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Systematic review and Meta-analysis of the effects of air pollution exposure on nasal mucosal immune-inflammatory markers in experimental animal models of AR

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Research Article

Keywords: Air pollutants, Allergic rhinitis, Inflammatory markers, Immune response, Animal models, Meta-analysis, Systematic review

Posted Date: September 24th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9432775/v1

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Abstract

Air pollution is strongly associated with the onset and aggravation of allergic rhinitis (AR), yet its immune and pathological mechanisms remain incompletely understood. Animal studies have provided important evidence, but methodological differences across studies have led to inconsistent results. A quantitative synthesis is therefore needed.

This study conducted a systematic review and meta-analysis to assess the effects of air pollution on immune-inflammatory markers in the nasal mucosa of AR animal models. The aims were to estimate the direction and magnitude of these effects, explore sources of heterogeneity, and provide evidence for understanding the underlying mechanisms.

Following PRISMA guidelines, PubMed, Web of Science, Embase, and the Cochrane Library were searched from inception to December 2025. Eighteen eligible studies were included, all using rodent models. More than 10 immunoinflammatory markers were analyzed, including immune cells, epithelial barrier proteins, cytokines, inflammasomes, and immunoglobulins. Stata 18.0 was used, and pooled effects were calculated as standardized mean differences (SMDs) with 95% confidence intervals under a random-effects model.

The results showed that air pollution significantly increased eosinophil infiltration, elevated IL-1β, IL-4, IL-5, and IL-13 levels, reduced ZO-1 expression, and increased OVA-IgE. Overall, air pollution may aggravate AR by disrupting the epithelial barrier, activating innate immunity, and promoting Th2-type inflammation. However, the effects varied by pollutant type and exposure duration, and evidence regarding IFN-γ remained inconsistent. Further well-designed studies are needed to clarify time-dependent mechanisms and support clinical translation.

1. Introduction

Allergic rhinitis (AR) is a non-infectious, chronic inflammatory disease of the nasal mucosa that's precisely mediated by immunoglobulin E (IgE). In the pathogenesis of AR, the imbalance between T helper cell 1 (Th1) and T helper cell 2 (Th2) plays a crucial role, specifically presenting a situation where Th2-type inflammatory mediators are dominant. (Galli et al.,2008).When allergens subtly stimulate the nasal mucosa, the nasal mucosa will promptly respond, presenting allergic manifestations such as paleness, edema, and increased secretions. Subsequently, this triggers a series of common allergic symptoms in patients with AR, including nasal congestion, nasal itching, sneezing, and runny nose(Wallace et al.,2008).Looking back over the past four decades, the incidence rate of AR has shown a continuous upward trend. In European countries, the prevalence of AR ranges from 23% to 30%. In the United States, it is approximately between 12% and 30%, while in the United Kingdom, it reaches 26%. Globally, 10%-20% of the population is severely affected by this condition(Siddiqui et al.,2021).Air pollution, which refers to the presence of substances in the air that pose threats to human health, has emerged as a significant public health challenge on a global scale in recent years. A substantial body of epidemiological evidence indicates that in recent years, when individuals are exposed to ambient air

pollutants such as fine particulate matter (PM2.5), ozone (O3), sulfur dioxide (SO2), and diesel exhaust particles (DEP), there is a clear positive correlation with the incidence of AR. Plus, such exposure greatly raises the risk of other allergic diseases, including asthma, atopic dermatitis, and allergic conjunctivitis, as well as making their acute flare-ups more frequent(Luo a et al.,2023;Agache et al.,2024；Pan et al.,2023；Lu et al.,2021).

A substantial body of existing evidence strongly indicates that the activation of the systemic inflammatory state serves as the crucial pathophysiological basis for the health damage caused by exposure to air pollutants(Zhang et al.,2019;Goodman et al.,2015;Glencross et al.,2020).Multiple studies have focused on the impacts of different air pollutants on nasal health. The results indicate that PM2.5 can exacerbate the degree of oxidative stress in the nasal cavity of patients with AR by disrupting the crucial nasal epithelial barrier. Subsequently, this triggers a type II inflammatory response in the nasal cavity, ultimately leading to more severe nasal symptoms(Yuan et al.,2025;Li et al.,2024;Mariani et al.,2021).Meanwhile, air pollutants such as O3, NO2, and SO2 are also closely associated with the exacerbation of nasal allergies and inflammatory responses(Ye et al.,2024；Wang et al.,1995；Peden et al.,1995).However, some studies haven't strongly confirmed this correlation. A cohort study involving 905 Nordic individuals based on this issue found no link between PM2.5, PM10, and the risk of AR. Likewise, another cohort study with 1,286 Canadian participants also discovered no significant connection between PM2.5 exposure and the risk of developing AR (To et al.,2020；Pindus et al.,2016).

Currently, the specific cellular and molecular mechanisms underlying how air pollution affects AR remain shrouded in mystery and have not been fully elucidated. In the field of clinical research, due to the constraints of numerous factors, it is extremely difficult to conduct an in-depth analysis of the causal chain. Ethical considerations, like the hanging Sword of Damocles, constantly restrict the boundaries of research. The accuracy of exposure assessment is difficult to guarantee, which may lead to biases in research results. Plus, individual differences mean that each patient's situation varies greatly, making research even more challenging. Given these limitations in clinical research, animal models with standardized exposure conditions have become a crucial tool for exploring how air pollution affects the pathological mechanisms of AR. Many researchers have dedicated themselves to the research in this field. They have skillfully used allergens such as ovalbumin (OVA) to successfully construct AR animal models. On this basis, they have in-depth explored the impacts of different air pollutant exposures on a series of immune-inflammatory markers in the nasal mucosa. These impacts cover multiple levels, including the epithelial barrier that maintains the integrity of the nasal mucosa, the innate immune cells that play an important role in immune defense, the precise regulation of adaptive immune cells in the immune response, the complex interactions of various factors in the cytokine network, and the crucial role of inflammasomes in the inflammatory response, all of which are included in the research scope.

In the field of medical research, existing clinical meta-analyses have clearly revealed the substantial epidemiological burden borne by AR(Luoa et al.,2023;Luob et al.,2023).Even so, the limitations of clinical studies make it difficult for us to accurately infer the causal relationship of the cytokine network in the occurrence and development of AR from these studies. In this context, conducting mechanism analysis

using animal models serves as a bridge between clinical phenomena and immunological fundamentals, offering the possibility for us to conduct in-depth exploration of the mysteries of AR. Of particular concern is that the exposure time is likely to play a crucial regulatory role in the immune effects induced by air pollution. Different exposure durations, similar to different "switches," may trigger distinct immune response patterns. Short-term exposure may primarily lead to damage to the epithelial barrier and activation of the innate immune system(Li et al.,2023).Prolonged exposure may lead to the continuous accumulation and amplification of immune effects(Ye et al.,2022).Numerous animal studies have explored this theme, yet the existing evidence is marked by significant heterogeneity, with some findings even being contradictory. Take, for instance, the impact of air pollution on the Th1/Th2 balance. While most studies report a notable increase in Th2 cytokines like IL-4, IL-5, and IL-13, opinions diverge regarding the trend of IFN-γ, a hallmark cytokine of Th1 cells(Zhang et al.,2025;Zhang et al.,2023;Park et al.,2025;Ye et al.,2022;Guo et al.,2017;Zhang et al.,2025). These discrepancies likely arise from variations in research design, pollutant types, exposure parameters (including time, concentration, and route), animal strains, and detection methods.Given this complex landscape, there is an urgent call for research that quantitatively integrates and systematically evaluates the scattered evidence to provide a clearer, more unified understanding of AR's immunological underpinnings.

Systematic reviews and meta-analyses are considered the gold standard in evidence-based medicine, providing a solid and reliable foundation of evidence that supports both the exploration of underlying mechanisms and their practical application in clinical settings. Unfortunately, up to this point, there hasn't been a single study that has carried out a systematic review and meta-analysis that takes the time dimension into account when examining how exposure to air pollution affects nasal mucosal immune-inflammatory markers in animal models of AR.

Against this backdrop, this study innovatively employs systematic review and Meta-analysis to comprehensively integrate pre-clinical evidence regarding the impact of air pollution exposure on nasal mucosal immune-inflammatory markers in AR animal models. Particular emphasis is placed on the differential effects observed across different exposure time windows, namely short-term, medium-term, and long-term exposure. Specifically, this study has well-defined objectives. Firstly, it aims to precisely quantify the overall effects of air pollution exposure on various key inflammatory markers. Secondly, through subgroup analysis based on exposure time, it seeks to explore the dynamic evolution patterns of these effects. Thirdly, it assesses the influence of different pollutant types, exposure routes, and animal strains on the heterogeneity of the effects. Fourthly, it constructs a comprehensive evidence framework for understanding the immunopathological mechanisms of AR exacerbated by air pollution from a temporal perspective, thereby providing guidance for future research.

2. Methods

This study was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and has been registered on the International

Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD420251265574.

2.1 Search strategy

To comprehensively explore relevant research, a systematic search was conducted in the PubMed, Web of Science, Embase, and Cochrane Library databases, with the time span set from the establishment of each database to December 2025. In terms of the search strategy, a sophisticated approach of combining subject terms (including MeSH/Emtree) with free-text words was adopted. First, an extensive search was carried out through electronic retrieval methods, followed by a meticulous step of manually screening the reference lists of eligible articles to ensure that all relevant studies were comprehensively and exhaustively included. Regarding the detailed search formula, it can be found in Supplementary Table S1 materials.Additionally, to avoid overlooking any relevant studies, we also manually searched through relevant reviews and the reference lists of the studies we included.

2.2 Inclusion and exclusion criteria

In this study, the research team meticulously defined the inclusion and exclusion criteria, strictly adhering to the PICOTS framework. When it came to the inclusion criteria, they set strict limits on the participants, showing a preference for animal models with allergic rhinitis. For intervention measures, the animals had to be exposed to one or more common ambient air pollutants like PM2.5, PM10, O3, DEP, SO2, NO2, and so on. The exposure routes were varied, including whole-body inhalation and nasal instillation. The control group was made up of animals not exposed to the target pollutants, with clean air or solvents typically used as controls. The main outcome indicators centered on the quantitative levels of immune-inflammatory markers measured in nasal mucosal tissue, nasal lavage fluid, or serum. The indicators for primary analysis were diverse, encompassing inflammatory cells such as eosinophils, neutrophils, macrophages, and lymphocyte counts, cytokines like IL-1β, IL-4, IL-5, IL-13, IL-17, TNF-α, IFN-γ, IL-25, IL-33, and more, as well as immunoglobulins (total IgE, ova-IgE), epithelial barrier proteins (such as ZO-1), and inflammasome components (such as NLRP3). This study focused on published randomized controlled trials (RCTs) in animals that employed either double-blind or single-blind designs, as well as parallel group or crossover designs. For the ease of academic reference, Supplementary Table S2 offers a detailed and clear description of the PICOTS framework.

