Exhibit 318

ORIGINAL ARTICLE

Long-Term Exposure to Low Concentrations of Ambient Benzene and Mortality in a National English Cohort

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Abstract

Background: Benzene affects human health through environmental exposure in addition to occupational contact. However, few studies have examined the associations between long-term exposure to low concentrations of ambient benzene and mortality risks in nonoccupational settings.

Methods: This prospective cohort study consists of 393,042 participants without stroke, myocardial infarction, or cancer at baseline from the UK Biobank. Annual average concentrations of benzene for each year during follow-up were measured using air dispersion models. The main outcomes were all-cause mortality and mortality from specific causes. Cox proportional-hazards models with time-varying exposure measurements were used to estimate the hazard ratios and 95% confidence intervals (CIs) for mortality risks. Restricted cubic spline models were used to estimate exposure–response relationships.

Measurements and Main Results: With each interquartile range increase in the average annual concentration of benzene, the adjusted hazard ratios of mortality risk from all causes, cardiovascular disease, cancer, and respiratory disease were 1.26 (95% CI, 1.24–1.27), 1.24 (95% CI, 1.21–1.28), 1.27 (95% CI, 1.25–1.29), and 1.25 (95% CI, 1.20–1.30), respectively. The monotonically increasing exposure–response curves showed no threshold and plateau within the observed concentration range. Furthermore, the effect of benzene exposure on mortality persisted across different subgroups and was somewhat stronger in younger and White people (P for interaction < 0.05).

Conclusions: Long-term exposure to low concentrations of ambient benzene significantly increases mortality risk in the general population. Ambient benzene represents a potential threat to public health, and further investigations are needed to support timely pollution regulation and health protection.

Keywords: benzene; mortality; long-term exposure; cohort study

Benzene holds significant importance as an industrial chemical, with widespread use in production (1), but it is also one of the most common air pollutants released into the environment (2). The main source of outdoor benzene exposure for the public is road transport, contributing approximately 85% of outdoor benzene (3, 4). Apart from producing from combustion reactions like many other air pollutants (e.g., particulate matter with an aerodynamic diameter ⩽2.5 μm [$PM_{2.5}$] and nitrogen dioxide [NO_2]), benzene is also a volatile organic compound that is likely to occur near industry and gas stations (5, 6). The International Agency for Research on Cancer classified benzene as a group 1 carcinogen (7). Benzene exposure has been linked with qualitative and

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At a Glance Commentary

Scientific Knowledge on the Subject: Benzene is one of the most common air pollutants, affecting human health through environmental exposure in addition to occupational contact. Previous studies were focused mainly on the health impacts of exposure to high concentrations of benzene on occupational populations.

What This Study Adds to the Field: The results of this large national cohort study suggest that long-term individual exposure to low concentrations of ambient benzene elevated mortality risk from all causes and a wide range of specific causes in the general population. Furthermore, the monotonically increasing exposure–response curves showed no threshold and plateau within the observed exposure range.

quantitative disruptions in blood cells (8, 9) and a number of diseases, such as hematologic malignancies (10, 11). Furthermore, epidemiological research has examined the prolonged impacts of exposure to high concentrations of benzene on occupational populations. These studies primarily used occupational cohorts or case–control study designs involving benzene concentrations of less than 1 ppm (3.19 mg/m^3) to more than 10 ppm (31.9 mg/m^3) (12–18). The outcomes of these investigations have consistently demonstrated that benzene is among the most significant hazardous air pollutants, incurring substantial risks of cancer, cardiovascular disease (CVD), and respiratory disease.

As a ubiquitous air contaminant, benzene might affect human health through environmental exposure in addition to occupational contact (5). Considering the widespread global distribution of low concentrations of ambient benzene and its exposure to a large population, benzene might pose a potential health risk to the global population. However, the potential health effects of low concentrations of benzene in ambient air among the general population have been historically overlooked. To our knowledge, only two previous epidemiological studies have investigated the associations of long-term exposure to low concentrations of ambient benzene and the risk of mortality in nonoccupational settings, primarily because of the lack of benzene monitoring data (19, 20). Furthermore, these two studies were limited by a lack of individual exposure assessment, single-city study design, or restricted health outcomes. Thus, the effects of benzene exposure on different causes of death are still uncertain. There is an urgent need to assess the overall impact of individual benzene exposure on human health and to provide evidence to support the development of regulatory strategies.

