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Increased mortality risk from airborne exposure to polycyclic aromatic hydrocarbons

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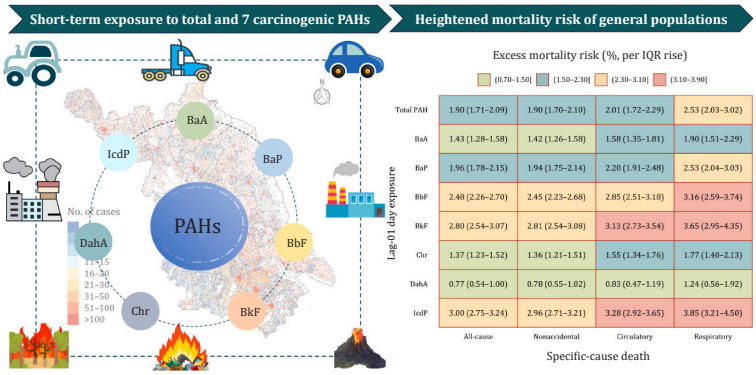
HIGHLIGHTS

- A large-scale individual-level case-crossover study to assess PAHs-mortality associations in eastern China.
- Excess mortality risks of 1.38–2.53% were linked to each 16.9-ng/m^3 increase in total PAH.
- Each 1.6-ng/m^3 rise in exposure to BaP at lag-01 day was associated with 2.2% and 2.53% increments in odds of circulatory and respiratory deaths.
- C-R analysis demonstrated a threshold-free, monotonously raised risk of mortality linked to PAHs exposure.
- Greater PAHs-associated risks of mortality were observed in the oldest-old and single dwellers.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: The potential health effects of airborne polycyclic aromatic hydrocarbons (PAHs) among general population remained extensively unstudied. This study sought to investigate the association of short-term exposure to low-level total and 7 carcinogenic PAHs with mortality risk.
Methods: We conducted an individual-level time-stratified case-crossover study in Jiangsu province of eastern China, by investigating over 2 million death cases during 2016–2019. Daily concentrations of total PAH and its 7 carcinogenic species including benzo[*a*]anthracene (BaA), benzo[*a*]pyrene (BaP), benzo[*b*]fluoranthene (BbF), benzo[*k*]fluoranthene (BkF), chrysene (Chr), dibenz[*a*,*h*]anthracene (DahA), and indeno[1,2,3-cd]pyrene (IcdP), predicted by well-validated spatiotemporal models, were assigned to death cases according to their residential addresses. We estimated mortality risk associated with short-term exposure to increase of an interquartile range (IQR) for aforementioned PAHs using conditional logistic regression.

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Results: An IQR increase (16.9 ng/m^3) in 2-day (the current and prior day) moving average of total PAH concentration was associated with risk increases of 1.90% (95% confidence interval [CI]: 1.71–2.09) in all-cause mortality, 1.90% (95% CI: 1.70–2.10) in nonaccidental mortality, 2.01% (95% CI: 1.72–2.29) in circulatory mortality, and 2.53% (95% CI: 2.03–3.02) in respiratory mortality. Risk increases of cause-specific mortality ranged between 1.42–1.90% for BaA (IQR: 1.6 ng/m^3), 1.94–2.53% for BaP (IQR: 1.6 ng/m^3), 2.45–3.16% for BbF (IQR: 2.8 ng/m^3), 2.80–3.65% for BkF (IQR: 1.0 ng/m^3), 1.36–1.77% for Chr (IQR: 1.8 ng/m^3), 0.77–1.24% for DahA (IQR: 0.8 ng/m^3), and 2.96–3.85% for IcdP (IQR: 1.7 ng/m^3).
Conclusions: This study provided suggested evidence for heightened mortality risk in relation to short-term exposure to airborne PAHs in general population. Our findings suggest that airborne PAHs may pose a potential threat to public health, emphasizing the need of more population-based evidence to enhance the understanding of health risk under the low-dose exposure scenario.

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are widespread environmental contaminants primarily formed during incomplete combustion of fuels or pyrolysis of organic materials [1]. Given their cytotoxicity, mutagenicity, and carcinogenicity [2,3], 16 PAHs were categorized as priority contaminants by the United States Environmental Protection Agency (USEPA) [4]. Accumulated evidence from occupational population cohorts linked increased mortality risks of cancers with exposure to high-level PAHs [5–7], and the most of these studies employed benzo[*a*]pyrene (BaP) as a proxy to assess the adverse health effects of PAHs [2]. Yet, the most sensitive gene sets regulated by PAHs and BaP were distinctly different in vitro transcriptional benchmark dose models, suggesting that the carcinogenicity of BaP could not reflect that of overall PAHs [8]. In view of the diversity and toxicity of PAHs, their health risks should be separately quantified, so as to further determine components requiring priority management.

Despite the declining trend in atmospheric PAHs emission, China released 106 thousand tons PAHs into the air in 2007, contributing to more than one-fifth global emission of PAHs [9]. However, due to the lack of fine-scale and full-coverage airborne PAHs data, population-based evidence under low-level PAHs exposure remains extensively scarce [10,11]. To our knowledge, only one recent quasi-experiment study linked PAHs exposure to cancer mortality in general public [12], but associations with a wider spectrum of death causes (e.g., all-cause and cardiopulmonary diseases) have not been investigated in both developed and developing countries. Given the co-existence of extensive PAHs emission and high population density in China, sustained low-dose exposure to atmospheric PAHs may pose an innegligible public health threat. Nowadays, motivated by recent advances of satellite remote sensing, spatio-temporal assessments of PAHs exposure should be feasible for a better understanding of the health impacts in association with mortality, particularly in low-dose exposure scenario.

Here, we conducted an individual-level case-crossover study, by involving more than 2 million death cases in Jiangsu Province, China. We primarily aimed to establish the concentration-response (C-R) associations of mortality risks with airborne total and 7 carcinogenic PAHs. The secondary purpose was to identify susceptible population by comparing the estimated health risk across subgroups.

2. Method

2.1. Health outcome data

Province-wide death records during 1 January 2016 to 31 December 2019 were obtained from the Death Surveillance System in Jiangsu Provincial Center for Disease Control and Prevention. Individual information including cause of death, age, sex, ethnicity, education level, marital status, and residential addresses were extracted. Cause of death was coded according to the 10th Revision of International Classification of Disease (ICD-10), and we included all-cause, nonaccidental (A00-R99), circulatory (I00-I99), and respiratory (J00-J99) mortality for analysis. The wide-distributed death cases at a 1 × 1-km resolution were geographically illustrated in Fig. 1a.

2.2. Environmental exposure assessment

Pollutants of interest in this study were total PAH and its 7 species, in which total PAH is a large class of organic chemicals composed of two or more condensed benzene rings arranged in different configurations, and these components comprising of benz[*a*]anthracene (BaA), benzo[*b*]fluoranthene (BbF), benzo[*k*]fluoranthene (BkF), BaP, chrysene (Chr), dibenz[*a*,*h*]anthracene (DahA), indeno[1,2,3-cd]pyrene (IcdP) are probable human carcinogens determined by USEPA [1,4]. We used a previously developed four-dimensional spatiotemporal deep forest (4D-STDF) model [13,14] to separate ambient PAHs from the total $PM_{2.5}$ mass. The nonlinear relationship was established by considering their photochemical reactions with the inclusion of major polluted gases (sulphur dioxide, nitrogen dioxide, and carbon monoxide) [15], as well as meteorological reanalysis (e.g., temperature and radiation), and other surface- and population-related auxiliary factors. This dataset was created at a spatial resolution of 10 km on a daily basis since 2013, and it has been extensively validated at a total of 126 long-term operational stations across China [13], using the widely used out-of-sample approach (random division of data samples into ten folds, with 9 folds used for model training and the remaining 1 fold for testing). The validation results demonstrated an average cross-validation coefficient (CV-R^2) of 0.65 and a root-mean-square error (RMSE) of 66.69 ng/m^3 between the daily PAH retrievals and measurements. The average concentrations of total PAH and its 7 carcinogenic species for study areas between 2016 and 2019 were shown in Fig. 1b.

