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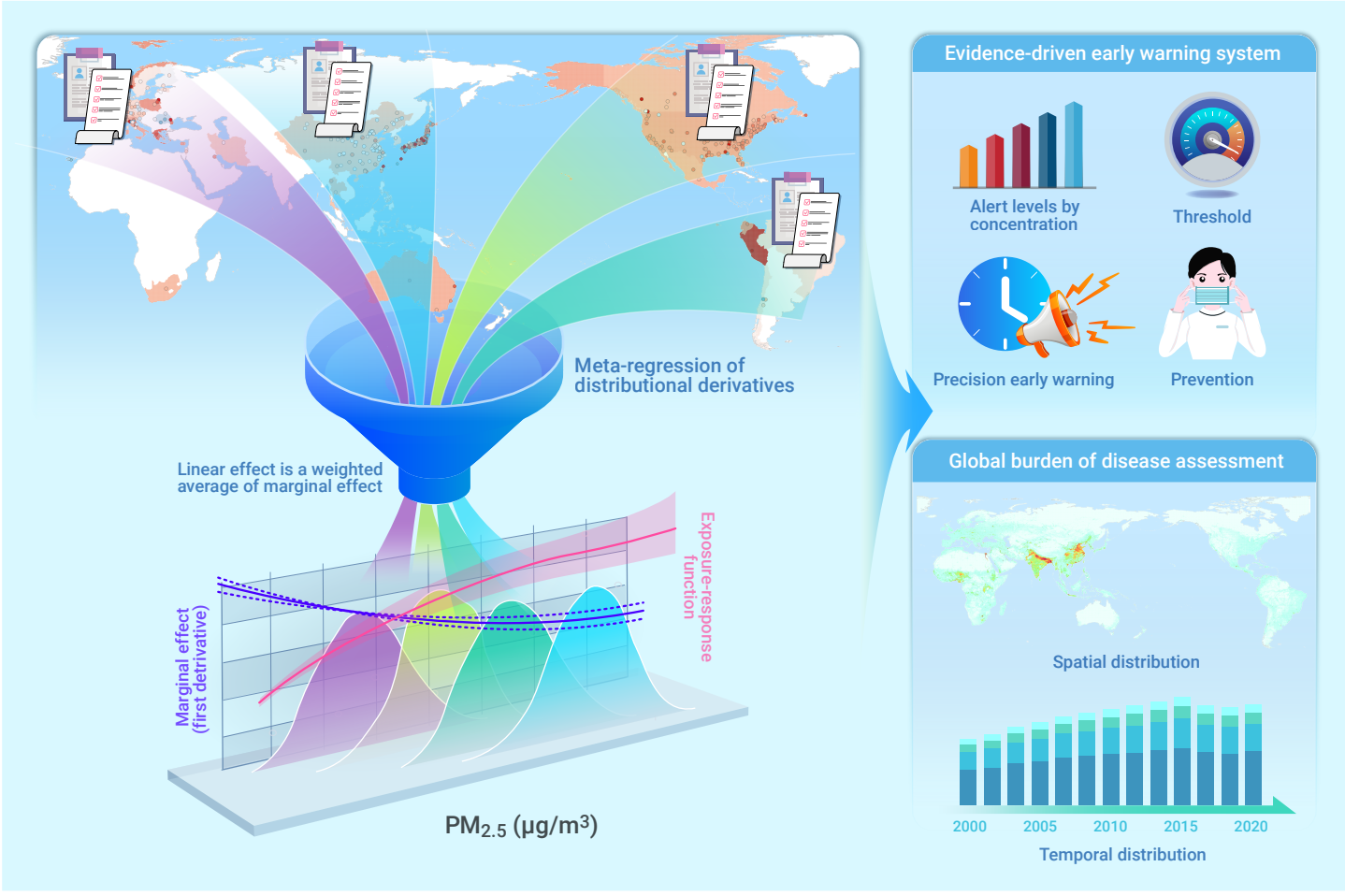
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Growing $PM_{2.5}$ variability across regions triggers extreme pollution and endangers public health.
- A new method was developed for global evidence synthesis of non-linear health risks.
- Short-term exposure to $PM_{2.5}$ causes over 670,000 deaths globally each year.
- Early warning systems are crucial to mitigate health impacts from extreme air pollution peaks.

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Rising $PM_{2.5}$ variability fuels mortality from pollution extremes

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Fine particulate matter ($PM_{2.5}$) pollution is a leading cause of the global mortality burden, but public health risks from short-term fluctuations, in addition to long-term exposure, have been insufficiently studied. Potentially influenced by climate change, the daily variability of $PM_{2.5}$ has significantly increased over the past 60 years, particularly in densely populated regions of East Asia, South Asia, and western North America. To quantify the short-term mortality burden exacerbated by this growing variability, we developed a novel method, the Meta-Regression of Distributional Derivatives (MR-ODDs), to construct nonlinear exposure-response relationships from published summary statistics without requiring individual-level data. Using this approach, we estimate that an average of 672,867 (95% CI: 579,452–740,680) deaths per year globally were attributable to short-term $PM_{2.5}$ exposure between 2000 and 2023. The mortality burden is especially pronounced in regions where intensifying climate variability drives more frequent extreme pollution events. Western North America, in particular, has emerged as the region with the fastest-rising risk from such events. These findings indicate that extreme pollution events pose a new and growing threat to global public health, demanding a shift in policy from managing annual average concentrations to focusing on early warning and intervention for extreme pollution peaks.

INTRODUCTION

Anthropogenic climate change is escalating the frequency and intensity of extreme weather events (e.g., heatwaves), sand dust storms and wildfires, posing profound threats to human survival.[1-4] A growing body of evidence shows that these climate-driven disturbances are tightly linked to a surge in extreme fine particulate matter ($PM_{2.5}$) pollution events, amplifying the adverse health impacts of climate change.[5-8] However, current global health impact assessments have primarily focused on long-term $PM_{2.5}$ exposure levels,[9-18] leaving the health risks posed by increased short-term variability (i.e., frequent extreme pollution events) unquantified. This knowledge gap hinders our ability to fully understand how climate change affects public health through air pollution and to develop effective response strategies.

Quantifying the health risks of $PM_{2.5}$ variability is challenging. It represents an "out of distribution" problem dominated by extreme events that defy the linear assumptions of traditional meta-analysis.[19,20] Large-scale, multi-center studies can capture non-linear effects but are fundamentally constrained by data privacy and sharing barriers, leaving a fragmented and outdated picture of global risk.[21,22] Consequently, a globally applicable, generalizable exposure-response relationship for extreme $PM_{2.5}$ events remains elusive.

Here we overcome these barriers by developing a novel framework, the Meta-Regression of Distributional Derivatives (MR-ODDs), to construct nonlinear exposure-response functions directly from published summary statistics, without requiring private individual-level data. Using this approach, we reveal the substantial global mortality burden attributable to short-term $PM_{2.5}$ and its spatiotemporal evolution over recent decades. To facilitate continuous evidence synthesis, we launch a living online platform that routinely updates the risk function with new findings. This work provides a new paradigm for evidence-based risk assessment and a critical tool for monitoring the evolving health impacts of air pollution extremes in the context of a changing climate.