Hence, in the present study, we comprehensively investigated the associations between individual long-term exposure to low concentrations of ambient benzene and the risk of mortality in a large prospective cohort. We aimed to provide scientific evidence for developing public health measures to regulate ambient benzene pollution.

Methods

Study Population

We sourced data from the UK Biobank for the present study. Details of the rationale, study design, and survey methods can be found elsewhere (https://www.ukbiobank.ac.uk) (21, 22). Briefly, the UK Biobank is a population-based cohort study consisting of more than 500,000 participants aged 37–73 years in the UK National Health Service (NHS) who attended one of the 22 centers across the United Kingdom for baseline assessment from 2006 to 2010. Individuals completed a computer-based questionnaire on baseline information, medical history, and treatments and underwent a standardized portfolio of clinical measurements. The UK Biobank has approval from the National Information Governance Board for Health and Social Care and the NHS North West Multicenter Research Ethics Committee, and all participants gave written informed consent. Of the 502,479 UK Biobank participants, we excluded those with prior cancer, myocardial infarction, or stroke at baseline ($n = 56{,}568$), missing data on benzene exposure ($n = 8$), or missing covariate data ($n = 52{,}861$), yielding an analytic cohort of 393,042 participants.

Exposure Assessment

Annual average concentrations of benzene (2006–2020) were obtained from the Department for Environment Food & Rural Affairs (DEFRA), which collects high-resolution, near-surface air pollution data in the United Kingdom (https://uk-air.defra.gov.uk). The data are used in official government publications and have been widely used in existing publications (23–25). This system generated annual concentration maps of diverse air pollutants with a resolution of 1 × 1 km. This is achieved through an air dispersion model that relies on multiple sources derived from the National Atmospheric Emissions Inventory, incorporating data from secondary inorganic aerosol measurements and models accounting for various sources such as dust resuspension. Subsequently, the estimated concentrations underwent calibration by integrating actual measurements obtained from background sites within DEFRA's Automatic Urban and Rural Network. To ensure the reliability of models, DEFRA carries out a comprehensive set of comparisons between modeled and measured annual mean air pollutant concentrations. These evaluations show strong agreement between the observed data and the model's output values. Detailed summary statistics regarding the model's performance can be accessed at https://uk-air.defra.gov.uk/data/pcm-data.

On the basis of an existing study (26), we estimated benzene exposures for each participant. Using the residential address history provided by UK Biobank, we linked the annual average benzene concentrations to each participant using a unique code (ukgridcode) corresponding to individual 1 × 1 km cells in the annual concentration map.

Mortality Ascertainment

Information on vital status, date of death, and the underlying cause of death was sourced from the NHS Information Centre (England and Wales) and the NHS Central Register (Scotland). Specific causes of death were defined on the basis of codes from the International Classification of Diseases, 10th Revision: *1*) CVD (codes I00–I99), ischemic heart disease (codes I20–I25), and cerebrovascular disease (codes I60–I69); *2*) cancer (codes C00–C97), leukemia (codes C91–C95), multiple myeloma (codes C90), non-Hodgkin's lymphoma (NHL; codes C82–C85), respiratory cancer (codes

C32–C34), and lung cancer (codes C33–C34); and *3*) respiratory diseases (codes J00–J99). Participants were followed up from the date of attendance at the recruitment center until death or the end of the follow-up period (December 18, 2020), whichever came first.

Covariates

The baseline survey collected detailed information on sociodemographic information, lifestyle factors, physical measurements, and medical history. The covariates were chosen *a priori* on the basis of previous epidemiology studies of air pollution and mortality (27–33): age (years), gender (female or male), ethnicity (White or non-White), education level (with or without degree level or professional education), Townsend deprivation index (TDI), drinking status (never drinkers, former drinkers, or current drinkers), smoking status (never-smokers, former smokers, or current smokers), body mass index (kg/m^2), physical activity (never activity, low activity, medium activity, or high activity), hypertension (yes or no), hyperlipidemia (yes or no), diabetes (yes or no), solid-fuel cooking or heating (yes or no), exposure to tobacco smoke at home (h/wk), exposure to tobacco smoke outside the home (h/wk), and annual average concentration of residential $PM_{2.5}$ exposure ($\mu g/m^3$). TDI is an area-based proxy measure for socioeconomic status, and higher scores represent higher degrees of area-based socioeconomic deprivation.