To control potential confounding effects caused by other air pollutants, we derived daily estimates of fine particulate matter ($PM_{2.5}$) and maximum 8-h average ozone (O_3) data from the CHAP dataset [13,16]. The daily $PM_{2.5}$ (1 km × 1 km) and O_3 (10 km × 10 km) datasets were generated utilizing satellite-derived spatiotemporal machine-learning models, combined with ground-based observations. Estimates of $PM_{2.5}$ dataset had a good consistency with ground-based $PM_{2.5}$ measurements, with the average CV-R^2 of 0.92 and RMSE of 6.32 μg/m^3 in different years [13]. Validation results of O_3 estimates showed a high CV-R^2 of 0.87 and a low RMSE of 17.10 μg/m^3 during 2013–2020 [16]. The detailed information in relation to $PM_{2.5}$ and O_3 datasets was described in our prior publications [13,16,17]. Daily temperature and dew point temperature data (0.1° × 0.1°) were derived from European Centre for Medium-Range Weather Forecasts (ECMWF) datasets to account for potential confounding effects caused by meteorological factors. Relative humidity was calculated using the method recommended by the National Weather Service [18].

Daily estimates of PAHs and air pollutants, as well as meteorological factors, were assigned to the deceased according to their dates of death and residential addresses. Specifically, we firstly geocoded residential latitude and longitude of each death case, and linked the death location with the closest spatial grid cell of the aforementioned environmental

variables, and then extracted the time-dependent estimates on the current (lag-0) and prior (lag-1) days of death. Environmental exposures of 2-day moving mean (lag-01) were calculated by averaging the estimates of lag-0 and lag-1 day.

2.3. Statistical analysis

Basic characteristics of study population were summarized as counts and percentages, and environmental exposures of air pollutants and meteorological factors were presented as mean, standard deviation (SD), and percentiles. We calculated Pearson's correlation coefficients (ρ) to measure the correlation between air pollutants and meteorological factors estimated at lag-0 day. Individual-level, time-stratified case-crossover (TSCC) design was utilized to assess the associations of short-term exposure to total and 7 carcinogenic PAHs with mortality risk. All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), and two-sided tests with *P*-value <0.05 were considered to be statistically significant.

2.3.1. Main analysis

In TSCC design, each case serves as its own control, and the matched case-control pair is viewed as a stratum. Briefly, the death date of each individual was defined as case day, and the same days in other weeks within the same calendar month and year were chosen as control days. Such a self-matching design allows for the control of individual-level confounding variables (e.g., demographic characteristics and gene susceptibility) without significant changes within a month, effectively mitigating potential bias caused by long-term time trends of environmental exposures [19]. This well-established approach has been widely used to evaluate the associations between short-term exposure to air pollution and health outcomes (e.g., mortality and morbidity) [19–22].

For each cause of death, we created a case-crossover dataset, and ran conditional logistic regression model to investigate its association with PAHs. Considering the potential collinearity between total PAH and its 7 carcinogenic species, we included each PAH composition separately in the model. Several predefined variables, including daily mean temperature, relative humidity, and national public holiday, were incorporated as adjusted covariates. Temperature and relative humidity were included in the model as the natural cubic spline (NCS) terms with 6 and 3 degrees of freedom (df) [22–24] respectively to capture their nonlinear associations with risk of death; public holiday was included as a binary indicator to account for vocation effects. We estimated PAHs-related mortality risk at multiple exposure windows (lag-0, lag-1, and lag-01 day), and reported corresponding excess mortality risk (%) and 95% confidence interval (CI) associated with an interquartile range (IQR) rise of each PAH composition. In line with prior studies [19,23], the lag-01 day was selected as main exposure metric in subsequent analyses to capture the delayed and accumulated effects. We investigated the C-R relationships via fitting PAHs as a NCS term with 3 df [22,25], and examined the nonlinearity using likelihood ratio tests [21]. Given the limited constraint of extreme values, the C-R associations were plotted for the concentration ranges between 1st and 99th percentiles of PAHs [26].

2.3.2. Subgroup and sensitive analyses

We performed subgroup analyses stratified by age, sex, residence, education level, and marital status, to identify potential susceptible population. To ensure statistical power, widowed, unmarried, and divorced individuals were unified as the single, while those with unknown marital status were excluded from stratified analyses. In age-specific analysis, we divided the full dataset into four groups of <65, 65–74, 75–84, and ≥85 years old, and testified the linear trend of PAHs-associated risks based on the median age in each group [27]. We examined the potential effect modifications in other subgroups through two-sample z-test [25,28].

Several sensitive analyses were conducted to check the robustness of the estimated PAHs-mortality associations. First, bi- and tri-pollutant models were fitted by additionally adjusting for ambient $PM_{2.5}$ and/or O_3. Second, we changed df of NCS function for temperature (5−7) and relative humidity (2−4) to check the impacts of different modelling specifications. Third, alternative lag windows of meteorological factors were applied to capture their potential lagged confounding effects.

3. Results

We identified over 2 million deaths between 2016 and 2019, with 92.0% from nonaccidental cause, 37.9% from circulatory cause, and 11.9% from respiratory cause (Table 1). Of the 2070101 all-cause death cases, nearly one-fifth occurred before the age of 65, and more than half were men. During the study periods, the average concentration of total

