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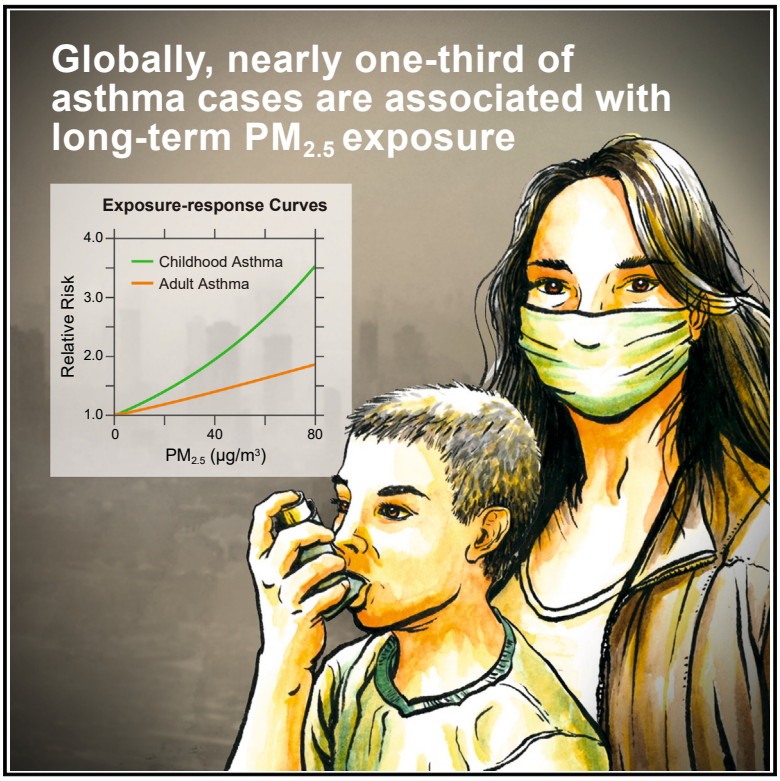
# Long-term exposure to $PM_{2.5}$ has significant adverse effects on childhood and adult asthma: A global meta-analysis and health impact assessment

## Graphical abstract




## Highlights

- Long-term exposure to $PM_{2.5}$ increases asthma risk in both children and adults
- In 2019, nearly one-third of global asthma cases were associated with $PM_{2.5}$ exposure
- Elaborate database for evaluating $PM_{2.5}$-associated asthma risk and its confidence level
- Exposure-response curves for assessing global burden of asthma attributable to $PM_{2.5}$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## In brief

As a major health threat, asthma is affecting more than 250 million people worldwide. Here, we find that long-term exposure to ambient $PM_{2.5}$ significantly increases the risk of asthma, and the increased risk not only presents in children but also in adults. In 2019, nearly one-third of the global asthma cases were associated with $PM_{2.5}$ exposure, posing dramatic threats to public health. Our findings highlight the urgent need for stricter legislation and effective personal maneuvers against air pollution to alleviate asthma risk and burden.


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# Long-term exposure to $PM_{2.5}$ has significant adverse effects on childhood and adult asthma: A global meta-analysis and health impact assessment

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**SCIENCE FOR SOCIETY** Asthma is currently an incurable disease that severely impairs quality of life, with recurring symptoms such as wheezing, coughing, and shortness of breath. As of today, ~4% of the world's population suffers from asthma, with more than 30 million new cases arising annually. Evidence suggests that long-term exposure to fine particulate matter ($PM_{2.5}$) may be an important risk factor for developing asthma. However, inconsistencies in findings from earlier epidemiological studies have left this potential health risk under debate. Drawing on evidence from ~25 million participants worldwide, we demonstrate that long-term exposure to $PM_{2.5}$ significantly increases asthma risk in both children and adults and is associated with ~30% asthma cases globally. Our findings highlight the urgent need for policymakers to enforce stringent legislation to continuously combat air pollution, while personal maneuvers, such as wearing masks, can also help reduce individual exposure and mitigate asthma risk.

## SUMMARY

Asthma affects more than 250 million people worldwide, making it a globally significant health threat. As one of the most important potential risk factors, the effects of long-term exposure to ambient fine particulate matter ($PM_{2.5}$) on asthma, especially in adults, remains unclear. Here, we comprehensively addressed this issue by integrating a systematic review, meta-analysis, exposure-response analysis, and health impact assessment based on evidence that emerged until May 2023. We show that, for every 10 $\mu g/m^3$ increment in $PM_{2.5}$, the risk of childhood and adult asthma (i.e., prevalence, incidence, and mortality of all asthma types) increases by 21.4% (95% confidence interval [CI]: 11.4%–32.3%) and 7.1% (95% CI: 1.6%–12.9%), respectively. We estimate that, in 2019, nearly one-third of the global asthma cases are associated with $PM_{2.5}$ exposure. These findings emphasize that long-term $PM_{2.5}$ exposure significantly increases asthma risk in both children and adults. Continuous efforts regarding air pollution mitigation are therefore urgently needed.

## INTRODUCTION

Asthma is a disease affecting more than 250 million people worldwide, making it a globally significant health threat.[1] There exists evidence that long-term fine particulate matter ($PM_{2.5}$) exposure might be one of the most important potential risk factors for asthma. However, the associations reported in previous epidemiological studies are inconsistent, leaving the effects of long-term $PM_{2.5}$ exposure on asthma under debate. On the other hand, asthma is incurable at present and can be easily triggered, leading to recurring symptoms such as wheezing, coughing, and shortness of breath, which significantly reduce the quality of life. In severe cases, asthma can be life-threatening and may require emergency medical interventions. Moreover, the treatment and management of asthma involve long-term medication and medical services, imposing a heavy financial burden on patients and their families as well as the whole society. Given the widespread impact of asthma among populations, there is an urgent need to clarify its association with long-term $PM_{2.5}$ exposure, which could help formulate policies and promote individual actions to

alleviate such a big disease burden, especially since air pollution is a preventable risk factor.

For childhood asthma, many studies have examined its association with long-term $PM_{2.5}$ exposure, including several meta-analyses.[2–13] However, the results of these meta-analyses remain highly inconsistent.[3–12] Furthermore, the studies included in these meta-analyses are almost exclusively from high-income and low-exposure Western countries and thus may not be globally representative. For adult asthma, very few studies in earlier years have explored its association with long-term $PM_{2.5}$ exposure, mainly due to the lack of asthma cohorts with long enough follow-up periods to identify new-onset adult asthma cases or deaths. With the widespread use of electronic health records and the establishment of high-resolution global and regional $PM_{2.5}$ datasets toward kilometer range,[14,15] relevant epidemiological studies have proliferated recently; however, the emerging evidence revealed contradictory results, leaving the association inconclusive.[16,17]

In this study, we comprehensively explored the effects of long-term $PM_{2.5}$ exposure on asthma by conducting a global meta-analysis and health impact assessment based on a large body of emerging evidence involving 25,789,433 participants worldwide, including evidence from several low- and middle-income countries (LMICs). Focusing on long-term postnatal exposure, we find that $PM_{2.5}$ significantly increases the risk of asthma both in children and adults, and globally, nearly one-third of asthma cases are associated with long-term $PM_{2.5}$ exposure, underscoring the severe threats it poses to public health. These findings provide an important basis for policy making; i.e., continuous efforts in air pollution reduction are an effective way to mitigate the risk and burden of asthma. Stricter legislations aimed at air pollution reduction and personal maneuvers against air pollution are therefore urgently needed.

## RESULTS

### Methods summary

To examine the associations between long-term $PM_{2.5}$ exposure and risk of asthma, we first conducted a systematic review of literature published in English until May 2023 and established an elaborate database (MPIC environment-related asthma risk [MEAR] dataset; Data S1),[18] which summarizes the association of long-term $PM_{2.5}$ exposure with risk of asthma incidence, prevalence, and mortality (experimental procedures; Notes S1–S3). This database comprises 1,027 records of the exposure-response associations observed based on 25,789,433 participants involved in cohort, case-control, and cross-sectional studies conducted across 22 countries and regions (including 6 LMICs) that complement evidence in areas with much higher $PM_{2.5}$ exposure levels, relatively poor health care systems, and different demographics, greatly enhancing the global representativeness of our follow-up analyses.

Using the MEAR database,[18] we performed a series of meta-analyses to synthesize asthma exposure-response associations, which encompass several sets of sensitivity tests to demonstrate the robustness of our findings (experimental procedures; Note S4). We then conducted a dedicated exposure-response analysis to examine the exposure-response effects of asthma at different $PM_{2.5}$ exposure levels over the global exposure range (experimental procedures; Note S5). After establishing, through the meta-analysis and exposure-response analysis, that long-term $PM_{2.5}$ exposure significantly increases the risk of asthma, we further assessed the related public health threat by estimating the fatal, non-fatal, and overall burden of asthma attributable to long-term $PM_{2.5}$ exposure. Additionally, we estimated the global $PM_{2.5}$-attributable burden of lower respiratory infections (LRIs), lung cancer, and chronic obstructive pulmonary disease (COPD) in order to compare the global burden of asthma with these well-documented $PM_{2.5}$-associated respiratory diseases (experimental procedures).

### Descriptive statistics

As shown in Figure 1, our database search for the systematic review of the association between long-term $PM_{2.5}$ exposure and asthma yielded 3,406 literature (defined as scientific papers published in journals) after removing duplicates. Of these, 3,212 were excluded by title and abstract screening. From the remaining 194, we further excluded 135 after reviewing the full text, leaving 41 on childhood asthma and 18 on adult asthma meeting the full eligibility criteria (Note S1). In this work, childhood asthma is defined as asthma existing among populations with an age under 20 (<20 years), and adult asthma is defined as asthma existing among populations with an age above 20 ($\geq$20 years). Main characteristics of the literature meeting the full eligibility criteria are summarized in Tables S1 and S2. Literature excluded during the full-text review and the corresponding reasons for exclusion are listed in Table S3.

For childhood asthma, we identify 43 studies (defined as epidemiological research or projects involved in the literature) across 15 countries and regions, including 5 studies conducted in 2 LMICs (Table S4). The 43 studies cover 15,647,826 participants with 1,703,973 asthma cases and provide 724 records on relative risks associated with long-term $PM_{2.5}$ exposure (Data S1). For adult asthma, we identify 25 studies across 20 countries and regions, including 1 study conducted in 6 LMICs. The 25 studies cover 10,141,607 participants with 303,366 asthma cases and provide 303 relative risk records (Data S1).

Importantly, with the inclusion of several studies conducted in LMICs, our systematic review encompasses evidence at $PM_{2.5}$ levels covering most of the worldwide exposure ranges (from 0.2 $\mu g/m^3$ to 169.8 $\mu g/m^3$ for children and from 3.0 $\mu g/m^3$ to 79.2 $\mu g/m^3$ for adults)[17,19–21]; i.e., over 90% of the global population is exposed to $PM_{2.5}$ within the aforementioned concentrations (Figure S1). Moreover, according to the risk of bias assessment (experimental procedures), all the literature/studies meeting full eligibility criteria are rated with a Newcastle-Ottawa Scale (NOS) score equal to or greater than 7 (Data S1 and S2), indicating that the selected literature/studies are of a high quality to make an appropriate evaluation of the association between long-term $PM_{2.5}$ exposure and risk of asthma (see more details in Note S6).