Statistical Analysis

Participant baseline characteristics and annual average concentrations of benzene exposure were presented using descriptive statistics. A figure showing the benzene exposure distribution of UK Biobank participants was plotted. Continuous variables were presented as mean with SD, and categorical variables were displayed as counts with percentages. Pearson correlation coefficients among air pollutants were calculated.

To quantify associations of long-term benzene exposure with all-cause and cause-specific mortality risk, the Cox proportional-hazards model with time-varying exposure measurements was fitted. We used the variance inflation factor to evaluate multicollinearity in the fitted models. Variables with variance inflation factors ≥ 5 indicate significant multicollinearity and should be removed from the model (34). Finally, we incorporated these confounders for adjustment: age, gender, ethnicity, education level, TDI, drinking status, smoking status, body mass index, physical activity, hypertension, hyperlipidemia, diabetes, solid-fuel cooking or heating, exposure to tobacco smoke at home, exposure to tobacco smoke outside the home, and annual average concentration of residential $PM_{2.5}$ exposure. Figure E1 in the online supplement presents the conceptual model for the exposure–outcome relationship. The proportional-hazards assumption was tested using Schoenfeld residuals, and no violation was detected. Hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were used to present the results. To further assess the exposure–response relationships of benzene concentration and risk of all-cause mortality and cause-specific mortality, we fitted restricted cubic splines models and chose five knots (at the 5th, 27.5th, 50th, 72.5th, and 95th centiles) according to the Akaike information criterion optimality principle (35).

We conducted subgroup analyses to investigate potential modification effects and explore possible population heterogeneity according to age, gender, ethnicity, smoking status, baseline hypertension, baseline hyperlipidemia, and baseline diabetes. The interactions were examined using the likelihood ratio test, which involved comparing models with and without interaction terms.

We also examined the robustness of the results by conducting several sensitivity tests. First, we excluded participants who died within the first year of follow-up. Second, we restricted our analyses to participants who had resided at their current addresses for more than five years. Third, we included only participants who reported no poor health at baseline. Fourth, we replaced the covariate $PM_{2.5}$ with NO_2 to perform a sensitivity analysis. Fifth, we drew a directed acyclic graph using DAGitty version 3.1 (https://www.dagitty.net) to determine the minimal sufficient adjustment set (*see* Figure E2). Then, we adjusted this minimal sufficient adjustment set to perform a sensitivity analysis.

All *P* values reported were two sided; *P* values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using R software (version 4.1.2).

Results

Table 1 shows the baseline characteristics of participants according to survival status. Our analysis included 393,042 participants (213,777 women and 179,265 men) with a mean baseline age of 56.1 years (SD, 8.1 yr). We observed 20,390 deaths during a median follow-up period of 11.7 years (4,145 deaths of CVD, 10,236 deaths of cancer, and 1,469 deaths of respiratory disease). Participants who died during follow-up tended to be male and current smokers, with lower levels of education and socioeconomic status. In addition, they were less likely to engage in physical activity and had a higher prevalence of preexisting diseases. Figure E3 presents the distribution of the mean values of the annual average concentrations of individual benzene exposure during the study period among UK Biobank participants. The concentration of benzene exposure ranged from 0.01 to 1.13 $\mu g/m^3$, with a mean of 0.48 (SD, 0.13) $\mu g/m^3$. Table E1 shows a weak correlation between benzene and $PM_{2.5}$ (Pearson correlation coefficient = 0.335) and a moderate correlation between benzene and NO_2 (Pearson correlation coefficient = 0.527).