This study has set up strict exclusion criteria to ensure the quality and relevance of the research included. First off, any studies that don’t have a properly set up parallel control group that operates at the same time are out of the running. In these cases, the allergic rhinitis models weren’t exposed to filtered air or carriers, so it’s impossible to make meaningful comparisons. We’re also leaving out non-original studies, like reviews and commentaries, as well as those that don’t use experimental designs or are conducted in vitro or ex vivo. Studies that use models for non-allergic rhinitis, non-mammalian models, or models where the allergic rhinitis induction hasn’t been properly validated are excluded too. On top of that, we’re not including studies where the main exposure isn’t a clearly defined ambient air pollutant, or where the individual effects of pollutants can’t be separated out—like those using tobacco smoke as the

main exposure or involving occupational exposure. Finally, we're ruling out studies where the quantitative outcome data can't be converted, extracted from predefined biomarkers, obtained from the authors, or where the full text isn't available.

2.3 Data extraction

To ensure the efficient management of research and the accurate extraction of data, we utilized EndNote software to systematically manage the studies that had been determined for inclusion. After removing duplicate documents, Pan and Lv independently conducted literature screening and data extraction based on pre-set criteria. In case of any disagreements during this process, the two would reach a consensus through in-depth discussions or by consulting a third researcher, Li.. Additionally, cross-validation was performed on all articles that met the data extraction criteria to guarantee the reliability of the data.Literature screening was initially conducted based on titles and abstracts, followed by a full-text review to determine the final included studies. We employed a pre-designed data extraction form to collect relevant information, specifically including the first author, publication year, animal species, strain, gender, sample size, AR modeling method, pollutant type, and exposure protocol (including exposure route, concentration, frequency, and duration), as well as outcome measurements. For data in charts and graphs, we used software such as WebPlotDigitizer for digital extraction. When a study reported multiple pollutant groups or multiple time points, we treated each as an independent comparison and extracted the data separately.

To ensure the accuracy of the data, two researchers independently digitized each graph, calibrated at least three different axis points from pixels to data points, and cross-checked the extracted values with the numerical data in the original article. During the data extraction process, for studies that did not directly report the standard deviation, we employed a hierarchical approach for estimation and conversion. If the standard error of the mean (SEM) was reported, the standard deviation was calculated using the formula SD = SEM × √n. If the 95% confidence interval (CI) of the mean was reported, the standard deviation was calculated according to the formula SD = √n × (upper limit of CI-lower limit of CI) / 3.92. If only the inter-quartile range or range was reported, an empirical formula was used for estimation (Hozo et al., 2005). All conversion processes were meticulously documented to ensure transparency. For the means and standard deviations obtained in this way, we calculated the standardized mean difference as the effect size. We also acknowledged that this selection strategy could introduce bias, so we planned to evaluate it specifically in the sensitivity analysis. If any discrepancies came up during data extraction that couldn't be resolved, the corresponding author would step in to help resolve and negotiate, ensuring the study could move forward smoothly.

2.4 Characteristics of included studies

This meta-analysis meticulously incorporated 18 preclinical studies, encompassing a total of 297 model animals suffering from allergic rhinitis. Of these animals, 149 were assigned to the control group while 148 were placed in the exposure group.During the analysis process, a rich and diverse experimental model system was adopted, covering different animal strains, various pollutant types, different exposure

protocols, and diverse detection methods, aiming to comprehensively and systematically evaluate the impact of air pollution exposure on nasal mucosal immune inflammation markers.

2.5 Animal models and demographics

In this study, researchers selected mice, rats, and guinea pigs as experimental models. Among them, mice were the primary model, with a quantity of 144, accounting for 48.5%. Rats came next, with 122, accounting for 41.1%. Guinea pigs had a relatively smaller number, 31, accounting for 10.4%. To simulate different allergic reaction backgrounds, multiple standard strains were chosen for the study. BALB/c mice were used in 6 studies, C57BL/6 mice in 4 studies, Sprague-Dawley (SD) rats in 5 studies, Norway rats in 1 study, and Hartley guinea pigs in 2 studies. In terms of gender distribution, 12 studies used only female animals, and 6 studies used male animals. All the animals involved were young adults, with mice ranging from 6 to 8 weeks old, except for one study that included 36-week-old mice. Rats varied in age from 4 to 12 weeks, and all guinea pigs were precisely 5 weeks old, aligning with the typical age range for such research.

3. Results

3.1Study selection

The entire research screening process is laid out clearly in FIGURE 1 When it came to searching the literature, we methodically combed through four well-respected databases and pulled out a whopping 11,965 relevant records at first. Subsequently, we conducted a duplicate removal process on the retrieved literature, eliminating 4,925 duplicate documents. Then, a preliminary screening was carried out based on the titles and abstracts, and 6,946 documents that did not meet the requirements were excluded. The remaining 94 documents entered the full-text evaluation stage.After reviewing those 94 documents in detail, we found that 54 of them met our initial inclusion criteria. But our investigation didn't stop there; we dug deeper and ended up excluding another 36 documents. Here's why: 14 documents didn't set up a clear allergic rhinitis model, so they didn't meet our need for accuracy in the model; 2 documents could not provide the full-text or abstract, and the incomplete information made them difficult to be included in the analysis; 7 documents did not report the outcome indicators relevant to the research, lacking key data; 4 documents did not set up a control group, which did not comply with the control principle of scientific research. After several rounds of this screening process, we were left with 18 documents that met all our inclusion criteria and made it to the Meta-analysis stage.

3.2 Characteristics of included studies

Out of the 18 studies, a whopping 15 used ovalbumin (OVA) solution as their go-to sensitization method. On top of that, three studies opted for ragweed pollen and dust mites respectively for sensitization. All these studies together reported a total of 17 different immunoinflammatory markers. These markers can be mainly grouped into categories based on different immune mechanisms. First, there are immunoglobulin profiles, with IgE being looked at in four studies and OVA-IgE in 12. Then, there are

cytokine levels, with eight studies examining IL-4, six looking at IL-5, seven at IL-13, three at IL-17, two at TNF-α, seven at IFN-γ, three at IL-1β, and three at both IL-25 and IL-33. Next, there are inflammatory cell counts, with eosinophils (Eos) being present in 12 studies, neutrophils (Neu) reported in four, and macrophages (Mac) and lymphocytes (Lym) mentioned in a total of three studies. Moving on, epithelial barrier proteins were also looked at, with ZO-1 being reported in three studies. Lastly, there are inflammasome components, with NLRP3 having relevant data in three studies. Since the research sets for these different markers vary, to make sure our analysis results are accurate and reliable, we'll be conducting independent Meta-analyses for each marker (or closely related marker groups). When it comes to the overall evaluation of the full-text, 18 studies (Fukuoka et al.,2016;Guo et al.,2017;Iijima et al.,2001;Iijima et al.,2004;Jung et al.,2021;Li et al.,2021;Li et al.,2024;Li et al.,2025;Li et al.,2019;Park et al.,2025;Piao et al.,2021;Sun et al.,2021;Sun et al.,2023;Wagner et al.,2002;Wang et al.,2017;Ye et al.,2022;Zhang et al.,2025;Zhang et al.,2023)met all the inclusion criteria and were successfully included in the Meta-analysis. The specific number of studies (k) and the total number of animals (N) for each marker are detailed in the following table and subsequent sections. You can find a summary of the basic characteristics of the included studies in Supplementary Table S3 materials.

3.3 Risk bias evaluation

Following the predetermined inclusion and exclusion criteria, the two independent reviewers smoothly reached a consensus on which articles to incorporate, with no disputes arising. To gauge the methodological rigor of the selected studies, the SYRCLE tool(Hooijmans et al., 2014). For each included study, a detailed assessment was conducted from ten dimensions, namely random sequence generation, similarity of baseline characteristics, allocation concealment, random housing, blinding of implementers, random outcome assessment, blinding of outcome assessors, incomplete outcome data, selective reporting of outcomes, and other biases. Based on the evaluation results, each study was determined to be in a state of "low risk", "high risk", or "uncertain risk". In case of differences, they were resolved through group discussions or communication with the corresponding authors.

The findings reveal that the overall risk of bias in the studies is moderate. When it comes to selective reporting and baseline comparability, the majority of studies excelled, earning a low-risk rating.However, only a few studies described the random sequence generation process, and very few studies reported on allocation concealment. Regarding the blinding of experimental implementation and outcome assessment, the reporting situation varied. Based on these circumstances, most studies were rated as having an "unclear risk" or a "high risk" in the above aspects, which implies that the studies may be subject to selection bias, implementation bias, and measurement bias.Detailed evaluation results can be found in FIGURE 2and Supplementary Table S4.

3.4 Statistical analysis

In the statistical analysis phase, we selected the professional and powerful Stata 18.0 software as the analysis tool. For continuous outcome indicators, we calculated the standardized mean difference (SMD) and the 95% confidence interval (CI), which served as the key indicators for measuring the effect

size. If the research did not directly provide the data on the mean and standard deviation, we would conduct scientific estimations from data such as the standard error, confidence interval, or inter-quartile range according to the methods provided in the Cochrane Handbook. When assessing the heterogeneity among studies, we employed Cochrane's Q test with a significance level set at $p < 0.10$ and used the I^2 statistic for comprehensive judgment. Generally, when $I^2 \leq 25\%$, we consider that there is low-level heterogeneity among the studies; when $25\% < I^2 \leq 50\%$, it indicates moderate heterogeneity; if $I^2 > 50\%$, it means high-level heterogeneity. Given that we anticipated high heterogeneity in this field of research, we primarily used the DerSimonian-Laird random-effects model to combine the effect sizes.

When extracting data and selecting effect sizes, the original studies' inclusion of multiple time points, concentrations, and measurement sites can introduce methodological variability. To tackle this, we developed a clear, standardized set of decision-making guidelines aimed at identifying the most representative effect estimate for each outcome indicator in every study, ensuring consistency in our main analysis.Our approach involved a three-tiered selection process. First, when studies presented various exposure concentration groups, we focused on the highest concentration group—a step applied to six studies. Next, for studies with multiple time-point measurements within a chosen concentration group, we selected the data point with the largest absolute standardized mean difference (SMD), a method used in two studies. Finally, if multiple anatomical sites were measured at that time point, we chose the site with the largest absolute SMD, relevant to just one study.We acknowledge that prioritizing the strongest effects could introduce selection bias, potentially inflating the true effect size. To address this concern, we conducted a thorough sensitivity analysis, examining how our selection criteria influenced the stability and reliability of our findings, ensuring our conclusions remain robust despite these methodological challenges.

To thoroughly understand the underlying reasons for the differences we observed, we carried out pre-planned subgroup analyses using a variety of stratification factors. These factors included different types of pollutants like PM2.5, O3, DEP, and SO2, as well as varying exposure times categorized as short-term (up to 7 days), medium-term (8 to 30 days), and long-term (over 30 days). We also considered different animal strains, such as mice, rats, and guinea pigs, and exposure routes including whole-body inhalation and nasal instillation. For key indicators like IL-4, IL-5, IL-13, OVA-IgE, and EOS, we conducted additional cross-subgroup analyses looking at both pollutant types and exposure times. To measure how much each potential factor contributed to the differences in effect size, we used both univariate and multivariate Meta-regression methods. Given that some subgroups were based on evidence from just a single study, we adopted a stratified reporting approach in this paper. For subgroups with two or more studies ($n \geq 2$), we provided detailed effect sizes in the main text. For those with only one study ($n = 1$), we briefly described the overall trends in the main text and included detailed data in a supplementary material table. It's crucial to note that all findings should be interpreted carefully, taking into account the significant influence of the number of studies involved.