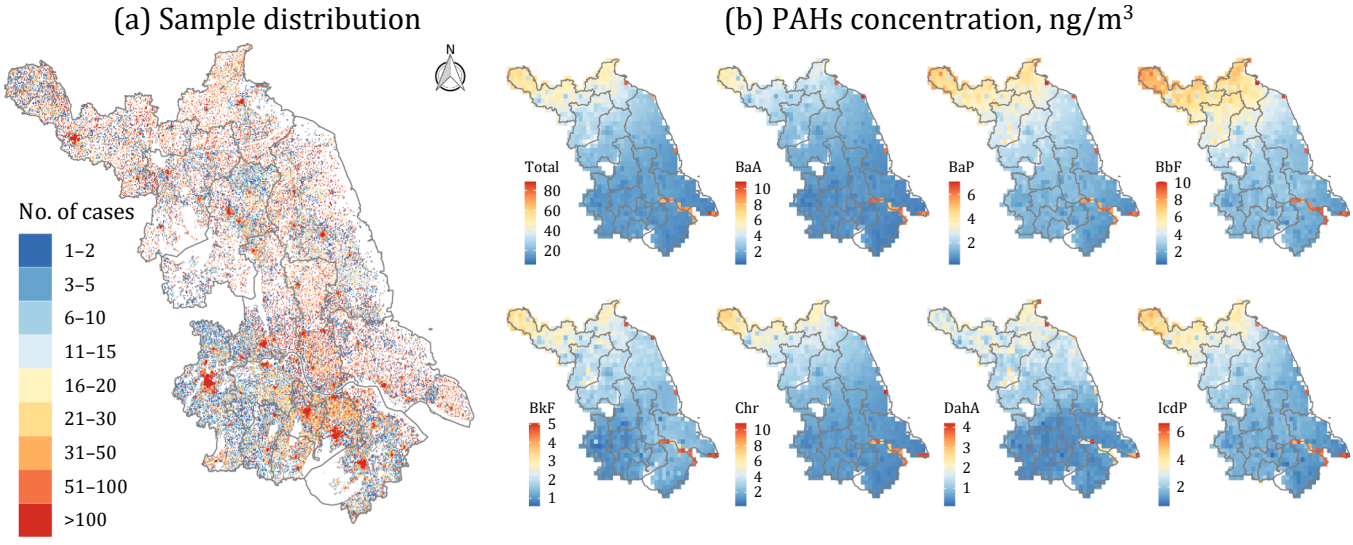


Fig. 1. The spatial distribution of study population and average PAHs concentration during 2016–2019 in Jiangsu province, China. Note: The grids with different colors in Fig. 1a indicated the number of death cases at a 1 × 1-km resolution. Abbreviations: PAH, polycyclic aromatic hydrocarbon; BaA, benzo[*a*]anthracene; BaP, benzo[*a*]pyrene; BbF, benzo[*b*]fluoranthene; BkF, benzo[*k*]fluoranthene; Chr, chrysene; DahA, dibenz[*a*,*h*]anthracene; IcdP, indeno[1,2,3-cd]pyrene.

Table 1
Descriptive characteristics of study population during 2016–2019.

Characteristics	Case number (%)
All-cause death	2070101 (100.0)
Nonaccidental (ICD code: A00-R99)	1905209 (92.0)
Circulatory (ICD code: I00-I99)	785567 (37.9)
Respiratory (ICD code: J00-J99)	247336 (11.9)
Age at death, yrs	75.5 ± 14.9
<65	409558 (19.8)
[65, 75)	407995 (19.7)
[75, 85)	670463 (32.4)
≥85	582085 (28.1)
Sex	
Men	1139734 (55.1)
Women	930367 (44.9)
Ethnicity	
Han	2065700 (99.8)
Others	4401 (0.2)
Education level (yrs)	
Middle school and below (≤9)	1927709 (93.1)
Above middle school (>9)	142392 (6.9)
Marital status	
Married	1316863 (63.6)
Widowed	653678 (31.6)
Unmarried	73167 (3.5)
Divorced	19833 (1.0)
Unknown	6560 (0.3)
Residence	
Urban	921284 (44.5)
Rural	1148817 (55.5)

Table 2
Summary statistics of air pollutants and meteorological conditions on case days and control days from all-cause death during 2016–2019.

Variables	Mean	SD	Percentiles				
			P_1	P_{25}	P_{50}	P_{75}	P_{99}
On case days (n = 2070101)							
Total PAH, ng/m^3	24.6	29.6	4.7	9.2	14.6	26.3	159.3
BaA	2.2	3.3	0.2	0.6	1.0	2.2	17.1
BaP	2.3	2.9	0.3	0.8	1.3	2.4	14.9
BbF	3.8	4.4	0.4	1.3	2.2	4.2	22.7
BkF	1.7	1.4	0.4	1.0	1.3	2.0	7.2
Chr	2.6	4.2	0.3	0.6	1.1	2.5	21.6
DahA	1.0	1.1	0.1	0.4	0.6	1.1	5.2
IcdP	2.2	2.4	0.3	0.9	1.4	2.5	12.1
$PM_{2.5}$, μg/m^3	50.0	30.5	12.1	28.3	42.0	63.0	154.5
O_3, μg/m^3	103.8	44.2	28.5	69.9	95.1	132.4	223.7
Meteorological conditions							
Temperature, ℃	15.0	9.6	-2.6	6.4	15.2	23.3	32.1
Relative humidity, %	65.3	14.2	32.9	55.4	65.7	75.6	92.8
On control days (n = 7028213)							
Total PAH, ng/m^3	24.4	29.4	4.6	9.1	14.5	26.0	158.6
BaA	2.2	3.3	0.2	0.6	0.9	2.2	17.0
BaP	2.2	2.8	0.3	0.8	1.3	2.4	14.8
BbF	3.7	4.4	0.4	1.3	2.1	4.1	22.7
BkF	1.7	1.4	0.4	1.0	1.3	2.0	7.2
Chr	2.5	4.1	0.3	0.6	1.1	2.4	21.4
DahA	1.0	1.1	0.1	0.4	0.6	1.1	5.2
IcdP	2.2	2.3	0.3	0.8	1.4	2.5	12.0
$PM_{2.5}$, μg/m^3	49.5	30.6	12.1	27.9	41.3	62.4	155.1
O_3, μg/m^3	103.3	43.9	28.5	69.6	94.7	131.4	222.4
Meteorological conditions							
Temperature, ℃	15.0	9.5	-2.6	6.5	15.3	23.3	31.7
Relative humidity, %	65.3	14.2	32.8	55.4	65.8	75.8	92.7

Abbreviations: SD, standard deviation; PAH, polycyclic aromatic hydrocarbon; BaA, benzo[*a*]anthracene; BaP, benzo[*a*]pyrene; BbF, benzo[*b*]fluoranthene; BkF, benzo[*k*]fluoranthene; Chr, chrysene; DahA, dibenz[*a*,*h*]anthracene; IcdP, indeno[1,2,3-cd]pyrene; $PM_{2.5}$, particulate matter in aerodynamic diameter ≤2.5 μm; O_3, ozone.

PAH was 24.6 (SD: 29.6) ng/m^3 on case days and 24.4 (29.4) ng/m^3 on control days (Table 2). The mean concentration on case days of 7 carcinogenic species together accounted for 64.2% of total PAH, ranging from 1.0 (1.1) ng/m^3 for DahA to 3.8 (4.4) ng/m^3 for BbF. Total PAH was highly correlated with 6 carcinogenic PAHs ($\rho \geq 0.9$) with exception for DahA, and moderately or weakly ($-0.6 < \rho < 0.6$) correlated with ambient $PM_{2.5}$, O_3, and meteorological conditions (Fig. S1).