Long-term exposure to low concentrations of benzene significantly increases the risk of all-cause and cause-specific mortality (Figure 1). In the fully adjusted models, the HRs of mortality from all causes, CVD, cancer, and respiratory disease were 1.26 (95% CI, 1.24–1.27), 1.24 (95% CI, 1.21–1.28), 1.27 (95% CI, 1.25–1.29), and 1.25 (95% CI, 1.20–1.30) for each interquartile range increase ($0.22\ \mu g/m^3$) in benzene. For two subtypes of CVD mortality, the adjusted HRs were 1.23 (95% CI, 1.18–1.28) for ischemic heart disease and 1.22 (95% CI, 1.16–1.29) for cerebrovascular disease. Similar associations were also observed for mortality from respiratory cancer (HR, 1.29; 95% CI, 1.25–1.34), lung cancer (HR, 1.29; 95% CI, 1.24–1.34), and different types of hematopoietic malignancy, with HRs of 1.27 (95% CI, 1.15–1.39) for leukemia, 1.45 (95% CI, 1.30–1.62) for multiple myeloma, and 1.27 (95% CI, 1.16–1.39) for NHL. Figure 2 illustrates the monotonic nonlinear increase in the exposure–response relationships of benzene exposure with all-cause, CVD, cancer, and respiratory disease mortality (*P* for nonlinearity < 0.001). Similar exposure–response patterns were observed

Table 1. Baseline Characteristics of Participants Included

Characteristic	All ($N = 393,042$)	Alive ($n = 372,652$)	Dead ($n = 20,390$)
Age, yr, mean (SD)	56.1 (8.1)	55.8 (8.1)	61.3 (6.6)
Gender (female), *n* (%)	213,777 (54.4)	205,509 (55.1)	8,268 (40.5)
Ethnicity (White), *n* (%)	357,814 (91.0)	338,880 (90.9)	18,934 (92.9)
Educational level, *n* (%)			
Degree levels or professional qualifications	329,599 (83.9)	315,183 (84.6)	14,416 (70.7)
None of the above	63,443 (16.1)	57,469 (15.4)	5,974 (29.3)
Townsend deprivation index, mean (SD)	−1.4 (3.0)	−1.4 (3.0)	−0.9 (3.3)
Smoking, *n* (%)			
Never	219,312 (55.8)	211,186 (56.7)	8,126 (39.9)
Previous	133,574 (34.0)	125,262 (33.6)	8,312 (40.8)
Current	40,156 (10.2)	36,204 (9.7)	3,952 (19.4)
Drinking, *n* (%)			
Never	16,665 (4.2)	15,667 (4.2)	998 (4.9)
Previous	13,169 (3.4)	11,937 (3.2)	1,232 (6.0)
Current	363,208 (92.4)	345,048 (92.6)	18,160 (89.1)
Body mass index, kg/m^2, mean (SD)	27.4 (4.8)	27.3 (4.7)	28.2 (5.4)
Physical activity, *n* (%)			
None	23,776 (6.0)	21,528 (5.8)	2,248 (11.0)
Low	26,658 (6.8)	24,620 (6.6)	2,038 (10.0)
Medium	339,421 (86.4)	323,406 (86.8)	16,015 (78.5)
High	3,187 (0.8)	3,098 (0.8)	89 (0.4)
Hypertension, *n* (%)	98,878 (25.2)	91,294 (24.5)	7,584 (37.2)
Hyperlipidemia, *n* (%)	60,444 (15.4)	54,773 (14.7)	5,671 (27.8)
Diabetes, *n* (%)	4,970 (1.3)	4,458 (1.2)	512 (2.5)
Annual average concentration of residential $PM_{2.5}$, μg/m^3, mean (SD)	10.0 (1.1)	10.0 (1.1)	10.1 (1.1)
Solid-fuel cooking or heating, *n* (%)	34,816 (8.9)	33,491 (9.0)	1,325 (6.5)
Exposure to tobacco smoke at home, h/wk, mean (SD)	0.4 (4.1)	0.4 (4.0)	0.6 (4.6)
Exposure to tobacco smoke outside the home, h/wk, mean (SD)	0.4 (2.2)	0.4 (2.2)	0.5 (2.5)

Definition of abbreviation: $PM_{2.5}$ = particulate matter with an aerodynamic diameter of ⩽2.5 μm.