### Meta-analysis results

Based on our data inclusion criteria of the meta-analyses (experimental procedures; Note S4), 46 records of relative risk on childhood asthma were selected (Figure 2). By pooling these records, a significant association between long-term $PM_{2.5}$ exposure and increased risk of childhood asthma is observed (Table 1;

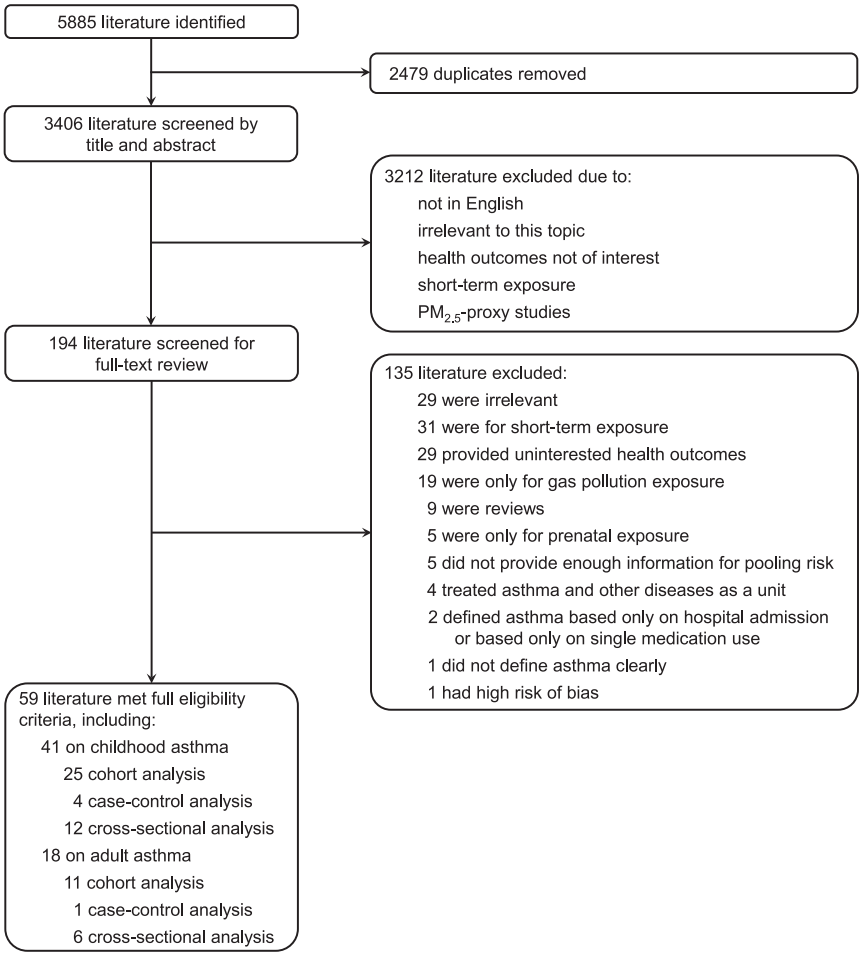


**Figure 1. Literature/study selection processes**

Figure 2). According to the results of the random-effects meta-analysis, for every 10 μg/m$^3$ increment in $PM_{2.5}$, the risk for all-type asthma increases by 21.4% (pooled retalive risk [RR]: 1.214; 95% confidence interval [CI]: 1.114–1.323). Further subgroup analyses upon exposure window and health outcome occurrence age show that the increased risk is more associated with early-life $PM_{2.5}$ exposure and that the health outcome is more likely to occur with age; i.e., the risk increases with age (Table S5). Notably, the heterogeneity among studies on childhood asthma is extremely high ($I^2$: 92.2%, $p < 0.0001$). By conducting additional sensitivity analyses and subgroup analyses, we find that the remarkable inter-study heterogeneity may come from the inconsistency in asthma definitions, exposure estimate approaches, exposure windows, and confounding adjustment strategies as well as the different chemical compositions of $PM_{2.5}$ across regions (Note S7; Tables S5–S9). This finding highlights the requirement of standardized methodology in future studies to improve the accuracy of asthma risk estimates. Despite the large heterogeneity, the confidence and certainty of the evidence is high; especially, 34 of the 46 records fitted to the meta-analysis reported a relative risk with a value greater than 1 (RR > 1). We further estimate that the risk of active childhood asthma associated with a 10 μg/m$^3$ increment in $PM_{2.5}$ is 1.194 (95% CI: 1.082–1.318), slightly lower than but essentially similar to the risk of all-type childhood asthma.

For adult asthma, 18 records of relative risk were selected for inclusion of the meta-analysis (Figure 3). The pooled risk estimates suggest that the association between long-term $PM_{2.5}$ exposure and adult asthma is significant, but the risk is much lower than that of childhood asthma. According to the results of random-effects meta-analysis, every 10 μg/m$^3$ increment in $PM_{2.5}$ is associated with a 7.1% increase in the risk of all-type adult asthma (pooled RR: 1.071; 95% CI: 1.016–1.129). We note that the heterogeneity across studies on adult asthma is moderate ($I^2$: 77.8%, $p < 0.0001$) and would be distinctly reduced after excluding the cross-sectional study reporting extremely high risk (Table 1),[50] which may partly explain the source of inter-study heterogeneity. We further estimate that the risk of active adult asthma associated with a 10 μg/m$^3$ increment in $PM_{2.5}$ is 1.388 (95% CI: 0.979–1.967), much higher than the risk of all-type asthma (Table 1). Nevertheless, the large uncertainty range is worth noting, especially with the regard to the lack of statistical significance in the observed risk of active adult asthma. For adult-onset asthma, we estimate its risk associated with a 10 μg/m$^3$ increment in $PM_{2.5}$ as 1.093 (95% CI: 1.010–1.183).

## Exposure-response curves

The exposure-response curves fitted based on the random-effects regression model (experimental procedures) reveal weak supra-linear associations between long-term $PM_{2.5}$ exposure and the risk of asthma in both children and adults (Figure 4); i.e., asthma risk increases almost linearly with $PM_{2.5}$ exposure levels rather than a log-linear association simply assumed in previous studies.[64–69] Furthermore, similar to the results indicated by the meta-analyses, the exposure-response analyses show that the risk of asthma is much higher in children than in adults over the entire exposure range. More importantly, both the lower bounds of the inferred risk of childhood and adult asthma are clearly greater than 1, further confirming the significant association observed in the meta-analyses. Notably, owing to the great inter-study heterogeneity, the risk of childhood asthma indicated by the random-effects regression model exhibits a much wider uncertainty range than that indicated by the fixed-effects model (Figure 4A vs. Figure S2A), suggesting that the extremely high inter-study heterogeneity has limited the accuracy of the fitted exposure-response curves.

Subsequent sensitivity analysis that excludes cross-sectional studies when fitting the exposure-response curves shows a

