Associations of ambient exposure to benzene, toluene, ethylbenzene, and xylene with daily mortality: a multicountry time-series study in 757 global locations

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Summary

Background The presence of benzene, toluene, ethylbenzene, and xylene isomers (BTEX) in the environment is of increasing concern due to their toxicity and ubiquity. Although the adverse health effects of BTEX exposure have been documented, robust epidemiological evidence from large-scale, multicountry studies using advanced exposure assessment methodologies remains scarce. We aimed to assess the association of short-term ambient exposure to individual BTEX components and their mixture with daily total, cardiovascular, and respiratory mortality on a global scale.

Methods Daily data on mortality, meteorological factors, and air pollution were collected from 757 locations across 46 countries or regions. Data on individual chemicals (ie, benzene, toluene, xylenes [summation of ethylbenzene, m-xylene, p-xylene, and o-xylene]) and the aggregate mixture (ie, BTEX) were estimated using a chemistry–climate model. We examined the short-term associations of each individual chemical as well as the BTEX mixture with daily total, cardiovascular, and respiratory mortality in a multicountry framework. Using a two-stage time-series design, we first applied generalised additive models with a quasi-Poisson distribution to obtain location-specific associations, which were subsequently pooled using random-effects meta-analysis. Two-pollutant models were used to assess the independent effects of BTEX after adjusting for co-pollutants ($PM_{2·5}$, PM_{10}, nitrogen dioxide, sulphur dioxide, ozone, and carbon monoxide). Additionally, we assessed the overall exposure–response curves with spline terms.

Findings An IQR increment of BTEX concentration on lag 0–2 days (3-day moving average of the present day and the previous 2 days) was associated with increases of 0·57% (95% CI 0·49–0·65), 0·42% (0·30–0·54), and 0·68% (0·50–0·86) in total, cardiovascular, and respiratory mortality, respectively. The corresponding effect estimates for an IQR increment in individual chemicals (benzene, toluene, and xylenes) were 0·38–0·61%, 0·44–0·70%, and 0·41–0·65%, respectively. The associations remained significant after adjusting for co-pollutants, with a general decline in magnitude, except for a slight increase after adjustment for ozone. The shape of the exposure–response curves for all pollutants and causes of death was almost linear, with steeper slopes at low concentrations and no discernible thresholds.

Interpretation This global study provides novel evidence linking short-term exposure to ambient BTEX, both individually and as a mixture, with increased daily total, cardiovascular, and respiratory mortality. Our findings underscore the need for comprehensive air pollution mitigation policies, including stringent controls on BTEX emissions, to protect public health.

Funding Noncommunicable Chronic Diseases—National Science and Technology Major Project, National Natural Science Foundation of China, Shanghai Municipal Science and Technology Major Project, Shanghai B&R Joint Laboratory Project, and Shanghai International Science and Technology Partnership Project.

Lancet Planet Health 2025; 9: 101306

Published Online September 16, 2025
https://doi.org/10.1016/j.lanplh.2025.101306

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Introduction

Benzene, toluene, ethylbenzene, and xylene isomers (BTEX) are typical volatile organic compounds (VOCs) with ubiquity in atmospheric air.[1–5] These chemicals originate from various anthropogenic sources, including vehicle emissions, fuel evaporation, coal combustion, industrial emissions, and biomass burning.[5–7] From a public health perspective, BTEX are demonstrated as toxic, carcinogenic, and mutagenic compounds at the environmental level,[4,5] and are classified as hazardous air pollutants by the US Environmental Protection Agency. Notably, ambient BTEX exposure has also raised increasing concerns for air quality due to their high reactivity in atmospheric photochemical reactions and their role as key precursors in the formation of secondary organic aerosol and ozone.[8–10]

Both short-term and long-term exposure to BTEX have been associated with numerous adverse health outcomes.[2–4,11,12] Short-term exposure to BTEX has been linked to skin and mucous membrane irritation, impaired immune function, metabolic perturbation, and cardiopulmonary events.[4] Long-term exposure to BTEX has been associated with more severe health issues, including leukaemia, anaemia, adverse pregnancy outcomes, reproductive problems, kidney and liver damage, neurological disorders, and mortality.[2–4,11–13] Although these studies have explicitly stated the toxicity of BTEX chemicals, their limitations should be noted. Firstly, most existing evidence was derived from indoor occupational settings or highly polluted environments, primarily focusing on chronic toxicological effects. Consequently, questions remain regarding whether exposure to low-level ambient BTEX could induce acute adverse health effects. Additionally, current epidemiological evidence concerning acute health effects of BTEX on mortality remains limited, with only two studies identified to date.[14,15] These investigations were constrained by the single-city design, heterogeneous exposure contexts, and varying data quality, thereby limiting the representativeness and generalisability of the findings.[14,15] Furthermore, critical characteristics of the exposure–response relationship, including temporal lag patterns, potential non-linearity, and effect thresholds, remain to be elucidated. Despite the limited epidemiological evidence, it is biologically plausible that short-term exposure to BTEX could induce acute effects through several mechanisms. Inhalation of BTEX could directly simulate respiratory irritant receptors, leading to autonomic imbalance and subsequent cardiopulmonary events, such as arrhythmias and exacerbation of asthma and chronic obstructive pulmonary disease.[16–19] Additionally, BTEX can cause irritation of the respiratory tract and vascular mucosa, promoting inflammation and oxidative stress across multiple organ systems, ultimately contributing to an elevated risk of mortality.[18–21]

Despite the recognised health effects of BTEX, WHO has not yet established threshold levels for BTEX exposure in ambient air.[22] The European Commission introduced an annual limit value of 5 $\mu g/m^3$ for benzene in outdoor air to protect health, without encompassing the other toxic compounds of BTEX.[23] Furthermore, this standard was set based on the carcinogenicity of long-term exposure to benzene and did not consider the health effects of short-term exposure. Notably, the health effects of BTEX might be experienced in combination rather than in isolation, particularly in outdoor settings where multiple emissions overlap. Furthermore, the sources of BTEX pollution differ greatly across regions, countries, and communities, and might shift depending on local practices and regulations.[5–7] This variability poses a challenge for monitoring and establishing comprehensive air quality standards. Currently, the limited monitoring of BTEX and the scarcity of large-scale data further hinder efforts to examine the health effects of short-term exposure in the general population

Research in context

Evidence before this study

We searched PubMed, Web of Science, and Google Scholar from database inception until Dec 4, 2024, for articles in English. The following search terms were used: ("benzene" or "toluene" or "ethylbenzene" or "xylene*" or "BTEX" or "volatile organic compo*") and ("mortal*" or "death*" or "dead*" or "fatal*"). Extensive research has reported the detrimental health effects of BTEX (benzene, toluene, ethylbenzene, and xylene isomers) exposure. However, previous research has primarily focused on the chronic health effects of BTEX exposure in indoor occupational settings or heavily polluted environments, leaving a gap in the investigation of the acute health effects associated with low-level ambient BTEX exposure. To date, there has been insufficient effort and investment in environmental monitoring of the BTEX compounds, coupled with a lack of air quality regulations in most countries worldwide.

Added value of this study

This multicountry study employs a comprehensive time-series analysis to assess the associations of short-term exposure to individual chemicals and the aggregate mixture of ambient BTEX with total, cardiovascular, and respiratory mortality. Our findings reveal a significantly increased risk of mortality associated with ambient BTEX exposure, with the effect remaining robust after controlling for co-pollutants. The linear nature of the exposure–response curves indicates that there is no safe threshold for BTEX exposure, underscoring the substantial health risks even at low concentrations.

Implications of all the available evidence

Our study shows that low-level ambient BTEX exposure is associated with an elevated risk of mortality, addressing a critical gap in the existing literature and informing air quality regulations targeting BTEX emissions to protect public health.

and to subsequently establish appropriate air quality standards.