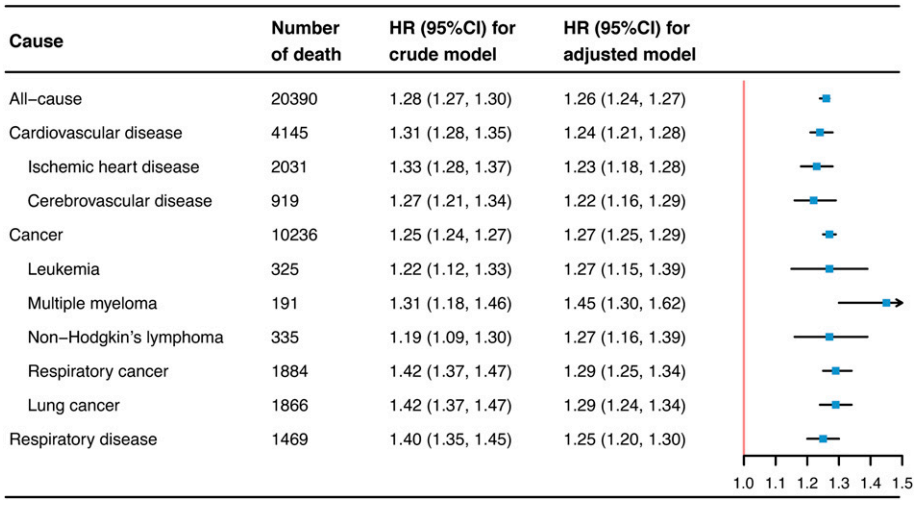

Figure 1. Associations between long-term exposure to benzene and the risk of all-cause and cause-specific mortality. Models were adjusted for age, gender, ethnicity, education level, Townsend deprivation index, drinking status, smoking status, body mass index, physical activity, hypertension, hyperlipidemia, diabetes, solid-fuel cooking or heating, exposure to tobacco smoke at home, exposure to tobacco smoke outside the home, and annual average concentration of residential exposure to particulate matter with an aerodynamic diameter ⩽2.5 μm. CI = confidence interval; HR = hazard ratio.

for death of ischemic heart disease, cerebrovascular disease, respiratory cancer, and lung cancer (*see* Figures E4 and E5). For subtypes of hematologic malignancy mortality, the curves showed a nonlinear relationship of benzene exposure with multiple myeloma, while linear exposure–response relationships were found for leukemia and NHL mortality (Figure 3).

We conducted stratified analyses according to potential risk factors (*see* Table E2). The results showed that White and younger people had a higher risk for all-cause mortality associated with long-term benzene exposure (P for interaction = 0.008 for age; HRs were 1.27 [95% CI, 1.25–1.30] for younger people and 1.25 [95% CI, 1.23–1.27] for older people; P for interaction < 0.001 for ethnicity; HRs were 1.27 [95% CI, 1.25–1.28] for White and 1.14 [95% CI, 1.09–1.19] for non-White).

In sensitivity analyses, to avoid the potential influence of undetected subclinical