| Refference | Study Name | Region | Health Outcome | Sample Size | Asthma Cases | Relative Risk (2 μg/m³) | Relative Risk (2 μg/m³) | Relative Risk (10 μg/m³) | Weight (FE) | Weight (RE) |
|---|---|---|---|---|---|---|---|---|---|---|
| Zhang et al., 2002 [19] | Four Chinese Cities Study | Mainland China | Prevalence of Ever Asthma | 7,392 | 172 | | 1.010 (0.984–1.036) | 1.052 (0.922–1.196) | 1.211% | 4.976% |
| Kim et al., 2004 [22] | EBCRHS | The United States | Prevalence of Current Asthma | 705 | 101 | | 1.000 (0.917–1.119) | 1.000 (0.647–1.751) | 0.082% | 1.955% |
| Akinbami et al., 2010 [35] | NHIS | The United States | Prevalence of Current Asthma | 27,462 | 2,581 | | 1.008 (0.988–1.024) | 1.040 (0.941–1.124) | 2.593% | 5.295% |
| Clark et al., 2010 [23] | / | Canada | Incidence | 19,524 | 3,254 | | 1.020 (0.980–1.061) | 1.105 (0.904–1.344) | 0.521% | 4.328% |
| Carlsten et al., 2011 [24] | CAPPS | Canada | Incidence | 186 | 23 | | 1.737 (1.137–2.655) | 15.792 (1.896–131.849) | 0.005% | 0.161% |
| Fuertes et al., 2013 [38] | LISA East | Germany | Prevalence of Current Asthma | 516 | / | | 0.917 (0.615–1.368) | 0.649 (0.088–4.794) | 0.005% | 0.180% |
| Nishimura et al., 2013 [37] | GALA II/SAGE II | The United States | Prevalence of Current Asthma | 1,314 | 514 | | 1.051 (0.714–1.549) | 1.284 (0.185–8.915) | 0.005% | 0.191% |
| Gehring et al., 2015 [36] | BAMSE | Sweden | Prevalence of Current Asthma | 4,008 | / | | 1.041 (0.889–1.218) | 1.220 (0.554–2.683) | 0.033% | 0.986% |
| Gehring et al., 2015 [36] | BAMSE | Sweden | Incidence | 4,008 | / | | 1.014 (0.840–1.225) | 1.074 (0.419–2.755) | 0.023% | 0.729% |
| Gehring et al., 2015 [36] | GINI/LISA North | Germany | Prevalence of Current Asthma | 2,684 | / | | 1.089 (0.607–1.956) | 1.534 (0.082–28.607) | 0.002% | 0.086% |
| Gehring et al., 2015 [36] | GINI/LISA North | Germany | Incidence | 2,684 | / | | 1.235 (0.624–2.441) | 2.869 (0.095–86.751) | 0.002% | 0.063% |
| Gehring et al., 2015 [36] | GINI/LISA South | Germany | Prevalence of Current Asthma | 3,549 | / | | 1.037 (0.687–1.564) | 1.199 (0.153–9.368) | 0.005% | 0.171% |
| Gehring et al., 2015 [36] | GINI/LISA South | Germany | Incidence | 3,549 | / | | 0.952 (0.562–1.610) | 0.780 (0.056–10.831) | 0.003% | 0.105% |
| Gehring et al., 2015 [36] | PIAMA | Netherlands | Prevalence of Current Asthma | 3,687 | 353 | | 1.238 (0.919–1.669) | 2.914 (0.656–12.949) | 0.009% | 0.315% |
| Mölter et al., 2015 [30] | MAAS | The United Kindom | Prevalence of Current Asthma | 920 | 249 | | 0.888 (0.056–14.144) | 0.551 (0.000–565965.606) | 0.000% | 0.004% |
| Tétreault et al., 2016 [39] | QICDSS | Canada | Incidence | 1,133,938 | 162,752 | | 1.087 (1.079–1.092) | 1.515 (1.462–1.551) | 23.498% | 5.573% |
| Chen et al., 2018 [40] | CCHH | Mainland China | Prevalence of Ever Asthma | 30,759 | 2,461 | | 1.014 (1.000–1.028) | 1.070 (1.000, 1.150) | 4.181% | 5.410% |
| Keet et al., 2018 [48] | / | The United States | Prevalence of Current Asthma | 7,810,025 | 999,683 | | 1.047 (1.028–1.063) | 1.255 (1.149, 1.357) | 2.954% | 5.331% |
| Kravitz-Wirtz et al., 2018 [41] | CDS 1997/2014 | The United States | Incidence | 4,535 | 667 | | 1.106 (1.027–1.186) | 1.655 (1.141–2.350) | 0.156% | 2.825% |
| Lavigne et al., 2018 [42] | OASIS | Canada | Incidence | 761,172 | 110,981 | | 0.999 (0.994–1.004) | 0.994 (0.968–1.020) | 30.132% | 5.581% |
| Pennington et al., 2018 [20] | KAPPA | The United States | Incidence | 23,100 | 2,650 | | 1.011 (0.993–1.029) | 1.054 (0.963–1.154) | 2.507% | 5.285% |
| Rice et al., 2018 [25] | / | The United States | Prevalence of Current Asthma | 1,242 | 219 | | 0.950 (0.303–2.980) | 0.884 (0.005–155.365) | 0.001% | 0.028% |
| Rice et al., 2018 [25] | / | The United States | Prevalence of Ever Asthma | 1,242 | 279 | | 0.976 (0.347–2.743) | 0.774 (0.003–235.034) | 0.001% | 0.023% |
| Chen et al., 2019 [49] | 2011 survey | Taiwan | Prevalence of Current Asthma | 6,346 | 742 | | 1.109 (1.057–1.164) | 1.678 (1.319–2.141) | 0.348% | 3.890% |
| Chen et al., 2019 [49] | 2016–2017 survey | Taiwan | Prevalence of Current Asthma | 11,585 | 1,819 | | 1.061 (1.011–1.113) | 1.343 (1.055–1.711) | 0.350% | 3.894% |
| Garcia et al., 2019 [31] | CHS | The United States | Incidence | 4,140 | 525 | | 1.053 (1.005–1.104) | 1.298 (1.025–1.640) | 0.369% | 3.958% |
| Jung et al., 2019 [43] | TMCHD | Taiwan | Incidence | 184,604 | 34,336 | | 1.092 (1.069–1.115) | 1.552 (1.397–1.723) | 1.856% | 5.180% |
| Fuertes et al., 2020 [9] | BIB | The United Kindom | Prevalence of Current Asthma | 2,592 | 407 | | 1.039 (0.902–1.196) | 1.210 (0.597–2.452) | 0.041% | 1.177% |
| Fuertes et al., 2020 [9] | EDEN | France | Prevalence of Current Asthma | 1,110 | 84 | | 0.671 (0.518–0.870) | 0.137 (0.037–0.499) | 0.012% | 0.410% |
| Fuertes et al., 2020 [9] | GASP II | Italy | Prevalence of Current Asthma | 486 | 26 | | 1.197 (0.778–1.844) | 2.462 (0.284–21.300) | 0.004% | 0.155% |
| Fuertes et al., 2020 [9] | RHEA | Greece | Prevalence of Current Asthma | 894 | 103 | | 1.047 (0.554–1.978) | 1.256 (0.052–30.307) | 0.002% | 0.072% |
| Fuertes et al., 2020 [9] | INMA-Guipuzcoa | Spain | Prevalence of Current Asthma | 400 | 31 | | 0.820 (0.447–1.505) | 0.371 (0.018–7.717) | 0.002% | 0.080% |
| Fuertes et al., 2020 [9] | INMA-Sabadell | Spain | Prevalence of Current Asthma | 581 | 91 | | 0.978 (0.680–1.406) | 0.893 (0.145–5.492) | 0.006% | 0.217% |
| Fuertes et al., 2020 [9] | INMA-Valencia | Spain | Prevalence of Current Asthma | 586 | 87 | | 1.306 (0.594–2.871) | 3.797 (0.074–194.961) | 0.001% | 0.048% |
| Gehring et al., 2020 [32] | PIAMA | Netherlands | Incidence | 3,687 | 221 | | 1.295 (0.965–1.737) | 3.643 (0.838–15.834) | 0.009% | 0.324% |
| Holst et al., 2020 [26] | / | Denmark | Incidence | 3,192,785 | 122,842 | | 1.020 (1.012–1.027) | 1.103 (1.061–1.145) | 14.056% | 5.549% |
| Min et al., 2020 [44] | SAFSP | Korea | Prevalence of Ever Asthma | 14,614 | 1,171 | | 0.993 (0.902–1.088) | 0.963 (0.596–1.524) | 0.093% | 2.106% |
| Olaniyan et al., 2020 [45] | / | South Africa | Incidence | 509 | 11 | | 0.941 (0.631–1.400) | 0.737 (0.100–5.380) | 0.005% | 0.181% |
| To et al., 2020 [33] | T-CHEQ | Canada | Incidence | 1,286 | 366 | | 0.925 (0.794–1.077) | 0.676 (0.315–1.450) | 0.035% | 1.040% |
| Lavigne et al., 2021 [27] | BORN | Canada | Incidence | 1,130,855 | 167,080 | | 1.053 (1.042–1.063) | 1.293 (1.231–1.357) | 8.596% | 5.511% |
| Olsson et al., 2021 [28] | MBR | Sweden | Incidence | 163,740 | 20,920 | | 1.034 (0.938–1.139) | 1.180 (0.726–1.919) | 0.087% | 2.018% |
| Xu et al., 2022 [46] | NCGOC2013 | Mainland China | Prevalence of Ever Asthma | 251 | 118 | | 1.044 (0.996, 1.096) | 1.240 (0.980–1.580) | 0.358% | 3.922% |
| Zhang et al., 2022 [47] | CCHH II | Mainland China | Prevalence of Ever Asthma | 30,325 | 1,250 | | 1.034 (1.018, 1.049) | 1.180 (1.095–1.272) | 3.656% | 5.383% |
| Pedersen et al., 2023 [29] | DNPR | Denmark | Incidence | 1,060,154 | 65,143 | | 1.066 (1.041–1.083) | 1.378 (1.225–1.488) | 2.174% | 5.238% |
| Tingskov Pedersen et al., 2023 [34] | COPSAC2010 | Denmark | Prevalence of Current Asthma | 700 | 146 | | 2.364 (1.000–5.480) | 73.864 (1.000–4941.157) | 0.001% | 0.041% |
| Tingskov Pedersen et al., 2023 [34] | COPSAC2010 | Denmark | Prevalence of Ever Asthma | 700 | 48 | | 5.432 (0.966–30.545) | 4727.431 (0.840–2658914.303) | 0.000% | 0.010% |
| **Fixed-effects model** | | | | | | | **1.035 (1.032–1.038)** | **1.187 (1.170–1.204)** | **100.0%** | |
| **Random-effects model** | | | | **15,647,826** | **1,703,973** | | **1.040 (1.022–1.058)** | **1.214 (1.114–1.323)** | | **100.0%** |
| ***Heterogeneity: $I^2$ = 92.2%, $P_{het}$ < 0.0001*** | | | | | | | | | | |

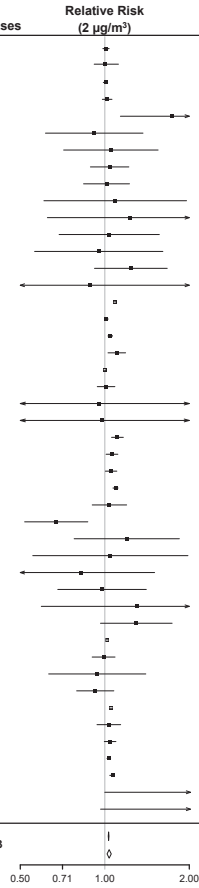


**Figure 2. Pooled risk estimates of childhood asthma associated with long-term $PM_{2.5}$ exposure**

Sample size and asthma cases refer to the population size and health outcomes included in the crude model or adjusted model (if available) applied by the study incorporated in the meta-analysis. Notably, as many studies did not provide such information for each adjusted model, the population size and health outcomes included in crude model were used as proxies under these circumstances; i.e., the actual number of sample size and asthma cases in the final models used to assess relative risks may be smaller than that shown here. As one study may report multiple relative risks on different bases (e.g., follow-up periods, confounding adjustment strategies, exposed populations, exposure windows, age of health outcomes occurrence, types of health outcomes, and $PM_{2.5}$ exposure estimate models/approaches), we applied data screening criteria to select the relative risks and conducted data preprocessing to maximize the use of these effect estimates without causing any duplication. For more details, please refer to Note S4. Moreover, for each study, the exact effect estimates participating in the meta-analysis are listed in column AL in Data S1. FE, fixed-effects model; RE, random-effects model. $I^2$ is the statistic value to assess the heterogeneity across studies, the higher the $I^2$, the larger the heterogeneity; $P_{het}$ is the p value of tests for heterogeneity. Data in parentheses are 95% CIs. Numbers shown in brackets indicate the reference number accompanied by the reference list. A slash ("/") indicates that the data are unavailable. For more details regarding these studies, please refer to Data S1.

much higher asthma risk in both children and adults, suggesting that the inclusion of cross-sectional studies may result in an underestimation of asthma risk (Figure S3). Despite this limitation, we keep the exposure-response curves fitted with the inclusion of cross-sectional studies as our main results because the evidence at higher exposure levels (>40 μg/m$^3$) that cover vast populations in LMICs is exclusively provided by these studies. This practice avoids the uninformed extrapolation of exposure-response curves, which may introduce even much greater uncertainty.

## $PM_{2.5}$-attributable global burden of asthma

By applying the aforementioned exposure-response curves into an epidemiological model,[70–75] we assessed the burden of asthma attributable to $PM_{2.5}$ (experimental procedure). We estimate that globally, long-term exposure to ambient $PM_{2.5}$ in 2019 caused 0.12 million (95% CI: 0.06–0.16) excess deaths through asthma, comparable to the deaths caused by fire, heat, and hot substances.[1] Moreover, these attributable excess deaths almost exclusively occurred in adults (over 90%; Table S10), and with largest contributions from India and China, followed by countries in Southeast Asia, Africa, and the Middle East. The exposure is also responsible for 63.5 million (95% CI: 40.4–82.5) prevalent asthma cases and 11.4 million (95% CI: 7.7–14.4) new asthma cases (Figure 5); i.e., almost one-third of the global asthma cases are associated with long-term $PM_{2.5}$ exposure, and children present the majority (over 60%; Table S10). It is worth noting that Northern America and Western Europe also contribute significantly to the attributable asthma prevalence and incidence despite their relatively lower $PM_{2.5}$ exposure levels.

