduce some bias (e.g., exposure misclassification), but this approach is commonly used in large-scale epidemiological studies due to its feasibility. To minimize potential exposure misclassification, we conducted a sensitivity analysis where we averaged air pollutant concentrations across four grid cells (approximately a 15 km radius) surrounding each participant's residential address (see Supplementary Methods in the Supporting Information). To address missing data for continuous covariates, we introduced a dummy variable to delineate participants with data from those without data. For categorical covariates with missing data, we established a "Missing" category. Hazard ratios (HRs) and 95% confidence intervals (CIs) associated with every interquartile range (IQR) increase in air pollutant measures, which represented an overall effect, were reported to allow for better comparisons with previous studies. We trimmed the data at 1%−99% percentiles of each air pollutant to reduce the bias to HRs from the scarce data at the two extremes. Exposure−response associations between long-term exposure and mortality were depicted by fitting a penalized spline with 2 degrees of freedom (df). For the heavy metal, we also analyzed the joint effect of Pd, Cd, and Hg by using the quantile g-computation.[19] This method offers a sophisticated analytical framework for estimating the joint impact of incrementing all of the exposure levels by one quantile.

To ensure the robustness of the estimated HRs, we performed four sensitivity analyses for both all-cause and cause-specific mortality (see details in Supplementary methods of Supporting Information).We also performed three subgroup analyses for all-cause mortality only according to age (<median of 58 years and ≥58 years), sex (female and male), and smoking status (recategorized to binary: nonsmoking and smoking, with the latter including previous and current smokers). For the five specific mortality outcomes—CRC, CVD, IHD, stroke, and AD—we also performed subgroup analyses by genetic risk (i.e., low, medium, and high PRS). For all subgroup analyses, statistically significant differences were tested based on the likelihood ratio tests comparing models with and without the cross-product multiplicative interaction term.

R version 3.6.3 (R Foundation for Statistical Computing) was used in all statistical models. Cox regression models and penalized splines were constructed using the "survival" package. Quantile g-computation in a survival setting was fitted using the "qgcomp" package. A two-sided p value <0.05 was regarded as statistically significant.

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RESULTS

Participants Characteristics

The cohort (n = 497,056) had a median age of 58.0 years at enrollment and consisted of 45.4% males, predominantly white adults (94.1%), and a larger proportion of urban residents (85.3%, Table 1). Median 3-year average concentrations of Pb, Cd, Hg, and B(a)P at baseline were 8.50 (IQR: 3.96) ng/m^3, 0.16 (IQR: 0.05) ng/m^3, 1.67 (IQR: 0.03) ng/m^3, and 0.07 (IQR: 0.01) ng/m^3, respectively. Three of the four air pollutants including Pb, Cd, and B(a)P showed high correlation (Spearman correlation coefficient > 0.6), whereas Hg had a smaller correlation with other air pollutants (Supporting Information: Figure S6).

Over a median follow-up period of 13.7 years, we identified 8.0% (n = 39,530) deaths, of which 4.0% (n = 19,891) were from cancer, 1.8% (n = 8706) from CVD, 0.6% (n = 3084) from respiratory disease, and 0.5% (n = 2669) from nervous system disease (Supporting Information: Table S1). Among the cancer deaths, lung cancer led to 3398 deaths and CRC led to 1990. Of the category of CVD deaths, the majority was from IHD (n = 4383), followed by stroke (n = 1676). For respiratory and nervous system diseases, COPD (n = 1218) and AD (n = 827) were the primary causes of deaths, respectively.

Association between Heavy Metals and Mortality

Based on the linear Cox regression models, we observed that both Pb and Cd were positively associated with all-cause (HR for Pb: 1.164, 95%CI 1.107−1.223; HR for Cd: 1.111, 95%CI 1.073−1.150), cancer (Pb: 1.118, 95%CI 1.042−1.198; Cd: 1.084, 95%CI 1.033−1.138), CVD (Pb: 1.198, 95%CI 1.075−1.335; Cd: 1.130, 95%CI 1.047−1.220), IHD (Pb: 1.221, 95% CI 1.046−1.425; Cd: 1.167, 95%CI 1.046−1.301), respiratory disease (Pb: 1.356, 95%CI 1.133−1.622; Cd: 1.236, 95%CI 1.088−1.404), and COPD (Pb: 1.482, 95%CI 1.112−1.974; Cd: 1.276, 1.042−1.562) mortality (Supporting Information: Table S1). The highest HRs were found for mortality from respiratory diseases and COPD, followed by IHD, CVD, and cancer. Hg was only positively associated with CRC mortality (HR: 1.087, 95%CI 1.004−1.178) in the linear Cox regression model. Exposure to the mixtures of Pb, Cd, and Hg was associated with increased risk of all-cause (HR: 1.070, 95%CI: 1.040−1.101), cancer (HR: 1.042, 1.002−1.083), CVD (HR: 1.086, 95%CI: 1.022−1.155), stroke (HR: 1.154, 95%CI: 1.003−1.328), and respiratory disease (HR: 1.113, 95%CI: 1.005−1.233) mortality for one quantile increase in concentrations of all three heavy metals (Supporting Information: Table S1).