MATERIALS AND METHODS

Calculation of variability

We utilized the time series data of $PM_{2.5}$ exposure from 5023 sites in the northern hemisphere from 1959 to 2022.[23] To ensure reliable estimation of $PM_{2.5}$ variability with robust sample sizes, we employed a 5-year sliding window approach, defining consecutive overlapping periods as 1959–1963, 1960–1964, ..., 2018–2022 (resulting in 60 periods with a 1-year step between adjacent windows). For each 5-year period, $PM_{2.5}$ variability was quantified through a standardized workflow. First, we preprocessed daily $PM_{2.5}$ time series data for each site by removing linear trends and annual cycles. The linear trends were eliminated via linear regression to isolate long-term directional changes, and annual cycles were removed using cyclic splines with 6 degrees of freedom per year to capture seasonally recurring patterns with sufficient flexibility. This preprocessing framework aligns with the variability quantification approach described by Zhang et al. for precipitation.[24] Subsequently, we calculated the temporal standard deviation (SD) of the residual daily values (after trend and cycle removal) as the metric of day-to-day variability.[25-27] To facilitate cross-site comparisons, each site's SD for a given 5-year period was normalized by its mean SD across the entire 1959 to 2022 period, yielding a dimensionless index relative to the site's long-term average variability. Specifically, this index represents the relative difference between the sliding 5-year SD and the historical mean SD. Therefore, a positive (or negative) value indicates that the $PM_{2.5}$ variability during that specific window is higher (or lower) than the historical baseline, while the magnitude reflects the proportional deviation. Finally, the long-term trend in normalized $PM_{2.5}$ variability was estimated via linear regression over the 60 periods, with results expressed as the percentage change per decade. To maintain epidemiological rigor, it is essential to distinguish between the interconnected concepts of short-term exposure, extreme events, and exposure $PM_{2.5}$ variability. In this study, short-term $PM_{2.5}$ exposure refers to the daily mean concentration, which acts as the direct biological hazard modeled in our exposure-response function. Extreme pollution events represent the acute hazards at the right tail of the daily exposure distribution (days exceeding the 95th percentile). This choice aligns with the fundamental statistical consensus for defining extremity and significance. $PM_{2.5}$ variability is a quantitative metric to describe the instability or variation of the $PM_{2.5}$ distribution. $PM_{2.5}$ variability itself does not directly cause the disease burden, but serves as a statistical driver that indicates the probability of extreme events occurring.

Meta-regression of distributional derivatives

According to the theory proposed by Yitzhaki,[28] when a linear model is used to approximate a non-linear relationship, the resulting linear estimator ($\hat{\beta}$) represents a weighted average of the derivative of the true underlying exposure-response function ($f'(x)$). This relationship is formally expressed as:

$$\hat{\beta} = \int \frac{\partial E(y|x)}{x} w(x)\,dx = \int f'(x)\,w(x)\,dx \quad (1)$$

where x is the exposure as a random variable, y is the outcome variable, $f'(x)$ is the first derivative of the exposure-response function (i.e., the marginal risk at a specific exposure level x), and $w(x)$ is a weighting function determined by the probability distribution of the exposure within the study population.

We then utilized spline functions as the foundational framework to conduct

a flexible basis function expansion of $f(x)$, followed by estimating the coefficients of the expanded basis functions via the meta-regression method, utilizing only linear estimators and exposure probability distributions for each study center. Once these coefficients were obtained, they were substituted back into the basis function expansion expression to derive $\hat{f}(x)$. Detailed calculation procedures are provided in the method part of Supplementary Information. The final non-linear exposure curve, $\hat{f}(x)$, was then obtained by integrating $\hat{f}(x)$ and setting a reference value at the Theoretical Minimum Risk Exposure Level (TMREL), where the risk is assumed to be zero. Specifically, the method can be specified as follows:

$$\hat{f}(x) = \int_{TMREL}^{x} \hat{f}(x)\,dx \tag{2}$$

Confidence intervals for $\hat{f}(x)$ were derived using 500 Monte Carlo simulations, propagating uncertainty from the estimation of the coefficients.

To evaluate the performance of MR-ODDs, we conducted statistical simulations using $PM_{2.5}$ time series data from 5,661 global sites,[29] which were then matched with additional covariates, including ozone (O_3), humidity, and temperature from relevant datasets. After excluding missing values, these sites were aggregated into distinct cities based on the Global Administrative Areas (GADM) framework, resulting in a final sample of 1,503 cities included in the simulations. For each city i and each day t, we utilized the aforementioned variables, pre-set exposure-response function for $PM_{2.5}$, and relevant exposure-response functions for other covariates (derived from the literature)[30–33] to compute the expectations $E(y_{i,t})$. The outcome variable $y_{i,t}$ was simulated under the assumption that it follows a Poisson distribution with mean $E(y_{i,t})$. We then applied both MR-ODDs (only linear estimates and exposure probability distributions) and the traditional two-stage method (complete original data) to derive the $PM_{2.5}$ exposure-response function, which were subsequently compared against the pre-set true exposure-response function. To quantitatively assess the performance of the two methods, Equation (1) was used to compute the "equivalent linear estimate" for each method, with these estimates further compared to the pre-set true value. We preset three exposure-response functions (linear, non-linear and non-linear with a threshold) and use three degrees of freedom for basis function to obtain nine scenarios. The predefined scenarios served strictly as benchmark "pre-set true value" for validating the framework's performance via simulation. For latter global evidence synthesis, the MR-ODDs framework was applied without any a priori assumptions. Finally, this procedure was replicated 500 times for each scenario, and results were aggregated across replications to mitigate sampling error with each replication treated as an independent sample. Detailed calculation procedures are provided in the method part of the Supplementary Information.

Meta-analysis

We utilized the MR-ODDs to obtain globally applicable exposure-response function between short-term exposure to $PM_{2.5}$ and all-cause mortality. We developed an online database to archive the center-specific estimates on effect of short-term exposure to $PM_{2.5}$ on all-cause mortality for MR-ODDs. The database (https://seed.bjmu.edu.cn/exposure/index) will be well-maintained and updated timely (The authors promise to make the database open-accessed after the manuscript publication). Therefore, this study conducted an updated meta-analysis on basis of a previous one,[19] which had collected relevant original studies before December 31, 2017 by a team entrusted by World Health Organization to develop the 2021 version of air quality guidelines. We performed a systematic literature search of following bibliographic databases and citation indexes: Medical Literature Analysis and Retrieval System Online (MEDLINE), Scopus, Literatura Latinoamericana y del Caribe en Ciencias de la Salud (LILACS), Western Pacific Region Index Medicus (WPRIM), Index Medicus for South-East Asia Region (IMSEAR), Index Medicus for the Eastern Mediterranean Region (IMEMR), and African Index Medicus (AIM). The aim is to identify peer-reviewed epidemiological studies examining the association between short-term exposure to $PM_{2.5}$ and mortality risk. The search included publications from October 1, 2018, to December 1, 2024. All literature search and analysis were accordant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Study selection was guided by a standardized PECO (Population, Exposure, Comparator, Outcomes) framework, with detailed eligibility criteria provided in the method part of Supplementary Information. All retrieved records were imported into EndNote for reference management, and duplicates were removed. Two investigators (P.Z., and J.D.) independently screened titles and abstracts, followed by a full-text evaluation of potentially eligible articles against pre-specified eligibility criteria. Disagreements were resolved through discussion or consultation with a third investigator (T.X.). We evaluated the quality of included studies using a domain-specific Risk of Bias (RoB) instrument developed by a World Health Organization expert panel in the Supplementary Information. Other detailed procedures (including search question, eligibility criteria, studies search and selection, data extraction, risk of bias analysis, data synthesis and analysis) were shown in the method section of the Supplementary Information (Tables S1-S2).