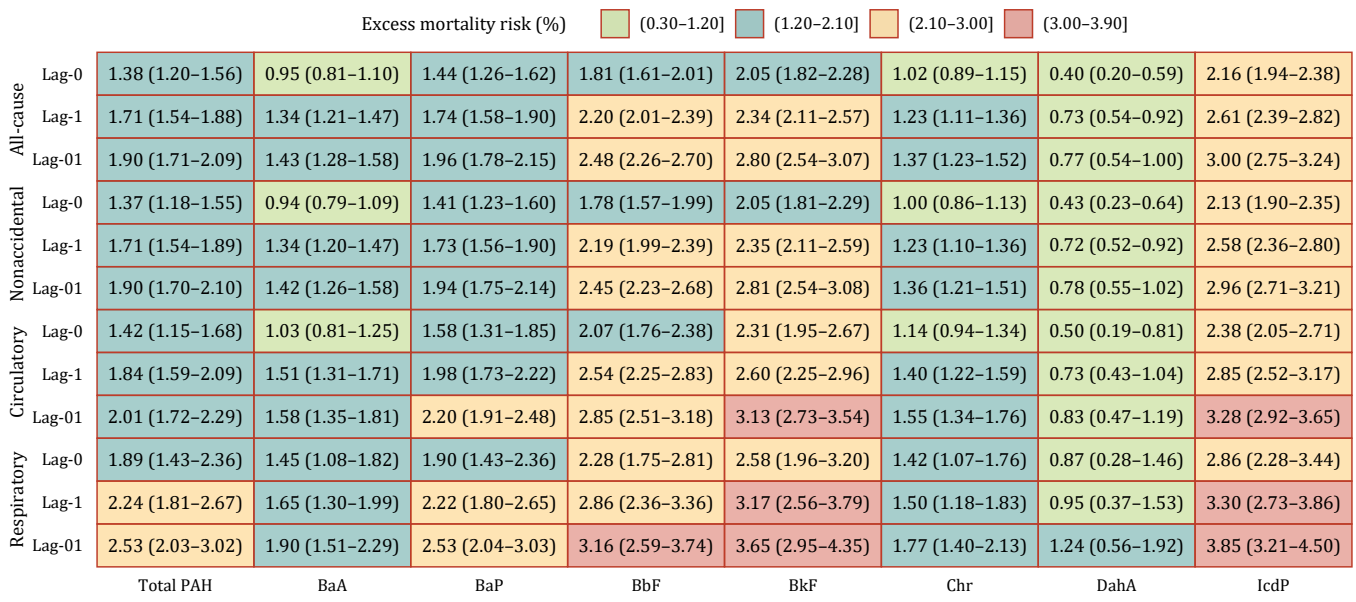
We estimated associations of mortality with short-term exposure to total and 7 carcinogenic PAHs, and observed consistent risk growths under multiple death causes and lag windows (Fig. 2). For instances, an IQR rise (16.9 ng/m^3) in 2-day moving average of total PAH concentration was associated with risk increases of 1.90% (95% CI: 1.71–2.09) in all-cause mortality, 1.90% (95% CI: 1.70–2.10) in nonaccidental mortality, 2.01% (95% CI: 1.72–2.29) in circulatory mortality, and 2.53% (95% CI: 2.03–3.02) in respiratory mortality. Varying magnitudes of risk increases in 7 carcinogenic PAHs were consistently seen, with excess risks of 1.42–1.90% for BaA (IQR: 1.6 ng/m^3), 1.94–2.53% for BaP (IQR: 1.6 ng/m^3), 2.45–3.16% for BbF (IQR: 2.8 ng/m^3), 2.80–3.65% for BkF (IQR: 1.0 ng/m^3), 1.36–1.77% for Chr (IQR: 1.8 ng/m^3), 0.77–1.24% for DahA (IQR: 0.8 ng/m^3), and 2.96–3.85% for IcdP (IQR: 1.7 ng/m^3). Sensitive analyses showed that these estimated associations changed slightly after adjusting for O_3 and changing df of temperature and relative humidity (Table S1). Despite a weakening in the effect size, the positive associations also largely remained via adjusting for $PM_{2.5}$ and extending the lag windows of meteorological factors.

C-R analysis illustrated relationships between cause-specific mortality and short-term exposure to total PAH and its 7 carcinogenic species. Overall, we revealed a significantly nonlinear ($P < 0.001$), monotonically increasing risk associated with acute exposure to PAHs, and found similar risk patterns in mortality of multiple causes linked to separate exposure to total PAH or its species (Fig. 3 & Fig. S2). For instance, in associations of total PAH exposure with death risk of different causes, C-R curves exhibited a steep incline below approximately 15 ng/m^3, while the slope gradually became less pronounced under higher PAH ranges. Notably, no distinct thresholds were detected within a wide concentration range of 4.7–159.3 ng/m^3.

The alike between-subgroup effect modification across total PAH and its 7 carcinogenic species was identified in analyses, stratified by sex, age, residence, and education level (Fig. 4 & Fig. S3). For instance, despite a higher risk of respiratory mortality in men (2.95%, 95% CI: 2.27–3.63) compared to women (2.06%, 95% CI: 1.33–2.78), we did not identify evident between-sex differences for 4 main causes of death related to total PAH exposure. We found linearly raised risks (P for trend ≤0.005) related to total exposure of all-cause, nonaccidental and circulatory mortality in older groups, with the greatest effects of 2.59–2.66% in the oldest-old population (age ≥85) compared to those aged younger than 65 years (1.23–1.37%), but did not detect significant linear trend of respiratory mortality (P for trend = 0.219), despite an increased risk in older stratum. Parallelly heightened risk associated with exposure to PAHs was found in urban-rural residents and cases with different education level. In analyses stratified by marital status, findings indicated greater risk increases for specific causes (excluding respiratory deaths) in single cases, when exposed to total PAH and its 6 carcinogenic species apart from DahA.

4. Discussion

To the best of our knowledge, this study represented the first attempt to assess the association between mortality risk and low-level airborne PAHs in the non-occupational population using a large-scale epidemiological survey. By analyzing data from over 2 million deaths, we provided novel evidence that even at extremely low levels, short-term exposure to airborne total and 7 carcinogenic PAHs was associated with an increased risk of death. Furthermore, our findings shed light on the impacts of this exposure on vulnerable population, specifically the



		Total PAH	BaA	BaP	BbF	BkF	Chr	DahA	IcdP
All-cause	Lag-0	1.38 (1.20–1.56)	0.95 (0.81–1.10)	1.44 (1.26–1.62)	1.81 (1.61–2.01)	2.05 (1.82–2.28)	1.02 (0.89–1.15)	0.40 (0.20–0.59)	2.16 (1.94–2.38)
	Lag-1	1.71 (1.54–1.88)	1.34 (1.21–1.47)	1.74 (1.58–1.90)	2.20 (2.01–2.39)	2.34 (2.11–2.57)	1.23 (1.11–1.36)	0.73 (0.54–0.92)	2.61 (2.39–2.82)
	Lag-01	1.90 (1.71–2.09)	1.43 (1.28–1.58)	1.96 (1.78–2.15)	2.48 (2.26–2.70)	2.80 (2.54–3.07)	1.37 (1.23–1.52)	0.77 (0.54–1.00)	3.00 (2.75–3.24)
Nonaccidental	Lag-0	1.37 (1.18–1.55)	0.94 (0.79–1.09)	1.41 (1.23–1.60)	1.78 (1.57–1.99)	2.05 (1.81–2.29)	1.00 (0.86–1.13)	0.43 (0.23–0.64)	2.13 (1.90–2.35)
	Lag-1	1.71 (1.54–1.89)	1.34 (1.20–1.47)	1.73 (1.56–1.90)	2.19 (1.99–2.39)	2.35 (2.11–2.59)	1.23 (1.10–1.36)	0.72 (0.52–0.92)	2.58 (2.36–2.80)
	Lag-01	1.90 (1.70–2.10)	1.42 (1.26–1.58)	1.94 (1.75–2.14)	2.45 (2.23–2.68)	2.81 (2.54–3.08)	1.36 (1.21–1.51)	0.78 (0.55–1.02)	2.96 (2.71–3.21)
Circulatory	Lag-0	1.42 (1.15–1.68)	1.03 (0.81–1.25)	1.58 (1.31–1.85)	2.07 (1.76–2.38)	2.31 (1.95–2.67)	1.14 (0.94–1.34)	0.50 (0.19–0.81)	2.38 (2.05–2.71)
	Lag-1	1.84 (1.59–2.09)	1.51 (1.31–1.71)	1.98 (1.73–2.22)	2.54 (2.25–2.83)	2.60 (2.25–2.96)	1.40 (1.22–1.59)	0.73 (0.43–1.04)	2.85 (2.52–3.17)
	Lag-01	2.01 (1.72–2.29)	1.58 (1.35–1.81)	2.20 (1.91–2.48)	2.85 (2.51–3.18)	3.13 (2.73–3.54)	1.55 (1.34–1.76)	0.83 (0.47–1.19)	3.28 (2.92–3.65)
Respiratory	Lag-0	1.89 (1.43–2.36)	1.45 (1.08–1.82)	1.90 (1.43–2.36)	2.28 (1.75–2.81)	2.58 (1.96–3.20)	1.42 (1.07–1.76)	0.87 (0.28–1.46)	2.86 (2.28–3.44)
	Lag-1	2.24 (1.81–2.67)	1.65 (1.30–1.99)	2.22 (1.80–2.65)	2.86 (2.36–3.36)	3.17 (2.56–3.79)	1.50 (1.18–1.83)	0.95 (0.37–1.53)	3.30 (2.73–3.86)
	Lag-01	2.53 (2.03–3.02)	1.90 (1.51–2.29)	2.53 (2.04–3.03)	3.16 (2.59–3.74)	3.65 (2.95–4.35)	1.77 (1.40–2.13)	1.24 (0.56–1.92)	3.85 (3.21–4.50)