Exposure−response curves suggested Pb was near linearly associated with increased risk of all-cause, cancer, CRC, CVD, IHD, stroke, respiratory disease, and COPD mortality, and near nonlinearly associated with lung cancer mortality (Figure 1A, Figures 2−4). Cd followed the same pattern but with relatively smaller HR values. In addition to CRC, our exposure−response curves suggested Hg was associated with higher risk of all-cause, cancer, and stroke mortality over certain concentrations, with all-cause and stroke mortality showing nonlinear relationships. We did not observe statistically significant positive exposure−response associations of heavy metals with nervous system disease including AD. Sensitivity analyses for all-cause mortality and cause-specific mortality were broadly consistent with the main results (Supporting Information: Figures S7−S17).

Table 1. Baseline Characteristics of Included Participants[a]

	Overall (n = 497,056)
Age, years, median (IQR)	58.00 [51.00, 64.00]
Sex, Male, n (%)	225694 (45.4)
Ethnicity, n (%)	
White	467591 (94.1)
Mixed	2924 (0.6)
Chinese	1566 (0.3)
Asian or Asian British	9779 (2.0)
Black or Black British	7969 (1.6)
Missing	7227 (1.5)
Household income, £, n (%)	
Less than 18,000	95405 (19.2)
18,000 to 30,999	106988 (21.5)
31,000 to 51,999	109945 (22.1)
Greater than 52,000	108616 (21.9)
Missing	76102 (15.3)
Urban, yes, n (%)	424223 (85.3)
Current employment status, n (%)	
In paid employment or self-employed	285031 (57.3)
Looking after home and/or family	13960 (2.8)
Retired	164375 (33.1)
Unemployed	28125 (5.7)
Missing	5565 (1.1)
Qualifications, n (%)	
College or University degree	159855 (32.2)
A level/GCSE/CSE or equivalent	185743 (37.4)
NVQ and other professional qualifications	57796 (11.6)
Missing	93662 (18.8)
Activity intensity, n (%)	
Moderate/vigorous activity	313129 (63.0)
Others	171962 (34.6)
Missing	11965 (2.4)
Smoking, n (%)	
Never	271469 (54.6)
Previous	170782 (34.4)
Current	51930 (10.4)
Missing	2875 (0.6)
Drinking, n (%)	
Never	22111 (4.4)
Previous	17698 (3.6)
Current	455643 (91.7)
Missing	1604 (0.3)
BMI, kg/m^2, n (%)	
<25	163516 (32.9)
25−30	210003 (42.2)
≥30	120558 (24.3)
Missing	2979 (0.6)
Diet quality, good, n (%)	363035 (73.0)
PRS for bowel cancer, mean (SD)	0.22 (1.05)
PRS for coronary artery disease, mean (SD)	−0.16 (0.96)
PRS for CVD, mean (SD)	−0.11 (0.98)
PRS for ischemic stroke, mean (SD)	−0.02 (0.93)
PRS for AD, mean (SD)	0.05 (1.00)
Pb, 3-year average, ng/m^3, median (IQR)	8.50 [6.89, 10.85]
Cd, 3-year average, ng/m^3, median (IQR)	0.16 [0.14, 0.19]
Hg, 3-year average, ng/m^3, median (IQR)	1.67 [1.66, 1.69]
B(a)P, 3-year average, ng/m^3, median (IQR)	0.07 [0.06, 0.07]

[a]IQR, interquartile range. BMI, body mass index. PRS, polygenic risk score. SD, standard deviation. CVD, cardiovascular disease. AD, Alzheimer's disease.