In this time-series study, we aimed to assess the association of short-term ambient exposure to individual BTEX components and their mixture with daily total, cardiovascular, and respiratory mortality across various countries and regions globally. We used data from the Multi-Country Multi-City (MCC) Collaborative Research Network and obtained BTEX data from the Community Earth System Model (CESM) Community Atmosphere Model with Chemistry (CAM6-Chem, version 6) to overcome the limitations of small sample size and sparse ground monitoring in exposure measurement. Our research provides a large, multicity analysis of the health effects of BTEX within a unified statistical framework, offering implications for policy development and emission control strategies.

Methods

Data collection

We obtained time-series data on daily mortality, air pollution, and meteorological conditions from 757 locations in 46 countries or regions from the MCC database, spanning the period of Jan 1, 2001, to Dec 31, 2019. Figure 1 illustrates the geographical distribution of the locations included in the analyses. Mortality data were sourced from authorities in each country or region. Based on ICD-10, causes of death were classified as cardiovascular deaths (ICD-10: I00–I99), respiratory deaths (ICD-10: J00–J99), and total deaths (non-external deaths [ICD-10: A00–R99] or all-cause deaths when data on non-external causes were unavailable [54·4% of the locations]). Environmental data were obtained from local monitoring stations for each location in the MCC network. Specifically, we collected daily average concentrations of $PM_{2·5}$, PM_{10}, nitrogen dioxide (NO_2), sulphur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO). Meteorological data on daily mean air temperature and relative humidity were also collected for each location.

To collect data on daily concentrations of BTEX, we used CAM6-Chem, a three-dimensional fully coupled global chemistry-climate model with a horizontal resolution of 0·9° latitude × 1·25° longitude (~90 × 125 km^2). A detailed description of the model simulation and validation has been published elsewhere.[24] Briefly, this model is known for its comprehensive chemistry mechanisms, facilitating the simulation of global trends in surface concentrations of BTEX. The global emission data were derived from the Copernicus Atmosphere Monitoring Service (CAMS) version 5.3,[25] which provides global monthly emissions of non-methane VOCs and 25 speciated VOCs (eg, benzene, toluene, and xylenes) from a variety of emission sources. These sources include power generation, refineries, industrial processes, road and non-road transportation, ship emissions, residential, solvents application and production, agriculture livestock and waste burning, solid waste and wastewater handling, and fugitive fuels emissions, with a spatial resolution at 0·1° latitude × 0·1° longitude. The CAMS version 5.3 emission data have been extensively evaluated against nine existing global and regional emission inventories, showing good agreement in regions such as Europe, the USA, China, and India.[25] CAMS provides global monthly VOC emissions, whereas CESM generates daily BTEX concentrations by linearly interpolating emissions between monthly timestamps, with meteorology (nudged to 6-h MERRA-2 [Modern Era Retrospective-analysis for Research and Applications, Version 2] data) and 30-min chemistry timesteps accounting for finer temporal variability. This approach guarantees robust daily exposure estimates despite the monthly emission input (appendix p 3). To validate the model, we compared simulated daily BTEX concentrations against ground-level observations from 290 sites (appendix pp 8–23) across the USA, Canada, and the EU, leveraging national monitoring networks and measurement data. Our validation revealed reasonable agreement for daily BTEX concentrations (root mean square error 0·43–0·53 parts per billion [ppb]), albeit with regional variations (appendix p 51)—slight overestimation in the USA (normalised mean bias 7·06%), Canada (7·70%), and the EU (12·64%). These discrepancies primarily reflect the global model's coarse resolution, simplified chemistry, and inherent uncertainties in emission inventory, as detailed in the appendix (pp 4–5). Despite these biases, the model retains sufficient validity for detecting exposure–response gradients.

In the CESM model, ethylbenzene, m-xylene, p-xylene, and o-xylene are collectively represented as a single entity (referred to as "xylenes" in this study). This grouping reflects their structural similarity (molecular formula C_8H_{10}), shared emission sources (eg, industrial solvents) and chemical pathways (reacting with hydroxyl radical to form secondary organic aerosol), and combined representation in the input emission inventory, which provide xylenes emissions as an aggregated category rather than as individual species. Such lumping is common in atmospheric models to balance computational efficiency with minimal impacts on simulated chemistry, as justified by previous studies.[24,26,27] Finally, the location-specific time-series data on BTEX were extracted by linking the grid cell containing the location-specific coordinates during 2001–19.

Statistical analysis

In this time-series study, we applied a two-stage analytic framework to examine the associations of short-term exposure to individual BTEX components and their mixture with daily total, cardiovascular, and respiratory mortality. In the first stage, we conducted quasi-Poisson generalised addictive models to estimate the location-specific associations of BTEX with cause-specific mortality. Consistent with previous studies,[28,29] we controlled for the following covariates in the models: a natural cubic spline function with 7 df per year to control for long-term time trends and seasonality, an indicator variable for the day of the week to control for short-term variations within the week and day-of-the-week trends, and a natural cubic

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spline with 6 df for air temperature to account for confounding effects of weather conditions. For the appropriate lag time for temperature, we selected a lag of 0–3 days (moving average of the present day and the previous 3 days) according to previous studies.[28,29] We included linear term of BTEX with single lags of 0, 1, 2, and 3 days, 2-day moving average (lag 0–1), 3-day moving average (lag 0–2), and 4-day moving average (lag 0–3), and generalised cross-validation scores were calculated to determine the optimal lag time for BTEX.

In the second stage, a random-effects meta-analytical model was performed to pool the location-specific estimates. The multilevel meta-analytical approach accommodates flexible random effects within a hierarchical structure, whereby locations are nested within countries, and provides improved country-specific risk estimates of the associations through the best linear unbiased predictions (BLUPs).[30] The BLUP methodology allows for the sharing of information across the pooled associations at the same hierarchical level, thus enhancing precision of estimates for locations with limited daily mortality records or short study period. Additionally, we examined the heterogeneity across locations using the Cochran Q test and I^2 statistic.

We conducted several secondary analyses to expand the main models. First, we fitted models with two pollutants to account for the potential confounding effects of co-pollutants ($PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3, and CO). Due to data availability for various air pollutants, the number of locations included in these sensitivity analyses varied. Although multipollutant models theoretically offer more complete adjustment, their application is limited by inconsistent availability of monitoring data across locations. The approach of two-pollutant models, maintaining an optimal balance between confounding control and data retention, has been widely used in previous global studies. To compare the estimates from the main and two-pollutant models, we evaluated the effects of BTEX in these models within the same subset of locations where data for both pollutants were available. In addition to Pearson correlation analysis, multicollinearity was assessed by calculating variance inflation factors (VIFs) for all two-pollutant models, and a VIF value less than 5 was considered acceptable collinearity. Second, we explored the potential effect modifiers (eg, gross domestic product [GDP] per capita, latitude, and annual average temperature, and fossil carbon dioxide [CO_2] emissions by industry and transport) on the associations between BTEX and total mortality by fitting meta-regression models with these modifiers separately. Location-specific CO_2 emissions data were derived from the Emissions Database for Global Atmospheric Research (EDGAR), with detailed information on data collection and evaluation provided in the appendix (p 7). Thirdly, we conducted stratified analyses following the above-mentioned two-stage analytical framework by pooling location-specific estimates across geographical regions classified by WHO, income group assigned by the World Bank, and socioeconomic indicators including income inequality (categorised by Gini index), population educational attainment, and health expenditure. Fourth, we examined the exposure–response curves for the associations of individual chemicals and BTEX with total, cardiovascular, and respiratory mortality at a global level. Our analysis followed the two-stage analytical framework. In the first stage, consistent with previous studies,[28,31] we replaced the linear term of a specific pollutant in the main models with a non-linear term through a natural spline function with two common knots placed at the approximate average of the 25th and 75th percentiles of the concentration distributions across locations (ie, 0·30 ppb and 0·60 ppb for benzene; 0·45 ppb and 0·85 ppb for toluene; 0·40 ppb and 0·85 ppb for xylenes; 1·15 ppb and 2·30 ppb for BTEX) to estimate location-specific associations. Then, the location-specific spline coefficients were pooled in the second stage through meta-analysis to generate the overall exposure–response curve. Finally, we performed weighted quantile sum (WQS) regression to identify the key contributors within the BTEX mixture. This approach constructs an index by weighting each component of BTEX based on its contribution to the overall effect of BTEX exposure on mortality while deriving weights (constrained to 0–1 and summing to 1) for each BTEX constituent (benzene, toluene, and xylenes).