Correspondingly, the global number of years of life lost (YLLs; indicating fatal burden), years of healthy life lost due to disability (YLDs; indicating non-fatal burden), and disability-adjusted life

**Table 1. Summary of pooled risk estimates of asthma associated with every 10 μg/m$^3$ increment in $PM_{2.5}$ exposure**

Childhood asthma

| | Included studies | Sample size | Asthma cases | Fixed-effects model | | Random-effects model | | Heterogeneity | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Relative risk | *p* | Relative risk | *p* | $I^2$ | $p_{het}$ |
| All-type asthma: main analysis | Fuertes et al.,[9] Zhang et al.,[19] Pennington et al.,[20] Kim et al.,[22] Clark et al.,[23] Carlsten et al.,[24] Rice et al.,[25] Holst et al.,[26] Lavigne et al.,[27] Olsson et al.,[28] Pedersen et al.,[29] Mölter et al.,[30] Garcia et al.,[31] Gehring et al.,[32] To et al.,[33] Tingskov Pedersen et al.,[34] Akinbami et al.,[35] Gehring et al.,[36] Nishimura et al.,[37] Fuertes et al.,[38] Tétreault et al.,[39] Chen et al.,[40] Kravitz-Wirtz et al.,[41] Lavigne et al.,[42] Jung et al.,[43] Min et al.,[44] Olaniyan et al.,[45] Xu et al.,[46] and Zhang et al.[47] | 15,647,826 | 1,703,973 | 1.187 (1.170–1.204)[b] | <0.0001 | 1.214 (1.114–1.323)[b] | <0.0001 | 92.2% | <0.0001 |
| Active asthma[a] | Fuertes et al.,[9] Pennington et al.,[20] Kim et al.,[22] Clark et al.,[23] Rice et al.,[25] Mölter et al.,[30] Keet et al.,[48] Chen et al.,[49] Garcia et al.,[31] Gehring et al.,[32] Tingskov Pedersen et al.,[34] Akinbami et al.,[35] Gehring et al.,[36] Nishimura et al.,[37] Fuertes et al.,[38] and Olaniyan et al.[45] | 7,928,665 | 1,013,139 | 1.158 (1.105–1.213)[b] | <0.0001 | 1.194 (1.082–1.318)[b] | 0.0004 | 38.0% | 0.0198 |
| Sensitivity analysis 1 | Pennington et al.,[20] Clark et al.,[23] Carlsten et al.,[24] Rice et al.,[25] Pedersen et al.,[29] Garcia et al.,[31] Gehring et al.,[32] To et al.,[33] Pedersen et al.,[34] Gehring et al.,[36] Nishimura et al.,[37] Fuertes et al.,[38] Tétreault et al.,[39] Kravitz-Wirtz et al.,[41] Lavigne et al.,[42] Jung et al.,[43] Olaniyan et al.,[45] and Xu et al.[46] | 7,701,044 | 692,960 | 1.196 (1.178–1.215)[b] | <0.0001 | 1.264 (1.120–1.427)[b] | 0.0001 | 94.7% | <0.0001 |
| Sensitivity analysis 2 | Fuertes et al.,[9] Zhang et al.,[19] Pennington et al.,[20] Kim et al.,[22] Carlsten et al.,[24] Rice et al.,[25] Lavigne et al.,[27] Olsson et al.,[28] Pedersen et al.,[29] Mölter et al.,[30] Keet et al.,[48] Chen et al.,[49] Garcia et al.,[31] Gehring et al.,[32] To et al.,[33] Tingskov Pedersen et al.,[34] Akinbami et al.,[35] Gehring et al.,[36] Fuertes et al.,[38] Tétreault et al.,[39] Chen et al.,[40] Kravitz-Wirtz et al.,[41] Lavigne et al.,[42] Jung et al.,[43] Min et al.,[44] Olaniyan et al.,[45] and Zhang et al.[47] | 12,433,952 | 1,577,245 | 1.202 (1.183–1.221)[b] | <0.0001 | 1.226 (1.109–1.355)[b] | <0.0001 | 92.7% | <0.0001 |
| Sensitivity analysis 3 | Pennington et al.,[20] Carlsten et al.,[24] Rice et al.,[25] Lavigne et al.,[27] Olsson et al.,[28] Pedersen et al.,[29] Garcia et al.,[31] Gehring et al.,[32] To et al.,[33] Tingskov Pedersen et al.,[34] Gehring et al.,[36] Fuertes et al.,[38] Tétreault et al.,[39] Kravitz-Wirtz et al.,[41] Lavigne et al.,[42] Jung et al.,[43] and Olaniyan et al.[45] | 4,487,170 | 566,232 | 1.217 (1.196–1.238)[b] | <0.0001 | 1.307 (1.121–1.524)[b] | 0.0006 | 95.3% | <0.0001 |

(*Continued on next page*)

**Table 1.** ***Continued***

| Childhood asthma | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Included studies | Sample size | Asthma cases | Fixed-effects model | | Random-effects model | | Heterogeneity | |
| | | | | Relative risk | *p* | Relative risk | *p* | $I^2$ | $p_{het}$ |
| Sensitivity analysis 4 | Fuertes et al.,[9] Zhang et al.,[19] Pennington et al.,[20] Kim et al.,[22] Clark et al.,[23] Rice et al.,[25] Lavigne et al.,[27] Olsson et al.,[28] Pedersen et al.,[29] Mölter et al.,[30] Keet et al.,[48] Chen et al.,[49] Garcia et al.,[31] Gehring et al.,[32] To et al.,[33] Tingskov Pedersen et al.,[34] Akinbami et al.,[35] Gehring et al.,[36] Nishimura et al.,[37] Fuertes et al.,[38] Tétreault et al.,[39] Chen et al.,[40] Kravitz-Wirtz et al.,[41] Lavigne et al.,[42] Jung et al.,[43] Min et al.,[44] Olaniyan et al.,[45] Xu et al.,[46] and Zhang et al.[47] | 15,646,940 | 1,703,804 | 1.187 (1.170–1.204)[b] | <0.0001 | 1.206 (1.107–1.314)[b] | <0.0001 | 92.6% | <0.0001 |

| Adult asthma | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Included studies | Sample size | Asthma cases | Fixed-effects model | | Random-effects model | | Heterogeneity | |
| | | | | Relative risk | *p* | Relative risk | *p* | $I^2$ | $p_{het}$ |
| All-type asthma: main analysis | Fisher et al.,[16] Wang et al.,[21] Schultz et al.,[50] So et al.,[51] Wang et al.,[52] Shin et al.,[53] Jacquemin et al.,[54] Havet et al.,[55] Wu et al.,[56] Nordeide Kuiper et al.,[57] Liu et al.,[58] Liu et al.,[59] Nachman and Parker,[60] Young et al.,[61] To et al.,[62] and Lee et al.[63] | 10,141,607 | 303,366 | 1.017 (1.005–1.029)[b] | 0.0063 | 1.071 (1.016–1.129)[b] | 0.0105 | 77.8% | <0.0001 |
| Active asthma[a] | Fisher et al.,[16] Schultz et al.,[50] Jacquemin et al.,[54] Havet et al.,[55] Nordeide Kuiper et al.,[57] Nachman and Parker,[60] and Young et al.[61] | 274,921 | 11,008 | 1.018 (0.934–1.111) | 0.6819 | 1.388 (0.979–1.967) | 0.0659 | 86.3% | <0.0001 |
| Sensitivity analysis 1 | Fisher et al.,[16] So et al.,[51] Wang et al.,[52] Shin et al.,[53] Jacquemin et al.,[54] Nordeide Kuiper et al.,[57] Liu et al.,[58] Liu et al.,[59] Young et al.,[61] To et al.,[62] and Lee et al.[63] | 9,973,318 | 288,681 | 1.012 (0.999–1.025) | 0.0688 | 1.072 (1.017–1.130)[b] | 0.0102 | 65.6% | 0.0003 |
| Sensitivity analysis 2 | Fisher et al.,[16] Wang et al.,[21] Schultz et al.,[50] So et al.,[51] Wang et al.,[52] Shin et al.,[53] Jacquemin et al.,[54] Havet et al.,[55] Wu et al.,[56] Liu et al.,[58] Liu et al.,[59] Nachman and Parker,[60] Young et al.,[61] To et al.,[62] and Lee et al.[63] | 10,138,179 | 302,821 | 1.017 (1.005–1.030)[b] | 0.0067 | 1.087 (1.022–1.156)[b] | 0.0077 | 79.0% | <0.0001 |
| Sensitivity analysis 3 | Fisher et al.,[16] So et al.,[51] Wang et al.,[52] Shin et al.,[53] Jacquemin et al.,[54] Liu et al.,[58] Liu et al.,[59] Young et al.,[61] To et al.,[62] and Lee et al.[63] | 9,969,890 | 288,136 | 1.012 (0.999–1.026) | 0.0768 | 1.102 (1.028–1.182)[b] | 0.0063 | 68.2% | 0.0002 |

(*Continued on next page*)

**Table 1. *Continued***

| Adult asthma | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Fixed-effects model | | Random-effects model | | Heterogeneity | | |
| | Included studies | Sample size | Asthma cases | Relative risk | *p* | Relative risk | *p* | $I^2$ | $p_{het}$ | |
| Sensitivity analysis 4 | Fisher et al.,[16] Wang et al.,[21] So et al.,[51] Wang et al.,[52] Shin et al.,[53] Jacquemin et al.,[54] Havet et al.,[55] Wu et al.,[56] Nordeide Kuiper et al.,[57] Liu et al.,[58] Liu et al.,[59] Nachman and Parker,[60] Young et al.,[61] To et al.,[62] and Lee et al.[63] | 10,138,232 | 302,864 | 1.016 (1.004–1.028)[b] | 0.0082 | 1.051 (1.009–1.094)[b] | 0.0155 | 62.6% | 0.0002 | |

Sample size and asthma cases refer to the population size and health outcomes included in the crude model or adjusted model (if available) applied by the study incorporated in the meta-analysis. Notably, as many studies did not provide such information for each adjusted model, the population size and health outcomes included in the crude model were used as proxies under these circumstances; i.e., the actual number of sample size and asthma cases in the final models used to assess relative risks may be smaller than that shown here. Sensitivity analyses were conducted based on the main analysis. Sensitivity analysis 1 excludes studies conducting cross-sectional analysis in the meta-analysis. Sensitivity analysis 2 excludes studies conducting case-control analysis in the meta-analysis. Sensitivity analysis 3 includes only studies conducting cohort analysis in the meta-analysis. Sensitivity analysis 4 excludes studies reporting extremely high risk (childhood asthma: Carlsten et al.[24] and Tingskov Pedersen et al.[34]; adult asthma: Schultz et al.[50]) in the meta-analysis, which is defined as relative risks with value greater than 10 when associated with every 10 $\mu g/m^3$ increment in $PM_{2.5}$ exposure. *p* is the *p* value of tests for pooled relative risks, and $p_{het}$ is the *p* value of tests for heterogeneity. $I^2$ is the statistic value to assess the heterogeneity across studies, the higher the $I^2$, the larger the heterogeneity.

[a]Includes only studies reporting relative risks for active asthma (defined as asthma with medication use or symptoms occurring during the past 24 months) in the meta-analysis.

[b]$p < 0.05$. Data in parentheses are 95% CIs.

years (DALYs; sum of YLLs and YLDs, indicating overall burden) of asthma attributable to $PM_{2.5}$ are 3.1 million (95% CI: 1.7–4.2), 2.5 million (95% CI: 1.6–3.2), and 5.6 million (95% CI: 3.3–7.4), respectively, which are in the same order of the magnitude as the attributable burden of previously well-known $PM_{2.5}$-associated respiratory diseases: lung cancer, LRIs, and COPD (Figure S4). These findings reveal that the increased risk of asthma associated with long-term $PM_{2.5}$ exposure causes a substantial disease burden, imposing remarkably adverse health effects on public health. Furthermore, the overall adverse health effects of long-term $PM_{2.5}$ exposure might have been significantly underestimated previously, as its role in asthma has not been explicitly considered in earlier health impact assessments.

## DISCUSSION

Since the 21st century, new cases of asthma have continued to increase,[1] especially in LMICs.[76] As of today, about ~4% of the world's population suffers from asthma, with more than 30 million new cases each year,[1] and the numbers are expected to be growing.[77] There is evidence suggesting that long-term exposure to $PM_{2.5}$ may be one of the significant risk factors for asthma. However, the confidence and certainty of the evidence remains unknown, as not all previous studies have reported increased risk. Here, we comprehensively addressed this issue and explored the effect of long-term $PM_{2.5}$ exposure on asthma by integrating a systematic review, meta-analysis, exposure-response analysis, and health impact assessment.