4. Meta-analysis conclusion

4.1 Primary outcome

When looking at the main research findings concerning cellular-level regulation, exposure to air pollution has clearly had a significant impact.In this context, a meta-analysis of 11 studies indicates that exposure to air pollution strongly promotes an increase in EOS levels [n = 12, SMD = 2.39, (95% CI: 1.04–3.75), p = 0.001, I^2 = 90.0%](Refer to FIGURE 4A for detailed information).Moreover, exposure to air pollution also significantly promotes the expression of Th2-type cytokines. Specifically, in the case of IL-4, [n = 8, SMD = 2.44, (95% CI: 0.85–4.02), p = 0.003, I^2 = 89.3%](Refer to FIGURE 5A),In the research on IL-5 [n = 7, SMD = 3.72, 95% CI: 1.88–5.56, p < 0.001, I^2 = 85.9%](As shown inFIGURE 5B),Analysis of IL-13 indicated that [n = 7, SMD = 4.62, (95% CI: 2.21–7.03), p < 0.001, I^2 = 92.7%](Refer toFIGURE 5C).A meta-analysis based on 12 studies found that the level of OVA-IgE was also significantly elevated [SMD = 3.57, (95% CI: 2.16–4.98), p < 0.001, I^2 = 90.9%](Refer to FIGURE 3B).These five key indicators strongly suggest that exposure to air pollution significantly promotes the core allergic processes.

4.2 Exploratory results

For the indicators with a small number of studies (number of studies n ≤ 5) under this circumstance, although the results obtained can provide some preliminary clues, the strength of the evidence is relatively limited. In terms of pro-inflammatory and tissue damage effects, exposure to air pollution exhibits multi-faceted impacts. It may up-regulate the expression of IL-1β [n = 3 studies, SMD = 3.88, (95% CI: 1.35–6.40), p = 0.003, I^2 = 87%](Refer to FIGURE 5F for details),It may also upregulate the expression of the NLRP3 inflammasome [n = 3, SMD = 3.45 95% CI = 1.69–5.22, p = 0.02, I^2 = 75.7%] (see FIGURE 5H).In addition, exposure to air pollution may disrupt the expression of the tight junction protein ZO-1 [n = 3, SMD = -3.90, (95% CI: -6.96 to -0.85), p = 0.01, I^2 = 85%] (as shown in FIGURE 6.These results further confirm that exposure to air pollution has extensive pro-inflammatory and tissue-damaging effects. Regarding the uncertain trends presented in a small number of studies on this basis, lymphocytes tend to promote infiltration, [n = 2, SMD = 6.04, (95% CI: 0.09–11.99), p = 0.047, I^2 = 64.8%] (see FIGURE 4C).The effects of some other indicators are not clear. For example, the overall effect of IFN-γ is not significant, and there is extremely high heterogeneity, [n = 7, SMD = 0.77, (95% CI: -1.72-3.25), p = 0.55, I^2 = 94.1%] (see FIGURE 5G for details).The overall effect of Neu is also not significant [n = 4, SMD = 0.66, (95% CI: -0.97-2.29), p = 0.43, I^2 = 81.1%] (as shown in FIGURE 4B),The overall effect of IL-17 did not reach statistical significance [n = 3, SMD = 2.07, (95% CI: -0.38-4.50), p = 0.10, I^2 = 77.3%] (see FIGURE 5D),IL-33 exhibited a non-significant upward trend [n = 2, SMD = 1.40, (95% CI: -0.40-3.20), p = 0.13, I^2 = 87.1%] (seeFIGURE 5E).Finally, the overall pooled effect of total serum IgE also did not reach significance [n = 4, SMD = 1.32, (95% CI: -1.47-4.10), p = 0.36, I^2 = 93.6%] (as shown in FIGURE 3A).

4.3 Subgroup analysis

Given the high heterogeneity among the included studies, to delve deeper into the root causes of the variation in effect sizes, we conducted a systematic subgroup analysis focusing on the key methodological and experimental factors in the study design. The analysis spanned a wide range of

dimensions, including pollutant types, exposure routes, exposure durations, and animal species. Moreover, we further carried out a cross-analysis of pollutants and exposure times. These subgroup analyses aim to identify the key potential factors that may explain the variation in immunological indicators, and to provide reasonable and possible explanations for the heterogeneity of the results from both biological and experimental design perspectives.

We carried out subgroup analyses categorized by pollutant types, and the findings highlighted the distinct effects each pollutant had on different immune markers.Regarding the impact of O3, it significantly upregulated EOS [n = 4, SMD = 3.04 (95% CI: 1.03–5.03), p = 0.003, I^2 = 85.9%]. Meanwhile, the level of ova-IgE also increased significantly [n = 6, SMD = 4.03 (95% CI: 1.79–6.27), p < 0.001, I^2 = 93.5%]. In addition, O3 also significantly upregulated the levels of IL-4, lymphocytes, and NLRP3, and significantly downregulated the levels of IFN-γ and tight junction protein ZO-1. For PM2.5, its impact was more extensive.It significantly upregulated IL-13 [n = 3, SMD = 6.31 (95% CI: 1.79–10.84), p = 0.01, I^2 = 86.8%]. The EOS level also increased significantly [n = 5, SMD = 3.05 (95% CI: 1.20–4.91), p = 0.001, I^2 = 86.3%]. The IL-4 level was also significantly upregulated [n = 5, SMD = 3.31 (95% CI: 1.31–5.31), p = 0.001, I^2 = 84.3%]. The IL-5 level also increased significantly [n = 4, SMD = 2.70 (95% CI: 0.97–4.43), p = 0.002, I^2 = 75.1%]. The level ova-IgE was significantly upregulated [n = 6, SMD = 3.39 (95% CI: 1.41–5.36), p = 0.001, I2 = 88.4%]. The NLRP3 level increased significantly [n = 2, SMD = 2.83, (95% CI: 1.82–3.84), p < 0.001, I^2 = 85.7%]. The IL-1β level was also significantly upregulated [n = 2, SMD = 3.16, (95% CI: 2.01–4.31), p < 0.001, I^2= 93.2%]. In addition, PM2.5 also significantly upregulated the levels of lymphocytes and IL-33 and significantly downregulated the ZO-1 level.In terms of other pollutants, exposure to diesel exhaust particles (DEP) was shown in individual studies to significantly downregulate the levels of IL-4, total serum IgE, and ZO-1. Exposure to sulfur dioxide (SO2) also demonstrated a significant upregulatory effect on indicators such as EOS, IL-4, IL-5, IL-13, IFN-γ, and IL-1β. However, due to the small sample size of these results and the non-significant heterogeneity, caution should be exercised when extrapolating these results (Table S5 in the supplementary materials).

When we carried out a stratified analysis based on how animals were exposed to pollutants, we discovered that pollutants had varying impacts on different immune indicators depending on the exposure route. For instance, when animals breathed in pollutants through their whole bodies, several immune indicators underwent notable changes. The level of EOS was significantly up-regulated [n = 7, SMD = 3.15 (95% CI: 1.67–4.64), p < 0.001, I^2 = 85.4%]. The level of ova-IgE also increased significantly [n = 8, SMD = 3.99 (95% CI: 2.15–5.83), p < 0.001, I^2 = 92.5%]. The level of IL-4 was significantly up-regulated [n = 5, SMD = 2.99 (95% CI: 1.91–4.07), p < 0.001, I^2= 45.5%], and the levels of IL-5 [n = 4, SMD = 4.83 (95% CI: 1.69–7.96), p = 0.003, I^2 = 90.1%] and IL-13 [n = 5, SMD = 4.87 (95% CI: 2.33–7.39), p < 0.001,I^2 = 88.9%] were also significantly up-regulated. Moreover,the mode of intranasal administration of pollutants has also led to a series of changes in immune indicators. The level of IL-5 was significantly up-regulated [n = 3, SMD = 3.10 (95% CI: 0.42–5.78), p = 0.002, I^2 = 83.4%], the level of ova-IgE [n = 4, SMD = 3.07 (95% CI: 0.36–5.79), p = 0.03, I^2 = 89.3%], and the level of NLRP3 was significantly up-regulated [n = 2, SMD =

2.83 (95% CI: 1.82–3.84), $p < 0.001$, $I^2 = 85.7\%$]. The level of IL-1β was significantly increased [n = 2, SMD = 3.16 (95% CI: 2.01–4.31), $p < 0.001$, $I^2 = 93.2\%$]. Meanwhile, the level of ZO-1 was significantly down-regulated [n = 2, SMD =-5.37 (95% CI:-7.19– 3.55), $p < 0.001$, $I^2 = 67\%$]. In addition, evidence from a single study indicates that systemic inhalation of pollutants can also up-regulate the levels of lymphocytes, NLRP3, IL-1β, and IL-17 and down-regulate the level of ZO-1. Intranasal administration of pollutants can also up-regulate the level of lymphocytes.(Supplementary Material Table S6).

In the subgroup analysis based on the duration of exposure, when in the short-term exposure stage of pollutants (≤ 7 days), the EOS level was significantly up-regulated [n = 5, SMD = 1.51 (95% CI: 0.07–2.96), $p = 0.02$, $I^2 = 67\%$]. The analysis based on two studies indicated that short-term exposure not only led to the above-mentioned changes but also potentially up-regulated the levels of IFN-γ, NLRP3 inflammasome, and IL-1β, while reducing the expression of tight junction protein ZO-1. Moreover, all these changes were statistically significant ($p < 0.05$). As the exposure time enters the middle stage (8–30 days), multiple immune indicators exhibit more significant changes. The level of IL-13 is significantly upregulated [n = 5, SMD = 3.63 (95% CI: 1.04–6.22), $p < 0.001$, $I^2 = 92.3\%$]. The level of IL-4 also increases significantly [n = 6, SMD = 2.06 (95% CI: 0.30–3.81), $p = 0.01$, $I^2 = 91.3\%$]. The levels of IL-5 [n = 4, SMD = 2.35 (95% CI: 1.39–3.31), $p < 0.001$, $I^2 = 56.8\%$] and ova-IgE [n = 5, SMD = 2.39 (95% CI: 1.20–3.58), $p < 0.001$, $I^2 = 75.9\%$] also rise significantly. Based on this, the analysis of two studies suggests that middle-stage exposure may also upregulate IL-17 [n = 2, SMD = 1.12 (95% CI: 0.22–2.02), $p = 0.02$, $I^2 = 62.9\%$].When the exposure time is extended to the long-term period (> 30 days), the EOS level increases significantly again [n = 3, SMD = 3.41 (95% CI: 0.59–6.23), $p = 0.02$, $I^2 = 90.5\%$], and the ova-IgE level also rises significantly [n = 4, SMD = 6.57 (95% CI: 2.34–10.80), $p = 0.002$, $I^2 = 95.8\%$]. Evidence from single studies suggests that different exposure times may also have an impact on other inflammatory indicators. For detailed information, please refer to the supplementary materials. The overall trend shows that the effect size of long-term exposure is greater, which indicates that there may be a cumulative effect between the exposure time and the inflammatory response(Supplementary Material Table S7)