Several sensitivity analyses were performed to test the robustness of the results. First, we varied the df in the smoothness of calendar day (6–10 per year). Second, we prolonged the lag time of temperature from lag 0–3 days to lag 0–7 days, lag 0–10 days, lag 0–14 days, and lag 0–21 days. Third, we incorporated a natural spline function with 3 df for daily mean relative humidity at lag 0–3 days in the models within the 552 locations with available data. Finally, we excluded 18 locations without at least 5 years of data, as well as 55 locations with a missing data rate of more than 10%.

All analyses were performed with R software (version 4.1.0) with the use of the mgcv and mixmeta packages to fit location-specific models in the first stage and random-effects models in the second stage, respectively. Results were presented as the percentage changes and the corresponding 95% CIs of mortality associated with an IQR increase in location-specific concentrations of individual BTEX components and their mixture.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

During the study period, a total of 62·4 million deaths were recorded, including 15·8 million cardiovascular deaths and 7·1 million respiratory deaths (table 1, appendix pp 24–27). Figure 1 and the appendix (pp 52–53) show the annual average concentrations of BTEX, benzene, toluene, and xylenes for each location. The annual average concentrations of benzene, toluene, xylenes, and BTEX across 757 locations were 0·50 ppb (SD 0·29), 0·69 ppb (0·35), 0·68 ppb (0·38),

and 1·86 ppb (1·00), respectively. Correspondingly, the country-specific annual average concentrations ranged from 0·01 ppb to 2·86 ppb for benzene, from 0·01 ppb to 4·39 ppb for toluene, from 0·01 ppb to 2·58 ppb for xylenes, and from 0·03 ppb to 9·68 ppb for BTEX (table 1).

Descriptive statistics on weather conditions and the six considered co-pollutants are provided in the appendix (pp 28–31). Strong inter-correlations were observed among benzene, toluene, xylenes, and BTEX, with Pearson correlation coefficients (r) ranging from 0·82 to 0·97 (appendix p 32). Consistent correlation patterns were observed for BTEX and individual chemicals, showing weak to moderate correlations with other co-pollutants (PM_{10}: r=0·27 to 0·31; $PM_{2·5}$: r=0·43 to 0·47; NO_2: r=0·45 to 0·50; SO_2: r=0·27 to 0·31; O_3: r=–0·22 to –0·17; CO: r=0·33 to 0·37) and weather conditions (temperature: r=–0·35 to –0·13; humidity: r=0·01 to 0·07), with limited variability across different BTEX chemicals.

We used BTEX concentration on lag 0–2 days in the main analysis models because it produced the smallest mean generalised cross-validation scores and the largest effect estimate (appendix p 33). Generally, the estimates of associations of benzene, toluene, xylenes, and BTEX with mortality were highest at lag 1 day, with these associations drastically attenuating on lag 2 and 3 days.

At lag 0–2 days, each IQR increment in benzene, toluene, xylenes, and BTEX concentrations was associated with increases of 0·50% (95% CI 0·42–0·57), 0·58% (0·50–0·66), 0·59% (0·50–0·67), and 0·57% (0·49–0·65) in total mortality, respectively (table 2). We observed heterogeneity across location-specific estimates of associations for individual BTEX components and their mixture (I^2 ranging from 48·1% to 50·9%; Cochran's Q-test p<0·0001). We observed significant and larger effect estimates associated with an IQR increment in BTEX for several countries, including Mexico (ten locations, 1·55%), China (15 locations, 1·33%), Philippines (13 locations, 1·15%), and Thailand (62 locations, 0·94%). The effect estimates for several countries were close to the overall estimate associated with BTEX, including Moldova, South Africa, and Greece.

Similarly, we observed positive and significant associations of BTEX with both cardiovascular and respiratory mortality. Notably, the effect estimates of associations were higher for respiratory mortality, while those for cardiovascular mortality were even smaller than the estimates for total mortality. Both cardiovascular and respiratory mortality showed wider confidence intervals than total mortality (figure 2). Each IQR increase in benzene, toluene, xylenes, and BTEX concentrations was associated with 0·38% (95% CI 0·27–0·48), 0·44% (0·33–0·56), 0·41% (0·29–0·53), and 0·42% (0·30–0·54) increases in cardiovascular mortality, respectively (appendix pp 34–36). The corresponding increases in respiratory mortality for the same increases in benzene, toluene, xylenes, and BTEX were 0·61% (0·45–0·77), 0·70% (0·52–0·87), 0·65% (0·47–0·84), and 0·68% (0·50–0·86), respectively (appendix pp 37–39). Country-specific estimates for cause-specific analyses are presented in the appendix (pp 34–39). Consistently, we observed significant and larger effect estimates associated with an IQR increment in BTEX for Mexico, China, and the Philippines, compared with other countries, with corresponding increases of 0·81–0·90% in cardiovascular mortality and 1·19–1·88% in respiratory mortality.

After adjustment for co-pollutants (ie, PM_{10}, $PM_{2·5}$, NO_2, SO_2, and CO), the effect estimates of the associations between BTEX and total mortality generally decreased but remained significant (table 3). For instance, an IQR increment of BTEX concentration on lag 0–2 days (368 locations available) was associated with an increase of 0·24% (95% CI 0·11–0·36) in total mortality with adjustment for PM_{10} and 0·45% (0·34–0·57) without adjustment but considering only the locations with available PM_{10} data. Notably, the effect estimates associated with an IQR increase in BTEX concentrations slightly increased after adjustment for O_3. An IQR increment of BTEX concentrations on lag 0–2 days (405 locations available) was associated with an increase of 0·43% (0·33–0·53) in total mortality without adjustment for O_3, and associated with an increase of 0·48% (0·37–0·60) with adjustment for O_3 for the locations with O_3 data available. Additionally, VIF values ranged from 1·26 to 1·84, well below the threshold indicating problematic multicollinearity (appendix pp 40–41), suggesting minimal collinearity in the two-pollutant models.

We observed significant effect modification by GDP per capita, annual average temperature, latitude, and industrial CO_2 emission on the association between BTEX exposure and total mortality (appendix p 42). The results of the stratified analyses are presented in the appendix (pp 43–44). The WHO region exhibiting the highest risk of mortality associated with BTEX exposure was the Western Pacific region (0·88%, 95% CI 0·45 to 1·32), followed by the Americas region (0·64%, 0·21 to 1·07) and the European region (0·15%, –0·28 to 0·58). Additionally, countries with low income and middle income, higher income inequality, lower education attainment level, and lower health expenditure exhibited a higher risk of mortality associated with BTEX compared with their counterparts.

The exposure–response curves for the associations of benzene, toluene, xylenes, and BTEX with total mortality are shown in figure 3. These curves showed an approximately monotonic increase in risk associated with these four pollutants. Notably, the curves exhibited steeper slopes at low concentrations with no discernible thresholds, indicating heightened sensitivity to exposure. Additionally, the shapes of the exposure–response curves for cardiovascular and respiratory mortality differentiated slightly from those for total mortality (appendix p 54). For instance, the curve for the association between BTEX and respiratory mortality showed steeper slopes at high exposure ranges.