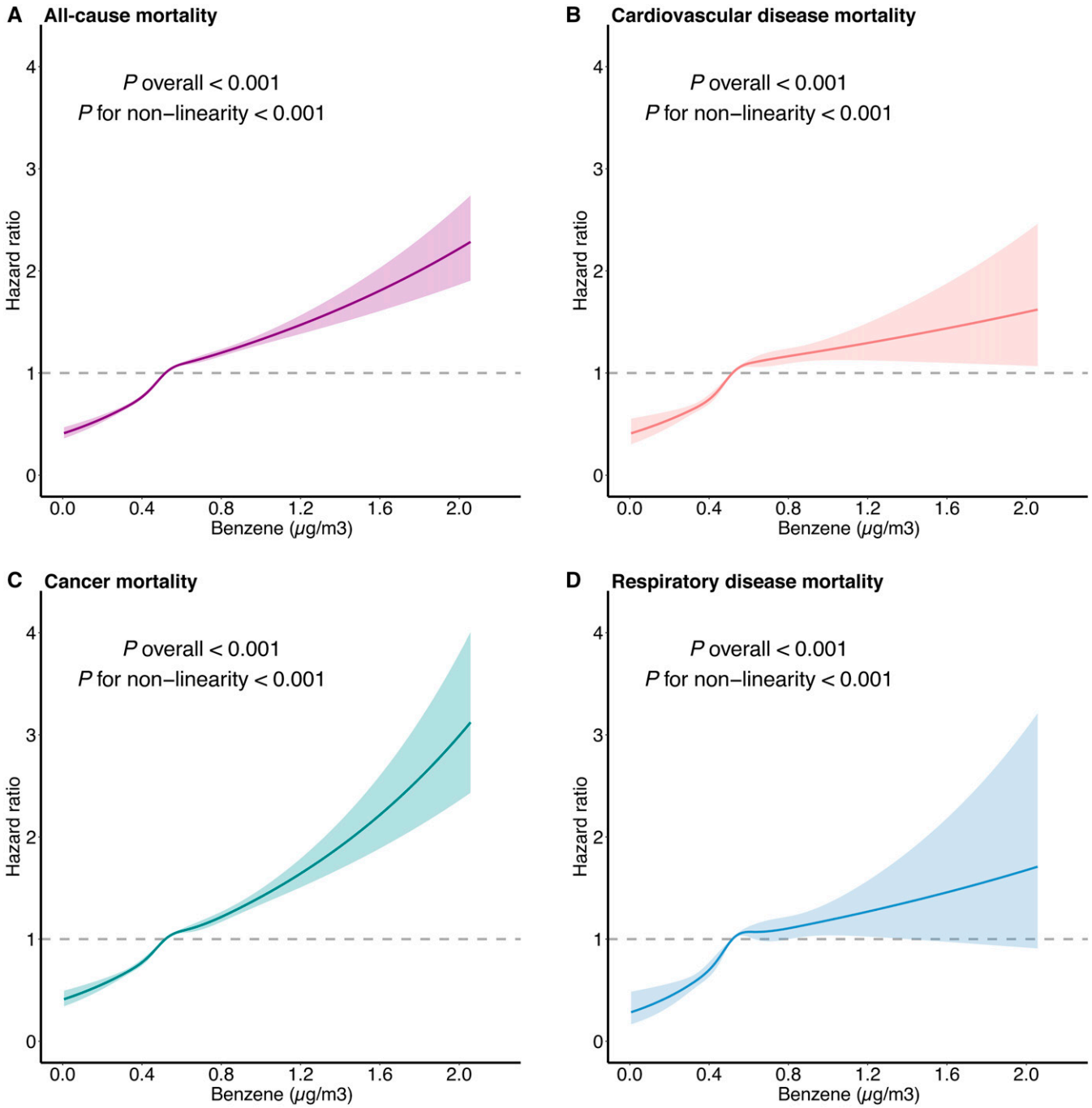

Figure 2. (*A–D*) Concentration–response curves of the effects of exposure to benzene on all-cause mortality (*A*), cardiovascular disease mortality (*B*), cancer mortality (*C*), and respiratory disease mortality (*D*). Models were adjusted for age, gender, ethnicity, education level, Townsend deprivation index, drinking status, smoking status, body mass index, physical activity, hypertension, hyperlipidemia, diabetes, solid-fuel cooking or heating, exposure to tobacco smoke at home, exposure to tobacco smoke outside the home, and annual average concentration of residential exposure to particulate matter with an aerodynamic diameter ≤2.5 μm.

disease at baseline, we excluded the participants who died during the first year of follow-up, and the results were identical to those in the main analysis (*see* Table E3). Sensitivity analyses showed no substantial change when we excluded participants living at their current addresses for less than five years (*see* Table E4) or included only individuals without poor self-reported health at baseline (*see* Table E5). The associations between long-term benzene exposure and mortality risk did not change materially when adjusting for NO_2 (*see* Table E6). In addition, the results of adjusting the directed acyclic graph–determined minimal sufficient adjustment set did not change (*see* Table E7).