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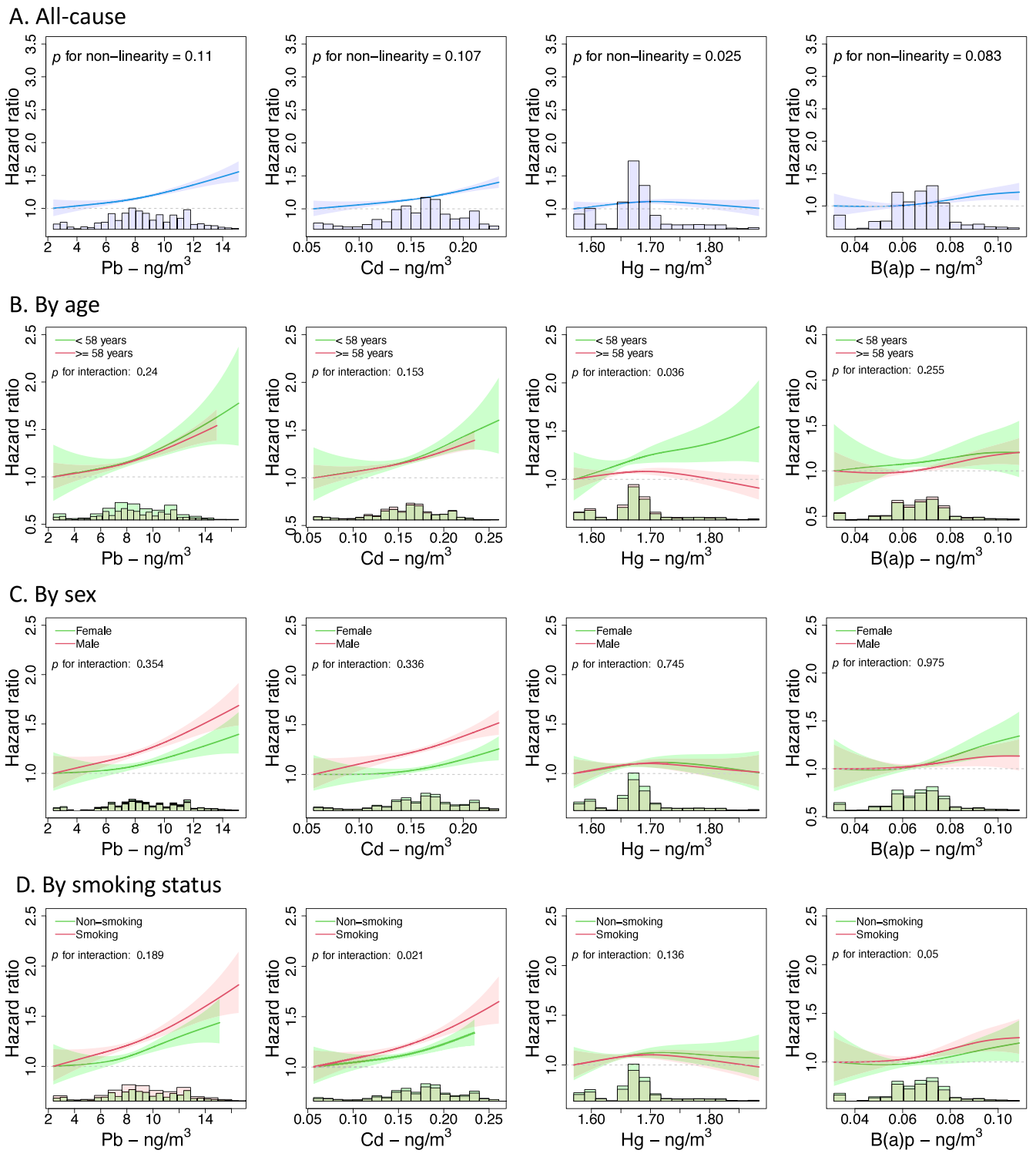

Figure 1. Exposure−response relationships between heavy metals and B(a)P and all-cause mortality. (A) Total population, (B) By age, (C) By sex, (D) By smoking status. Dark lines represent the point hazard ratios and shaded areas represent their 95% confidence intervals. Data were trimmed from 1% to 99% percentiles of concentration, and the 1% percentile concentration in the UK was set as the reference for each air pollutant. The histogram represents the concentration distribution of each air pollutant.

Our subgroup analyses for all-cause mortality suggested participants aged <58 years (p for interaction = 0.036 for Hg), males, smokers (p for interaction = 0.021 for Cd) may be more susceptible to the negative impact of heavy metals, though the p values for some interaction were not statistically significant (Figure 1B−D). For CVD mortality, we also observed participants with low genetic risk were more susceptible to the negative impact of Pb (p for interaction = 0.034) and Cd (p for interaction = 0.051) but less susceptible to the negative impact of Hg (p for interaction = 0.023) over their high concentrations (Supporting Information: Figure S18). Similar patterns were also identified for stroke mortality (p for interaction = 0.031 for Pb and 0.039 for Cd). On the contrary, Pb and Cd were less associated with IHD mortality in