A summary analysis of the studies by animal strain reveals that when mice are used as experimental subjects, significant changes occur in their immune indicators. Specifically, the levels of IL -13 are significantly elevated [n = 4, SMD = 2.74 (95% CI: 0.06–5.43), $p < 0.001$, $I^2 = 90.9\%$], the levels of IL-5 are also significantly increased [n = 4, SMD = 2.59 (95% CI: 0.83–4.36), $p = 0.004$, $I^2 = 68\%$], the levels of ova-IgE are significantly elevated [n = 6, SMD = 2.17 (95% CI: 0.79–3.55), $p = 0.002$, $I^2 = 83.3\%$], the levels of IL-1β are also significantly increased[n = 2, SMD = 3.16 (95% CI: 2.01–4.31), $p < 0.001$, $I^2 = 93.2\%$], and the levels of ZO-1 are significantly reduced [n = 3, SMD =-3.90 (95% CI:-6.96– 0.85), $p = 0.01$, $I^2 = 85\%$].In addition, single-study evidence also observed changes in the Lym level in mice. When rats were exposed to pollutants, the changes in immune indicators were more significant. In rats, the level of IL-13 increased significantly [n = 3, SMD = 8.07 (95% CI: 1.37–14.76), $p < 0.001$, $I^2 = 94.2\%$], the EOS level rose significantly [n = 4, SMD = 4.90 (95% CI: 2.73–7.07), $p < 0.001$, $I^2 = 81.1\%$], the ova-IgE level increased

significantly [n = 4, SMD = 9.49 (95% CI: 3.55–15.43), p = 0.002, I^2 = 94.1%], the IL-4 level also increased significantly [n = 4, SMD = 3.33 (95% CI: 1.92–4.74), p < 0.001, I^2 = 67.5%], and the IL-5 level [n = 3, SMD = 6.32 (95% CI: 2.23–10.40), p < 0.001, I^2 = 93.4%].In addition, single-study evidence suggests that inflammasome-related factors NLRP3, IL-33, and IL-1β may also be involved in the immune response of rats. Regarding guinea pigs, only a significant effect on EOS was found [n = 2, SMD = 1.47 (95% CI: 0.66–2.27), p < 0.001, I^2 = 0.0%].(Supplementary Material Table S8)

Through a cross-analysis of pollutants and exposure time, we conducted an in-depth exploration of the impacts of different pollutants on various immune indicators under different exposure durations, and discovered some noteworthy results. When it comes to the combination of PM2.5 and medium-term exposure (PM2.5 × Medium-term), significant changes occur in multiple immune indicators. The level of ova-IgE increases significantly [n = 3, SMD = 3.13 (95% CI: 0.92–5.33), p = 0.005, I^2 = 83.2%]. The level of IL-4 also rises significantly [n = 4, SMD = 2.86 (95% CI: 0.93–4.79), p = 0.004, I^2 = 85.8%]. The level of IL-5 is significantly up-regulated [n = 3, SMD = 2.35 (95% CI: 0.95–3.76), p = 0.001, I^2 = 71.2%]. The level of EOS increases significantly [n = 3, SMD = 3.48 (95% CI: 0.97–5.99), p = 0.007, I^2 = 87.7%]. The level of IL-13 shows a significant change [n = 3, SMD = 6.31 (95% CI: 1.79–10.84), p = 0.001, I^2 = 86.8%]. On this basis, two studies have shown that the combination of PM2.5 and short-term exposure (PM2.5 × Short-term) also has a significant impact. The level of NLRP3 inflammasome increases significantly [n = 2, SMD = 2.83 (95% CI: 1.82–3.84), p < 0.001, I^2 = 85.7%], and the level of IL-1β rises significantly [n = 2, SMD = 3.16 (95% CI: 2.01–4.31), p < 0.001, I^2 = 93.2%].The combination of O3 and medium-term exposure (O3 × Medium-term) can significantly upregulate the ova-IgE level [n = 2, SMD = 1.76 (95% CI: 0.40–3.13), p = 0.01, I^2 = 68.9%]. The combination of O3 and long-term exposure (O3 × Long-term) has a significant impact on the levels of ova-IgE [n = 4, SMD = 6.57 (95% CI: 2.34–10.80), p = 0.002, I^2 = 95.8%] and EOS [n = 3, SMD = 3.41 (95% CI: 0.59–6.23), p = 0.02, I^2 = 90.5%].The combination of DEP and medium-term exposure (DEP × Medium-term), based on evidence from individual studies, suggests that it may down-regulate the levels of total serum IgE, IL-4, and EOS, while up-regulating the level of IL-33 (all p < 0.05). Regarding other cross-combinations, such as short-term exposure to O3, short-term exposure to DEP, and short-term exposure to SO2, due to the limited number of studies, the relevant findings are detailed in Table S9 of the supplementary materials.

4.4 Visual summary of subgroup analysis through forest plots

To conduct an in-depth exploration and systematic interpretation of the high heterogeneity among various studies, we carried out multi-dimensional and refined subgroup analyses focusing on key methodological and experimental factors. The analysis dimensions are diverse, comprehensively covering key elements such as pollutant types, exposure routes, exposure durations, animal species, and the cross-effects between pollutants and exposure times. To present these analysis results more intuitively and comprehensively, we carefully prepared five summary forest plots in the supplementary materials(Supplementary Figures S1-S5).These forest plots correspond to five major stratification

variables: pollutant type, exposure route, exposure duration, animal species, and the cross-analysis of pollutants and exposure time. From these forest plots, one can clearly observe the summary standardized mean difference (SMD), 95% confidence interval (95% CI), heterogeneity index (I^2 value), and statistical significance of each subgroup. This makes it simpler to directly compare how air pollution affects different immunological indicators under various experimental conditions. .

It can be clearly observed from the forest plot that there are differences among various experimental conditions. Under such circumstances, the impacts of some pollutants on specific inflammatory indicators exhibit a relatively consistent pattern. In the summary plot of pollutant types, the up-regulation effect of PM2.5 on IL-13 is extremely significant, with the SMD reaching 6.31, which is significantly stronger than that of O3. In terms of the impact on ova-IgE, the effects of the two are similar. The summary plot of exposure time shows that the effect size (SMD = 6.57) of long-term exposure on ova-IgE far exceeds that of medium-and short-term exposure. The summary plot of animal species indicates that the effect size of the inflammatory response in the rat model is generally higher than that in the mouse model. The cross-summary plot of pollutant × time (Supplementary Figure S5).Further investigations reveal that medium-term exposure to PM2.5 exerts the strongest synergistic effects on multiple indicators, while long-term exposure to O3 has the most significant specific effect on ova-IgE. To ensure the integrity and transparency of the methodology, 65 detailed forest plots of specific indicators within each subgroup are available in the supplementary materials. These results are presented in an intuitive visual format, complementing the tabular data. This presentation facilitates an in-depth biological interpretation of subgroup outcomes and closely links the quantitative synthesis with specific experimental conditions.

4.5 Publication bias and sensitivity analysis

This study strictly follows the relevant recommendations for systematic reviews and meta-analyses, using Begg's rank correlation test and Egger's linear regression test to evaluate publication bias among the 18 pre-clinical trials included (see Supplementary Table S10 for details). The goal is to uncover potential small-study effects and selective publication bias, though it’s important to note that when the number of studies is small ($k < 10$), the sensitivity of both Begg's and Egger's tests declines, making their conclusions less reliable (Sterne et al., 2011). To address this, the study adopts a stratified approach when interpreting publication bias results, recognizing that tests like these have limited statistical power with fewer studies—for example, IL-5 had only $k = 6$ studies, while indicators like IL-17, NLRP3, IL-1β, and ZO-1 had just $k = 3$ each. The findings for these indicators should therefore be treated as supplementary rather than definitive. Overall, during evidence synthesis, publication patterns varied across immune indicators, so extreme caution is needed when interpreting bias tests for those with limited studies. Instead, greater focus should be placed on each study’s methodological quality and experimental design features.

The test results clearly reveal that during the process of evidence synthesis, the publication patterns of different immune indicators exhibit significant heterogeneity. Specifically, the publication biases of 3 indicators are statistically significant ($p < 0.05$). For ova-IgE, $p < 0.001$ in the Begg's test and $p < 0.001$ in

the Egger's test. For IL-5, $p < 0.05$ in the Egger's test, and for IL-13, $p = 0.001$ in the Egger's test. These results suggest that in the Meta-analysis, the effect sizes of these indicators are likely to be overestimated. However, no significant publication bias was found in terms of indicators such as total IgE, Neu, Eos, IL-4, IFN-γ, and ZO-1 (the p-values of both Begg's and Egger's tests were greater than 0.05), which undoubtedly enhances the reliability of the results of our studies. It is important to emphasize that for indicators with a relatively small number of included studies, such as IL-7, NLRP3 inflammasome, IL-1β, and ZO-1 (the number of studies for each indicator k = 3), the statistical power of the publication bias test is limited. The negative results should be interpreted with caution and not be blindly trusted.

This systematic review carried out a thorough meta-analysis focusing on key outcome indicators like EOS, IL-4, IL-5, IL-13, and OVA-IgE. Before and after performing a sensitivity analysis, it also carefully evaluated how robust each result was and the overall quality of the evidence, with the relevant results displayed in FIGURE 7. Looking at the preliminary analysis in FIGURE 3FIGURE 4 and FIGURE 5, for EOS,a total of 12 studies were included. The pooled effect size was expressed as the standardized mean difference (SMD) = 2.39 (95% CI: 1.04 to 3.75, P = 0.001), with significant heterogeneity (I^2 = 90%, Tau^2 = 4.84). For OVA-IgE, 12 studies were also included, and the pooled SMD = 3.57 (95% CI: 2.16 to 4.98, P < 0.001), with significant heterogeneity (I^2 = 90.9%, Tau^2 = 4.79). Regarding cytokines, for IL-4, 8 studies were included, and the pooled SMD = 2.44 (95% CI: 0.85 to 4.02, P = 0.003), with significant heterogeneity (I^2 = 89.3%, Tau^2 = 4.21). For IL-5, 7 studies were included, and the pooled SMD = 3.72 (95% CI: 1.88 to 5.56, P < 0.001), with significant heterogeneity (I^2 = 92.7%, Tau^2 = 4.21). For IL-13, 7 studies were included, and the pooled SMD = 4.62 (95% CI: 2.21 to 7.03, P < 0.001), with significant heterogeneity (I^2 = 92.7%, Tau^2 = 8.71).