The WQS regression results (appendix pp 45–48) showed that benzene, toluene, and xylenes contributed differentially to the overall effect of BTEX on total mortality, with mean weights of 0·36, 0·31, and 0·34, respectively. While country-specific weight estimates varied, analyses

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For a list of **hazardous air pollutants** see https://www.epa.gov/haps/initial-list-hazardous-air-pollutants-modifications

For the **MCC Collaborative Research Network** see http://mccstudy.lshtm.ac.uk/

restricted to countries with sufficient data (≥15 locations) exhibited a consistently comparable pattern, with weights ranging from 0·25 to 0·47 for three chemicals and no consistent dominance by a single chemical. The results of sensitivity analyses remained robust. Generally, variations in the df in the term for the time trend, additional adjustment for relative humidity, and exclusion of locations with a missing data rate exceeding 10% or fewer than 5 years of data did not substantially change the effect estimates (appendix pp 49–50).

Discussion

To our knowledge, this is the largest ever global study to investigate the association between ambient BTEX exposure and mortality. The extensive dataset we analysed in the study, encompassing 757 locations across 46 countries or regions, allows for assessment of BTEX effects within a unified statistical framework. Overall, our findings provide supportive evidence regarding the acute health effects of ambient BTEX exposure and underscore the urgency of developing corresponding air quality policies.

Current epidemiological evidence on the associations between short-term exposure to BTEX and mortality in the general population remains limited and inconsistent, with only two prior studies having examined these relationships.[14,15] For instance, a time-series study in Hong Kong reported 5·8% (benzene) and 3·5% (TEX) increases in cardiovascular mortality associated with an IQR exposure increment, but exhibited low and non-significant effects for total or respiratory mortality.[14] Our analysis confirmed these positive associations while observing more modest effects of BTEX (0·57% globally and 1·33% for China), potentially reflecting differences in exposure levels and population vulnerability between the hyper-urbanised environment of Hong Kong and our diverse study locations. Similarly, another study in Taiwan found that current-day ambient benzene and xylenes were significantly associated with all-cause mortality (relative risk 1·055 for an IQR increment in benzene), but no significant association was identified between xylenes and cardiovascular mortality.[15] These discrepancies could be attributed to variations in the study periods, study populations, and analytical methods. Furthermore, the scarcity of comprehensive BTEX monitoring across different countries, coupled with a general paucity of data, has contributed to the limited number of epidemiological investigations. Overall, current epidemiological evidence regarding the health effects of ambient BTEX in non-occupational settings is limited, focusing on a few locations and predominantly on benzene without considering the non-cancer health effects.[4,32] Notwithstanding more conservative effect estimates compared to those single-city studies, this multicountry analysis establishes the first consistent and comprehensive evidence of BTEX–mortality associations at ambient exposure concentrations across heterogeneous environmental settings, substantially advancing the understanding of the health effects of BTEX. The robustness of primary findings across sensitivity analyses also strengthened the evidence by addressing key residual confounding concerns regarding temporal trends, meteorological factors, and selection bias.

Several biological pathways and mechanisms are likely involved in responding to short-term exposure to BTEX. The detrimental effects of BTEX on metabolic, endocrine, and immune function have been well elucidated, which might lead to increased mortality risk.[4,18,19,32,33] BTEX might also be associated with some subclinical changes reflecting inflammation, endothelial dysfunction, dyslipidaemia, and

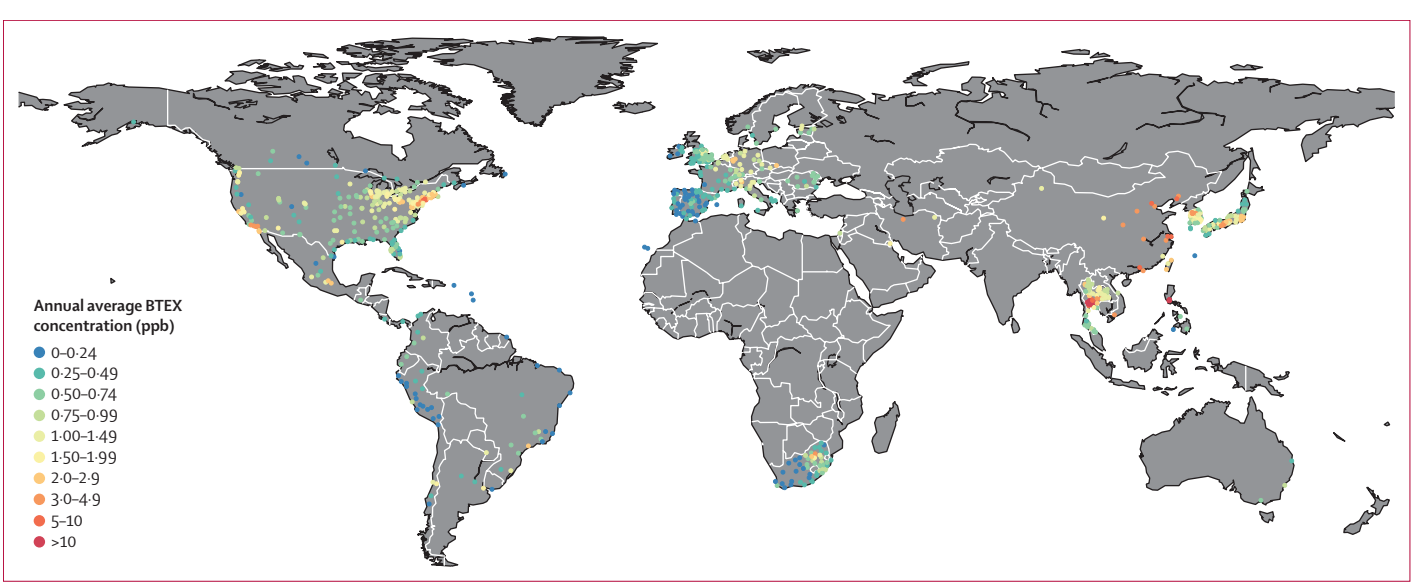

Figure 1: **Map of 757 locations included in the analyses**
BTEX=benzene, toluene, ethylbenzene, and xylene isomers (m-, p-, and o-). ppb=parts per billion.