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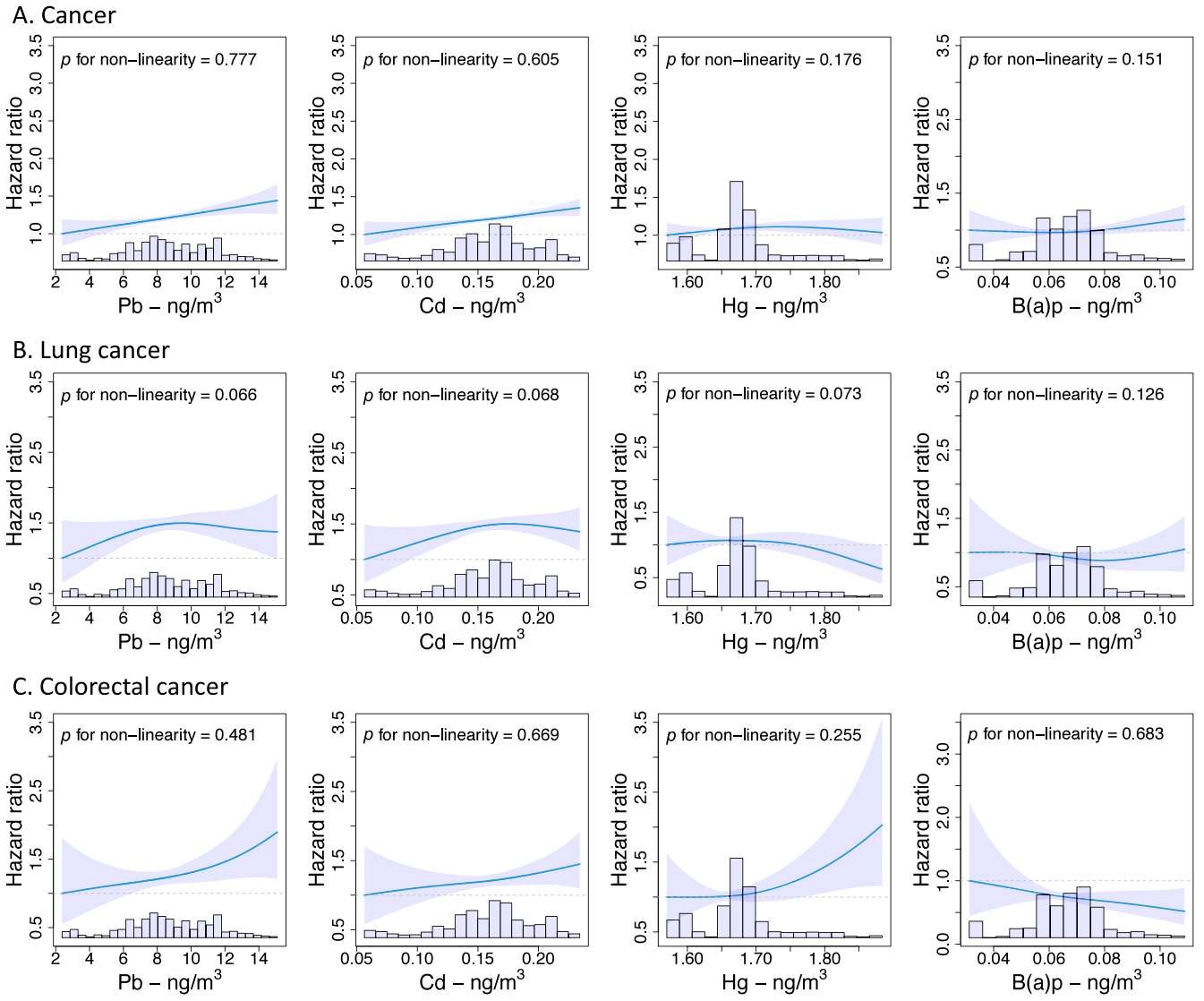

Figure 2. Exposure−response relationships between heavy metals and B(a)P and cancer-specific mortality. (A) Cancer, (B) Colorectal cancer, (C) Lung cancer. Dark blue lines represent the point hazard ratios and blue shaded areas represent their 95% confidence intervals. Data were trimmed from 1% to 99% percentiles of concentration, and the 1% percentile concentration in the UK was set as the reference for each air pollutant. The histogram represents the concentration distribution of each air pollutant.

participants with low genetic risk, with p for interaction of 0.046 and 0.093, respectively.