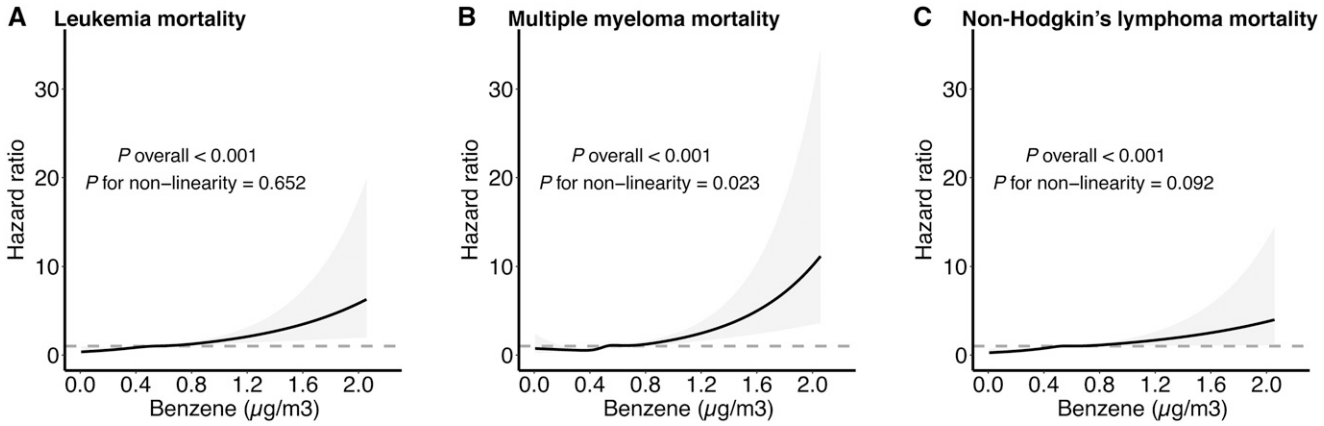

Figure 3. (*A–C*) Concentration–response curves of the effects of exposure to benzene on subtypes of hematologic malignancy mortality: leukemia (*A*), multiple myeloma (*B*), and non-Hodgkin's lymphoma (*C*). Models were adjusted for age, gender, ethnicity, education level, Townsend deprivation index, drinking status, smoking status, body mass index, physical activity, hypertension, hyperlipidemia, diabetes, solid-fuel cooking or heating, exposure to tobacco smoke at home, exposure to tobacco smoke outside the home, and annual average concentration of residential exposure to particulate matter with an aerodynamic diameter ⩽2.5 μm.

Discussion

In this study involving nearly 400,000 individuals from the United Kingdom, we explored the health effects associated with long-term exposure to low concentrations of ambient benzene, which has previously been an overlooked issue in the public health sector. To our knowledge, this is the first study to reveal that long-term individual exposure to low concentrations of ambient benzene elevated mortality risk from all causes and a wide range of specific causes in the general population. Furthermore, the monotonically increasing exposure–response curves showed no threshold and plateau within the observed exposure range. These findings highlight the necessity to develop effective, practical strategies to control ambient benzene concentration for general public health.

Prior studies have been informative for the adverse effects of benzene exposure on human health but were limited to highly exposed populations, such as a specific occupational group, and lacked individual measurements. In a retrospective cohort study performed on benzene-exposed Chinese workers, chronic benzene exposure increased a notable risk of overall mortality, respiratory disease mortality, lung cancer mortality, and death of hematopoietic, lymphoproliferative, and related disorders (36). According to research conducted in the United States, individuals with occupational exposure to benzene exhibited an overall standardized mortality ratio for leukemia of 337 and for multiple myeloma of 409, calculated by multiplying the relative risk by 100 (37). A cohort consisting of 20,625 employees from the French national electricity and gas company reported that long-term exposure to benzene was associated with an increased risk of nonaccidental mortality. However, no significant associations were observed for CVD and respiratory mortality (38). The reason for this may be due to the small number of deaths of CVD ($n = 165$) and respiratory disease ($n = 284$), limiting the statistical power to detect the effects.

The primary route of benzene exposure is through the air (39). For nonsmoking individuals in the general population, fuel-related emissions are the major sources of exposure (40). However, very few studies to date have examined the health effects of long-term exposure to low concentrations of ambient benzene exposure on the general population. In our study, we did a subgroup analysis according to the smoking status of participants and found that the association between benzene exposure and higher mortality was significant in both never- and ever-smokers. Similar to our findings, a previous cohort study composed of 58,760 residents in Toronto showed that each interquartile range (0.13 $\mu g/m^3$) increase in the baseline exposure to benzene was associated with an increase in all-cause mortality (HR, 1.04; 95% CI, 1.01–1.07) and cancer mortality (HR, 1.06; 95% CI, 1.02–1.11) (19). However, they did not observe significant associations between long-term benzene exposure and CVD and respiratory disease mortality. This difference may be due to a larger sample size and a more precise adjustment for individual-level risk factors, including smoking, in our study. A cohort study of 70,000 U.S. male veterans also revealed significant associations between benzene exposure and all-cause mortality (20); however, that study used data on county-level ambient benzene, which may result in potential exposure measurement error because of the notable within-city variations in benzene concentrations. Our findings also agree with earlier results from the U.S. NHANES (National Health and Nutrition Examination Survey), which was conducted in the general population of 16,968 participants, that blood benzene elevated the risk of total mortality and the mortality from cancer and heart disease, and these associations were also observed among nonsmokers (41). Of note, NHANES used a single baseline blood sample for each participant, and blood benzene is typically eliminated from the body within hours to days; thus, this exposure measurement may not represent long-term benzene exposure.