To make sure our research results were reliable and stable, we used a leave-one-out analysis to assess the outcomes. The results showed that no matter which single study we took out, there were no significant shifts in either the point estimate of the combined effect size or the 95% confidence interval. This clearly proves that our main conclusions don't rely too heavily on any one particular study.

FIGURE 7 Forest plot of sensitivity analysis for the effect of Air Pollution on (A) eosinophil counts, (B) IL-4, (C)IL-5, (D)IL-13, (E) ova-IgE.

5. Discussion

- This study creatively uses systematic review and meta-analysis to thoroughly combine pre-clinical evidence on how air pollution exposure affects nasal mucosal immune-inflammatory markers in animal models of allergic rhinitis (AR). The research shows that air pollution makes AR worse by working together to disrupt the epithelial barrier, activate innate immunity, and encourage Th2 response polarization.Moreover, the effect pattern and intensity are precisely regulated by the type of pollutants and the exposure time window. Subsequently, a systematic elaboration will be carried out from four aspects: mechanism integration, heterogeneity analysis, research limitations, and future prospects.

1.Mechanism integration: The "dynamic immune regulation network" of air pollution combined with augmented reality (AR)

- The study's findings offer robust backing and extend the "epithelial barrier hypothesis." Air pollutants, as external agents, mainly assault the nasal epithelium—the body's initial defense line. Our comprehensive meta-analysis reveals a notable decline in the expression of the tight-junction protein ZO-1 due to air pollution exposure, aligning closely with prior research. Studies have shown that particulate matter, like PM2.5, can heighten epithelial permeability by reducing occludin and claudin-1 levels and suppressing E-cadherin protein (Xian et al., 2020; Chuang et al., 2015). Once the nasal epithelial barrier is damaged, it not only allows allergens to penetrate more easily but also lays the groundwork and creates conditions for subsequent immune activation.
- Against the backdrop of impaired nasal epithelial barrier, air pollution further triggers the rapid response mechanism of innate immunity. Our analysis results indicate that under short-term exposure (no more than 7 days), the NLRP3 inflammasome is significantly activated, and the expression level of IL-1β is up-regulated. This finding is consistent with the conclusions of relevant studies on O3 exposure. Previous research has shown that acute ozone exposure can rapidly induce the release of inflammatory mediators, thereby promoting the occurrence of airway inflammation (Funabashi et al. 2004, Wagner et al. 2007).As a crucial pro-inflammatory factor, IL-1β can recruit and activate various immune cells, playing an important bridging role in the transition from innate immunity to adaptive immunity (Dinarello et al., 2018; Sim et al., 1994).
- The most conclusive finding of this study is that air pollution exerts a strong polarizing effect on the Th2-type immune response. Through Meta-analysis, we found that the levels of IL-4, IL-5, IL-13, and OVA-IgE were all significantly elevated, with a large effect size (SMD values were generally greater than 2.5). This finding provides strong mechanistic support for numerous epidemiological evidences and clearly explains the reason why exposure to air pollution increases the risk and severity of AR. Combining our results with existing mechanistic studies can more clearly outline the action pathways of different pollutants.Among the numerous phenomena revealed by the subgroup analysis, an undeniable fact comes to light: PM2.5 can be regarded as a multi-targeted attacker. Its exposure exerts a wide-ranging and significant up-regulatory effect on the core Th2-type immune indicators. Specifically, these indicators include IL-4 (SMD = 3.31, 95% CI: 1.31–5.31, P = 0.001), IL-5 (SMD = 2.70, 95% CI: 0.97–4.43, P = 0.001), IL-13 (SMD = 6.31, 95% CI: 1.79–10.84, P = 0.01), EOS (SMD = 3.05, 95% CI: 1.20–4.91, P = 0.001), and OVA-IgE (SMD = 3.39, 95% CI: 1.41–5.36, P = 0.001). This finding is consistent with previous research, which has shown that particulate matter (PM) can induce a Th2-biased microenvironment in the lungs, characterized by the overproduction of IL-4 and IL-13 (Kang et al., 2005). Moreover, PM can exacerbate Th2-dominant allergic inflammation in mice, accompanied by redox imbalance (Wang et al., 2020).Taking all these factors into account, PM2.5 is highly likely to worsen the pathological process of AR at multiple stages by jointly disrupting the epithelial barrier, activating innate immunity, and polarizing adaptive immune responses.
- In the subgroup analysis focusing on O3, a series of key findings have revealed its significant impact on AR. The analysis results indicate that O3 exposure significantly upregulates the levels of EOS

(SMD = 3.04, 95% CI: 1.03–5.04, P < 0.001) and OVA-IgE (SMD = 4.03, 95% CI: 1.79–6.27, P < 0.001).When exposed to O_3 for an extended period, its effect on OVA-IgE is more prominent (SMD = 6.57, 95% CI: 2.34–10.80, P = 0.002), suggesting that O3 has a cumulative immune-enhancing effect.This finding aligns with observations made in epidemiological studies, where some have reported that an increase in O3 concentration can lead to a 37% rise in the consultation rate among patients with AR(Kim et al., 2011). It also supports the results of our previous research involving an AR rat model, which demonstrated that O3 exposure can worsen eosinophilic inflammation in a concentration-dependent manner and trigger a Th2-skewed immune response (Bao et al., 2018).Based on relevant literature evidence, it is speculated that O3 may induce oxidative stress responses, promote the release of Th2 cytokines, and subsequently drive the recruitment and activation of eosinophils (Wiegman et al., 2020; Bao et al., 2017). Ultimately, this leads to the release of toxic mediators by eosinophils, causing damage to nasal mucosal tissues and continuously amplifying the inflammatory response.

- DEP:A complex immune adjuvant. Under DEP exposure conditions, most immune-related indicators show a downward trend. Among them, the change in Eos is the most significant, showing a decreasing trend (SMD = -1.46, 95% CI: -4.30–-1.37, P = 0.31), but it does not reach the level of statistical significance. IL-33 (SMD = 0.49, 95% CI: -0.40–1.38, P = 0.28) and IFN-γ (SMD = -0.31, 95% CI: -1.19–0.58, P = 0.50) show a non-significant downward trend.Other indicators such as IL-4, IL-13, and ZO-1 all showed a downward trend. It is worth noting that, except for EOS, the analysis results of the remaining indicators are based on single studies, and the evidence base is relatively limited, suggesting that the interpretation of the immunomodulatory effects of DEP should be approached with caution.Numerous studies have confirmed that DEP are potent immune adjuvants, which can catalytically promote the production of Th2 cytokines (such as IL-4, IL-5, and IL-13)(Takano et al.,1997; Diaz-Sanchez et al.,1997).It can also promote the synthesis of OVA-IgE(Diaz-Sanchez et al.,1994;Tsien et al.,1997).Thus, the effects of DEP are not singular and fixed but highly dependent on its particulate components (such as adsorbed polycyclic aromatic hydrocarbons)(Diaz-Sanchez et al.,1997;Kawasaki et al.,2001;Singh et al.,2004).Exposure routes, animal strains, sensitization status, and even some components may possess bidirectional Th1/Th2 regulatory activities. This complexity helps explain the heterogeneity observed in this meta-analysis, indicating that future research should focus more precisely on analyzing the immunomodulatory profiles of different DEP components.
- IIt's crucial to emphasize that when analyzing air pollution's impact, its effect on the Th1-representative cytokine IFN-γ shows significant variability. This finding defies the conventional "Th2 dominance/Th1 suppression" binary view. Reviewing the literature reveals that diesel exhaust particles (DEP) and their components don't statically regulate the Th1/Th2 balance but do so contextually. Under certain conditions, they can boost both Th1 and Th2 responses simultaneously. (Muranaka et al.,1986; Takano et al.,1997),Conversely, specific circumstances can lead to Th1 response suppression (Yioshno et al.,1998;Burstein et al.,1993).his intricate behavior suggests air pollution doesn't merely unidirectionally inhibit a single immune pathway but instead reprograms the "set-point" for immune balance.

- Based on the above research findings, we innovatively propose the concept of the "dynamic regulatory network of pollution exposure-immune response" to elucidate the mechanism by which air pollution exacerbates AR. During the acute phase (lasting no more than 7 days, which is the initiation stage), pollutants such as PM2.5 and O3 directly attack the epithelial barrier, leading to the destruction of ZO-1. Meanwhile, the innate immune system is activated (with the involvement of NLRP3/IL-1β), releasing "danger signals" and creating a pro-nflammatory microenvironment.Upon entering the sub-acute phase (8–30 days, which is the polarization stage), against the backdrop of impaired barriers and continuous pro-inflammatory signals, the immune response gradually tilts towards adaptive immunity. At this time, pollutants (especially PM2.5 and O3) act as immune adjuvants, strongly driving the differentiation of T cells into Th2 cells. Subsequently, this leads to a comprehensive and stable increase in Th2 cytokines (such as IL-4, IL-5, and IL-13) and OVA-IgE. Upon entering the chronic phase (lasting over 30 days and in the maintenance and amplification stage), persistent Th2 inflammation promotes the further infiltration and accumulation of effector cells, (EOS), in the nasal mucosa. OVA-IgE levels continue to climb, perpetuating a self-reinforcing cycle of chronic inflammation.

2. Heterogeneity Sources and Methodological Innovation

- Among the many studies included in this research, we've managed to pinpoint the main sources of heterogeneity, like pollutant types, exposure time windows, and animal strains. For example, there are notable differences in how immune indicators are regulated between PM2.5 and O3, and these differences even show up in distinct lineages. Animals from different strains, such as rats and mice, display varying intensities of immune responses, which might be tied to their genetic backgrounds and how sensitive they are to specific pollutants. These findings are really important because they not only shed light on the methodological differences in current pre-clinical studies when trying to mimic real-world exposure scenarios but also serve as a reminder for future research to exercise stricter control and make more detailed comparisons of these variables.
- When facing the methodological discrepancies that arise across various concentrations and time points, we implemented and rigorously validated the "maximum effect size integration strategy." During our post-hoc sensitivity analysis, as depicted in FIGURE 8, we observed that even substantial data heterogeneity is permissible within our research domain.In subgroup analysis and Meta-regression, we extracted the rules and maintained the direction of effects, statistical significance, and the robustness of the core conclusions for the primary outcomes (EOS, IL-4, IL-5, IL-13, OVA-IgE). For example, the standardized mean difference of EOS changed from 2.39 to 2.15, still showing a significant positive effect. This fully reflects that our core findings are insensitive to the data extraction method and are robust.In addition, exposure dose, duration, and anatomical location are indeed significant biological sources contributing to the variability of effects. The pre-established decision rules we set can effectively extract the most biologically meaningful signals from the complex methodological heterogeneity.