Fig. 2. Estimates of excess mortality risk (%) and 95% confidence interval for all-cause, nonaccidental, circulatory, and respiratory mortality associated with an interquartile range increase of exposure to total PAH (16.9 ng/m^3), BaA (1.6 ng/m^3), BaP (1.6 ng/m^3), BbF (2.8 ng/m^3), BkF (1.0 ng/m^3), Chr (1.8 ng/m^3), DahA (0.8 ng/m^3) and IcdP (1.7 ng/m^3). Abbreviations: PAH, polycyclic aromatic hydrocarbon; BaA, benzo[*a*]anthracene; BaP, benzo[*a*]pyrene; BbF, benzo[*b*]fluoranthene; BkF, benzo[*k*]fluoranthene; Chr, chrysene; DahA, dibenz[*a*,*h*]anthracene; IcdP, indeno[1,2,3-cd]pyrene.

oldest-old adults, which may thereby provide valuable insights for the development of effective risk prevention strategies.

Using an individual-level case-crossover design, we observed significant increases in risk of mortality associated with short-term exposure to airborne total and 7 carcinogenic PAHs among general population. These findings extended prior European cohort evidence from occupational population, including workers of asphalt [29], coke oven [30], and other industries [7], which linked shortened long-term survival to high-dose exposure to PAHs. It is worth noting that PAHs exposure in these studies was estimated through questionnaire [29], historical geographic models [30], or air sampling (BaP as the proxy) [7], which may not accurately reflect the PAHs exposure of workers. In the present study, we conducted individual-level exposure assessment using gridded PAHs estimates at residential addresses, and could largely reduce exposure bias and well quantify PAHs-associated health risks. In general population, great interests were primarily focused on assessing the health effects of PAHs through dietary intake and dermal contact [31,32], while there is a significant scarcity of epidemiological evidence concerning the underlying effects of airborne PAHs exposure [10]. Importantly, airborne exposure to PAHs may pose a greater risk to human health compared to dietary intake and dermal contact, as it directly affects target organs without undergoing liver detoxification [33]. This study provided robust evidence for PAHs-related mortality risks from general population perspective, and highlighted the urgent need for preventive measures to reduce PAHs exposure in airborne environments.

Greater PAHs-associated risks were estimated for cardiopulmonary deaths in our analysis. Echoing our results, recent studies have reported positive associations between exposure to PAHs and risks of circulatory (e.g., coronary heart disease and stroke) [34,35] and respiratory (e.g., chronic obstructive pulmonary disease and lung cancer) [36,37] diseases. These findings could be partially verified by prior toxicological and molecular mechanism studies. First, inhalation of PAHs has been shown to promote the expression of pro-inflammatory cytokines (e.g., CXCL8 and TNF-α) and trigger the invasion of macrophages and neutrophils into the lungs [38,39], thus leading to airway inflammation and impaired lung function [40]. Second, PAHs entering the circulation system through the alveolar capillary membrane may result in vascular endothelial dysfunction and atherosclerosis [41,42], thereby increasing the risk of coronary heart disease. Third, PAHs can cause damage to cardiac cells by disrupting the balance between the generation and elimination of free radicals [43], ultimately contributing to the development of cardiovascular diseases [44]. These possible mechanisms suggest that the cardiopulmonary systems may be particularly susceptible to the harmful effects of airborne PAHs. Additionally, alterations induced by PAHs in epigenetic mechanisms (e.g., DNA methylation, histone modification, and miRNA regulation) can accelerate the onset and progression of diverse diseases [45,46]. Also, exposure to PAHs, even in the low-dose scenario, may instigate oxidative stress, a pivotal initiator in the genesis of numerous acute and chronic ailments [47].

C-R analysis in our study demonstrated a threshold-free, monotonously raised risk of mortality associated with short-term exposure to airborne PAHs. Instead of observing a linear association, the slopes of C-R curves were consistently steeper at low doses for all-cause, non-accidental, and cardiopulmonary deaths. In eastern China, a similar C-R pattern was exhibited in a recent quasi-experiment study evaluating long-term associations between PAHs and cancer mortality [12]. Prior toxicological evidence also suggested that low-dose genotoxic compounds like PAHs may elicit a sharp increase in mortality risk, without a discernible no-effect threshold dose [2]. Currently, ambient air quality standard in China [48] only released a limit value for BaP, with a daily average concentration of 2.5 ng/m^3. However, based on the C-R curve of BaP stemmed from our rigorous epidemiology design and province-wide surveillance data, the existing standard may be inadequate and insufficient in protecting public health. In addition, there are no mandatory standards for airborne total and other specific PAHs exposure due to the wide lack of aggregated evidence from diverse populations and regions [10]. More population-based studies should be warranted in the coming decade, so as to comprehensively investigate the health effect of airborne PAHs and provide scientific support for the formulation of appropriate environment emission regulation.

Considering the decline in multi-organ function and metabolic capacity [49,50], older adults may be more susceptible to ambient air pollution. For instance, higher risk of death associated with ambient