We show that, for every 10 $\mu g/m^3$ increment in long-term exposure to $PM_{2.5}$, the risk of childhood and adult asthma increased by 21.4% (95% CI: 11.4%–32.3%) and 7.1% (95% CI: 1.6%–12.9%), respectively. The results highlight a significant association between long-term exposure to $PM_{2.5}$ and increased risk of asthma, and this association not only presents in children but also in adults. Subsequent sensitivity analyses consistently support these findings, demonstrating the robustness of our results (experimental procedures; Table 1, S8, and S9). We also find that both the risk of childhood and adult asthma increases almost linearly with $PM_{2.5}$ exposure levels rather than a log-linear association simply assumed in previous studies (Note S8). We further estimate that, in 2019, nearly one-third of the global asthma cases—63.5 million (95% CI: 40.4–82.5) prevalent cases and 11.4 million (95% CI: 7.7–14.4) new cases—are associated with long-term $PM_{2.5}$ exposure.

We observe that the risk of childhood asthma is much higher than that of adult asthma, which may reflect the age-related vulnerability. Moreover, the differences in asthma outcomes between children and adults, as well as the common lack of exposure data back in time and elaborate covariates records for adults, may also play a role in the observed risk difference. In addition, through the systematic review, we identified two studies exploring associations between $PM_{2.5}$ exposure and asthma mortality in adults.[51,52] However, as the evidence is still limited, it is difficult to conclude whether $PM_{2.5}$ affects asthma mortality differently than morbidity. By excluding relative risks of mortality from the meta-analysis, we observe that the pooled risk estimate of adult asthma for every 10 $\mu g/m^3$ increment in $PM_{2.5}$ is 1.069 (95% CI: 1.013–1.128) (shown as a sensitivity analysis 19 in Table S9). It indicates a statistically significant

| Refference | Study Name | Region | Health Outcome | Sample Size | Asthma Cases | Relative Risk (2 μg/m³) | Relative Risk (2 μg/m³) | Relative Risk (10 μg/m³) | Weight (FE) | Weight (RE) |
|---|---|---|---|---|---|---|---|---|---|---|
| Nachman and Parker., 2012 [60] | NHIS in US | The United States | Prevalence of Current Asthma | 109,485 | 7,664 | | 0.994 (0.973–1.014) | 0.970 (0.870–1.070) | 1.334% | 9.614% |
| Young et al., 2014 [61] | Sister Study | The United States | Incidence | 35,862 | 254 | | 1.107 (0.989–1.239) | 1.659 (0.945–2.916) | 0.045% | 0.827% |
| Jacquemin et al., 2015 [54] | ESCAPE | Europe# | Incidence | 17,909 | 1,257 | | 1.016 (0.950–1.086) | 1.082 (0.774–1.513) | 0.127% | 2.129% |
| To et al., 2015 [62] | ONBSS | Canada | Prevalence of Ever Asthma | 29,549 | 4,813 | | 1.027 (1.002–1.052) | 1.140 (1.010–1.290) | 0.954% | 8.376% |
| To et al., 2015 [62] | ONBSS | Canada | Incidence | 29,549 | / | | 1.006 (0.966–1.046) | 1.030 (0.840–1.250) | 0.361% | 4.812% |
| Fisher et al., 2016 [16] | NHS | The United States | Incidence | 104,254 | 934 | | 0.979 (0.936–1.023) | 0.900 (0.720–1.120) | 0.293% | 4.143% |
| Schultz et al., 2017 [50] | SHOW | The United States | Prevalence of Current Asthma | 3,375 | 502 | | 1.666 (1.410–1.968) | 12.816 (5.570–29.485) | 0.021% | 0.389% |
| Havet et al., 2018 [55] | EGEA | France | Prevalence of Current Asthma | 608 | 240 | | 0.924 (0.752–1.141) | 0.672 (0.240–1.932) | 0.013% | 0.251% |
| Wu et al., 2020 [56] | / | Taiwan | Prevalence of Ever Asthma | 9,131 | 101 | | 0.971 (0.910–1.036) | 0.863 (0.625–1.194) | 0.136% | 2.256% |
| Lee et al., 2021 [63] | NHIS in Korea | Korea | Incidence | 1,220,645 | 54,522 | | 1.016 (1.006–1.023) | 1.080 (1.030–1.120) | 8.138% | 13.937% |
| Liu et al., 2021a [58] | DNS | Denmark | Incidence | 23,093 | 528 | | 1.084 (1.009–1.162) | 1.495 (1.048–2.122) | 0.115% | 1.945% |
| Liu et al., 2021b [59] | CEANS | Sweden | Incidence | 20,387 | / | | 1.151 (0.887–1.490) | 2.016 (0.548–7.344) | 0.008% | 0.163% |
| Liu et al., 2021b [59] | DCH | Denmark | Incidence | 52,961 | / | | 1.097 (1.008–1.198) | 1.588 (1.040–2.465) | 0.077% | 1.359% |
| Nordeide Kuiper et al., 2021 [57] | RHINESSA | Norway/Sweden | Prevalence of Ever Asthma | 3,428 | 545 | | 1.002 (0.992–1.010) | 1.010 (0.960–1.050) | 7.111% | 13.762% |
| Shin et al., 2021 [53] | ONPHEC | Canada | Incidence | 5,116,497 | 218,005 | | 1.000 (0.994–1.000) | 1.000 (0.972–1.000) | 69.254% | 15.112% |
| So et al., 2022 [51] | DNAC | Danmark | Mortality | 3,083,227 | 1,506 | | 1.031 (0.971–1.093) | 1.166 (0.865–1.562) | 0.163% | 2.627% |
| Wang et al., 2022 [21] | SAGE | Six LMICs† | Prevalence of Ever Asthma | 45,690 | 6,178 | | 1.011 (1.004–1.018) | 1.057 (1.019–1.094) | 11.582% | 14.312% |
| Wang et al., 2023 [52] | UKBB | The United Kingdom | Incidence | 265,506 | 6,317 | | 1.068 (1.020–1.121) | 1.392 (1.103–1.769) | 0.255% | 3.747% |
| Wang et al., 2023 [52] | UKBB | The United Kingdom | Mortality | 265,506 | / | | 1.039 (0.842–1.290) | 1.210 (0.423–3.572) | 0.013% | 0.240% |
| **Fixed-effects model** | | | | | | | **1.003 (1.001–1.006)** | **1.017 (1.005–1.029)** | **100.0%** | |
| **Random-effects model** | | | | **10,141,607** | **303,366** | | **1.014 (1.003–1.025)** | **1.071 (1.016–1.129)** | | **100.0%** |
| ***Heterogeneity: $I^2$ = 77.8%, $P_{het}$ < 0.0001*** | | | | | | | | | | |

0.50 0.71 1.00 2.00

#Europe refers to European countries covered by the ESCAPE study, including Belgium, France, Germany, Italy, Spain, Sweden, Switzerland, and the United Kindom
†Six LMICs indicates six low- and middle income countries, including China, Ghana, India, Mexico, Russia, and South Africa

**Figure 3. Pooled risk estimates of adult asthma associated with long-term $PM_{2.5}$ exposure**

Sample size and asthma cases refer to the population size and health outcomes included in the crude model or adjusted model (if available) applied by the study incorporated in the meta-analysis. Notably, as many studies did not provide such information for each adjusted model, the population size and health outcomes included in the crude model were used as proxies under these circumstances; i.e., the actual number of sample size and asthma cases in the final models used to assess relative risks may be smaller than that shown here. As one study may report multiple relative risks on different bases (e.g., follow-up periods, confounding adjustment strategies, exposed populations, exposure windows, age of health outcomes occurrence, types of health outcomes, and $PM_{2.5}$ exposure estimate models/approaches), we applied data screening criteria to select the relative risks and conducted data preprocessing to maximize the use of these effect estimates without causing any duplication. For more details, please refer to Note S4. Moreover, for each study, the exact effect estimates participating in the meta-analysis were listed in column AL in Data S1. FE, fixed-effects model; RE, random-effects model. $I^2$ is the statistic value to assess the heterogeneity across studies, the higher the $I^2$, the larger the heterogeneity; $P_{het}$ is the p value of tests for heterogeneity. Data in parentheses are 95% CIs. Numbers shown in brackets indicate the reference number accompanied by the reference list. A slash ("/") indicates that the data are unavailable. For more details regarding these studies, please refer to Data S1.

association between long-term $PM_{2.5}$ exposure and asthma morbidity in adults.

For both children and adults, the risk of incident asthma is slightly higher, whereas the risk of prevalent asthma is slightly lower, when compared to the overall risk of asthma (Table 1, S5, and S6). Notably, despite these differences, the tests for subgroup difference did not suggest a statistically significant difference in risk estimates for various health outcomes or for heterogeneity across studies addressing the associations for these health outcomes (Tables S5 and S6). Based on this finding, we combined relative risks of prevalence, incidence, and mortality in the meta-analysis or exposure-response analysis by following the approach adopted by GBD studies.[73,74] Nevertheless, we acknowledge that this practice remains to be a simplification when fitting exposure-response curves and may introduce additional uncertainty in the assessment of attributable burden. Future studies are therefore encouraged to further examine the exposure-response associations for individual health outcomes if possible, which may help to obtain more accurate health impact assessments.

Our study mainly considers the effects of total $PM_{2.5}$. In fact, $PM_{2.5}$ consists of different compositions that may have varying toxicity, yielding different impacts on asthma. A couple of studies have examined the association of asthma with different $PM_{2.5}$ compositions[22–29,78,79] and observed a larger impact from organic mass and black carbon. For other $PM_{2.5}$ compositions,

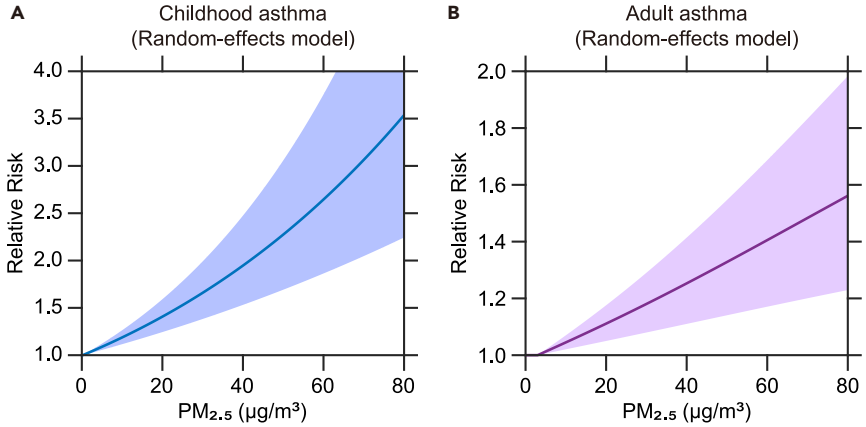


**Figure 4. Exposure-response curves of childhood asthma and adult asthma**

(A) Inferred relative risk and its uncertainty range for childhood asthma (blue line and shaded area) based on a random-effects meta-regression model. The threshold $PM_{2.5}$ concentration is 0.2 μg/m³ ($RR = 1, x \leq 0.2$).

(B) The same as (A) but for adult asthma (purple line and shaded area). The threshold $PM_{2.5}$ concentration is 3.0 μg/m³ ($RR = 1, x \leq 3.0$).

Note that the range of the y axis is different for (A) and (B). For the equations and parameters used to estimate the exposure-response curves, please refer to Table S18. For more details regarding the establishment of exposure-response curves, please refer to experimental procedures and Note S5.