3. Research Limitations and Future Prospects

- The limitations of this study are mainly reflected in several aspects. We only retrieved English-language literature, which may lead to language bias. There are relatively few studies on some markers (such as IL-17, IL-25, IL-33) and specific subgroups (such as SO2 exposure), resulting in limited statistical power. Therefore, the research conclusions need to be interpreted with caution. Thirdly, even though we tried to understand the sources of heterogeneity by doing subgroup analyses, there's still some heterogeneity that we couldn't explain. This might be due to differences in how allergic rhinitis was modeled across studies or variations in the sensitivity of the detection methods used. Fourthly, our study mainly focused on the effects of single pollutants, but in reality, air pollution is a complex mix, and different pollutants might interact in ways that are either synergistic or antagonistic—effects that our analysis didn't capture.Finally, there are species differences in the pathogenesis and immune responses between animal models and human allergic rhinitis. Therefore, caution should be exercised when extrapolating the research findings to humans.
- Based on the findings and limitations of this study, we present the following recommendations for future research. First, standardization and real-world simulation should be promoted.Future studies should use standardized exposure plans and carry out immune monitoring at multiple time points, and also try to create a mixed pollutant exposure model that better mirrors real-world conditions. There's also a requirement for in-depth exploration of mechanisms. Research shouldn't just stop at Th1/Th2 differentiation but should delve deeper into how pollutants alter immune homeostasis through epigenetic regulation, like FOXP3 methylation(Prunicki et al., 2018). Finally, it is necessary to strengthen translational research. The key markers identified in this study (such as EOS, IL-13, OVA-IgE) can serve as candidate biomarkers for population studies and be validated and applied within the framework of exposome research and precision prevention strategies.

6. Conclusion

- This study systematically evaluated the impact of air pollution on nasal mucosal immune inflammation markers in an animal model of allergic rhinitis. The results showed that air pollution exacerbated nasal mucosal inflammation through multiple mechanisms, primarily including the disruption of the epithelial barrier, the activation of the innate immune system, and the enhancement of Th2-type immune inflammatory responses.Additionally, the research uncovered that air pollution's impact on the Th1 pathway varies significantly and depends on the context, highlighting the complexity of its effects on the immune system.These results provide important pre-clinical evidence for our in-depth understanding of the relationship between air pollution and allergic rhinitis.

This research introduces a groundbreaking concept: the "dynamic immune regulatory network," shedding light on how air pollution affects immune responses across varying timeframes. Initially, brief exposure to pollutants mainly compromises the immune barrier and triggers innate immune responses.Medium-term exposure causes polarization of Th2 cells, while long-term exposure results in the accumulation of immune effects. In response to the issue of heterogeneity in the methodology within this field, this study

has also developed and validated the "maximum effect size integration strategy", providing methodological guidance for handling complex animal experiment data. Through the application of these findings and methods, we can gain a better understanding of the immune system's response process to air pollution, offering important reference for future research, prevention, and treatment.

Current research still faces some limitations, including a lack of sufficient studies and inconsistent methodological quality. Given this, our study offers systematic quantitative evidence that helps clarify how air pollution affects the immune mechanisms underlying allergic diseases. Moving forward, future research should be more rigorous and standardized, and it should also consider real-world scenarios where people are exposed to multiple pollutants simultaneously, in order to better understand how different pollutants act over various time periods. It's also crucial to advance the validation and application of relevant biomarkers in population studies. These collective efforts will ultimately provide a solid scientific foundation for developing precise prevention and intervention strategies for allergic diseases linked to air pollution.

Declarations

Ethics approval

Not applicable. This study is a systematic review and meta-analysis of previously published studies and did not involve new experiments on humans or animals.

Consent to participate

This is not applicable.

Consent for publication

This is not applicable.

Conflict of interest

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

Funding

Author contributions

Zhuo Pan: Conceptualization, Methodology, Formal analysis, Writing – original draft.

Acknowledgements

This is not applicable.

Data availability

The data supporting the findings of this study are available within the article and its Supplementary Materials. Further information can be provided by the corresponding author upon reasonable request.

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64. Clinical trial number
65. This is not applicable

Figures

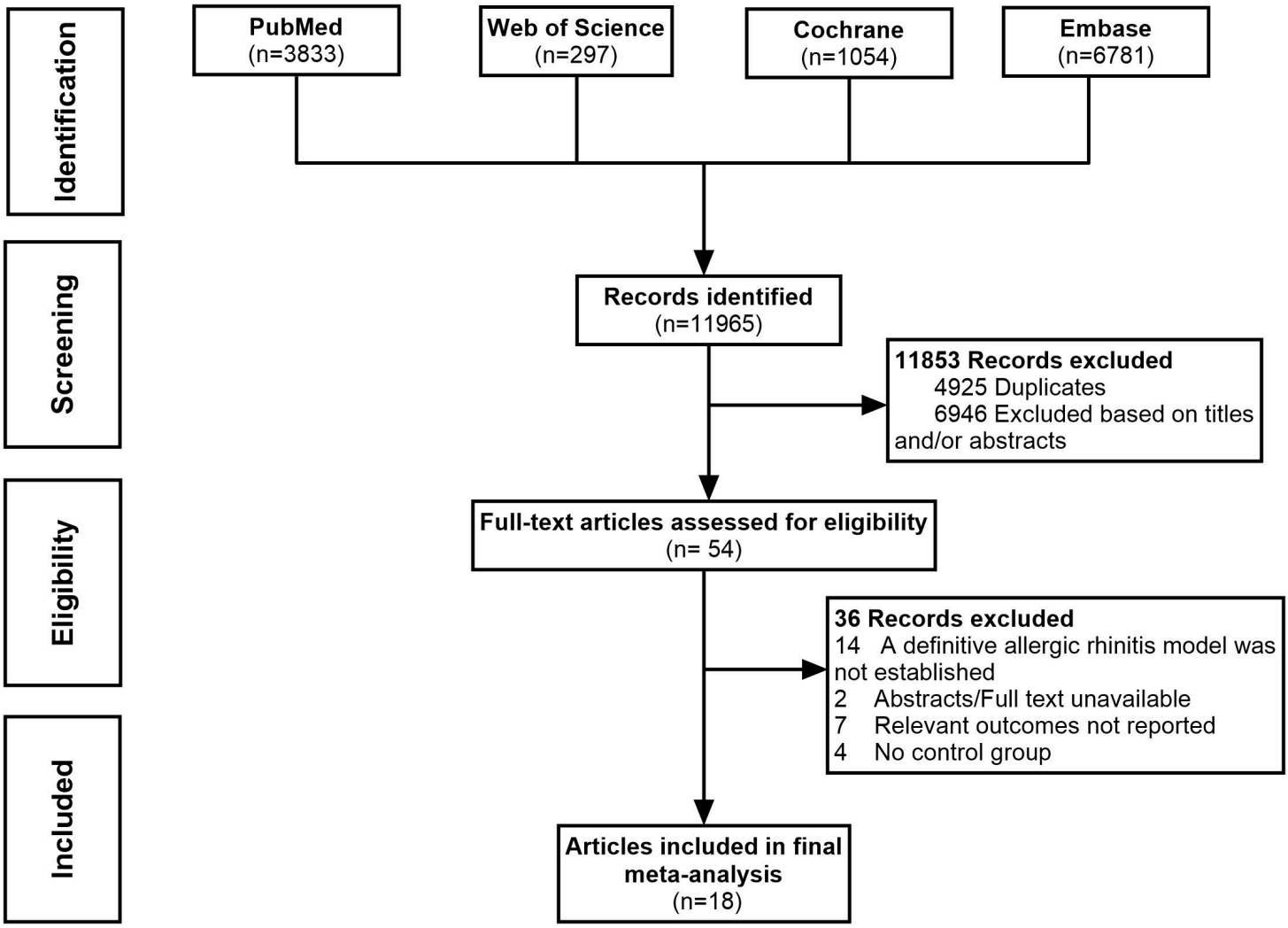


Figure 1

Flow chart of study selection.

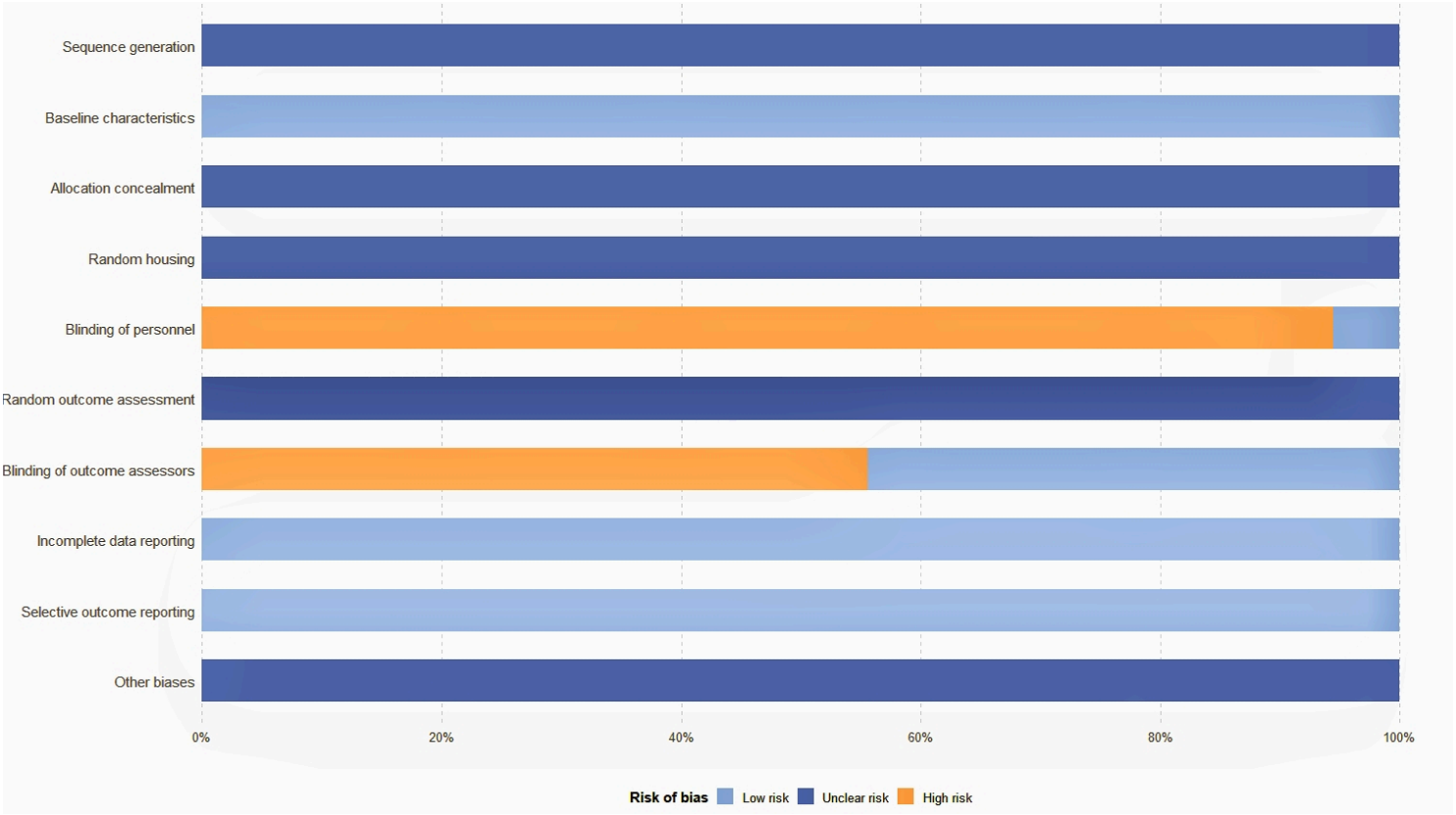


Figure 2

Summary of risk of bias assessment for included studies.