Burden of disease

Based on the exposure-response function derived above, we can evaluate the all-cause mortality burden attributable to short-term exposure to $PM_{2.5}$:

$$AF_{s,t} = 1 - \frac{1}{f[\max(x_{s,t},\ TMREL)]},\ AN_{s,t} = AF_{s,t} \times N_{s,t} \tag{3}$$

where s and t denote the s^{th} grid cell and the t^{th} day, AF denotes the attributable fraction, x denotes the concentration of $PM_{2.5}$, TMREL refers to theoretical minimum risk exposure level, AN denotes the attributable number, and N denotes the baseline number of daily deaths. The TMREL was set at 15 $\mu g/m^3$, according to the 24-hour average $PM_{2.5}$ guideline value established by the 2021 WHO Air Quality Guidelines. We then selected the 5% days with the highest concentration in each grid cell, and separately calculated the attributable number for these days and determined their proportion in the total disease burden. Environmental data on daily $PM_{2.5}$ concentrations is derived from MERRA-2 dataset (https://disc.gsfc.nasa.gov/), corrected using data from the Atmospheric Composition Analysis Group at Washington University (https://sites.wustl.edu/).[34] Baseline data were computed using population data from LandScan (https://landscan.ornl.gov/) and mortality data from the Global Burden of Disease (GBD) database, maintained by the Institute for Health Metrics and Evaluation (IHME) (https://vizhub.healthdata.org/gbd-results/). The Detailed calculation procedures are described in the Supplementary Information.

RESULTS

Global $PM_{2.5}$ variability is intensifying

To assess the possible impact of climate change on air pollution patterns, we analyzed long-term observational data (1959–2022) from 5,023 sites worldwide. The analysis reveals a significant long-term increasing trend in daily $PM_{2.5}$ variability across several key regions (Figure 1). Among sites with over 40 years of data, more than half (1,687) showed increased $PM_{2.5}$ variability. This phenomenon was particularly pronounced in western North America, East Asia, and South Asia, indicating that these densely populated regions are experiencing more frequent and intense extreme pollution events. Since the 21st century, $PM_{2.5}$ variability has grown most rapidly in northwestern North America, with its anomaly increasing by 8.25% per year (p-value < 0.01), followed by the Western Pacific (4.26% per year; p-value < 0.01) and South Asian regions (0.64% per year; p-value = 0.02). This aligns with recent reports of wildfires and adverse meteorological conditions occurring in the context of a changing climate, reflecting a shift in the threat posed by $PM_{2.5}$ pollution.

Nonlinear health effects of short-term $PM_{2.5}$ exposure

Statistical simulation validation demonstrated that the MR-ODDs method performs excellently in capturing both linear and nonlinear relationships (including complex scenarios with thresholds), with performance comparable or even more robust in certain complex scenarios than the traditional two-stage method that relies on original data (Figure 2). Specifically, to capture a more complex nonlinear relationship (e.g., the threshold-linear function), the spline regression needs a larger number of degrees of freedom. For such scenarios (e.g., degrees of freedom > 5), the two-stage method faced convergence failures in the first stage for cities with small sample sizes, which either

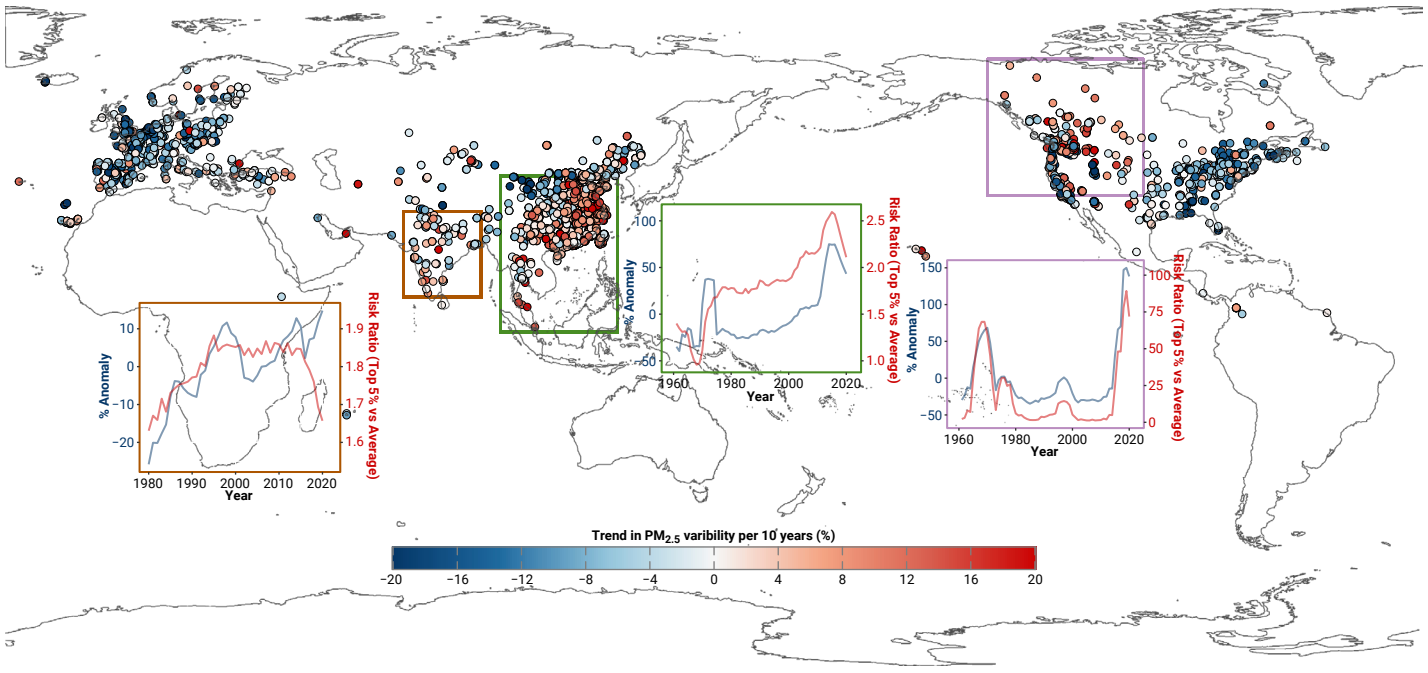

Figure 1. Trend in daily $PM_{2.5}$ variability, 1961-2020 $PM_{2.5}$ variability at each site was calculated from its time series data; linear trends of variability were derived via regression analysis, expressed as percentage changes per decade. Regions enclosed in purple, brown, and green boxes indicate three areas with significantly increased variability. The left y-axis represents the standardized $PM_{2.5}$ variability index. Positive (negative) values indicate that the variability during a given 5-year window is higher (lower) than the historical average, with the magnitude reflecting the proportional deviation. Corresponding line graphs show variability trends across different regions and the changing trend of the ratio of mortality risk on the top 5% most polluted $PM_{2.5}$ days to the average mortality risk.