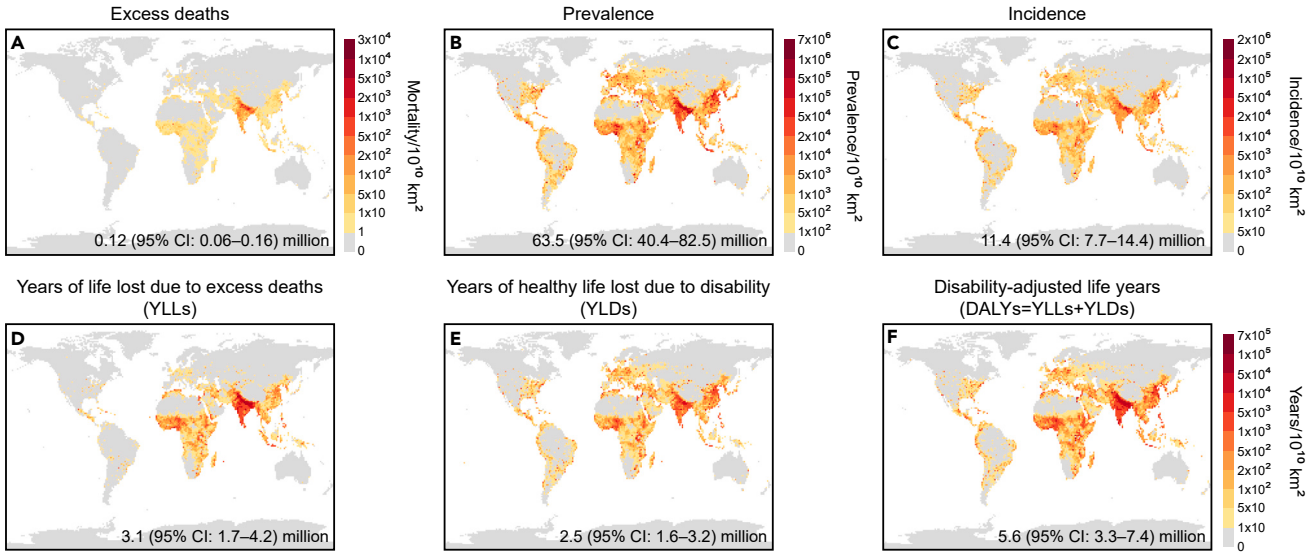


**Figure 5. Global distribution of $PM_{2.5}$-attributable burden of asthma in 2019**

(A) Global distribution of excess deaths attributable to long-term ambient $PM_{2.5}$ exposure through asthma.

(B) Global distribution of asthma prevalence attributable to long-term ambient $PM_{2.5}$ exposure.

(C) The same as (B) but for asthma incidence.

(D–F) The same as (A) but for YLLs (indicating fatal burden), YLDs (indicating non-fatal burden), and DALYs (denoted as the sum of YLLs and YLDs, indicating the overall burden), respectively.

The number in the lower right corner represents the global total attributable burden, with a 95% CI in parentheses.

especially inorganic aerosols (e.g., sulfate, nitrate, ammonia, and sea salt), the observations are more diverse, and no consistent conclusion has been drawn. Given that the compositions of $PM_{2.5}$ are largely constrained by emission sources, it is also important to explore the association of asthma risk with different emission sources, especially because the findings could provide direct suggestions for future pollution control and abatement aimed at effectively mitigating adverse health effects. However, there are not yet enough related evidence and consistent conclusions on which type of emission sources have larger adverse effects on asthma, warranting further research to address this important issue.

The observed association between $PM_{2.5}$ and asthma might be affected by exposure to other air pollutants due to the correlations among various exposures. Regarding to long-term exposure, in general, $PM_{2.5}$ is observed to be positively correlated with most other pollutants, such as $NO_2$ and $SO_2$,[9,20,24,26,29–34,48,49,53–59,78–85] while its correlation with ozone varies across regions.[28,29,33,35,53,55,57,59,85] For $PM_{2.5}$ compositions, their correlations with other exposures are more complicated (see more discussions in Note S9).[21,26,28,29] To consider the potential confounding effects from exposure to co-pollutants, we conducted additional sensitivity analyses (experimental procedures). We observe that, after considering the adjustment for most of the co-pollutants, the pooled risk estimates remain largely unchanged; except that after considering the adjustment for $NO_2$, the observed effect sizes are slightly attenuated but still indicate the role of $PM_{2.5}$ exposure in increasing asthma risk (Table S11).

Limitations in exposure assessment may also affect risk estimate. For instance, coarse spatial resolution data can lead to under- or overestimation of exposure levels because both high and low $PM_{2.5}$ concentrations are averaged within a grid or area. Moreover, most epidemiological studies assessed personal exposure based on residential address, which may miss exposure during daily activities such as studying, working, and outdoor exercising. In the future, if epidemiological surveys can provide more details for individual exposure trajectories at the same time the resolution of $PM_{2.5}$ data are enhanced, a better exposure assessment could be achieved, potentially enabling more accurate risk estimates. Furthermore, the inclusion of studies based on exposure data with limited capability of assessing non-traffic-related emissions and/or estimating exposure back in time may affect the observed risk as well. By excluding these studies, the pooled risk estimates remain robust (shown as sensitivity analyses 5 and 15 in Table S8), further demonstrating the high confidence level in associations between long-term $PM_{2.5}$ exposure and risk of asthma.

Our study has several distinct strengths. First, the studies and participants involved in our meta-analyses have a large sample size and are geographically diverse, ensuring the global representativeness. Specifically, the included studies covered 15.6 million children from 15 countries and regions and 10.1 million adults from 20 countries and regions. As far as we know, this sample size is almost an order of magnitude larger than those in previous meta-analyses (Tables S12–S15; Figure S5). Second, we adequately considered the inter-study differentiation in conducting the meta-analyses. We noted that the acquisition of asthma exposure-response associations in different studies is often based on methods and variables with large variance, which may bias the results of the meta-analyses. To minimize the bias, we set strict data inclusion criteria

for our main analyses (Note S4). By conducting additional sensitivity analyses with the alteration in data inclusion criteria (sensitivity analyses in Tables 1, S8, and S9), we demonstrate the robustness of our main findings and explore the potential impacts of inter-study differentiation on asthma risk estimate (experimental procedures).

Our study may help partly explain the inconsistency in previous meta-analyses on childhood asthma and the positive but statistically nonsignificant association with adult asthma observed by Jacquemin et al.[54] (Data S3; Tables S13–S15). By pooling only 2 studies for prevalence and 2 for incidence, Gasana et al.[3] reported a positive but nonsignificant association (Data S3; Tables S13 and S14; Figure S5). Although there are no clear criteria for the minimum number of records or studies to be included in a meta-analysis, the quite limited evidence tends to weaken the credibility of the results.[7] By collecting a larger number of studies, Bowatte et al.[5] and Khreis et al.[7] reported a statistically significant positive association, whereas Anderson et al.,[4] Gehring et al.,[36] Mölter et al.,[30] Shao et al.,[8] Fuertes et al.,[9] the HEI Special Report,[13] and Jacquemin et al.[54] observed statistically nonsignificant association or null association. According to the stratified subgroup analyses upon asthma definitions and $PM_{2.5}$ estimate approaches (Table S7), relative risks with a wider uncertainty range are observed within studies based on the traditional land-use regression (LUR) model and parental/self-reporting. This may reflect the potential limitations in the application of the traditional LUR model and the recall bias in self-reporting, which may introduce additional uncertainty and is likely to affect the accuracy of risk estimates. These limitations may partly contribute to the nonsignificant or null association observed in the latter seven meta-analyses, in which most of the included studies applied the traditional LUR model to estimate $PM_{2.5}$ and adopted parental/self-report data to identify asthma cases (see more discussions in Note S7).[86–93]

Another key strength of our study is the inclusion of evidence from LMICs, which enables the fitting of exposure-response curves based on evidence covering most of the worldwide $PM_{2.5}$ exposure range. This means that the exposure-response curves established in our study could be applied to assess the city- to global-scale attributable burden of asthma as well as air pollution reduction-associated asthma health benefits (e.g., health benefit obtained from policy-driven air pollutant reduction under different scenarios). Moreover, our exposure-response curves were derived based on a detailed exposure-response analysis (experimental procedures; Note S5) and, thus, are of greater precision than those applied previously (Figure S6; Table S16). As a result, one of the most important implications of this strength is to suggest strong overestimation in previous assessments of the attributable burden of childhood asthma (see more discussions in Note S8).

Despite these advances, several limitations need to be noted. First, evidence from LMICs is still limited. Compared with high-income countries, studies conducted in LMICs are an order of magnitude less, and most studies performed cross-sectional analyses that cannot measure incidence and were susceptible to bias. Ideally, high-quality cohort studies covering areas with different levels of $PM_{2.5}$ exposure, economic development, and health care as well as populations with various characteristics (e.g., different age compositions and ethnicities) would be optimal for studying global burden, and therefore, more such studies conducted in LMICs are warranted. Second, the high heterogeneity across studies on childhood asthma should be of aware, especially as it restricts the effects of the exposure-response analysis—the uncertainty range of the exposure-response curves estimated based on the random-effects meta-regression model is much larger than that from the fixed-effects model. In addition, the high heterogeneity that remains in most of the sensitivity analyses calls for standardization in methodology, including harmonization of asthma identification, health outcome type, and its occurrence period as well as confounding adjustment (e.g., environmental tobacco status and exposure to other pollutants) (Note S7).

Moreover, the explanation for observations from subgroup and sensitivity analyses may be limited due to the investigation of one factor at a time. If possible, future studies should conduct meta-regression or more stratified subgroup analyses to address this limitation and better detect factors affecting the inter-study heterogeneity once more evidence emerges (see more discussions in Note S10). Also, the common limitations in fitting exposure-response curve and assessing $PM_{2.5}$-attributable disease burden are also present in the current study (see more discussions in Note S11). In particular, the inclusion of cross-sectional studies and the underestimation in baseline burden of asthma incline to make our estimates conservative. In addition, our study mainly focuses on the effects of postnatal $PM_{2.5}$ exposure, while increasing evidence suggests that prenatal exposure may also play an important role in asthma onset. Therefore, the overall adverse effects of long-term $PM_{2.5}$ exposure might be even more pronounced. To improve the accuracy of risk and burden estimate as well as enhance the understanding of the association between long-term $PM_{2.5}$ exposure and asthma, future studies are encouraged to repeat and update the synthesis with the help of the elaborate MEAR[18] database we established once more evidence emerges.

In summary, our study provides robust evidence that long-term exposure to $PM_{2.5}$ significantly increases the risk of asthma. In addition, the explicit systematic review, sensitivity analyses, and subgroup analyses provide important and informative new insights for future studies. More importantly, our health impact assessments indicate that the increased risk causes substantial disease burden, posing remarkable threats to public health. These findings provide an important basis for policy making: controlling $PM_{2.5}$ is an effective way to significantly reduce the risk and burden of asthma. Furthermore, given the inexplicit consideration of the role of long-term $PM_{2.5}$ exposure on asthma in earlier health impact assessments, the overall adverse health effects of $PM_{2.5}$ might be significantly underestimated. In other words, combating air pollution can actually save more lives and avoid greater disease burden than previously thought. Stricter legislation and other, more effective measures aimed at air pollution reduction are therefore urgently needed.

## EXPERIMENTAL PROCEDURES

### Systematic review: Search strategy, inclusion criteria, and data extraction

The systematic review of the associations between long-term $PM_{2.5}$ exposure and asthma was registered with PROSPERO (CRD42022363032, available

from https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=363032). Briefly, we first searched PubMed for literature published in English before May 2023 by using the keywords listed in Table S17. We further searched Google Scholar, Web of Science, and Science Direct for any other publications related to this topic. Next, we hand searched the reference lists for all related literature, including that covered by previous reviews. We then screened literature based on the stringent criteria described in Note S1. The literature search and screening were independently performed by two investigators (R.N. and Y.C.), and disagreements were resolved by discussion with a third investigator (H.S.).