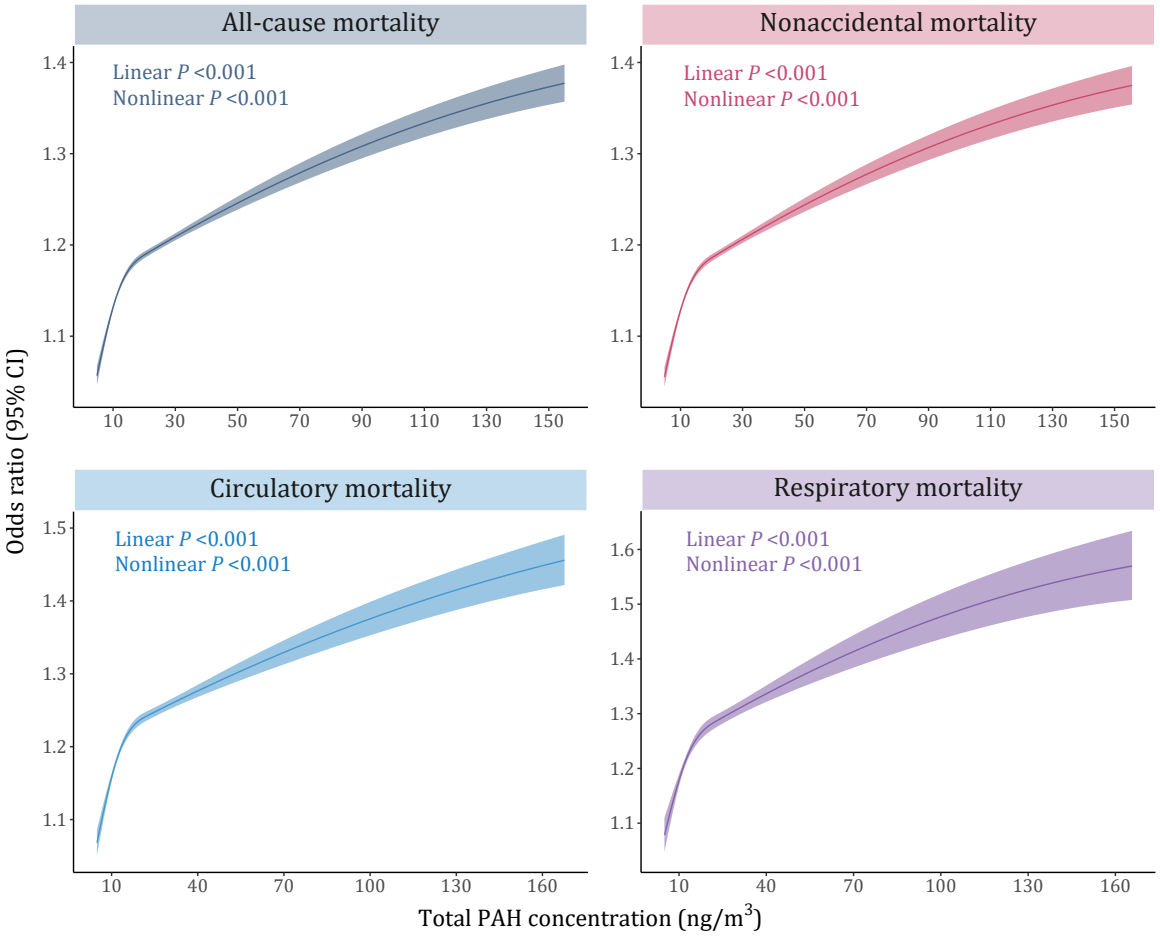


Fig. 3. Concentration-response associations between exposure to total PAH at lag-01 day and mortality risk. Notes: Linear *P* indicates the statistical significance of the exposure-risk association estimated in conditional logistic models fitting PAHs as a linear term, while nonlinear *P* represents degree of violation from a linear relationship; the odds ratio was estimated based on the minimum exposure level; the solid lines and shaded bands indicate the changes in mortality risk and corresponding 95% confidence intervals, respectively. Abbreviations: PAH, polycyclic aromatic hydrocarbon; CI, confidence interval.

Subgroup	A All-cause: Excess mortality risk (%)	A All-cause: *P*-value*	B Nonaccidental: Excess mortality risk (%)	B Nonaccidental: *P*-value*	C Circulatory: Excess mortality risk (%)	C Circulatory: *P*-value*	D Respiratory: Excess mortality risk (%)	D Respiratory: *P*-value*
Sex		0.918		0.802		0.903		0.113
Men	1.92 (1.66–2.18)		1.86 (1.60–2.13)		2.03 (1.62–2.43)		2.95 (2.27–3.63)	
Women	1.89 (1.60–2.17)		1.94 (1.65–2.24)		1.98 (1.57–2.39)		2.06 (1.33–2.78)	
Age, yrs		0.005		<0.001		0.001		0.219
<65	1.37 (0.94–1.80)		1.23 (0.76–1.69)		1.36 (0.56–2.16)		1.59 (-0.42–3.64)	
[65, 75)	1.40 (0.96–1.85)		1.37 (0.91–1.83)		1.21 (0.50–1.92)		2.28 (0.87–3.71)	
[75, 85)	1.89 (1.56–2.22)		1.89 (1.55–2.23)		2.03 (1.55–2.50)		2.42 (1.63–3.22)	
≥85	2.63 (2.28–2.98)		2.66 (2.30–3.02)		2.59 (2.10–3.08)		2.83 (2.07–3.58)	
Residence		0.739		0.685		0.964		0.532
Urban	1.84 (1.52–2.17)		1.82 (1.49–2.16)		2.02 (1.52–2.52)		2.79 (1.95–3.63)	
Rural	1.95 (1.71–2.18)		1.95 (1.71–2.20)		2.00 (1.65–2.35)		2.42 (1.81–3.04)	
Education level, yrs		0.936		0.692		0.745		0.090
≤9	1.90 (1.70–2.09)		1.91 (1.70–2.11)		2.00 (1.71–2.29)		2.45 (1.95–2.96)	
>9	1.94 (1.04–2.85)		1.68 (0.73–2.65)		2.27 (0.75–3.82)		5.14 (2.12–8.24)	
Marital status		0.066		0.036		0.165		0.836
Married	1.70 (1.47–1.94)		1.66 (1.42–1.91)		1.80 (1.44–2.17)		2.58 (1.92–3.24)	
Single	2.29 (1.96–2.61)		2.34 (2.00–2.68)		2.34 (1.87–2.82)		2.46 (1.70–3.22)	

Fig. 4. Subgroup-specific estimates of excess mortality risk (%) and 95% confidence interval for all-cause, nonaccidental, circulatory, and respiratory mortality associated with an interquartile range increase of exposure to total PAH at lag-01 day. Note: * *P*-value <0.05 indicates statistically significant effect heterogeneity between strata. Abbreviation: PAH, polycyclic aromatic hydrocarbon.

$PM_{2.5}$ in the elderly was identified from two national case-crossover analyses based on millions of American [20] and Brazilian [28]. In line with these findings, we also found dramatically greater PAHs-related risks of death in Chinese older populations. Ambient formaldehyde, another persistent organic pollutant, has more adverse health effects on very old population [24]. Synthetic evidence suggested that senior dwellers, particularly the oldest-old, may be more vulnerable to airborne toxic substances, thereby sufferring from greater health risk in exposure to airborne PAHs. The systemic review revealed higher PAHs concentration in the indoor compared with outdoor environments [51], and traffic emission and biomass combustion may be the major contributors of indoor PAHs [52]. Considering that the oldest-old stays indoors more, improving indoor air quality (e.g., using clean energy) may be of great importance to mitigate PAHs-related health hazards and drive healthy longevity and well-being over life course.

In our stratified analysis, single individuals were at higher risks of mortality when being exposed to PHAs. This solitary status may lead to social isolation and loneliness [53], which can exacerbate the psychical frailty [54] and physical vulnerability [55]. Such sub-health condition may render single persons more susceptible to environmental hazardous substances including PAHs, thereby heightening their exposure-related risk of mortality. Given variability in exposure, contamination sources, and individual susceptibility, accurately assessing exposure levels of PAHs and their adverse effects on various demographic groups remains a key challenge. Future large-scale and precision-designed population-based investigations are still needed to fully understand health impacts of short- and long-term exposure to ambient PAHs, for the sake of developing appropriate government regulatory policies and individual preventive measures.

Some limitations should be noted in this study. First, though the risk effects of PAHs exposure were largely robust in bi- and tri-pollutant analyses considering the potential bias confounded by $PM_{2.5}$ and O_3, it is still challenging in epidemiologic studies to completely separate the health effects of PAHs from $PM_{2.5}$ and O_3, due to the nature of co-exposure and shared sources of multiple air pollutants. Second, although time-invariant confounding factors were well controlled in the case-crossover design and we further adjusted for daily temperature and relative humidity, the estimated associations may be partially affected by some residual or unmeasured time-varying confounding (e.g., indoor air quality and time activity pattern). Third, the study was conducted in a single province of China, even though it encompasses a considerably large population (~ 85 million in 2020). The generalization of our results may be limited, and the findings should be cautiously interpreted to other regions or countries.