halted progression to the second stage or forced the exclusion of these cities. For detailed results and sensitive analysis on the statistical simulation, please see the Supplementary Information (Figures S1-S2, Tables S3-S4).

To precisely quantify the burden of disease from short-term $PM_{2.5}$ exposure, we first needed to construct an exposure-response function that accurately describes the risk. Through a systematic literature review, we integrated over 700 effect estimates from 85 studies across 35 countries (Figure 3B). Using our newly developed Meta-Regression of Distributional Derivatives (MR-ODDs) method, we constructed a globally applicable exposure-response function for short-term $PM_{2.5}$ exposure and all-cause mortality (Figure 3A, Table S5). The literature search process, study selection results (Figure S3, Tables S6-S7), risk of bias assessment (Figures S4-S5, Table S8), and sensitivity analysis (Figures S6-S7) for the meta-analysis are detailed in the Supplementary Information. The systematic review will be updated once a while, with a re-generated exposure-response function released via the online database (https://seed.bjmu.edu.cn/exposure/index). The function exhibits a significant non-linear characteristic. At low concentration ranges (e.g., 0–50 μg/m^3), the mortality risk rises sharply with increasing $PM_{2.5}$ concentration; at high concentrations (>200 μg/m^3), the slope of the curve gradually flattens. This "high risk at low concentration" pattern implies that even minor fluctuations in $PM_{2.5}$, especially in areas with low background concentrations, can lead to disproportionate health damage. Furthermore, sensitivity analyses exploring alternative exposure distribution assumptions (Figures S8-S9) and varying lag specifications (Figure S10) both produced results highly concordant with the main analysis, corroborating the robustness of our findings.

Global burden of disease from short-term $PM_{2.5}$ exposure

We combined our nonlinear exposure-response function with global daily $PM_{2.5}$ concentration data to assess the global disease burden. The results show that between 2000 and 2023 an average of 672,867 deaths (95% CI: 579,452–740,680) per year were attributable to short-term $PM_{2.5}$ exposure, equivalent to 10 (8–12) deaths per 100,000 population. The geographical distribution of the disease burden is highly uneven, with Asia accounting for approximately 78% of the deaths, followed by Africa (17%). High-burden areas are concentrated in heavily polluted and densely populated regions of East Asia, South Asia, and West Asia (Figure 4A). In terms of temporal trends, the global number of deaths attributable to short-term $PM_{2.5}$ exposure increased during the study period, from about 470,000 in 2000 to about 760,000 in 2023, with the growth mainly coming from Asia. Detailed disease burden results are provided in Figures S11-S12 and Tables S9-S10 of the Supplementary Materials.

Intensified impacts from $PM_{2.5}$ episodes

Notably, the geographic hotspots of this escalating mortality burden coincide closely with regions experiencing intensified $PM_{2.5}$ variability (Figure 1). This spatial alignment demonstrates that the increasingly frequent and intense extreme pollution events might act as a key driver of the rising health risks. To quantify the relative severity of extreme pollution events, we evaluated the ratio of mortality risk on the top 5% most polluted days to the overall historical average risk ($RR_{top5\%}$). Conceptually, this ratio is derived by dividing the expected attributable risk on days exceeding the 95th percentile of the $PM_{2.5}$ distribution by the expected baseline risk across the entire historical exposure distribution (applying a TMREL of 15 μg/m^3). Utilizing this metric, we observed substantial increases in $RR_{top5\%}$ across western North America, East Asia, and South Asia. Most strikingly, in western North America, the risk ratio has risen sharply over the past decade. By 2020, the mortality risk on extreme pollution days was 100-fold higher than the 1960-2020 average. This pattern was further confirmed by the spatial distribution of the disease burden estimates (Figure 5A). Regions with an elevated $RR_{top5\%}$ were primarily concentrated in western North America, eastern South America, southern Africa, Australia, and northern Europe. Trend analysis (Figure 5B) showed that the $RR_{top5\%}$ increased most markedly in western North America (0.38 increase per year; p-value = 0.03), whereas it exhibited a significant downward trend in eastern North America (0.59 reduction per year; p-value < 0.01).

Furthermore, we found an inverse relationship between the average risk (i.e., the annual fraction of deaths attributable to short-term $PM_{2.5}$) and the $RR_{top5\%}$ (Figure 6). Countries with a lower average risk exhibited a larger $RR_{top5\%}$, indicating that their mortality risk is highly concentrated on a small number of high-pollution days. Globally, 157 countries and territories had a death fraction below the global average of 1.23%, and among these regions, ~50% of the disease burden associated with short-term $PM_{2.5}$ exposure was concentrated on the 5% of days with the highest $PM_{2.5}$ concentrations on average. This finding underscores the urgent need for air pollution early