Association between B(a)P and Mortality

Exposure to B(a)P was associated with a 1.063-fold (95%CI: 1.022−1.106) increased risk of all-cause mortality (Supporting Information: Table S2). No statistically significant associations were identified with cause-specific mortality based on the linear Cox regression model; however, the exposure−response curves additionally identified positive associations of long-term exposure to B(a)P with the risk of IHD and stroke mortality (Figure 3). Sensitivity analyses for all-cause mortality and cause-specific mortality were broadly consistent with the main results, though for some mortality categories (e.g., AD) B(a)P became statistically significant when using different exposures (e.g., air pollutant concentration across four nearest grid cells to the participants' residential address or 2-year average concentrations as exposures, Supporting Information: Figures S7−S17). No modifying effects of age, sex, or smoking status were identified for associations of B(a)P with all-cause mortality (Figure 1). Participants with low genetic risk seemed to be less susceptible to the negative impact of B(a)P on CRC, CVD, and AD and more susceptible to the negative impact on IHD, although none of the interaction p-values were statistically significant (Supporting Information: Figure S18).

DISCUSSION

Although heavy metals and POPs are recognized as a major environmental risk factor for mortality, their direct impact via inhalation—a major exposure route alongside ingestion through water and food and the corresponding exposure−response associations in the general population—have remained largely unquantified. In this large-scale prospective cohort study, we evaluated the direct toxicity of long-term exposure to ambient heavy metals (Pb, Cd, and Hg) and B(a)P. Our findings showed that heavy metals were associated with an increased risk of mortality across all or parts of the categories: all-cause, cancer, lung cancer, CRC, CVD, IHD, stroke, respiratory disease, and COPD mortality. For B(a)P,

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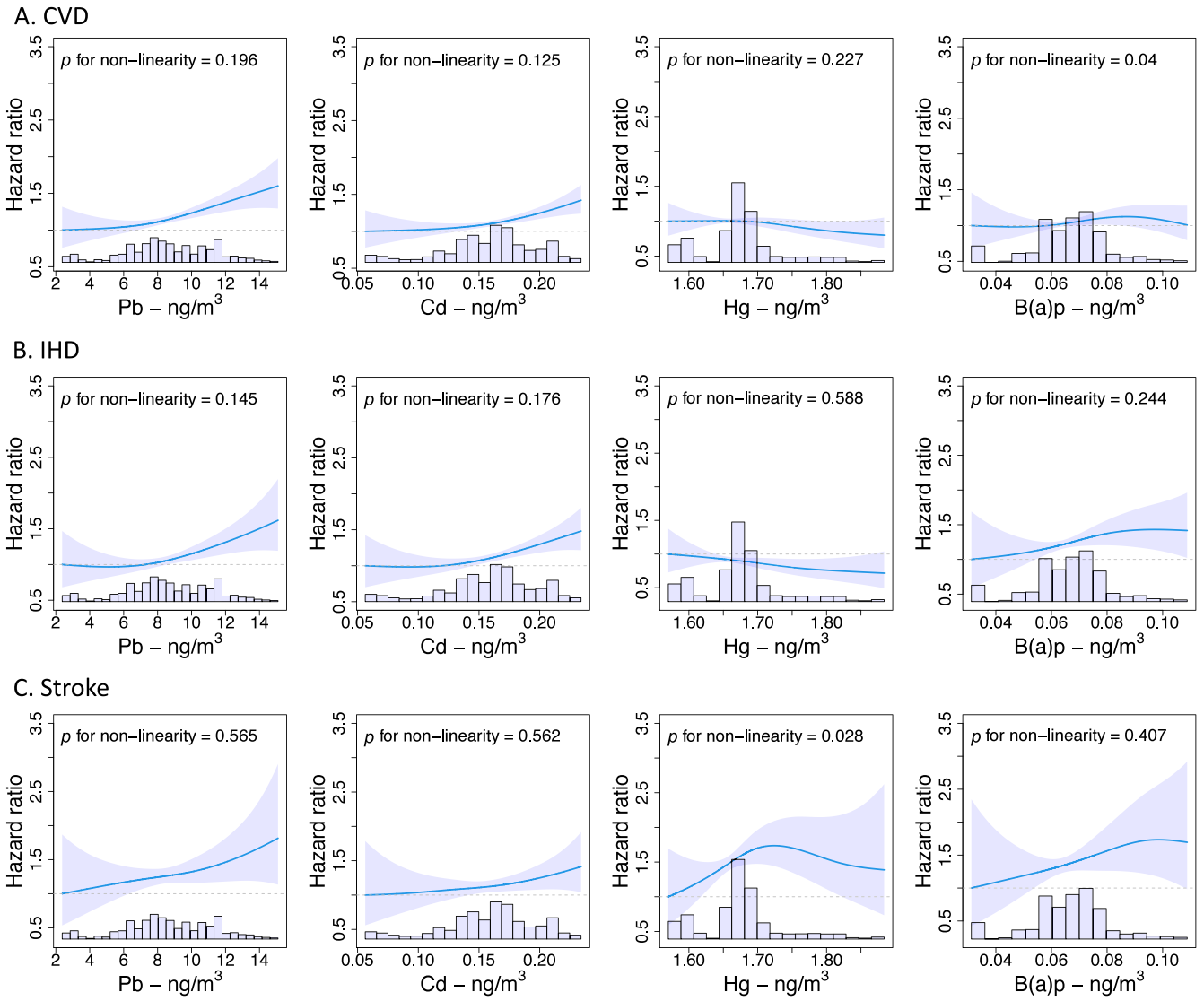