For literature meeting all inclusion criteria, we assessed the risk of bias using the NOS.[94] Note that the risk of bias assessment was conducted for each of the studies covered in the literature and was based on the ultimately adopted analysis method. To help distinguish the concepts of "literature," "study," and "analysis," we clearly defined these terminologies in Note S2. For literature utilizing cross-sectional analysis, an adapted NOS was applied.[95] The risk of bias assessment was cross-validated by two investigators (R.N. and Y.C.), with a third investigator (H.S.) adjudicating any disagreements. Studies with NOS scores below 6 were considered to be of poor quality and were excluded.[96] The scoring details for assessing the quality of studies are presented in Data S2. We further tested the publication bias by trim-and-fill method and present corresponding funnel plots in Figure S7.

Based on the systematic review, we established an elaborate database for associations between long-term $PM_{2.5}$ exposure and risk of asthma—the MEAR dataset (Data S1).[18] We manually extracted any possibly useful information for further analyses, including study region, study name, study design with analysis methods, demographics of the study population, sample size, number of asthma cases, definitions of asthma diagnosis, asthma type, characteristics of the studied areas, exposure estimate approaches, exposure windows, characteristics of exposure concentrations, health outcomes, confounding adjustment strategies, and so on (when available) (please see more details in Note S3). Of these, health outcomes include the types of the outcomes and quantitative exposure-response associations with CIs, which are often expressed as relative risk, hazard ratio, or odds ratio. In this study, we collectively named them relative risks. The data were extracted by one investigator (R.N.), with a second investigator (Y.C.) randomly selecting 10% for review and a third investigator (H.S.) adjudicating any disagreements.

The data were ultimately organized into a user-friendly database, the MEAR dataset (Data S1),[18] comprising 1,027 records of the exposure-response associations observed based on 25,789,433 participants involved in cohort, case-control, and cross-sectional studies. In the subsequence analyses, we incorporated evidence obtained from all three study designs, which involved 14.5 million, 3.2 million, and 8.1 million participants, respectively. We took this practice because evidence from LMICs is almost exclusively provided by cross-sectional studies; thus, the inclusion of these studies complements evidence for asthma risk in areas with much higher $PM_{2.5}$ exposure levels, relatively poor health care systems, and different demographics, greatly enhancing the global representativeness of the follow-up analyses. Moreover, this practice also improves the accuracy of the exposure-response curves used to assess the global burden of asthma attributable to $PM_{2.5}$ by helping avoid uninformed extrapolation of exposure-response associations observed at low concentrations to higher concentrations.

## Meta-analyses

Using the elaborate MEAR database generated from the systematic review,[18] we performed meta-analyses to quantify the associations between long-term $PM_{2.5}$ exposure and risk of asthma. We noticed that one study may report multiple relative risks on different bases (e.g., different follow-up periods, confounding adjustment strategies, exposed populations, exposure windows, health outcome occurrence ages, health outcome types, and $PM_{2.5}$ exposure estimate approaches). To maximize the application of these effect estimates without causing duplication of information, we set strict data screening criteria and performed data preprocessing for data integration. For more details, please refer to Note S4.

The meta-analyses were performed by applying both the fixed-effects and random-effects model. We used the statistic $I^2$ to assess the heterogeneity across studies, and considered substantial heterogeneity with values of $I^2$ greater than 75%.[97] Several sets of sensitivity analyses were conducted to assess the robustness of the results and to explore the causes of heterogeneity. We then compared our meta-analyses results with those of other studies and explored the causes of inconsistencies in previous findings. We additionally conducted subgroup analyses upon asthma outcomes, study regions, exposure windows, health outcome occurrence ages, and study qualities to examine the potential group difference and to further explore the causes of inter-study heterogeneity and inconsistencies in the results of previous studies. Considering the limitation of subgroup analysis that only one factor is investigated at a time, we conducted additional stratified subgroup analyses to investigate multiple factors simultaneously (e.g., taking asthma definitions and $PM_{2.5}$ exposure estimate approaches into account at the same time) (Note S10).

Notably, the above analyses were conducted for estimating risk of all-type asthma. We further conducted meta-analyses to explore the risk of active asthma by identifying corresponding studies. In this work, active asthma is defined as asthma with symptoms or medication use occurring in the past 24 months, slightly differing from previous studies, which typically defined active asthma by considering a threshold of 12 months. We took this approach in order to include as many studies/evidence on this health outcome as possible, since several studies have reported relative risk for asthma with symptoms occurring in the past 24 months[48,54,37] In addition, adult-onset asthma is identified through studies on adult asthma incidence, which measure new asthma cases developed in adulthood. Relative risks incorporated in the meta-analyses (including sensitivity analyses and subgroup analyses) are labeled with an asterisk in Data S1. All analyses were performed in R (v.4.1.2) with the *metafor* package.

## Sensitivity tests for meta-analysis

To test the robustness of our meta-analyses and explore the potential cause of the inter-study heterogeneity, we conducted several sets of sensitivity analyses. The first set was designed to test the sensitivity of meta-analyses to the potential bias from the inherent limitations of cross-sectional and case-control analyses. To achieve the purpose, we performed meta-analyses by excluding studies conducting cross-sectional analysis, excluding studies conducting case-control analysis, and only including studies conducting cohort analysis, respectively (sensitivity analyses 1–3 in Table 1). We observe that the effect size increases for both childhood and adult asthma after the exclusion of cross-sectional studies, suggesting that the inherent limitations of cross-sectional studies may cause underestimation of asthma risk. A second set of sensitivity analyses was conducted by excluding studies reporting extremely high risks; i.e., relative risk with a value greater than 10 (for every 10 $\mu g/m^3$ increment in $PM_{2.5}$) and by excluding studies contributing high weights in the meta-analyses to test their impact on the pooled risk estimates and to discern whether they are the source of inter-study heterogeneity (sensitivity analysis 4 in Table 1 and sensitivity analyses 7 and 8 in Tables S8 and S9).

The third set of sensitivity analyses was conducted to explore the impacts of the inclusion of studies representing high-risk populations. By excluding the study by Carlsten et al.,[24] which was conducted exclusively based on children with family history of asthma and allergic diseases, the effect size for childhood asthma is largely unchanged (RR of 1.209 in sensitivity analysis 13 vs. RR of 1.214 in the main analysis; Table S8). Further excluding studies covering only urban/suburban areas where the prevalence of asthma has been found to be higher than in rural areas, the effect size still remains at similar level (RR of 1.247 in sensitivity analysis 14 vs. RR of 1.214 in the main analysis; Table S8). These results emphasize that the significant association between long-term $PM_{2.5}$ exposure and childhood asthma is not affected by the inclusion or exclusion of studies representing high-risk populations, further demonstrating the robustness of our findings.

The fourth set of sensitivity analyses was performed by altering the data inclusion criteria of the meta-analyses. For example, we selected the relative risks restricted to non-movers rather than those for all participants (sensitivity analysis 6 in Tables S8 and S9) or selected relative risks related to the earliest exposure windows (e.g., birth address exposure or the exposure during the first year of lifetime, shown as sensitivity analysis 9 in Tables S8 and S9) and related to the health outcomes occurring during the earliest follow-up periods (sensitivity analysis 11 in Tables S8 and S9) instead of incorporating the full records. We find that the observed effect size remains significant in all of the above sensitivity analyses, indicating that the association between

long-term $PM_{2.5}$ exposure and asthma risk is independent of the data inclusion criteria.

The fifth set of sensitivity analyses was conducted to consider the potential confounding effects from exposure to co-pollutants. In these meta-analyses, we replaced relative risks obtained with the single-pollutant model with those obtained with adjustment for co-pollutants (Table S11). We find that the pooled risk estimates remain largely unchanged. After considering the adjustment for $NO_2$, the pooled effect size is slightly attenuated for both childhood and adult asthma but still indicates a role of $PM_{2.5}$ exposure in increasing asthma risk.

We noticed that the pooled risk of adult asthma significantly increased after excluding the relative risk, providing the largest weight in the meta-analysis. This relative risk was reported by Shin et al.[53] and was obtained with the main confounding adjustment strategy based on the Ontario Population Health and Environment Cohort (ONPHEC) study. It indicated no association between long-term $PM_{2.5}$ exposure and adult asthma. In fact, results observed from the same study but obtained with different confounding adjustment strategies and follow-up periods/populations were inconsistent. For example, by applying the basic confounding adjustment strategy, a positive association was observed by Shin et al.[53]—every 3.5 $\mu g/m^3$ increment in $PM_{2.5}$ is associated with a 1% increase in risk of adult asthma (RR: 1.01; 95% CI: 1.00–1.02) (Data S1). Based on the same study, but with a shorter follow-up period and fewer participants, Weichenthal et al.[98] also reported a positive association—every 3.2 $\mu g/m^3$ increment in $PM_{2.5}$ is associated with a 2% increase in risk of adult asthma (RR: 1.02; 95% CI: 1.00–1.04). By incorporating the above two relative risks instead of the previous one in the meta-analysis (sensitivity analyses 17 and 18 in Table S9), the pooled risk also significantly increased, suggesting that the exact extent to which long-term $PM_{2.5}$ exposure affects asthma in adults may be still ambiguous, and our main result tends to underestimate the impact. Future studies are therefore encouraged to provide additional evidence to further illustrate the association between long-term $PM_{2.5}$ exposure and adult asthma.

## Exposure-response analysis

We explored the exposure-response effect of asthma at different exposure levels by conducting a dedicated exposure-response analysis. More specifically, we fitted the exposure-response curves for childhood and adult asthma by constructing exposure-response functions (ERFs) based on the generalized global exposure mortality model (GEMM) proposed by Burnett et al.,[99] which updated the previous GEMM[100] to adapt it to the meta-data analytic framework.

The mathematical form of the generalized GEMM is as follows:

$$RR_{GEMM}(x) = \begin{cases} 1 & x < x_0 \\ exp\left(\dfrac{\theta \times log\left(1+\dfrac{x-x_0}{\alpha}\right)}{\left(1+exp\left(-\dfrac{(x-x_0-\mu)}{\tau \times r}\right)\right)}\right) & x \geq x_0 \end{cases} \quad \text{(Equation 1)}$$

where $RR_{GEMM}$ is the inferred relative risk, and $x$ is the annual mean $PM_{2.5}$ exposure concentration. $x_0$ is the threshold concentration below which it is assumed that there is no effect on mortality or morbidity of asthma. Here, $x_0$ is taken as the minimum fifth percentile concentration of $PM_{2.5}$ observed by studies selected for exposure-response analysis (labeled with # in Data S1). $r$ is the $PM_{2.5}$ exposure range, which is determined by the difference between the minimum 5$^{th}$ and the maximum 95$^{th}$ percentile concentration of $PM_{2.5}$ observed by the aforementioned studies. $\alpha$, $\mu$, and $\tau$ are parameters used to determine the shape of the exposure-response curves. Following Burnett et al.,[99] the parameters have sampling distribution specified as $\alpha \sim U(1, r)$, $\mu \sim U(0, r)$, and $\tau \sim U(0.1, 1)$— i.e., $\alpha$, $\mu$, and $\tau$ are specified by randomly sampling from 1 to $r$, from 0 to $r$, and from 0.1 to 1, respectively. In the present work, we randomly sampled $\alpha$, $\mu$, and $\tau$ 10,000 times to create 10,000 curves that range from supra-linear and near linear to sub-linear.