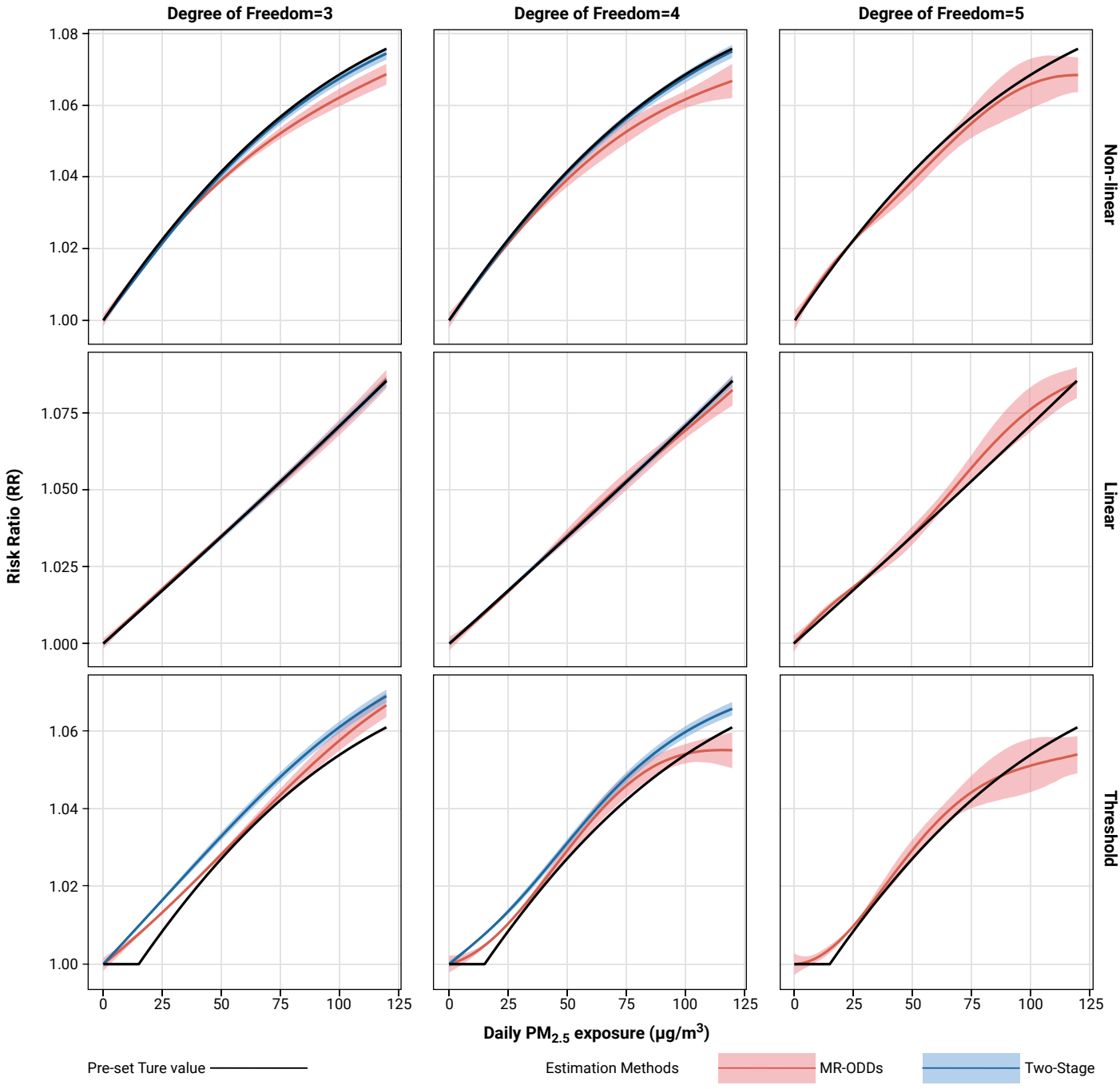

Figure 2. Performance of meta-regression of distributional derivatives (MR-ODDs) method in simulation This figure illustrates the performance of MR-ODDs: the black line represents the preset true value; the pink and blue lines represent the curves from MR-ODDs and the two-stage method, respectively; the pink and blue ribbons denote the confidence intervals of the two methods.

warning systems in these regions to mitigate the associated health risks.

DISCUSSION

Our study confirms that $PM_{2.5}$ variability is increasing in multiple global regions during the past 60 years, accompanied by increasing risk ratios and attributable deaths in these areas. To address this challenge, we developed the MR-ODDs method, which was verified to be effective through statistical simulations. This method was subsequently applied to identify the association between short-term $PM_{2.5}$ exposure and all-cause mortality, providing guidance for more precise prevention and control of the health hazards caused by short-term $PM_{2.5}$ exposure. Subsequently, using the exposure response function obtained through this method, we evaluated the global disease burden attributed to short-term exposure to $PM_{2.5}$, identified key areas, and provided policy recommendations to better mitigate the health impacts of $PM_{2.5}$.

Anthropogenic climate change and emissions significantly amplify the frequency and intensity of extreme $PM_{2.5}$ pollution events in regions like Western North America, East Asia, South Asia, and Australia, with rising temperatures, altered atmospheric dynamics, and climate-fueled wildfires as key drivers.[1-4] In Western North America, climate change has caused higher regional temperatures,[35,36] longer fire seasons[37] and drier fuels.[38] Human-caused climate change added 4.2 million hectares of forest fire area in western US forests (1984–2015), nearly doubling the area without it.[39] In East Asia, sustained emissions,[40,41] weather conditions,[42,43] weakened northerly winds,[44,45] a diminished East Asian winter monsoon,[45] reduced Arctic sea ice,[46] and decreased relative humidity[47] boost extreme winter haze. In South Asia,