	Locations, n	Study periods	Total deaths, n	Benzene, ppb	Toluene, ppb	Xylenes, ppb	BTEX, ppb
Total	757	2001–19	62 388 145	0·50 (0·29)	0·69 (0·35)	0·68 (0·38)	1·86 (1·00)
Argentina	3	2005–15	686 333	0·17 (0·16)	0·29 (0·28)	0·34 (0·36)	0·80 (0·80)
Australia	3	2001–09	460 144	0·09 (0·16)	0·20 (0·16)	0·31 (0·25)	0·59 (0·51)
Brazil	18	2001–18	3 247 414	0·22 (0·32)	0·16 (0·19)	0·18 (0·23)	0·56 (0·73)
Canada	26	2001–15	1 865 249	0·15 (0·12)	0·22 (0·22)	0·32 (0·34)	0·69 (0·67)
Chile	4	2004–14	325 462	0·27 (0·27)	0·22 (0·19)	0·41 (0·40)	0·89 (0·83)
China	15	2001–15	1 050 276	1·25 (1·07)	1·43 (1·04)	1·76 (1·17)	4·44 (3·18)
Colombia	5	2001–13	665 943	0·12 (0·08)	0·17 (0·09)	0·22 (0·13)	0·50 (0·30)
Costa Rica	1	2001–17	30 145	0·06 (0·04)	0·13 (0·09)	0·20 (0·13)	0·39 (0·25)
Czech Republic	4	2001–15	447 089	0·37 (0·25)	0·18 (0·15)	0·86 (1·01)	1·42 (1·28)
Ecuador	2	2014–18	112 264	0·11 (0·05)	0·21 (0·09)	0·26 (0·11)	0·58 (0·25)
Estonia	5	2001–18	142 221	0·37 (0·27)	0·11 (0·09)	0·25 (0·23)	0·73 (0·56)
Finland	1	2001–14	94 173	0·64 (0·34)	0·20 (0·11)	0·33 (0·20)	1·17 (0·63)
France	18	2001–15	1 542 061	0·24 (0·23)	0·08 (0·08)	0·22 (0·25)	0·55 (0·56)
French Caribbean*	2	2001–15	43 589	0·01 (0·01)	0·01 (0·00)	0·01 (0·01)	0·03 (0·01)
French Guiana	1	2001–15	6 708	0·01 (0·01)	0·01 (0·01)	0·01 (0·01)	0·03 (0·02)
Germany	12	2001–15	1 987 652	0·44 (0·30)	0·20 (0·15)	0·78 (0·68)	1·42 (1·10)
Greece	1	2001–10	287 969	0·27 (0·15)	0·12 (0·07)	0·22 (0·11)	0·61 (0·31)
Guatemala	1	2009–16	62 715	0·12 (0·09)	0·15 (0·09)	0·42 (0·25)	0·69 (0·41)
Iran	2	2002–15	817 913	0·62 (0·43)	1·15 (0·80)	1·35 (0·95)	3·12 (2·18)
Ireland	6	2001–07	289 406	0·11 (0·11)	0·03 (0·04)	0·11 (0·15)	0·26 (0·29)
Israel	1	2001–20	194 176	0·19 (0·11)	0·30 (0·20)	0·36 (0·23)	0·86 (0·53)
Italy	16	2001–10	645 420	0·35 (0·32)	0·14 (0·14)	0·38 (0·42)	0·87 (0·87)
Japan	47	2001–15	17 049 293	0·30 (0·23)	0·40 (0·38)	0·68 (0·68)	1·38 (1·27)
Kuwait	1	2001–16	70 321	0·54 (0·27)	0·60 (0·25)	0·85 (0·36)	2·00 (0·85)
Mexico	10	2001–14	2 531 393	0·20 (0·23)	0·44 (0·48)	0·58 (0·65)	1·22 (1·29)
Moldova	4	2001–10	59 906	0·31 (0·22)	0·08 (0·06)	0·20 (0·18)	0·59 (0·44)
Netherlands	5	2001–16	315 931	0·40 (0·30)	0·18 (0·14)	0·66 (0·59)	1·24 (1·01)
Norway	1	2001–18	59 919	0·27 (0·16)	0·10 (0·06)	0·19 (0·14)	0·56 (0·36)
Panama	1	2013–16	11 457	0·07 (0·03)	0·12 (0·06)	0·18 (0·08)	0·37 (0·17)
Paraguay	1	2004–19	48 037	0·40 (0·25)	0·30 (0·13)	0·34 (0·12)	1·04 (0·45)
Peru	18	2008–14	633 137	0·04 (0·06)	0·09 (0·08)	0·11 (0·10)	0·24 (0·22)
Philippines	13	2006–19	774 295	2·71 (1·78)	4·39 (2·83)	2·58 (1·57)	9·68 (6·17)
Portugal	6	2001–18	916 754	0·15 (0·25)	0·05 (0·09)	0·07 (0·07)	0·27 (0·38)
Puerto Rico	1	2009–16	26 564	0·01 (0·01)	0·04 (0·02)	0·05 (0·02)	0·09 (0·04)
Romania	8	2001–16	656 964	0·35 (0·26)	0·08 (0·07)	0·21 (0·18)	0·65 (0·49)
South Africa	52	2001–13	7 027 333	0·23 (0·34)	0·17 (0·28)	0·31 (0·53)	0·71 (1·13)
South Korea	36	2001–18	2 256 451	0·45 (0·31)	0·45 (0·37)	0·69 (0·65)	1·59 (1·29)
Spain	52	2001–14	1 739 544	0·12 (0·11)	0·04 (0·04)	0·11 (0·11)	0·26 (0·24)
Sweden	3	2001–16	425 806	0·26 (0·17)	0·08 (0·06)	0·21 (0·19)	0·55 (0·41)
Switzerland	8	2001–13	154 647	0·35 (0·30)	0·12 (0·12)	0·39 (0·38)	0·87 (0·79)
Taiwan	3	2001–14	372 598	0·31 (0·19)	0·55 (0·36)	1·00 (0·70)	1·87 (1·20)
Thailand	62	2001–08	1 501 027	2·86 (5·29)	4·19 (8·52)	2·17 (4·34)	9·22 (18·13)
UK	67	2001–16	3 128 767	0·22 (0·19)	0·09 (0·08)	0·38 (0·41)	0·68 (0·65)
Uruguay	1	2012–16	153 554	0·05 (0·05)	0·07 (0·07)	0·08 (0·08)	0·20 (0·20)
USA	208	2001–06	7 367 725	0·18 (0·18)	0·49 (0·59)	0·72 (0·94)	1·39 (1·64)
Viet Nam	2	2009–13	102 400	0·97 (0·83)	0·92 (0·83)	0·62 (0·57)	2·51 (2·21)

Concentrations of pollutants in ppb are shown as mean (SD). Xylenes exposure is a summation of ethylbenzene, m-xylene, p-xylene, and o-xylene. BTEX=benzene, toluene, ethylbenzene, and xylene isomers (m-, p-, and o-). ppb=parts per billion. *Guadeloupe and Martinique.

Table 1: **Summary statistics of locations, study periods, total deaths, and BTEX components in 757 locations included in the study**

oxidative stress, which are common in the physiological responses to air pollution.[32,34–36] Additionally, as BTEX is primarily inhaled into the body through the respiratory tract, it might irritate the respiratory system and result in respiratory symptoms (eg, inflammation, oedema, cough, and asthma) and reduced lung function.[3,20,37] In the present study, we found higher mortality risks due to respiratory diseases compared to cardiovascular disease mortality, potentially explained by the direct contact of BTEX with the lungs.

Our findings unveiled significant spatial heterogeneity in the health effects of BTEX, with substantially elevated risks observed in low-income and middle-income countries of