5. Conclusions

This study provided novel evidence that short-term exposure airborne total and 7 carcinogenic PAHs is associated with an increased risk of all-cause, nonaccidental, circulatory and respiratory mortality. C-R associations suggested a significantly increased mortality risk in exposure to PAHs, even at extremely low doses. Additionally, growing vulnerability to PAHs-related risk was seen in older population. These findings may substantially expand current knowledge on the acute health effects of PAHs in general population, and highlight the crucial needs for the development of appropriate public health regulation with regard to airborne PAHs.

CRediT authorship contribution statement

Yunquan Zhang: Writing – review & editing, Supervision, Software, Methodology, Funding acquisition, Conceptualization. **Jing Wei:** Resources, Methodology, Data curation. **Yaqi Wang:** Writing – original draft, Visualization, Software, Methodology, Formal analysis. **Hao Zheng:** Resources, Methodology, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2024.134714.

References

[1] Kim, K.-H., Jahan, S.A., Kabir, E., Brown, R.J.C., 2013. A review of airborne polycyclic aromatic hydrocarbons (PAHs) and their human health effects. Environ Int 60, 71–80.
[2] Bostrom, C.E., Gerde, P., Hanberg, A., Jernstrom, B., Johansson, C., Kyrklund, T., et al., 2002. Cancer risk assessment, indicators, and guidelines for polycyclic aromatic hydrocarbons in the ambient air. Environ Health Perspect 110 (Suppl 3 (Suppl 3)), 451–488.
[3] Hertz-Picciotto, I., Herr, C.E.W., Yap, P.-S., Dostál, M., Shumway, R.H., Ashwood, P., et al., 2005. Air pollution and lymphocyte phenotype proportions in cord blood. Environ Health Perspect 113 (10), 1391–1398.
[4] Mallah, M.A., Changxing, L., Mallah, M.A., Noreen, S., Liu, Y., Saeed, M., et al., 2022. Polycyclic aromatic hydrocarbon and its effects on human health: an overeview. Chemosphere 296, 133948.
[5] Bosetti, C., Boffetta, P., La Vecchia, C., 2007. Occupational exposures to polycyclic aromatic hydrocarbons, and respiratory and urinary tract cancers: a quantitative review to 2005. Ann Oncol 18 (3), 431–446.
[6] Armstrong, B., Hutchinson, E., Unwin, J., Fletcher, T., 2004. Lung cancer risk after exposure to polycyclic aromatic hydrocarbons: a review and meta-analysis. Environ Health Perspect 112 (9), 970–978.
[7] Petit, P., Maître, A., Persoons, R., Bicout, D.J., 2019. Lung cancer risk assessment for workers exposed to polycyclic aromatic hydrocarbons in various industries. Environ Int 124, 109–120.
[8] Chang, Y., Huynh, C.T.T., Bastin, K.M., Rivera, B.N., Siddens, L.K., Tilton, S.C., 2020. Classifying polycyclic aromatic hydrocarbons by carcinogenic potency using in vitro biosignatures. Toxicol Vitr 69, 104991.
[9] Shen, H., Huang, Y., Wang, R., Zhu, D., Li, W., Shen, G., et al., 2013. Global atmospheric emissions of polycyclic aromatic hydrocarbons from 1960 to 2008 and future predictions. Environ Sci Technol 47 (12), 6415–6424.
[10] Baan, R., Grosse, Y., Straif, K., Secretan, B., El Ghissassi, F., Bouvard, V., et al., 2009. A review of human carcinogens–Part F: chemical agents and related occupations. Lancet Oncol 10 (12), 1143–1144.
[11] IARC monographs on the evaluation of carcinogenic risks to humans: Outdoor air pollution, 2013. World Health Organization, Geneva.
[12] Li, Y., Fan, Z., Lu, W., Xu, R., Liu, T., Liu, L., et al., 2023. Long-term exposure to ambient fine particulate matter-bound polycyclic aromatic hydrocarbons and cancer mortality: a difference-in-differences approach. Chemosphere 340, 139800.
[13] Wei, J., Li, Z., Lyapustin, A., Sun, L., Peng, Y., Xue, W., et al., 2021. Reconstructing 1-km-resolution high-quality $PM_{2.5}$ data records from 2000 to 2018 in China: spatiotemporal variations and policy implications. Remote Sens Environ 252, 112136.
[14] Wei, J., Li, Z., Chen, X., Li, C., Sun, Y., Wang, J., et al., 2023. Separating daily 1 km $PM_{2.5}$ inorganic chemical composition in China since 2000 via deep learning integrating ground, satellite, and model data. Environ Sci Technol 57 (46), 18282–18295.
[15] Wei, J., Li, Z., Wang, J., Li, C., Gupta, P., Cribb, M., 2023. Ground-level gaseous pollutants (NO_2, SO_2, and CO) in China: daily seamless mapping and spatiotemporal variations. Atmos Chem Phys 23 (2), 1511–1532.
[16] Wei, J., Li, Z., Li, K., Dickerson, R.R., Pinker, R.T., Wang, J., et al., 2022. Full-coverage mapping and spatiotemporal variations of ground-level ozone (O_3) pollution from 2013 to 2020 across China. Remote Sens Environ 270, 112775.