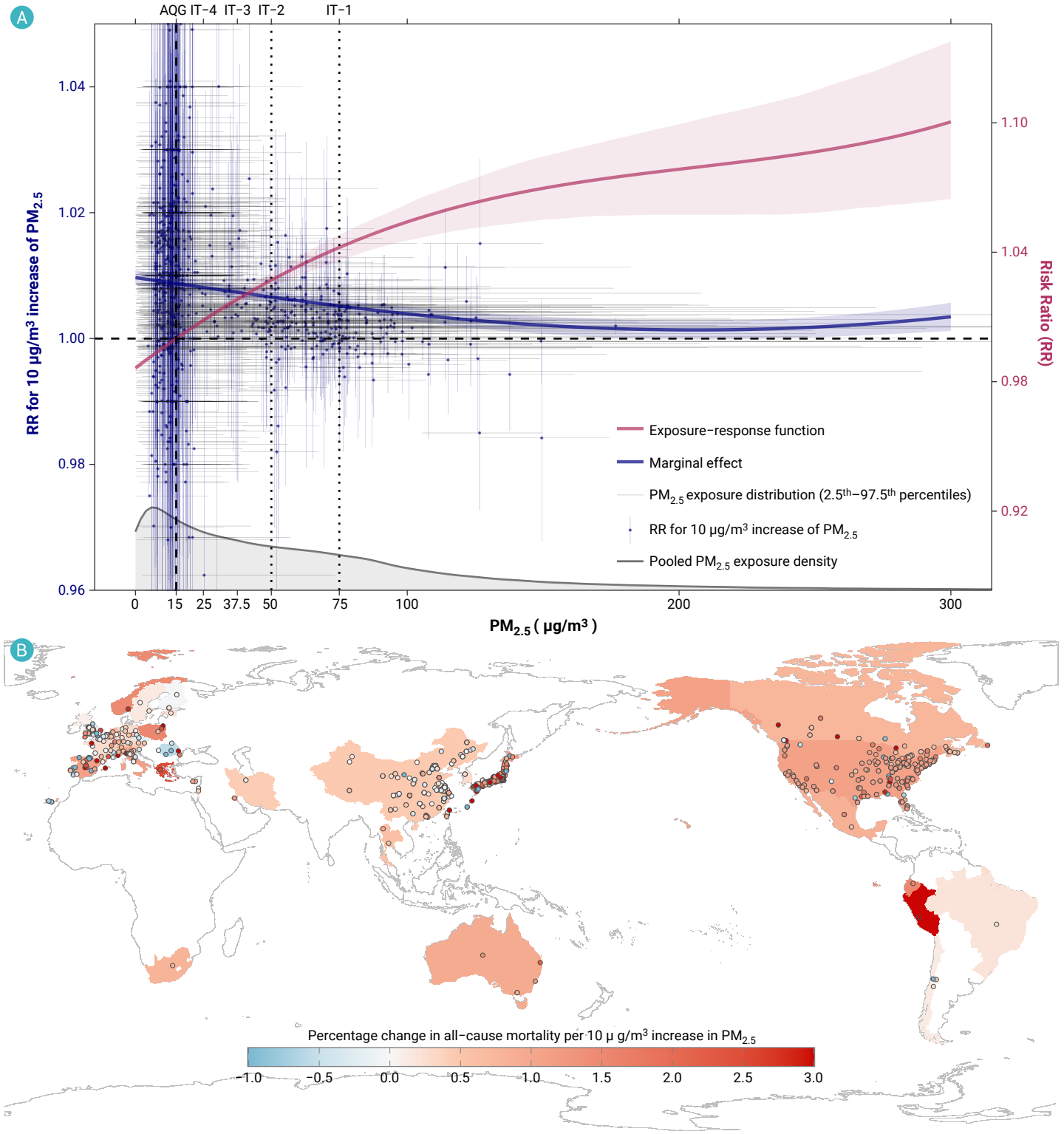

Figure 3. Exposure-response function derived by the meta-regression of distributional derivatives (MR-ODDs) method (A) This figure shows the exposure-response function from MR-ODDs derived from literature-collected data: the bold blue line indicated marginal effect; red line indicate the exposure-response function; blue points indicate the mean concentration and health effect of included study centers; the horizontal lines and vertical lines on the blue dots indicate the 2.5-97.5th percentile of short-term $PM_{2.5}$ exposure of included study centers and 95%CI of health effect from included study centers, respectively. (B) This figure shows the spatial distribution of the included study centers and pooled effect for each country.

anthropogenic emissions[48,49] and atmospheric stagnation[50] may increase extreme events. Regions like Delhi see 100-150 annual days with $PM_{2.5}$ exceeding 100 μg/m^3,[51] and India's pollution event frequency may rise by 20-120 days yearly by 2050 (vs 2018).[52] In Australia, the effect of climate change is becoming apparent in the increasing numbers of extreme fire events.[53,54] A globally anomalous 2019–2020 fire season in Australia burned over 5 million ha of Eucalyptus forests,[55] and climate change has increased the likelihood of such extreme fire weather conditions by at least 30%.[56] Global regional studies have shown that, possibly driven by anthropogenic emissions and climate change, the frequency of extreme $PM_{2.5}$ pollution events has increased, yet the annual average population-weighted $PM_{2.5}$ concentration has exhibited modest changes. This aligns closely with our research findings, which reveal

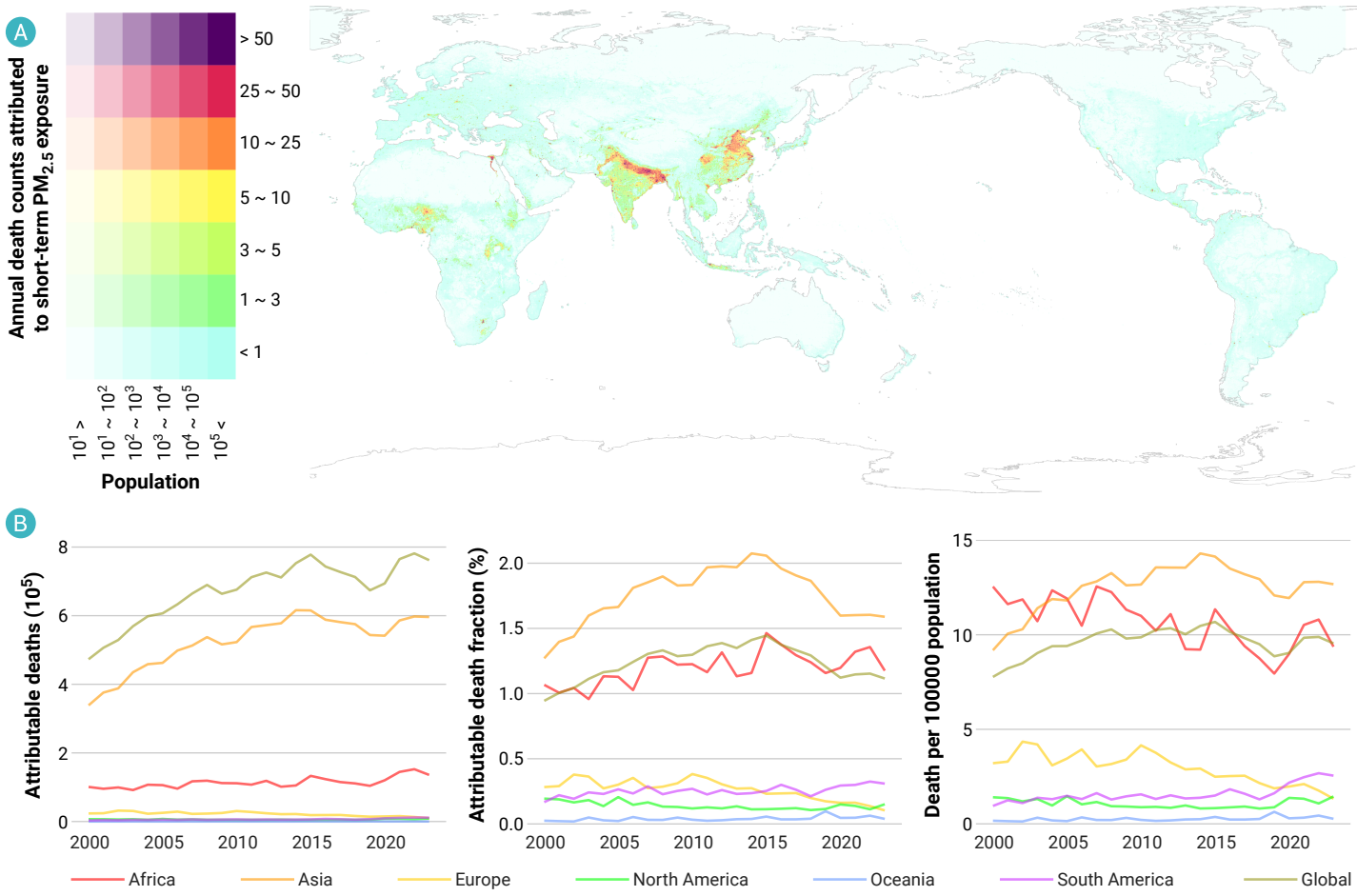

Figure 4. Spatiotemporal trends in deaths attributable to short-term $PM_{2.5}$ exposure (A) This figure presents the annual number of deaths attributable to short-term $PM_{2.5}$ exposure. (B) This figure displays the attributable deaths, attributable death fraction and the number of deaths per 100,000 population across different continents over years.

a growing variability in $PM_{2.5}$ across specific regions. It further underscores the importance and urgency of preventing and managing short-term $PM_{2.5}$ exposure to safeguard human health. While most regions show aligned trends, India is a notable post-2015 exception with increasing variability but declining $RR_{top5\%}$. Mathematically, variability isolates de-trended fluctuations, whereas $RR_{top5\%}$ relies on absolute peak concentrations, which fell as emission controls lowered the baseline. Furthermore, these regional estimates warrant caution since India's sparse monitoring sites fail to cover most major cities.