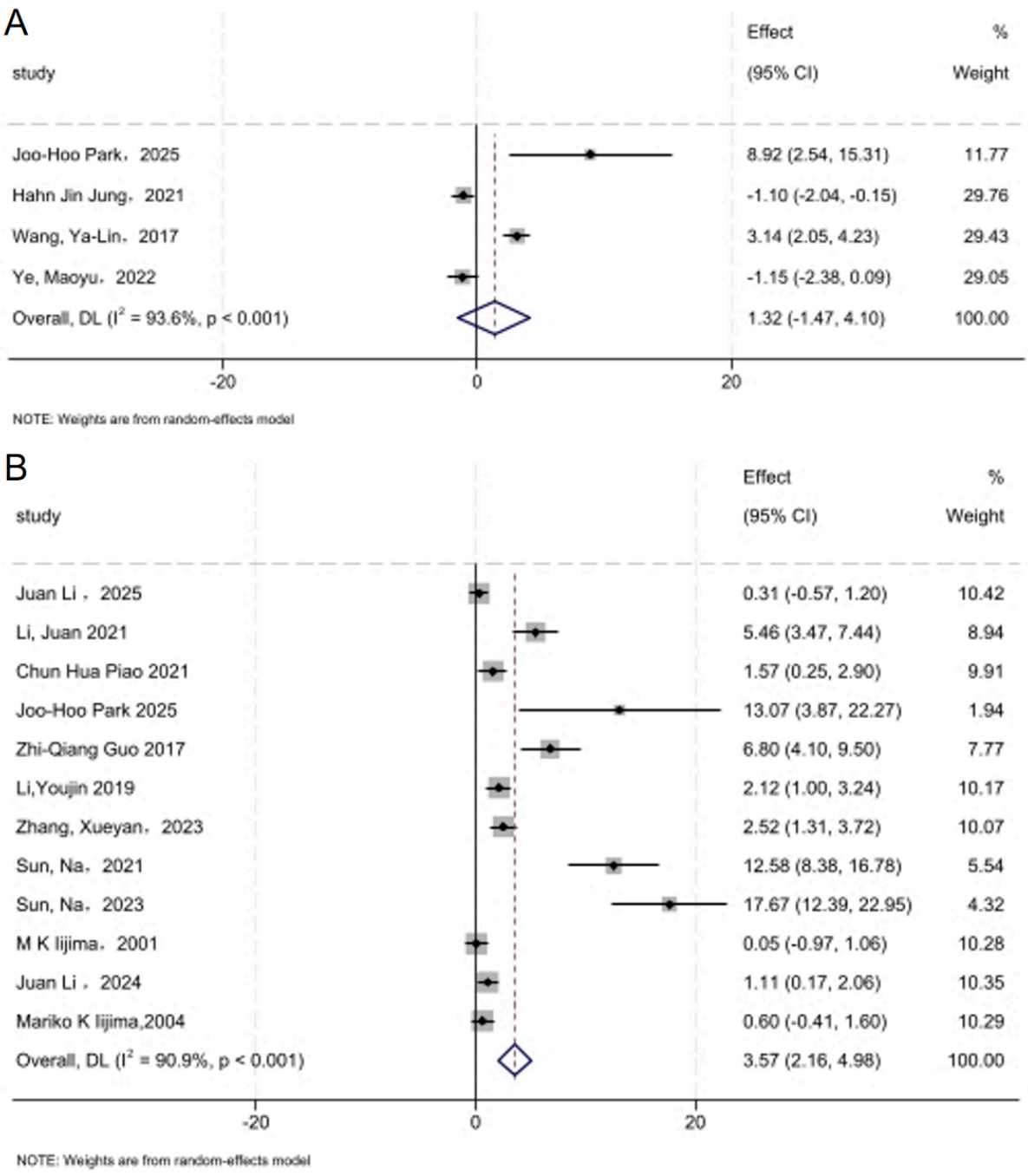


Figure 3

Forest plot of the effect of Air Pollution on (A) IgE ,(B) ova-IgE.

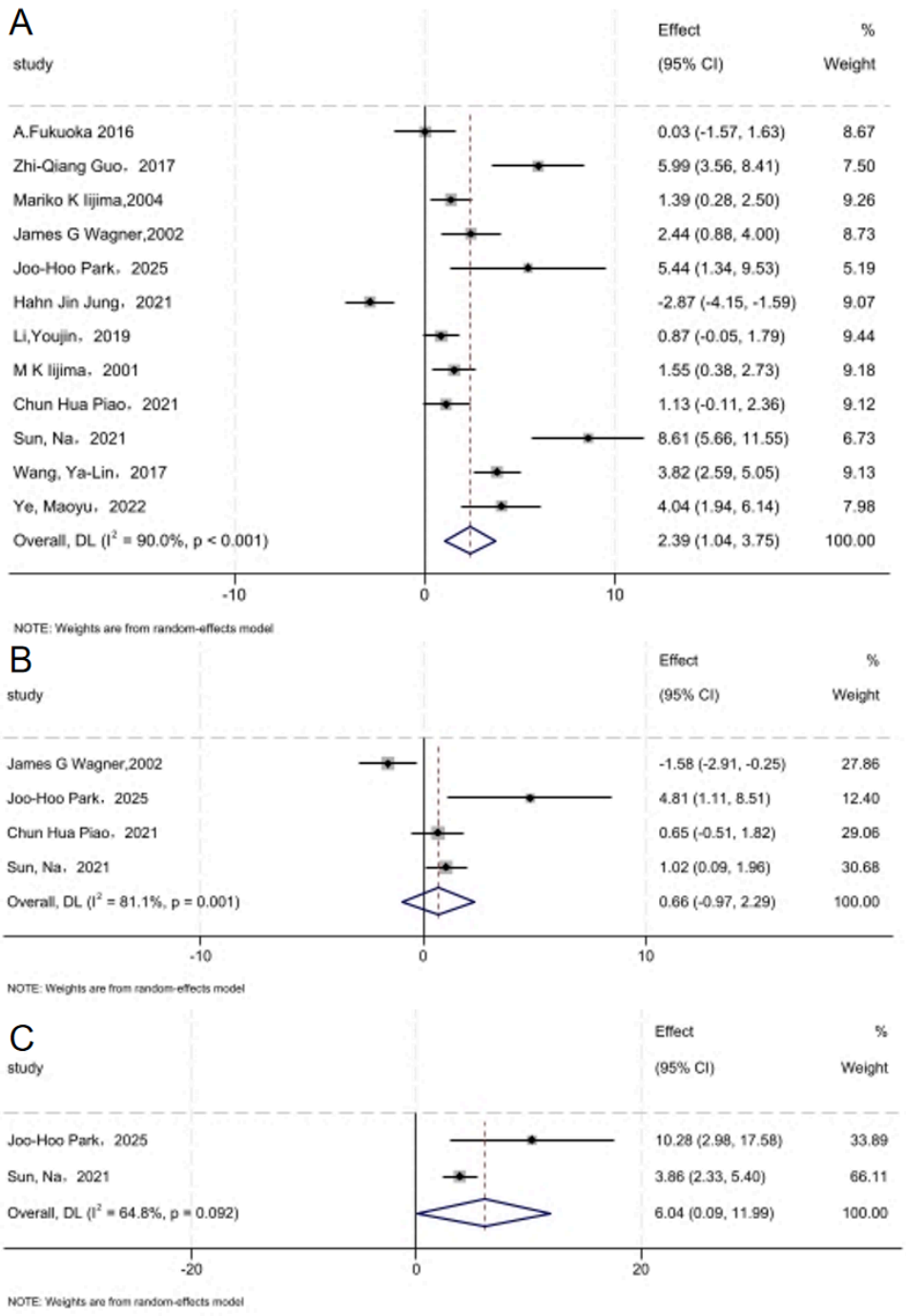


Figure 4

Forest plot of the effect of Air Pollution on (A) eosinophil counts, (B) neutrophil counts ,(C) lymphocyte counts.

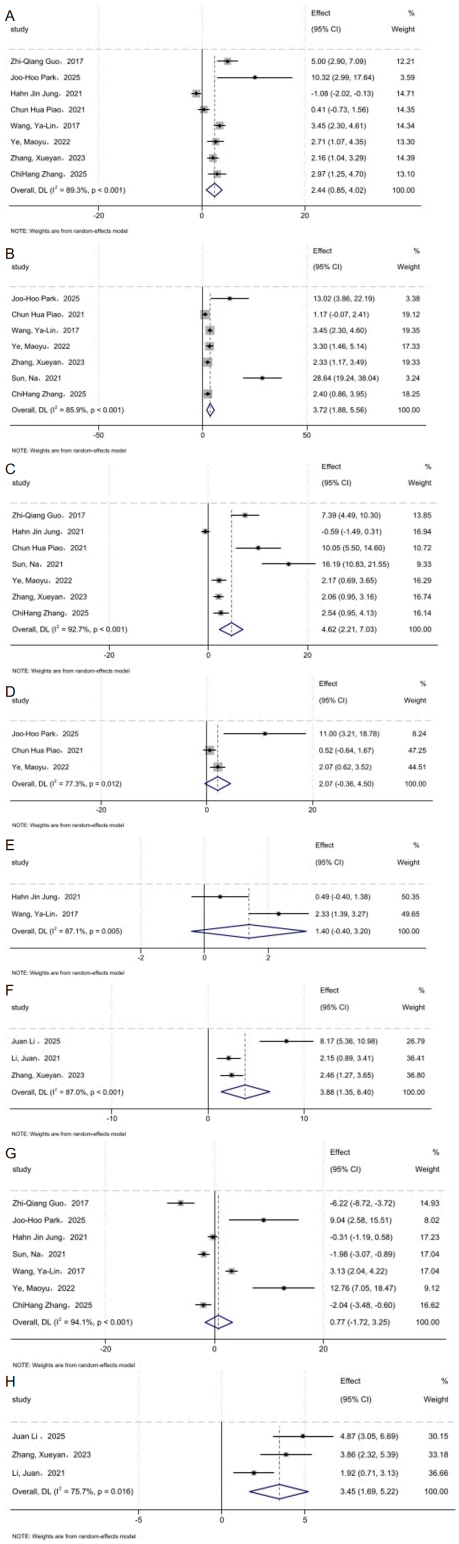


Figure 5

Forest plot of the effect of Air Pollution on (A) IL-4, (B) IL-5, (C) IL-13, (D)IL-17, (E)IL-33, (F)IL-1β, (G)IFN-γ, (H)NLRP3.