Figure 3. Exposure−response relationships between heavy metals and B(a)P and cardiovascular disease (CVD) mortality. (A) Total CVD, (B) Ischemic heart disease (IHD), (C) Stroke. Dark blue lines represent the point hazard ratios and blue shaded areas represent their 95% confidence intervals. Data were trimmed from 1% to 99% percentiles of concentration, and the 1% percentile concentration in the UK was set as the reference for each air pollutant. The histogram represents the concentration distribution of each air pollutant.

the significant association was limited to all-cause mortality in the linear model, although exposure−response curves also suggested positive associations between B(a)P exposure and the risk of IHD and stroke mortality. Hg and B(a)P seemed to exhibit lower toxicity compared to Pb and Cd. Exposure−response curves demonstrated monotonically increased risk for most mortality outcomes. Age, smoking status, and genetic factors were found to modify susceptibility to heavy metals. Our findings are supported by prior epidemiological and experimental studies elucidating several pathophysiological mechanisms, such as elevated inflammatory responses and endothelial oxidative stress, DNA methylation, and mitochondrial dysfunction.[6,20−28]

We found Pb and Cd were associated with 1.111−1.164 times increased risk for all-cause mortality for each IQR increment in their concentrations. Of the specific causes of mortality, they were most strongly associated with respiratory diseases, including COPD, followed by IHD, CVD, and cancer. Hg was less toxic and was positively associated only with CRC in the linear model. Our findings align with previous studies exploring effects of heavy metals in biomaterials,[7,29−31] or bound to ambient PM,[32,33] on health consequences. For instance, a recent meta-analysis of 34 population-based studies across several regions revealed significant associations of Cd and Pb levels in blood or urine with all-cause, CVD, and cancer mortality, whereas the adverse effects of Hg on mortality were inconclusive.[7] A US Medicare cohort study also demonstrated long-term Pb exposure from $PM_{2.5}$ was associated with 1.007−1.038 times increased risk for all causes of deaths, except COPD and lung cancer mortality, with Pb more strongly associated with IHD and CVD mortality than respiratory and cancer mortality.[33] The HRs were slighter lower than our estimates of 1.118−1.482, possibly due to lower Pb concentrations in $PM_{2.5}$ (mean ± SD: 2.47 ± 7.12 vs 8.7 ± 2.9 ng/m^3) in this study. Compared to an HR of 0.990 (0.983−0.997) in this study, our study suggested Pb was most associated with COPD mortality (HR: 1.482, 95%CI 1.112−1.974), although both studies suggested an association