The curves were fitted by relating $log(RR(c_{95})) - log(RR(c_5))$ to $log(RR)$ in the mathematical form of the generalized GEMM (Equation 1). $RR(c_{95})$ and $RR(c_5)$ represent the relative risk at the 95$^{th}$ percentile and 5$^{th}$ percentile of $PM_{2.5}$ concentration, respectively. Notably, when fitting the curves, we did not take the absolute lowest and highest values of the observed $PM_{2.5}$ in order to avoid the extremely strong marginal effects caused by these rarely occurring concentrations, as it would additionally introduce substantial uncertainty.

We then assigned weight to these curves based on their Akaike information criterion (AIC) scores. The lower the AIC score, the better the fit of the curve; therefore, it is assigned more weight. The next step is to get the ensemble estimates of relative risk at a given $PM_{2.5}$ exposure level based on these fitted exposure-response curves. Assuming that the parameter $\theta$ of the curve is normally distributed with a mean of $\theta_p$ and a standard deviation of $\theta_{sep}$, we randomly sampled the value of $\theta$ for each of the exposure-response curves and then calculated the corresponding relative risk at different $PM_{2.5}$ exposure levels. $\theta_p$ and $\theta_{sep}$ are the predicted parameter and its standard error, respectively. The number of the random samples is determined by the weight assigned to each curve. Considering that fitting a large number of curves will flatten the ensemble weights, we avoid this by selecting only the curves whose weight is greater than random chance. For a given $PM_{2.5}$ exposure level, an ensemble with 10,000 estimates of relative risk is created. The final ERF is constructed by fitting the ensemble mean of the relative risk in the mathematical form of Equation 1.

We applied both the fixed-effects and random-effects meta-regression models for the curve fitting by using the rma.uni routine in the metafor package in R (v.4.1.2). For the random-effects model, we adopt the following options: method="REML", control=list(maxiter=500). We display the parameters of the constructed ERFs in Table S18. We further conducted sensitivity analyses to reconstruct ERFs by excluding exposure-response associations obtained from cross-sectional analyses. This practice is consistent with the inclusion criteria of GBD studies[70,71,73,74] and aims to test the sensitivity of the results to potential bias from the inherent limitations of cross-sectional analyses.

## Assessment of $PM_{2.5}$-attributable burden of disease

Following the widely accepted methodology of health impact assessments adopted by World Health Organization (WHO) and GBD studies,[70–75] we estimated the $PM_{2.5}$-attributable burden of asthma at grid level (0.1° Longitude [Lon] × 0.1° Latitude [Lat]) with six metrics: excess deaths, prevalence, incidence, YLLs, YLDs, and DALYs.

To describe the methodology in detail, we take the calculation of $PM_{2.5}$-attributable asthma incidence (i.e., new cases) among children as the example. For each grid and age group, the attributable incidence ($\Delta Incidence_{grid,age}$) could be calculated as follows:

$$\Delta Incidence_{grid,age} = Incedence_{grid,age} \times Pop_{grid,age} \times PAF_{grid} \quad \text{(Equation 2)}$$

where $Incedence_{grid,age}$ is the baseline incidence (per $10^5$ population) of childhood asthma among a specific age group in the geographic grid, $Pop_{grid,age}$ is the corresponding population of children among this specific age group in the geographic grid, and $PAF_{grid}$ is the population attributable fraction, defined as $\left(\frac{RR_{grid}-1}{RR_{grid}}\right)$. $RR_{grid}$ is relative risk of childhood asthma and is derived from the exposure-response analysis yielded in this study. More specifically, based on the $PM_{2.5}$ exposure level in each grid, $RR_{grid}$ could be calculated by applying the ERF estimated with the random-effects regression model with the parameters shown in Table S18. By replacing the baseline childhood asthma incidence ($Incidence_{grid,age}$) in Equation 2 with baseline childhood asthma mortality, prevalence, YLLs, and YLDs, the $PM_{2.5}$-attributable excess deaths, prevalence, YLLs, and YLDs of childhood asthma could be obtained. We then summed the attributable YLLs and YLDs to obtain the $PM_{2.5}$-attributable DALYs of childhood asthma. Notably, until this step, what we had obtained was still the grid-level $PM_{2.5}$-attributable burden among different age groups. To derive the country-level attributable burden, the values of the grids belonging to the same country were summed, and then the values of different age groups were added together. The global attributable burden was then estimated by aggregating the country-level attributable burden.

The $PM_{2.5}$-attributable burden of adult asthma is calculated in the same manner, and the sum of the attributable burden of childhood and adult asthma gives the overall attributable burden of asthma. We further estimated the $PM_{2.5}$-attributable burden of LRIs, lung cancer, and COPD using the same method and procedure to enable a comparison between global burden of asthma and those well-documented $PM_{2.5}$-associated respiratory diseases. Notably, to maintain the consistency for attributable burden assessment across diseases, $RR_{grid}$ for LRIs, lung cancer, and COPD is also calculated based on ERFs obtained with the random-effects meta-regression model by

applying the GEMM (Figure S8), and the ERFs are provided by Burnett et al.[100] Moreover, there is no study to date addressing the association between long-term $PM_{2.5}$ exposure and asthma mortality among children. We estimated the correspondingly attributable excess deaths by assuming that the relative risk for morbidity or mortality can be applied equally to both, by following the WHO and GBD studies.[70–75,101,102] Furthermore, the RR of LRIs, lung cancer, and COPD provided by Burnett et al.[100] is for mortality. We applied it to assess attributable YLDs by taking the same assumption. It should be mentioned that this assumption may introduce additional uncertainties. However, given the low proportion (4.8%) of excess deaths among children in excess deaths among total populations (Table S10) and the small contribution from YLDs to the overall attributable burden of LRIs, lung cancer, and COPD (Figure S4), it can be expected that the uncertainty potentially introduced by this assumption will only have a limited impact on the attributable burden assessment and will not change the main findings.

The data other than RR required for the attributable burden assessment are publicly available. The data source and corresponding processing details are documented as follows. The age-specific country- or region-level baseline burden of $PM_{2.5}$-associated respiratory diseases (including asthma, LRIs, lung cancer, and COPD) was taken from GBD 2019). In other words, grids belonging to the same country or region share the same baseline mortality, incidence, prevalence, YLLs, and YLDs. The gridded $PM_{2.5}$ exposure data for 2019 at the resolution of 0.1° Lon × 0.1° Lat were obtained from IHME database). The population dataset for 2015 and 2020 with spatial distribution at a native resolution of 0.0083° Lon × 0.0083° Lat was taken from GPW v.4. To maintain the consistency of data resolution, the GPW v.4 dataset was subsequently re-gridded to a resolution of 0.1° Lon × 0.1° Lat and linearly interpolated to obtain the estimate for 2019.

### Uncertainties and limitations

In line with previous studies,[70,71,73,74] the 95% CIs given in this study present the uncertainties arising from statistical errors in each risk estimate (i.e., relative risks reported by studies meeting the full eligibility criteria of the systematic review). In the fixed-effects meta-analyses, the 95% CI of pooled risk estimate was calculated based on the sampling error variance (i.e., uncertainty range of the relative risk reported in each study). In the random-effects meta-analyses, the 95% CI additionally accounts for the effects of inter-study heterogeneity, and to be consistent with previous meta-analyses, the DerSimonian-Laird estimator was adopted to obtain the 95% CI.[103] In the exposure-response analysis, the 95% CI of exposure-response curves (i.e., inferred relative risks at different exposure levels) was quantified with the bootstrapping approach by following Burnett et al.[99,100] The detailed processes are as follows.

As mentioned above, an ensemble of the relative risks at any given $PM_{2.5}$ exposure levels was obtained in fitting the exposure-response curves. This means that the standard deviation of the logarithm of relative risks in the ensemble could be calculated, and we denote it as $SD_E(log(RR))$. We then fitted $SD_E(log(RR))$ to the logarithm of ensemble mean with the generalized linear method and derived the coefficient $SD_{approx}$ (Table S18). Next, we assigned all the uncertainties to the parameter $\theta$ in Equation 1 by applying 1.96 times standard deviation ($SD_{approx}$) to $\theta$, expressed as $\theta \pm 1.96 \times SD_{approx}$. Therefore, the 95% CI of the exposure-response curves could be obtained by applying the $SD_{approx}$ to Equation 1. In the global burden assessment, the 95% CI was estimated based on the 95% CI of exposure-response curves.

In addition to the statistical errors in risk estimate, other aspects can introduce uncertainties into global burden assessment. We discuss these aspects, especially the impacts of limitations in exposure-response analysis on global burden assessment, in great detail in Note S11.

## RESOURCE AVAILABILITY

### Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Yafang Cheng (yafang.cheng@mpic.de).

### Materials availability

This study did not produce novel materials.

### Data and code availability

The original data used for this study can be accessed as described below.

- Age-specific country- and region-level population data and baseline burden of asthma, LRIs, lung cancer, and COPD were taken from Global Burden of Disease (GBD) 2019 (http://ghdx.healthdata.org/gbd-results-tool, last access: May 4, 2024).
- Gridded population datasets for 2015 and 2020 with spatial distribution at a native resolution of 0.0083° Lon × 0.0083° Lat were taken from the Gridded Population of the World (GPW) v.4 (https://sedac.ciesin.columbia.edu/data/collection/gpw-v4, last access: May 4, 2024).
- Gridded $PM_{2.5}$ exposure data for 2019 at a resolution of 0.1° Lon × 0.1° Lat were obtained from the Institute for Health Metrics and Evaluation (IHME) database (https://ghdx.healthdata.org/record/global-burden-disease-study-2019-gbd-2019-air-pollution-exposure-estimates-1990-2019, last access: May 4, 2024).
- In the uncertainty analyses, gridded population datasets for 2019 from WorldPop (https://hub.worldpop.org/geodata/listing?id=64, last access: May 10, 2024) and LandScan (https://landscan.ornl.gov/, last access: May 10, 2024) as well as the gridded $PM_{2.5}$ exposure data at a resolution of 0.1° Lon × 0.1° Lat and 0.01° Lon × 0.01° Lat from ACAG (https://sites.wustl.edu/acag/datasets/surface-pm2-5/, last access: May 10, 2024) were used.
- Datasets generated in this study (MEAR dataset) have been deposited at Zenodo (https://doi.org/10.5281/zenodo.13376288 or https://zenodo.org/records/13376288) and are publicly available as of the date of publication.
- Codes used for conducting meta-analyses are available from the R package "metafor" (https://wviechtb.github.io/metafor/, last access: August 15, 2024).
- Codes used to obtain 5th and 95th percentiles of the $PM_{2.5}$ concentrations can be found in the GBD studies (https://github.com/ihmeuw/ihme-modeling/tree/master/gbd_2019/risk_factors_code/air/relative_risk, last access: May 10, 2024).
- Codes used to perform exposure-response analyses can be found in Burnett et al.[99,100]
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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## AUTHOR CONTRIBUTIONS

Y.C. led the project. Y.C. and R.N. designed the study. R.N., Y.C., and H.S. performed the research, analyzed the data, and interpermeated the results. R.T.B. and Y.G. discussed the results and commented on the manuscript. R.N. wrote the manuscript with input from Y.C., H.S., Y.G., and R.T.B.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

## SUPPLEMENTAL INFORMATION

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