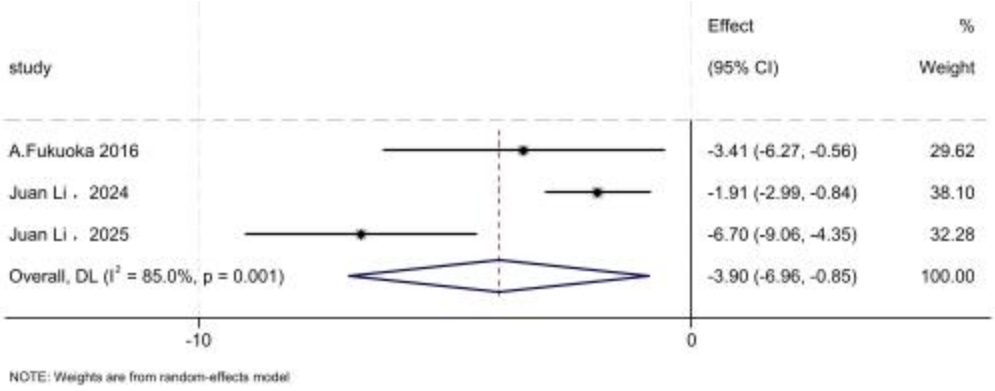


Figure 6

Forest plot of the effect of quercetin on ZO-1

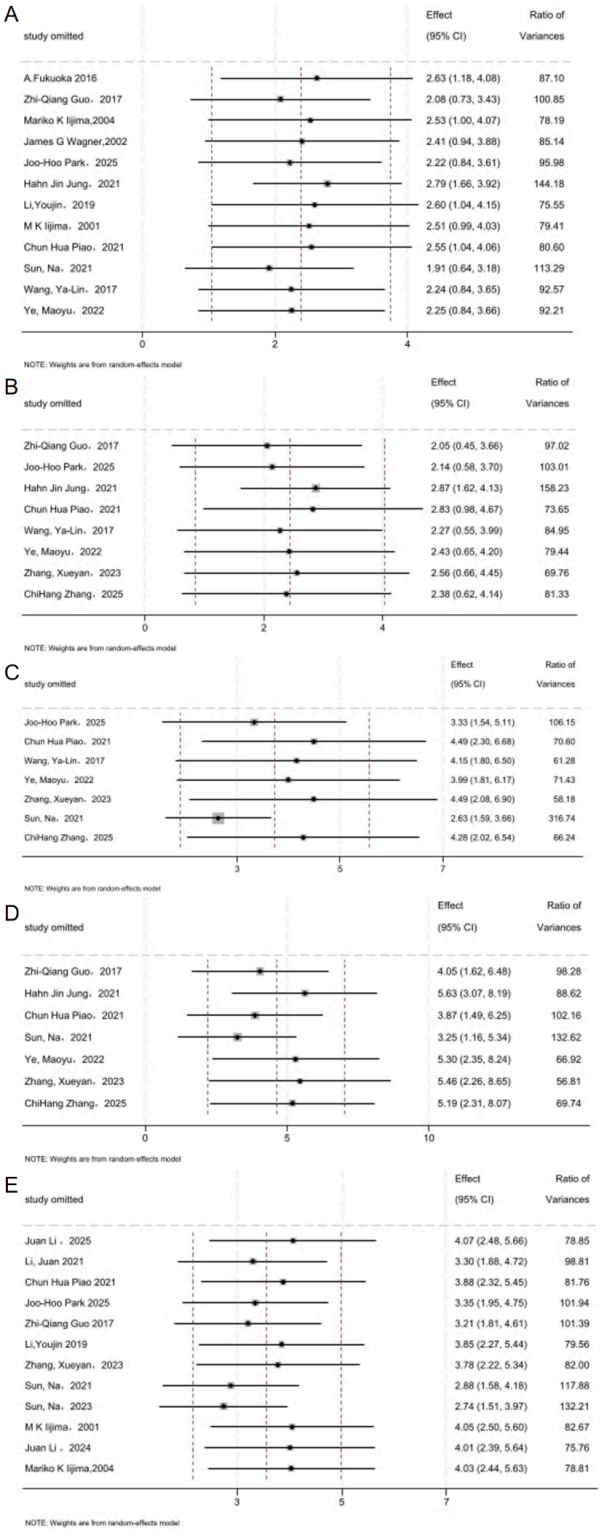


Figure 7

Forest plot of sensitivity analysis for the effect of Air Pollution on (A) eosinophil counts, (B) IL-4, (C)IL-5 , (D)IL-13, (E) ova-IgE.

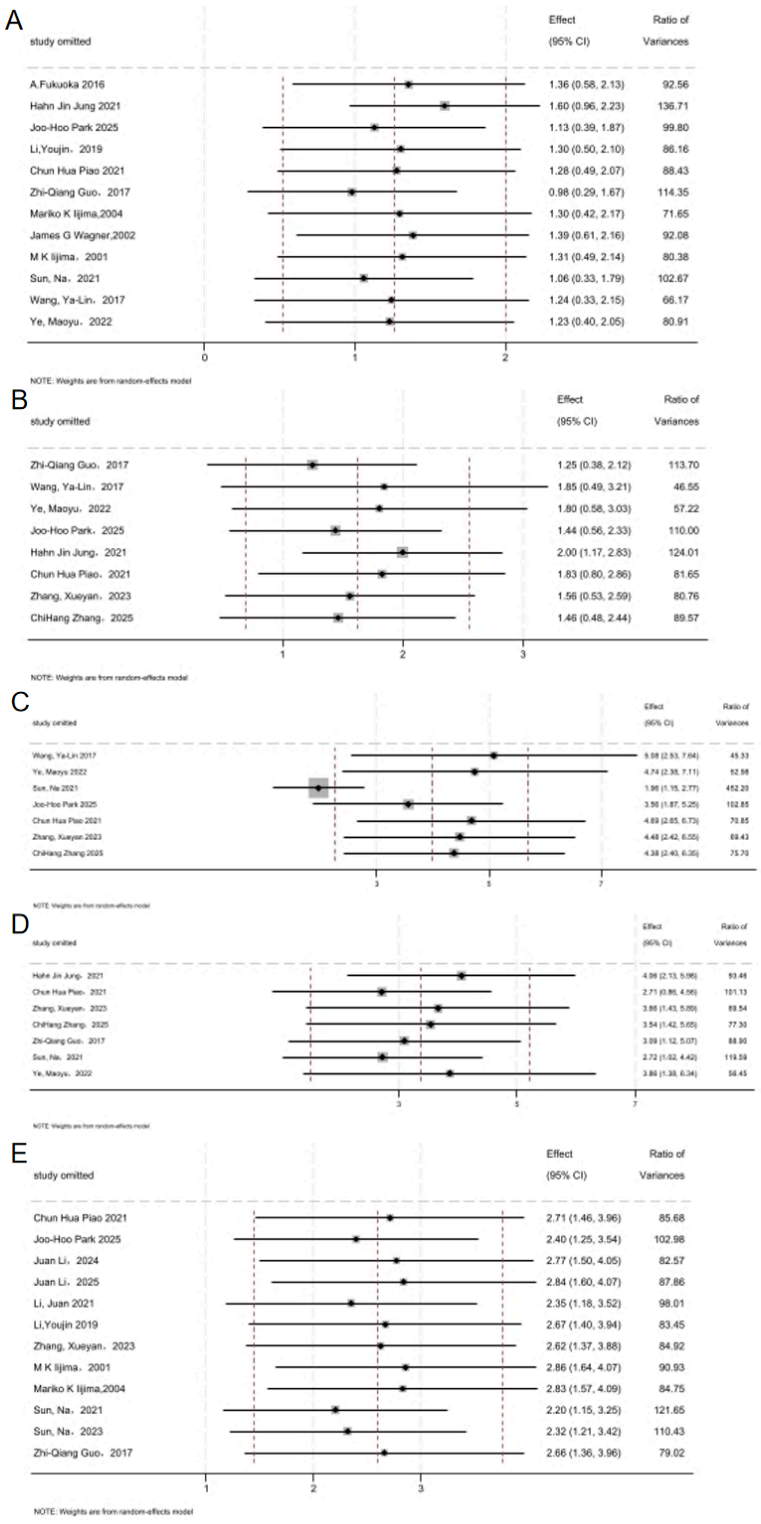


Figure 8

Post-hoc sensitivity analysis.

Supplementary Files

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- IFNPollutantxTimeInteractionSubgroupAnalysis.jpg
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- IL4Subgroupanalysisofexposureroutes.jpg
- IL5PollutantxTimeInteractionSubgroupAnalysis.jpg
- IL5Subgroupanalysisofanimalstrains.jpg
- IL5Subgroupanalysisofexposureduration.jpg
- IL5Subgroupanalysisofexposureroutes.jpg
- IL5Subgroupanalysisofpollutants.jpg
- NLRP3PollutantxTimeInteractionSubgroupAnalysis.jpg
- NLRP3Subgroupanalysisofanimalstrains.jpg
- NLRP3Subgroupanalysisofexposureduration.jpg

- NLRP3Subgroupanalysisofexposureroutes.jpg
- NLRP3Subgroupanalysisofpollutants.jpg
- SupplementaryFigure1.png
- SupplementaryFigure2.png
- SupplementaryFigure3.png
- SupplementaryFigure4.png
- SupplementaryFigure5.png
- SupplementaryTable1.docx
- SupplementaryTable10.docx
- SupplementaryTable2.docx
- SupplementaryTable3.docx
- SupplementaryTable4.docx
- SupplementaryTable5.docx
- SupplementaryTable6.docx
- SupplementaryTable7.docx
- SupplementaryTable8.docx
- SupplementaryTable9.docx
- lymPollutantxTimeInteractionSubgroupAnalysis.jpg
- lymSubgroupanalysisofanimalstrains.jpg
- lymSubgroupanalysisofpollutants.jpg
- lymSubgroupanalysisofexposureduration.jpg
- lymSubgroupanalysisofexposureroutes.jpg
- neuPollutantxTimeInteractionSubgroupAnalysis.jpg
- neuSubgroupanalysisofanimalstrains.jpg
- neuSubgroupanalysisofexposureduration.jpg
- neuSubgroupanalysisofexposureroutes.jpg
- neuSubgroupanalysisofpollutants.jpg
- ovaIgEPollutantxTimeInteractionSubgroupAnalysis.jpg
- ovaIgESubgroupanalysisofanimalstrains.jpg
- ovaIgESubgroupanalysisofexposureduration.jpg
- ovaIgESubgroupanalysisofexposureroutes.jpg
- ovaIgESubgroupanalysisofpollutants.jpg
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- renamed541bd.jpg

- renamed6e3ec.jpg
- renamedba0c4.jpg
- renamedd9b1e.jpg
- totalIgESubgroupanalysisofanimalstrains.jpg
- totalIgESubgroupanalysisofexposureroutes.jpg
- totalIgEPollutantxTimeInteractionSubgroupAnalysis.jpg
- totalIgESubgroupanalysisofexposureduration.jpg
- totalIgESubgroupanalysisofpollutants.jpg
- zo1PollutantxTimeInteractionSubgroupAnalysis.jpg
- zo1Subgroupanalysisofexposureduration.jpg
- zo1Subgroupanalysisofpollutants.jpg
- zo1Subgroupanalysisofexposureroutes.jpg