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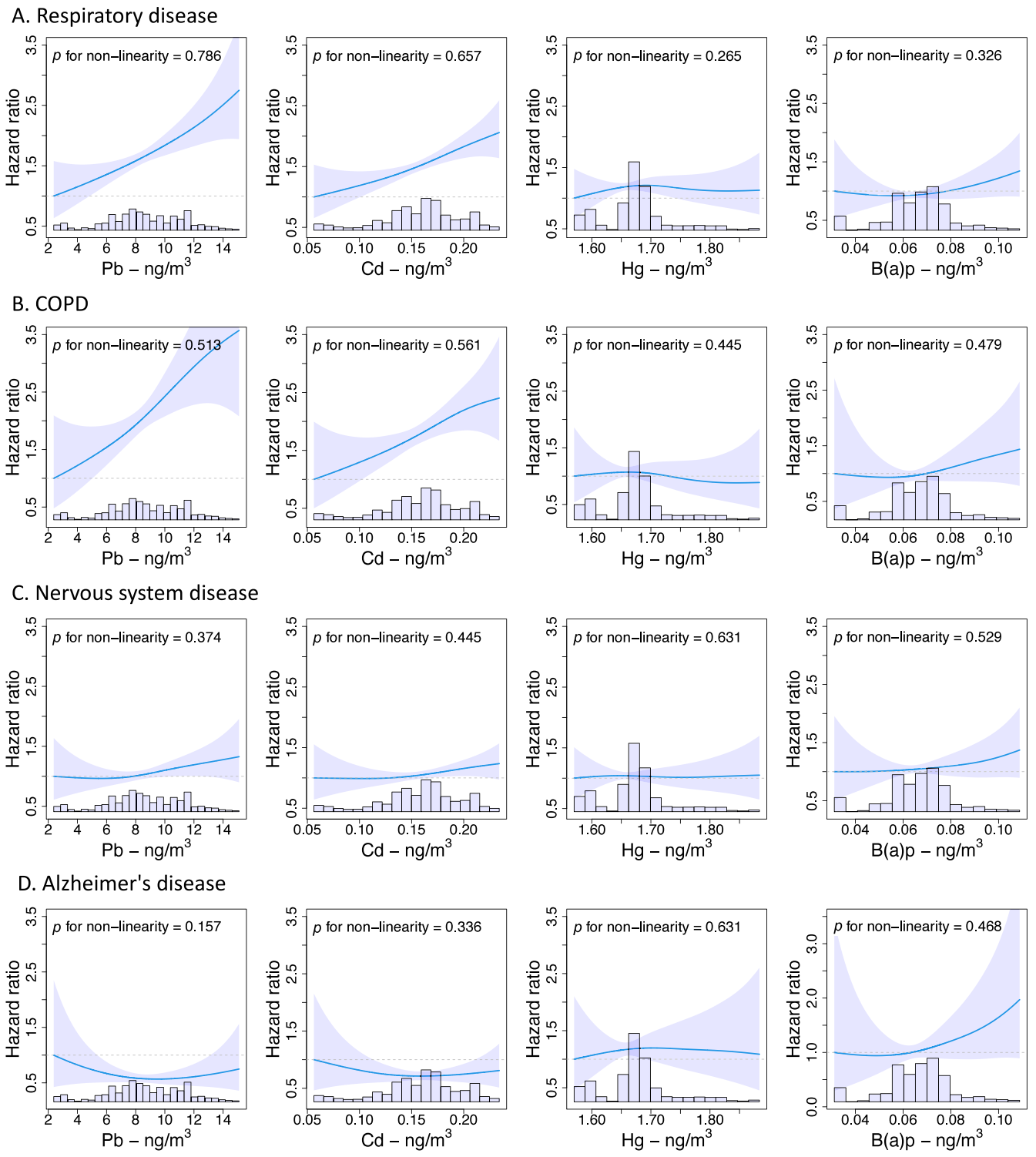

Figure 4. Exposure−response relationships between heavy metals and B(a)P and respiratory disease and nervous system disease mortality. (A) Respiratory disease, (B) Chronic obstructive pulmonary disease (COPD), (C) Nervous system disease, (D) Alzheimer's disease. Dark blue lines represent the point hazard ratios and blue shaded areas represent their 95% confidence intervals. Data were trimmed from 1% to 99% percentiles of concentration, and the 1% percentile concentration in the UK was set as the reference for each air pollutant. The histogram represents the concentration distribution of each air pollutant.

between Pb and respiratory disease. We observed that nearly 50% of respiratory deaths were due to COPD in both the US Medicare and the UK biobank cohorts; one possible reason for the conflicting finding is a potential nonlinear relationship between Pb and COPD mortality in the US was not captured by a linear model. In addition, a few studies have also explored the direct impact of air heavy metals on human health but primarily focused on cancer. For example, air Cd exposure was found to be associated with a higher risk of overall and prostate cancer-specific mortality risk among prostate cancer patients.[34]

Our study suggested exposure to mixtures of Pb, Cd, and Hg was associated with 1.040−1.154 times increased risk of all-

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cause, cancer, CVD, stroke, and respiratory disease mortality. Current epidemiological evidence for the joint effect of heavy metal exposure on mortality is limited.[35,36] Studies utilizing data from the American NHANES survey[35] and a Chinese cohort[36] have associated metal mixtures in blood or urine with an elevated risk of all-cause, cancer, and/or CVD mortality, with Cd potentially making the largest contribution. Given the complexity of environmental systems, further research is needed to understand the joint effects of heavy metals via various exposure routes.

In addition to all-cause-mortality, we found a positive association between long-term exposure to B(a)P and the risk of IHD and stroke mortality, which is partially in line with earlier studies focusing on occupational exposure.[37] As a group I carcinogen, B(a)P has been linked to multiple cancer outcomes in previous studies.[2] Our study did not identify positive associations with all- or cause-specific cancer mortality, which may be because of the low-level exposure during a short follow-up time. Furthermore, we found that B(a)P was less toxic than heavy metals, particularly Cd and Pb. This might be due to their varying emission sources: heavy metals are mainly emitted from industry and public power introduction, whereas POPs are from the residential combustion through coal and wood stoves/boilers in Europe.[5,38] Our findings seem to support that industry-sourced chemicals are more harmful than those from the residential combustion sector. However, our study included a limited number of chemicals and requires validation in future studies.