The MR-ODDs method exhibits three-tiered advantages that enhance its applicability in environmental health research. First, it integrates published effect estimates to bypass raw data privacy barriers, unlike traditional two-stage methods dependent on original health data. It enables analyses across 35 countries (six continents), more than twice the coverage of a prior 16-country multi-study.[21] Second, it supports high-dimensional spline modeling to capture non-linear relationships and threshold effects. This differs from linear meta-analyses that simplify exposure-response functions. Statistical simulations confirm its stability even in complex scenarios such as threshold-based effects. It also avoids the matrix instability inherent in two-stage methods while matching their performance without the need for raw data. Third, it is extensible to other pollutants like O_3 and PM_{10}, as well as other health outcomes including respiratory and cardiovascular diseases. It can even be applied to public health domains such as environmental justice and health disparity analysis, serving as a versatile tool for evidence synthesis. Furthermore, disease burden estimates reveal that the health impact of short-term $PM_{2.5}$ exposure is becoming increasingly concentrated on high-$PM_{2.5}$ pollution days across many global regions, particularly in western North America. This pattern is likely linked to the growing frequency and intensity of wildfires in western North America.[57-59] The finding further underscores the importance of air pollution early warning systems in these areas, as such systems play a critical role in mitigating the associated health risks.

Our study identifies a non-linear exposure-response function for short-term $PM_{2.5}$ exposure and all-cause mortality. Risk rises steeply at low concentrations (below 50 μg/m^3) and either plateaus or increases gradually at higher levels (above 200 μg/m^3). This pattern highlights the inadequacy of linear assumptions in $PM_{2.5}$ health risk assessments.[60,61] It also aligns with a growing body of evidence from multi-city studies. For instance, Chen et al. analyzed daily mortality data in China and observed a similar non-linear function. In their work, the steepest increase in mortality occurred at lower $PM_{2.5}$ concentrations.[22] This finding was further supported by a study within the Multi-Country Multi-City Collaborative Research Network, demonstrating consistently steeper slopes below approximately 50 μg/m^3 and flattening at higher levels for short-term effects.[21] While our results show such a non-linear exposure-response pattern, this should be interpreted cautiously. The apparent attenuation of risk at high concentrations may not solely reflect biological saturation. It could also arise from alternative epidemiological factors, such as the harvesting effect (mortality displacement)[62] or exposure measurement errors driven by avoidance behaviors (e.g., staying indoors during severe episodes).[63] Thus, we frame these findings as statistical associations rather than definitive mechanistic claims. The strong alignment between our non-linear exposure-response function and these robust findings, particularly those derived from the MCC network, is noteworthy. Given that a substantial proportion of cities included in our MR-ODDs analysis originate from or overlap with this network, it provides a plausible explanation for the observed consistency. Crucially, this validates the MR-ODDs method's capability to effectively capture and reconstruct complex non-linear short-term $PM_{2.5}$ exposure-response functions, even without direct access to original, granular daily exposure and mortality data. This methodological strength

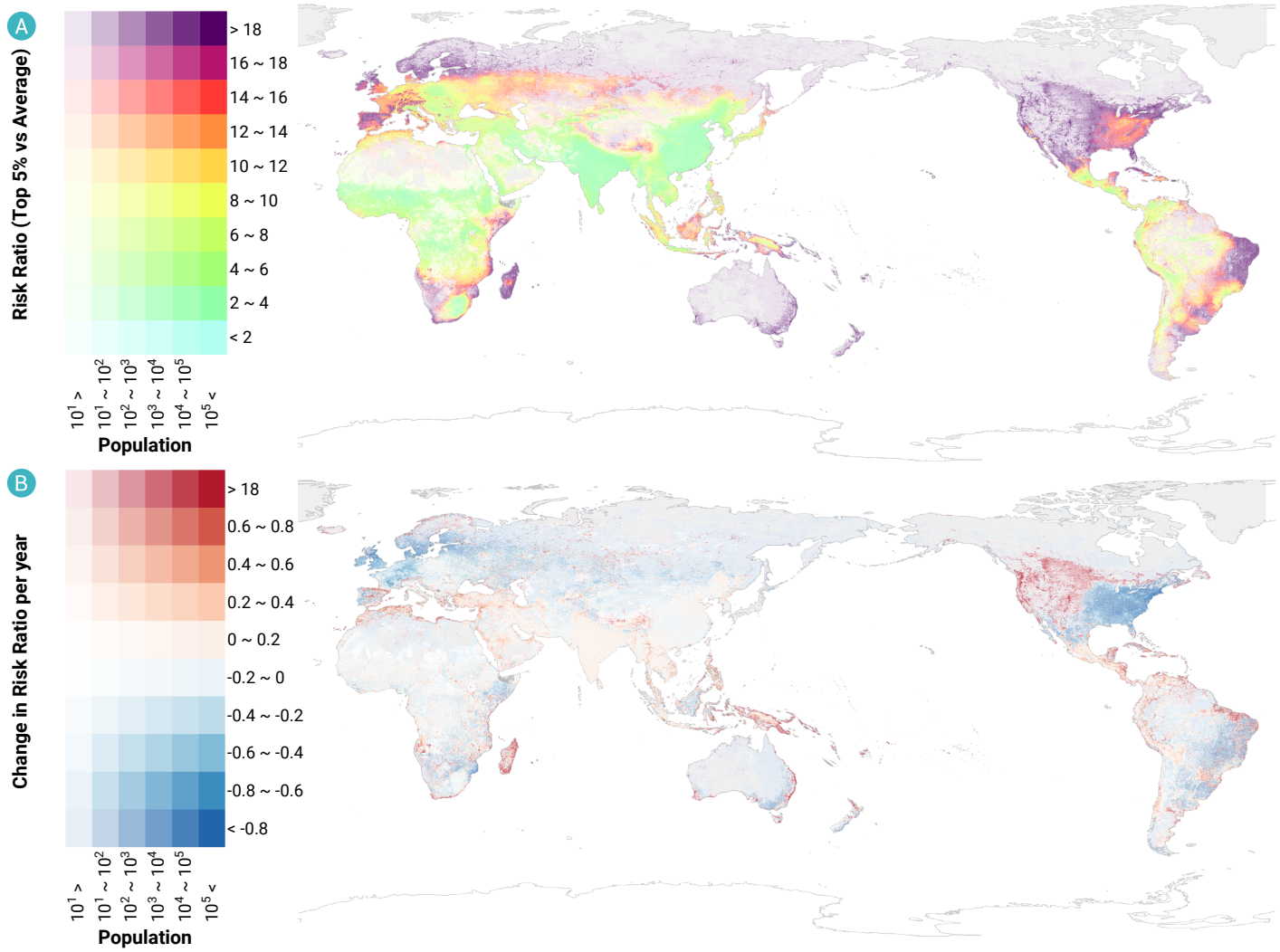

Figure 5. Contribution from top 5% pollution days to $PM_{2.5}$-related deaths and its spatiotemporal trends, 2000-2023 (A) This figure presents Spatial distribution of the risk ratio (top 5% vs average) at the pixel level. (B) This figure displays temporal trend in the risk ratio, with linear regression used to estimate pixel-level changes.

is vital for regions with limited data availability, enabling more precise acute health impact assessments.