Benefiting from sufficient sample size and a long follow-up period, we found significant exposure-dependent positive associations of long-term exposure to low concentrations of residential benzene with the risk of all-cause death and death of a wide range of specific causes. The specific causes of death include CVD, ischemic heart disease, cerebrovascular disease, cancer, leukemia, multiple myeloma, NHL,

respiratory cancer, lung cancer, and respiratory disease. The effect on mortality of benzene exposure persisted across different subgroups and was somewhat stronger in younger and White people. Besides, the associations remained unchanged regardless of adjustment for confounding effects from residence $PM_{2.5}$ or NO_2 concentrations, which suggested an independent association between benzene exposure and mortality. On one hand, our research furnished substantial data to affirm that long-term exposure to ambient benzene, even at extremely low concentrations, can be notably linked with increased mortality risk. This underscores the need for further investigation of ambient benzene pollution. On the other hand, analyses of a variety of specific causes of death and vulnerable groups provide useful implications for the development of effective risk prevention strategies.

The underlying biological mechanisms linking benzene exposure and mortality remain to be defined, but several explanations are possible. Benzene was found to be associated with dyslipidemia and depletion of circulating angiogenic cells (42). Studies conducted on humans and mice have indicated that exposure to benzene can lead to changes in plasma lipoprotein concentrations, subsequently triggering blood vessel inflammation and accelerating the progression of atherosclerosis (43, 44). In addition, benzene could induce cytotoxic interactions within the bone marrow (45), changes in immune system development (46) and respiratory function (47). Moreover, it has been identified as an important carcinogen (7). Thus, benzene exposure may lead to susceptibility to various diseases throughout life, in turn elevating the risk of mortality.

Several major strengths of our analysis should be underscored. First, apart from using a prospective study design to investigate the relationships between exposure and the outcomes of interest, incorporating a substantial sample size could significantly strengthen the robustness of our findings. Furthermore, the large UK Biobank population provided adequate cases to explore a wide range of potential causes of death. Second, a Cox hazards model with time-varying exposure was implemented as a strategy to control the influence of time-varying confounding effects of benzene, thus enhancing the accuracy and precision of our results.

However, the study also has certain limitations that must be acknowledged. First, this observational study could not fully control for all unknown or unmeasured confounding factors and was unable to demonstrate a causal relationship between benzene and mortality. Second, misclassification bias may occur when using an outdoor air pollution model for exposure assignment, given the lack of information about indoor benzene, which is higher than outdoor benzene. However, considering the monotonic increasing exposure–response curve, exclusively considering outdoor benzene exposure may underestimate its hazardous effects on health. Moreover, previous studies have demonstrated easy penetration of atmospheric benzene and that outdoor benzene highly affects indoor concentrations globally. The outdoor:indoor concentration ratio is 0.84 for developed places (48). Therefore, exploring the health effects of outdoor benzene holds significant public health implications. Third, as the participants in the UK Biobank were healthy volunteers, the potential for selection bias could not be entirely eliminated. Fourth, the majority of participants in this study were predominantly of White European descent, necessitating further validation of the generalizability of our conclusions to other ethnic populations.

Conclusions

We investigated the long-term effects of exposure to low concentrations of ambient benzene on mortality risk for different diseases in the UK Biobank. We found that exposure to ambient benzene was significantly associated with increased all-cause and cause-specific mortality risk in the general population. Further investigation into the potential human health risks posed by ambient benzene is essential to develop effective strategies for regulating its concentration and protecting public health. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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