Our monotonical exposure−response curves for most mortality outcomes are supported by previous studies using heavy metal concentrations in blood/urine.[39,40] For instance, the exposure−response curves for all-cause, CVD, IHD mortality in American adults associated with blood Pb showed a sublinear trend over 1 to 10 μg/dL.[39] In Korean adults, a significant increase in the risk of nonaccidental and cancer mortality was also observed at a blood Pb level between 1.5 and 6.0 μg/dL, although the curve flattened out at high concentrations.[41] Additionally, a recent exposure−response meta-analysis suggested the overall CVD mortality was linearly or sublinearly associated with blood/urinary Cd.[11] Limited prospective studies have constructed exposure−response associations of B(a)P with mortality in the general population, but one ecological study in Jiangsu Province of China found the cancer mortality risk associated with $PM_{2.5}$-bound B(a)P increased steeply below 1 ng/m^3 and then rose at a slower rate.[42]

Consistent with previous studies, our study suggested younger participants and smokers may be more susceptible to heavy metal exposure.[33,43] In addition, we observed that participants with a low genetic risk were more susceptible to adverse effects of high concentrations of Pb and Cd on composite CVD and stroke mortality, but these metals were less associated with IHD mortality in this group. This may imply, in comparison to the coronary arteries, that the cerebrovascular system is more susceptible to the toxic effects of Pb and Cd than to genetic influences. Meanwhile, we found participants with low genetic risk were less affected by the negative impact of Hg and B(a)P on CRC, CVD, and/or stroke mortality, although some interactions did not reach statistical significance. This finding partially aligns with a Chinese case-cohort study that indicated higher genetic risk exacerbated the detrimental effects of B(a)P on lung cancer.[44] While our findings are preliminary, they contribute to the literature by exploring the potential role of genetic modifiers in the context of heavy metal and POP exposure. Limited studies have explored the modifying effects of genetic effects, and further research with larger genetic data sets is needed to confirm our results. Genome-wide association studies have shown that an internal dose of heavy metal (e.g., Cd) can be affected by single nucleotide polymorphisms,[45−47] underscoring the importance of considering genetic factors in future investigations.

The strengths of this study lay in its large-scale, longitudinal design, the breadth of exposures considered, and its ability to provide novel and actionable evidence that can guide environmental and public health interventions. Our study had several limitations. First, we used baseline assessments of lifestyle, environmental, and socio-economic factors and did not track their changes over time. Future research would benefit from incorporating time-varying variables to capture these dynamics. Meanwhile, the reliance on self-reported questionnaires to gather data on several covariates could introduce inaccuracies, recall bias, or misclassification. Second, the study did not evaluate air pollution exposure in an indoor environment, which may bias the risk estimates. Third, we accounted for multiple known confounders, but there may be residual confounding (e.g., medication use), which could influence our results. Fourth, the utilization of ICD codes from death registries to ascertain all-cause and cause-specific mortality could be prone to a range of potential biases. Fifth, the study was limited to individuals of white European ancestry, making it difficult to generalize our findings to other ethnic groups. Future studies from diverse regions or populations will help validate our findings.

In conclusion, long-term exposure to heavy metals and B(a)P was monotonically associated with an elevated risk of multiple mortality outcomes, indicating there may be no safe threshold for these chemicals. Substantial benefits in public health could be achieved through stringent environmental regulations and clean air initiatives.

■ ASSOCIATED CONTENT

Data Availability Statement

The authors have no right to share the data obtained from the UK biobank. Air pollution data was publicly available and data sources have been provided.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/envhealth.4c00191.

Details on study population, covariates, and study population (Supplementary Methods); linear associations of air pollutants with all-cause and cause-specific mortality (Tables S1−S2); and flowchart of participants selection, distribution plot of air pollutants, Spearman correlation plot, sensitivity analyses, and stratified analyses by genetic factors (Figures S1−S18) (PDF)

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Author Contributions

F.Z. conceived the study and performed the data analysis. F.Z. and C.-G.G. drafted the manuscript. C.Y., F.W., W.W., and L.Z. contributed to interpretation of the data and critically revised the manuscript. F.Z., C.Y., and L.Z. obtained funding for the study. L.Z. supervised the study. All authors read the manuscript and had final responsibility for the decision to submit for publication.

Notes

The authors declare no competing financial interest.

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