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	Benzene	Toluene	Xylenes	BTEX
Total	0·50 (0·42 to 0·57)	0·58 (0·50 to 0·66)	0·59 (0·50 to 0·67)	0·57 (0·49 to 0·65)
Argentina	0·85 (0·46 to 1·25)	0·93 (0·48 to 1·40)	1·13 (0·62 to 1·65)	1·07 (0·60 to 1·55)
Australia	0·28 (0·01 to 0·56)	0·99 (0·48 to 1·50)	0·99 (0·43 to 1·55)	0·92 (0·41 to 1·43)
Brazil	0·48 (0·25 to 0·72)	0·69 (0·40 to 0·98)	0·75 (0·44 to 1·06)	0·68 (0·40 to 0·97)
Canada	0·66 (0·35 to 0·98)	0·64 (0·35 to 0·93)	0·58 (0·28 to 0·88)	0·65 (0·35 to 0·96)
Chile	0·28 (–0·12 to 0·67)	0·45 (–0·04 to 0·94)	0·59 (–0·02 to 1·21)	0·47 (–0·05 to 0·99)
China	1·07 (0·68 to 1·46)	1·31 (0·90 to 1·73)	1·43 (0·97 to 1·88)	1·33 (0·91 to 1·76)
Colombia	0·31 (–0·12 to 0·75)	0·26 (–0·24 to 0·76)	0·12 (–0·43 to 0·68)	0·25 (–0·27 to 0·76)
Costa Rica	0·59 (–0·13 to 1·32)	0·70 (–0·09 to 1·49)	0·75 (–0·18 to 1·68)	0·70 (–0·13 to 1·53)
Czech Republic	0·37 (–0·13 to 0·87)	0·26 (–0·22 to 0·74)	0·16 (–0·28 to 0·61)	0·25 (–0·24 to 0·74)
Ecuador	0·46 (–0·18 to 1·10)	0·40 (–0·32 to 1·13)	0·33 (–0·50 to 1·16)	0·40 (–0·34 to 1·15)
Estonia	0·07 (–0·53 to 0·68)	0·10 (–0·54 to 0·73)	–0·22 (–0·88 to 0·45)	–0·03 (–0·68 to 0·62)
Finland	0·15 (–0·49 to 0·78)	0·10 (–0·58 to 0·77)	0·00 (–0·74 to 0·75)	0·10 (–0·60 to 0·80)
France	0·00 (–0·32 to 0·32)	–0·11 (–0·42 to 0·20)	–0·26 (–0·57 to 0·04)	–0·14 (–0·45 to 0·18)
French Caribbean*	0·58 (–0·12 to 1·28)	0·88 (0·20 to 1·57)	0·92 (0·14 to 1·70)	0·85 (0·13 to 1·58)
French Guiana	0·52 (–0·20 to 1·25)	0·63 (–0·17 to 1·44)	0·64 (–0·31 to 1·59)	0·64 (–0·20 to 1·48)
Germany	0·46 (0·18 to 0·75)	0·36 (0·08 to 0·64)	0·27 (–0·02 to 0·56)	0·35 (0·06 to 0·64)
Greece	0·26 (–0·27 to 0·79)	0·75 (0·19 to 1·32)	0·81 (0·16 to 1·46)	0·56 (–0·03 to 1·16)
Guatemala	0·17 (–0·45 to 0·80)	0·35 (–0·37 to 1·08)	0·34 (–0·49 to 1·18)	0·33 (–0·42 to 1·08)
Iran	0·72 (0·21 to 1·23)	0·83 (0·31 to 1·35)	0·88 (0·30 to 1·47)	0·83 (0·29 to 1·38)
Ireland	0·46 (0·01 to 0·92)	0·43 (0·00 to 0·85)	0·24 (–0·09 to 0·58)	0·37 (–0·04 to 0·78)
Israel	0·70 (0·10 to 1·31)	0·81 (0·21 to 1·42)	0·83 (0·18 to 1·49)	0·81 (0·19 to 1·44)
Italy	0·63 (0·23 to 1·04)	0·73 (0·32 to 1·14)	0·68 (0·24 to 1·12)	0·68 (0·26 to 1·10)
Japan	0·71 (0·52 to 0·90)	0·83 (0·63 to 1·04)	0·79 (0·57 to 1·01)	0·82 (0·61 to 1·02)
Kuwait	0·60 (–0·09 to 1·29)	0·79 (0·05 to 1·55)	0·93 (0·06 to 1·81)	0·80 (0·02 to 1·59)
Mexico	0·80 (0·53 to 1·07)	1·52 (1·17 to 1·87)	1·61 (1·24 to 1·99)	1·55 (1·19 to 1·91)
Moldova	0·53 (–0·17 to 1·24)	0·66 (–0·10 to 1·43)	0·46 (–0·41 to 1·35)	0·58 (–0·22 to 1·39)
Netherlands	0·60 (0·14 to 1·05)	0·63 (0·16 to 1·10)	0·65 (0·19 to 1·12)	0·65 (0·19 to 1·11)
Norway	0·22 (–0·46 to 0·90)	0·28 (–0·43 to 1·00)	0·01 (–0·74 to 0·77)	0·17 (–0·56 to 0·92)
Panama	0·52 (–0·20 to 1·26)	0·61 (–0·19 to 1·41)	0·62 (–0·33 to 1·57)	0·60 (–0·24 to 1·44)
Paraguay	0·60 (–0·03 to 1·24)	0·43 (–0·28 to 1·14)	0·54 (–0·30 to 1·39)	0·59 (–0·14 to 1·32)
Peru	0·00 (–0·30 to 0·31)	0·48 (–0·04 to 1·00)	0·65 (0·05 to 1·26)	0·38 (–0·13 to 0·90)
Philippines	1·06 (0·66 to 1·46)	1·14 (0·72 to 1·56)	1·18 (0·74 to 1·62)	1·15 (0·73 to 1·58)
Portugal	0·10 (–0·12 to 0·31)	0·10 (–0·12 to 0·31)	0·30 (–0·06 to 0·66)	0·12 (–0·12 to 0·36)
Puerto Rico	0·53 (–0·17 to 1·24)	0·49 (–0·24 to 1·22)	0·44 (–0·40 to 1·30)	0·48 (–0·28 to 1·24)
Romania	0·61 (0·12 to 1·10)	0·80 (0·28 to 1·32)	0·52 (0·00 to 1·05)	0·69 (0·15 to 1·23)
South Africa	0·30 (0·12 to 0·48)	0·56 (0·35 to 0·76)	0·89 (0·64 to 1·15)	0·57 (0·35 to 0·78)
South Korea	0·71 (0·41 to 1·01)	0·77 (0·46 to 1·08)	0·73 (0·40 to 1·06)	0·77 (0·45 to 1·09)
Spain	–0·03 (–0·30 to 0·24)	0·04 (–0·22 to 0·30)	0·32 (0·01 to 0·63)	0·11 (–0·18 to 0·40)
Sweden	–0·42 (–0·92 to 0·09)	–0·33 (–0·83 to 0·17)	–0·32 (–0·76 to 0·12)	–0·40 (–0·89 to 0·09)
Switzerland	0·48 (–0·12 to 1·09)	0·40 (–0·22 to 1·01)	0·37 (–0·28 to 1·02)	0·45 (–0·19 to 1·09)
Taiwan	0·31 (–0·20 to 0·82)	0·69 (0·14 to 1·24)	0·77 (0·20 to 1·34)	0·69 (0·14 to 1·24)
Thailand	0·82 (0·50 to 1·15)	0·81 (0·50 to 1·13)	1·33 (0·97 to 1·68)	0·94 (0·60 to 1·27)
UK	0·27 (0·04 to 0·50)	0·19 (–0·05 to 0·42)	–0·02 (–0·27 to 0·23)	0·11 (–0·13 to 0·35)
Uruguay	1·25 (0·61 to 1·88)	1·30 (0·63 to 1·98)	1·68 (0·98 to 2·39)	1·48 (0·80 to 2·16)
USA	0·07 (–0·10 to 0·23)	0·48 (0·27 to 0·70)	0·48 (0·24 to 0·71)	0·46 (0·25 to 0·68)
Viet Nam	0·44 (–0·24 to 1·12)	0·55 (–0·16 to 1·28)	0·56 (–0·26 to 1·39)	0·52 (–0·23 to 1·28)

Data are % (95% CI). Xylenes exposure is a summation of ethylbenzene, m-xylene, p-xylene, and o-xylene. BTEX=benzene, toluene, ethylbenzene, and xylene isomers (m-, p-, and o-).
*Guadeloupe and Martinique.