[17] Wei, J., Li, Z., Cribb, M., Huang, W., Xue, W., Sun, L., et al., 2020. Improved 1km resolution $PM_{2.5}$ estimates across China using enhanced space–time extremely randomized trees. Atmos Chem Phys 20 (6), 3273–3289.
[18] Weather Forecast Office, Vapor pressure calculator; 2009.
[19] Wei, Y., Wang, Y., Di, Q., Choirat, C., Wang, Y., Koutrakis, P., et al., 2019. Short term exposure to fine particulate matter and hospital admission risks and costs in the medicare population: time stratified, case crossover study. BMJ 367, I6258.
[20] Di, Q., Dai, L., Wang, Y., Zanobetti, A., Choirat, C., Schwartz, J.D., et al., 2017. Association of short-term exposure to air pollution with mortality in older adults. JAMA 318 (24), 2446–2456.
[21] Liu, Y., Pan, J., Fan, C., Xu, R., Wang, Y., Xu, C., et al., 2021. Short-term exposure to ambient air pollution and mortality from myocardial infarction. J Am Coll Cardiol 77 (3), 271–281.
[22] Liu, Y., Pan, J., Zhang, H., Shi, C., Li, G., Peng, Z., et al., 2019. Short-term exposure to ambient air pollution and asthma mortality. Am J Respir Crit Care Med 200 (1), 24–32.
[23] Jiang, Y., Huang, J., Li, G., Wang, W., Wang, K., Wang, J., et al., 2023. Ozone pollution and hospital admissions for cardiovascular events. Eur Heart J 44 (18), 1622–1632.
[24] Ban, J., Su, W., Zhong, Y., Liu, C., Li, T., 2022. Ambient formaldehyde and mortality: a time series analysis in China. Sci Adv 8 (26), eabm4097.
[25] Zhang, Y., Wei, J., Shi, Y., Quan, C., Ho, H.C., Song, Y., et al., 2021. Early-life exposure to submicron particulate air pollution in relation to asthma development in Chinese preschool children. J Allergy Clin Immunol 148 (3), 771–782 e712.
[26] Shi, L., Rosenberg, A., Wang, Y., Liu, P., Danesh Yazdi, M., Réquia, W., et al., 2021. Low-concentration air pollution and mortality in American older adults: a national cohort analysis (2001–2017). Environ Sci Technol 56 (11), 7194–7202.
[27] Park, S.-Y., Freedman, N.D., Haiman, C.A., Le Marchand, L., Wilkens, L.R., Setiawan, V.W., 2017. Association of coffee consumption with total and cause-specific mortality among nonwhite populations. Ann Intern Med 167 (4).
[28] Ye, T., Xu, R., Yue, X., Chen, G., Yu, P., Coêlho, M.S.Z.S., et al., 2022. Short-term exposure to wildfire-related $PM_{2.5}$ increases mortality risks and burdens in Brazil. Nat Commun 13 (1), 7651.
[29] Igor, B., Paolo, B., Dick, H., Timo, P., Hans, K., Ole, S., et al., 2003. Mortality from obstructive lung diseases and exposure to polycyclic aromatic hydrocarbons among asphalt workers. Am J Epidemiol 158 (5), 468–478.
[30] Miller, B.G., Doust, E., Cherrie, J.W., Hurley, J.F., 2013. Lung cancer mortality and exposure to polycyclic aromatic hydrocarbons in British coke oven workers. BMC Public Health 13, 962.
[31] Beriro, D.J., Cave, M.R., Wragg, J., Thomas, R., Wills, G., Evans, F., 2016. A review of the current state of the art of physiologically-based tests for measuring human dermal in vitro bioavailability of polycyclic aromatic hydrocarbons (PAH) in soil. J Hazard Mater 305, 240–259.
[32] Domingo, J.L., Nadal, M., 2015. Human dietary exposure to polycyclic aromatic hydrocarbons: a review of the scientific literature. Food Chem Toxicol 86, 144–153.
[33] Gerde, P., Muggenburg, B.A., Lundborg, M., Dahl, A.R., 2001. The rapid alveolar absorption of diesel soot-adsorbed benzo[a]pyrene: bioavailability, metabolism and dosimetry of an inhaled particle-borne carcinogen. Carcinogenesis 22 (5), 741–749.
[34] Mallah, M.A., Mallah, M.A., Liu, Y., Xi, H., Wang, W., Feng, F., et al., 2021. Relationship between polycyclic aromatic hydrocarbons and cardiovascular diseases: a systematic review. Front Public Health 9, 763706.
[35] Mallah, M.A., Changxing, L., Mallah, M.A., Naveed, M., Liu, Y., Noreen, S., et al., 2022. Association of urinary polycyclic aromatic hydrocarbon metabolites and cardiovascular disease among US population: a cross-sectional study. Environ Res 209, 112775.
[36] Peng, K., Li, Z., Gao, T.-R., Lv, J., Wang, W.-J., Zhan, P., et al., 2023. Polycyclic aromatic hydrocarbon exposure burden: individual and mixture analyses of associations with chronic obstructive pulmonary disease risk. Environ Res 222, 115334.
[37] Holme, J.A., Vondráček, J., Machala, M., Lagadic-Gossmann, D., Vogel, C.F.A., Le Ferrec, E., et al., 2023. Lung cancer associated with combustion particles and fine particulate matter ($PM_{2.5}$) - The roles of polycyclic aromatic hydrocarbons (PAHs) and the aryl hydrocarbon receptor (AhR). Biochem Pharm 216, 115801.
[38] Podechard, N., Lecureur, V., Le Ferrec, E., Guenon, I., Sparfel, L., Gilot, D., et al., 2008. Interleukin-8 induction by the environmental contaminant benzo(a)pyrene is aryl hydrocarbon receptor-dependent and leads to lung inflammation. Toxicol Lett 177 (2), 130–137.
[39] Stading, R., Gastelum, G., Chu, C., Jiang, W., Moorthy, B., 2021. Molecular mechanisms of pulmonary carcinogenesis by polycyclic aromatic hydrocarbons (PAHs): implications for human lung cancer. Semin Cancer Biol 76, 3–16.
[40] Låg, M., Øvrevik, J., Refsnes, M., Holme, J.A., 2020. Potential role of polycyclic aromatic hydrocarbons in air pollution-induced non-malignant respiratory diseases. Respir Res 21 (1), 299.
[41] Iwano, S., Nukaya, M., Saito, T., Asanuma, F., Kamataki, T., 2005. A possible mechanism for atherosclerosis induced by polycyclic aromatic hydrocarbons. Biochem Biophys Res Commun 335 (1), 220–226.
[42] Kerley-Hamilton, J.S., Trask, H.W., Ridley, C.J.A., DuFour, E., Lesseur, C., Ringelberg, C.S., et al., 2012. Inherent and benzo[a]pyrene-induced differential aryl hydrocarbon receptor signaling greatly affects life span, atherosclerosis, cardiac gene expression, and body and heart growth in mice. Toxicol Sci 126 (2), 391–404.
[43] IARC monographs on the evaluation of carcinogenic risks to humans: Chemical agents and related occupations, 2009. World Health Organization, Geneva.
[44] Burstyn, I., Kromhout, H., Partanen, T., Svane, O., Langård, S., Ahrens, W., et al., 2005. Polycyclic aromatic hydrocarbons and fatal Ischemic heart disease. Epidemiology 16 (6), 744–750.
[45] Das, D.N., Ravi, N., 2022. Influences of polycyclic aromatic hydrocarbon on the epigenome toxicity and its applicability in human health risk assessment. Environ Res 213, 113677.
[46] Adegbola, P.I., Adetutu, A., 2024. Genetic and epigenetic modulations in toxicity: the two-sided roles of heavy metals and polycyclic aromatic hydrocarbons from the environment. Toxicol Rep 12, 502–519.
[47] Wu, X., Cao, X., Lintelmann, J., Peters, A., Koenig, W., Zimmermann, R., et al., 2022. Assessment of the association of exposure to polycyclic aromatic hydrocarbons, oxidative stress, and inflammation: a cross-sectional study in Augsburg, Germany. Int J Hyg Environ Health 244, 113993.
[48] Ambient air quality standards. Beijing: Ministry of Ecology and Environment of the People's Republic of China; 2012.
[49] López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The Hallmarks of aging. Cell 153 (6), 1194–1217.
[50] Campisi, J., Kapahi, P., Lithgow, G.J., Melov, S., Newman, J.C., Verdin, E., 2019. From discoveries in ageing research to therapeutics for healthy ageing. Nature 571 (7764), 183–192.
[51] Wang, M., Jia, S., Lee, S.H., Chow, A., Fang, M., 2021. Polycyclic aromatic hydrocarbons (PAHs) in indoor environments are still imposing carcinogenic risk. J Hazard Mater 409, 124531.
[52] Qi, H., Li, W.-L., Zhu, N.-Z., Ma, W.-L., Liu, L.-Y., Zhang, F., et al., 2014. Concentrations and sources of polycyclic aromatic hydrocarbons in indoor dust in China. Sci Total Environ 491-492, 100–107.
[53] Lasgaard, M., Friis, K., Shevlin, M., 2016. "Where are all the lonely people?" A population-based study of high-risk groups across the life span. Soc Psychiatry Psychiatr Epidemiol 51 (10), 1373–1384.
[54] Mishra, B., Pradhan, J., Dhaka, S., 2023. Identifying the impact of social isolation and loneliness on psychological well-being among the elderly in old-age homes of India: the mediating role of gender, marital status, and education. BMC Geriatr 23 (1), 684.
[55] Gale, C.R., Westbury, L., Cooper, C., 2018. Social isolation and loneliness as risk factors for the progression of frailty: the English Longitudinal Study of Ageing. Age Ageing 47 (3), 392–397.