Literature on the disease burden associated with short-term $PM_{2.5}$ exposure remains relatively scarce. Our estimate of 672,867 annual premature deaths is lower than the ~1 million premature deaths per year reported by Yu et al.[20] The numerical discrepancy is presumably driven by differences in exposure datasets and the use of distinct exposure-response functions. This methodological distinction is likely the primary driver of our modestly lower estimates. Similarly, Li et al. estimated the disease burden of short-term $PM_{2.5}$ exposure in China,[64] and their results were modestly lower than ours. Li et al. observed a reduction in the effect of their function when $PM_{2.5}$ concentrations exceeded 65 μg/m^3, which may lead to underestimation of disease burden. In contrast, the exposure-response function used in our study is more methodologically robust.

Our study also has several limitations. First, the data used to quantify $PM_{2.5}$ variability were derived exclusively from discrete monitoring stations and did not fully cover our key study regions. Consequently, extrapolations of increased $PM_{2.5}$ variability in these regions based solely on station data may be biased, even though station distribution is highly aligned with population distribution. It should be noted that while our study highlights the potential role of climate change in intensifying $PM_{2.5}$ variability, we did not perform a formal climate attribution analysis. The observed trends in pollution extremes result from a complex interplay between atmospheric dynamics, land-surface feedbacks (such as wildfires), and evolving emission trajectories. Future research using coupled Earth system models is needed to formally isolate the anthropogenic climate change signal from other drivers. Second, several assumptions underpinning MR-ODDs may not be valid in real-world settings. Specifically, the actual distribution of short-term $PM_{2.5}$ exposure may deviate from the assumed gamma distribution, and the quality of fit to the true exposure distribution is also highly dependent on the completeness of statistics reported in the literature. It is important to note that when raw, multi-center daily time-series data are available, the traditional two-stage approach remains the gold standard. The MR-ODDs framework serves as a robust alternative specifically designed for scenarios where data privacy restrictions prevent the pooling of raw health data, enabling global meta-assessments based on accessible summary statistics. Third, our study could not fully leverage multi-center studies that only reported pooled effect sizes. In our analysis, these multi-center studies were treated the same as single-center studies, which may diminish statistical power. We therefore advocate that, for multi-center studies, epidemiologists should disclose center-specific effect sizes and exposure distributions as fully as possible to enable improved data integration without compromising data privacy. Fourth, due to the lack of globally gridded daily mortality data, we applied national-level, annual average baseline mortality rates to all grid cells within a specific country across the entire year. While this is a practical and widely used approach in global assessments, it ignores spatiotemporal heterogeneity and may introduce specific biases. Temporally, this assumption likely leads to an underestimation of the overall disease burden. In many regions, extreme $PM_{2.5}$ events frequently peak during winter months, a period that also historically experiences the highest baseline mortality rates due to cold weather and seasonal

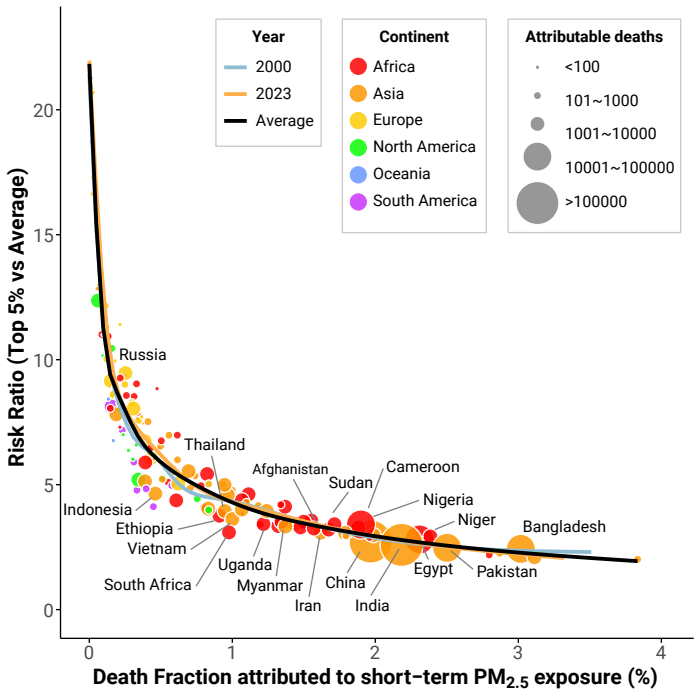

Figure 6. The relationship between the risk ratio and death fraction attributable to short-term $PM_{2.5}$ exposure from 2000 to 2023 Each point represents a country or region, where size of points indicates annual attributable deaths, their color denotes continent, and the curve is fitted via spline regression with line color representing year.

infections. Flattening the mortality rate across the year fails to capture the compound effect of these concurrent peaks. Spatially, this uniform application may introduce uncertainty, potentially overestimating or underestimating the local burden depending on whether highly polluted urban grid cells have lower or higher actual mortality rates compared to the national average due to discrepancies in healthcare access and demographic structures. Also, our estimation relies on a single global exposure-response function. While random effects were incorporated to address regional heterogeneity, severe data sparsity in regions like Africa precluded the development of robust region-specific functions. Consequently, this global function may not fully capture the distinct susceptibility and health conditions of all local populations.

CONCLUSION

In summary, this study clarifies the global pattern of $PM_{2.5}$ variability, validates a novel method for synthesizing environmental health evidence, and quantifies the disease burden of short-term exposure. The findings not only provide a methodological basis for global environmental health risk assessment but also lay a foundation for targeted pollution control and health protection strategies. Future research should further refine exposure-response modeling and improve data quality to enhance the accuracy and applicability of the results.

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AUTHOR CONTRIBUTIONS

Jianyu Deng: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing-original draft. Peng Zhou: Data curation, Investigation, Validation, Writing-review & editing. Jinting Guo: Software, Visualization, Writing-review & editing. Jingyi Wu: Validation, Data curation, Writing-review & editing. Pengfei Li: Conceptualization, Supervision,, Writing-review & editing. Tao Xue: Conceptualization, Methodology, Supervision, Project administration, Funding acquisition, Writing-review & editing. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not Applicable.

DATA AND CODE AVAILABILITY

Data are available from the corresponding author upon reasonable request.

SUPPLEMENTAL INFORMATION

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