Table 2: **Percentage changes and 95% CIs in daily total deaths associated with an IQR increment of BTEX concentrations on lag 0–2 days by country or region**

the Western Pacific and Americas regions (eg, Argentina, China, Mexico, Philippines, Thailand, and Uruguay). Notably, the Philippines, Thailand, and China were also characterised by prominently higher concentrations of BTEX, leading to substantial health risks that necessitate attention and concern. Overall, the heightened risks might be jointly determined by the environmental exposures and socioeconomic disadvantages, particularly in countries characterised by lower income, greater income inequality, lower educational attainment, and constrained health

expenditure. This pattern suggests that both higher exposure levels (eg, unregulated emissions) and limited adaptive capacity contribute to population vulnerability to BTEX exposure. Conversely, the European region exhibited lower and statistically non-significant effects, likely attributable to effective environmental regulations and mitigation interventions in the high-income countries. The steeper slopes of exposure–response curves at low BTEX concentrations were predominantly derived from locations with cleaner environments (eg, high-income countries), where populations with low baseline exposures exhibit heightened sensitivity to initial air pollution increments.[28] This pattern might reflect the differences in population vulnerability shaped by socioeconomic and environmental factors across locations. Furthermore, several significant effect modifiers could contribute to discrepancies across countries, including economic characteristic (GDP per capita), climatic variables (annual mean temperature and latitude), and emission source (emission by industry rather than by transport sector). Notably, rapidly developing economies that rely heavily on industrial emissions might experience distinct health effects compared with high-income countries where transport emissions are the predominant source of pollution. Other factors, such as differences in population characteristics, co-exposures, and regulatory standards might also play a role. Recognising these nuanced differences is crucial for tailoring public health interventions and regulatory policies. Additionally, the associations between BTEX and mortality were non-significant or negative in several countries (eg, Sweden, France, and Estonia). In these countries, the included locations and study periods were generally limited, which could diminish statistical power and introduce statistical uncertainties in the quantification of the health effects. Furthermore, these countries were generally high-income countries located in areas with low annual mean temperature and high latitude, which might decrease the BTEX–mortality association.

Disentangling the independent health effects of BTEX exposure from the potential confounding effects of other co-pollutants is pivotal for accurately determining the health risk. Our findings suggest that while the magnitude of risk estimates generally attenuated after adjustment for other co-pollutants, the associations remained significant when separately including co-pollutants in the two-pollutant models. Additionally, the health effects of BTEX might be modestly underestimated but would not substantially change, given the weak to moderate correlations of BTEX with other pollutants and the distinct patterns of measurement error from differentiated exposure measurement methods. These findings may be indicative of the independent effects of BTEX, but still warrant further investigation and validation. In addition, the risk estimates for BTEX slightly increased after adjustment for ozone, which might be interpreted as potential synergistic effects between BTEX and O_3 (eg, O_3-enhanced airway permeability and respiratory uptake of BTEX).[38] Although primary BTEX effects are established, the potential photochemical transformation effects warrant further investigation. Notably, our WQS regression analysis suggested comparable contributions of individual BTEX components to mortality risk. While these chemicals are highly correlated, the near-equivalent weights suggest that the observed health effects reflect combined toxicity rather than being driven by a single surrogate chemical. These health effects might reflect overlapping and complementary toxicological mechanisms beyond co-exposure.[4,20] Critically, the strong correlations among BTEX components—stemming from shared emission sources—further validate the scientific value of mixture-based risk assessment and underscore the practical need for integrated regulatory strategies targeting common BTEX emission sources.

Our findings underscore the need for coordinated strategies to reduce BTEX emissions and exposure. First, industrial and traffic emissions must be controlled through

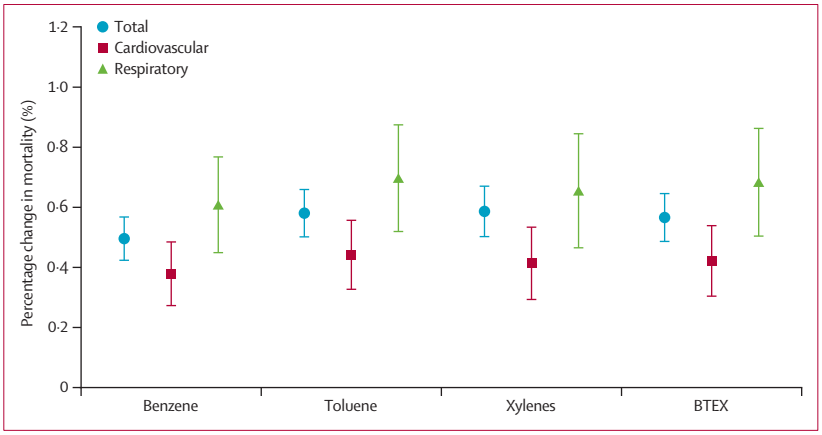

Figure 2: **Percentage changes and 95% CIs in daily total, cardiovascular, and respiratory deaths associated with an IQR increment of BTEX concentration on lag 0–2 days**
BTEX=benzene, toluene, ethylbenzene, and xylene isomers (m-, p-, and o-).

	Locations, n	Benzene	Toluene	Xylenes	BTEX
Basic model	368	0·41 (0·31–0·51)	0·46 (0·35–0·58)	0·47 (0·35–0·58)	0·45 (0·34–0·57)
+ PM_{10}	368	0·21 (0·10–0·33)	0·25 (0·12–0·37)	0·22 (0·10–0·35)	0·24 (0·11–0·36)
Basic model	358	0·37 (0·27–0·47)	0·43 (0·32–0·54)	0·40 (0·29–0·52)	0·42 (0·31–0·53)
+ $PM_{2·5}$	358	0·18 (0·05–0·30)	0·22 (0·07–0·38)	0·23 (0·08–0·39)	0·23 (0·08–0·39)
Basic model	345	0·34 (0·24–0·43)	0·40 (0·29–0·50)	0·40 (0·29–0·51)	0·39 (0·28–0·49)
+ NO_2	345	0·24 (0·14–0·34)	0·28 (0·17–0·39)	0·29 (0·17–0·40)	0·28 (0·17–0·39)
Basic model	316	0·43 (0·32–0·54)	0·46 (0·35–0·57)	0·48 (0·36–0·60)	0·46 (0·35–0·58)
+ SO_2	316	0·38 (0·25–0·50)	0·38 (0·26–0·51)	0·39 (0·26–0·52)	0·38 (0·25–0·51)
Basic model	405	0·38 (0·29–0·48)	0·44 (0·33–0·54)	0·44 (0·33–0·55)	0·43 (0·33–0·53)
+ O_3	405	0·41 (0·30–0·53)	0·48 (0·37–0·60)	0·50 (0·38–0·62)	0·48 (0·37–0·60)
Basic model	297	0·37 (0·26–0·48)	0·45 (0·34–0·56)	0·48 (0·36–0·60)	0·44 (0·33–0·56)
+ CO	297	0·32 (0·20–0·43)	0·39 (0·27–0·52)	0·43 (0·30–0·56)	0·39 (0·26–0·52)

Data are % (95% CI) unless otherwise indicated. Xylenes exposure is a summation of ethylbenzene, m-xylene, p-xylene, and o-xylene. BTEX=benzene, toluene, ethylbenzene, and xylene isomers (m-, p-, and o-). NO_2=nitrogen dioxide. SO_2=sulphur dioxide. O_3=ozone. CO=carbon monoxide.

Table 3: **Percentage changes and 95% CIs in daily total deaths associated with an IQR increment of BTEX concentrations on lag 0–2 days without and with adjustment for co-pollutants**

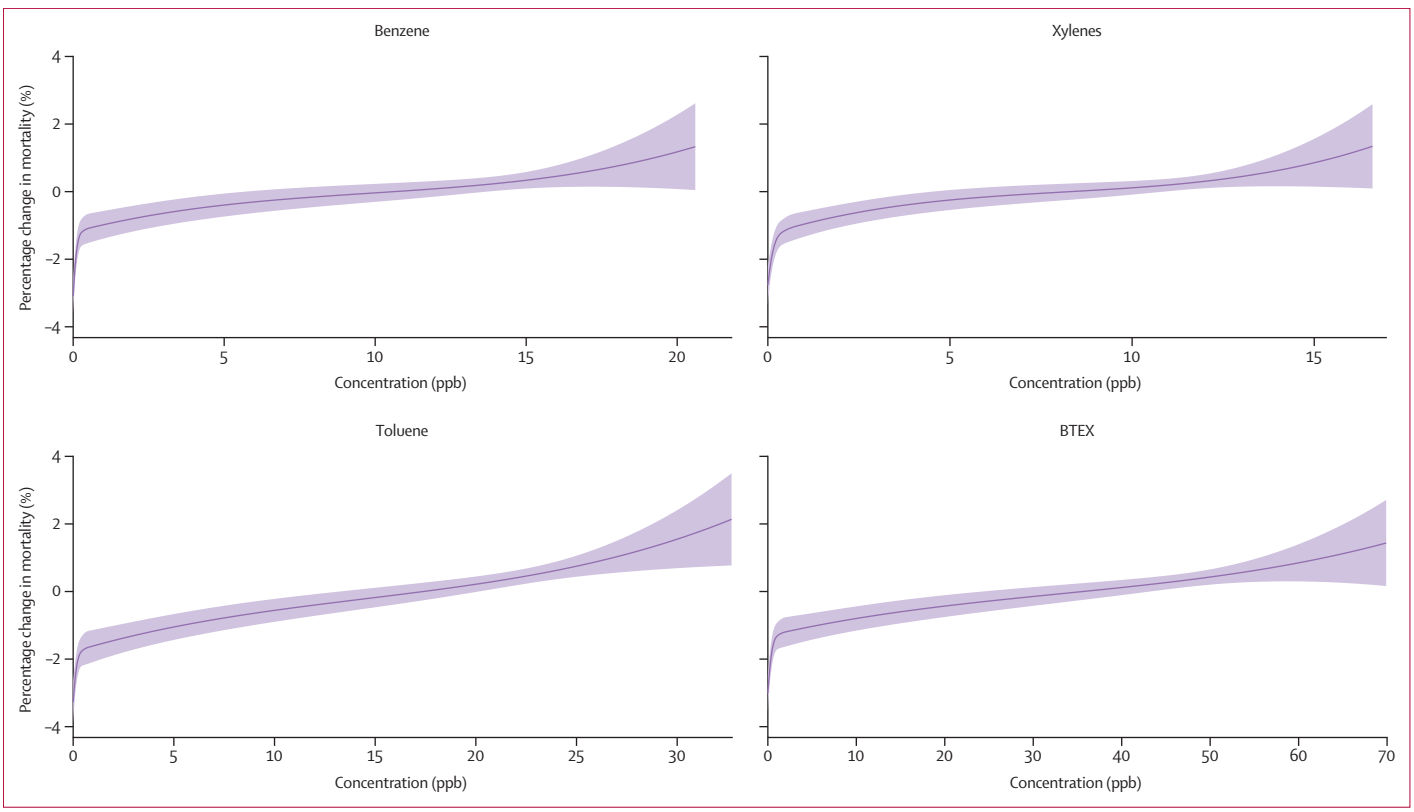

Figure 3: **Exposure–response curves for associations of benzene, toluene, xylenes, and BTEX with total mortality**
The y-axis represents the percentage change in daily mortality at a certain concentration relative to the median concentration. Shaded areas show 95% CIs. The x-axis represents concentrations of benzene, toluene, xylenes, and BTEX. BTEX=benzene, toluene, ethylbenzene, and xylene isomers (m-, p-, and o-). ppb=parts per billion.

effective interventions, including use of clean fuels, stricter fuel standards with lower BTEX content, improved exhaust treatment, and mandatory vapour recovery systems at gas stations.[5,7] Second, real-time BTEX monitoring networks should be established in high-risk areas (eg, traffic and industrial zones). Third, a BTEX-specific alert system is warranted to protect public health during peak exposure periods.

Several limitations should be noted. First, our evaluation only considered outdoor exposure, but there are growing concerns regarding the potentially higher concentrations and health risks of indoor exposure.[3,4,39–44] Subsequently, unaccounted indoor sources might lead to exposure misclassification, particularly in urban settings where they substantially contribute to total BTEX exposure, potentially negatively biasing risk estimates and obscuring regional variations in the BTEX–mortality associations. Moreover, BTEX exposure assessment carries inherent uncertainties stemming from multiple sources, including emission inventories, model resolution, and simulation configurations. Although model validation showed reasonable results at the grid scale, the current model resolution ($0{\cdot}9^{\circ} \times 1{\cdot}25^{\circ}$) might obscure fine-scale spatial heterogeneity critical for these short-lived compounds with local gradients near emission sources,[45] which remains a challenge for global-scale modelling. In time-series analyses, population-averaged exposures align better with aggregated mortality, but spatial variability of BTEX might amplify the measurement errors between the modelled and true ambient levels, further attenuating the effect estimates to null.[46] Consequently, exposure misclassification would potentially lead to an underestimation of the health effects. Second, potential variations in mortality coding practices across countries could disproportionately affect the estimates of the effects on cause-specific mortality due to the inevitable diagnostic errors in such a global study, while the effect estimates for total mortality were more robust against such errors. Third, the included locations were predominantly located in Europe, North America, and east Asia. Thus, our findings might have limited generalisability to regions with insufficient data (eg, Africa and south Asia). Furthermore, the country-specific estimates should be interpreted cautiously due to the limited number of locations and BTEX measurements in some countries. Fourth, our study focused on cities, while rural areas were not included. The associations between BTEX and mortality might differ in less urban settings due to factors such as differences in exposures, occupation, population characteristics, and access to health care. Lastly, we could not fully disentangle the effects of BTEX from other co-pollutants, and the

independent health effects of BTEX on mortality warrant further investigation.

In summary, this global investigation suggests significant associations between short-term ambient exposure to individual BTEX components or their mixture and daily total, cardiovascular, and respiratory mortality. Furthermore, these associations remain robust after adjusting for co-pollutants, indicating the potentially independent health effects of BTEX exposure. Our findings underscore the importance of developing comprehensive air quality policies that include BTEX monitoring and mitigation to protect public health.

Contributors

LZ and YX conducted the statistical analysis and drafted the manuscript. YH and HKa had equal contributions as senior authors and they contributed to the conception of the work and gave final approval of the version to be submitted. AG, YG, MH, and BA set up the collaborative network. FS, AMV-C, YG, ST, PHNS, EL, DR, NR, SB-B, ES, AZ, JK, SdNPdS, MB, and AG provided substantial scientific input in interpreting the results and drafting and revising the manuscript. YX, FS, AMV-C, RA, YG, ST, MdSZSC, PHNS, EL, PMC, NVO, SO, DR, JK, HO, MM, JJKJ, NR, MP, VH, SB-B, AS, KK, ES, AE, FM, PG, AZ, RR, MSc, MSt, YH, MH, CFSN, BA, MHD, EEFA, AO, JK, SR, GC, XS, PLCC, SdNPdS, JM, I-HH, NS, RMG, HKi, WL, AT, CI, BF, MSR, YLG, S-CP, SL, PM, VC, MB, AZ, JS, TND, DVD, AG, YH, and HKa provided the data and contributed to the interpretation of the results. YH and HKa verified the data. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data were collected within the MCC Collaborative Research Network and are not publicly available due to restrictions imposed by the data sharing agreement with the MCC participants of the included countries.

Acknowledgments

This work was supported by the Noncommunicable Chronic Diseases—National Science and Technology Major Project (2024ZD0529300), the National Natural Science Foundation of China (82430105), Shanghai Municipal Science and Technology Major Project (2023SHZDZX02), Shanghai B&R Joint Laboratory Project (22230750300), and Shanghai International Science and Technology Partnership Project (21230780200). YX and YH were partially funded by the Faculty Competition for Postdoctoral Fellows Program from the Division of Research & Innovation at Wayne State University. We gratefully acknowledge Cong Liu and Like Wang for their valuable contributions to manuscript revision and exposure model validation. We also appreciate the high-performance computing support and data storage from the Derecho (https://doi/org/10.5065/qx9a-pg09) supercomputers provided by the National Science Foundation (NSF) National Center for Atmospheric Research and sponsored by NSF.

Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

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