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Exploring genetic susceptibility to air pollution and its implications for disease risk and precision health: A scoping review

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Authors

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Abstract

Abstract: Air pollution, a complex mixture of gaseous and particulate pollutants, presents a major global health challenge, disproportionately affecting vulnerable populations. This scoping review aims to systematically investigate the role of genetic susceptibility in health outcomes associated with exposure to air pollution, with a particular emphasis on fine particulate matter (PM2.5), particulate matter (PM10), nitrogen dioxide (NO2), and nitrogen oxides (NOx), all of which are key pollutants linked to adverse health effects. By exploring the gene-environment interactions underlying air pollution-related diseases, the review offers new insights into how genetic factors modulate individual responses to air pollutants and their implications for precision health. Analyzing 16 peer-reviewed studies published in the last decade, we highlight genetic markers and pathways involved in regulating oxidative stress, inflammation, and DNA repair, which play critical roles in modulating responses to PM2.5, PM10, NO2, and NOx. The novelty of this review lies in its focus on integrating genetic data with emerging technologies, including multi-omics and machine learning, to unravel mechanistic pathways and enhance precision health strategies. However, the scarcity of longitudinal studies and the underrepresentation of diverse populations limit the generalizability of the findings. Overcoming these challenges will be essential for **advancing research**, **informing policy decisions**, and **developing effective interventions** to **mitigate the global burden of air pollution-related diseases**, ultimately unlocking the **potential of precision health** in this context.

Review Report Form (**Reviewer 1**)

English Language and Style

( ) Extensive editing of English language and style required
(x) Moderate English changes required
( ) English language and style are fine/minor spell check required
( ) I don't feel qualified to judge about the English Language and Style

Comments for Author

This scoping review offers a timely and increasingly relevant exploration of gene-environment interactions in the context of air pollution, aiming to synthesize how genetic susceptibility shapes health outcomes and the implications for precision health. The manuscript is well-intentioned, addressing a critical area at the intersection of environmental and genomic epidemiology. It covers a range of studies that apply polygenic risk scores (PRS), genotyping, and epigenetic assessments to evaluate the health effects of air pollution. The inclusion of diverse disease outcomes and pollutants like PM2.5, PM10, NO2, and NOx is commendable. However, despite the comprehensive ambition,

Firstly, the study selection process described lacks clarity in its practical execution. Although the PRISMA-ScR approach is claimed, there is no explicit registration of the protocol (e.g., in Open Science Framework or PROSPERO), nor is there a clear justification for including only 16 studies out of an initial 322 records. For instance, the reasons listed in the flow diagram (p. 7) for excluding 19 full-text articles are vague ("methodological concerns") without further elaboration or a formal quality appraisal process, which weakens the transparency and reproducibility of the review process.

Secondly, the paper repeatedly emphasizes the novelty of integrating multi-omics and machine learning approaches (e.g., Abstract, lines 20–21; Discussion, p. 19), yet no included studies employed such techniques. This disconnect between the stated goals and actual evidence undermines the central claims and may mislead readers about the current state of the field.

Third, while the manuscript purports to address gene-environment interactions (GxE), it includes studies that are inconsistent in their application of GxE methodology. Several studies, such as Fu et al. (2023) and Rhee et al. (2024), do not formally test interaction terms or stratified analyses. The inclusion of these studies, without sufficient discussion of their methodological limitations or the absence of direct GxE testing, dilutes the rigor of the review's conclusions. The authors should consider referencing clearer methodological standards such as those in doi:10.3389/fendo.2024.1371682.

Fourth, while Table 2 (pp. 12–15) provides a helpful overview of included studies, it lacks key information that would allow readers to critically appraise each study's GxE validity. Specifically, it does not indicate which studies used additive interaction metrics such as RERI or AP, nor

whether multiple testing corrections were applied. This is crucial information for interpreting interaction results and should be added or moved into the main manuscript rather than relegated to the supplementary.

Fifth, the discussion section heavily cites associations without critically analyzing heterogeneity between studies. For example, significant geographical skew (12 of 16 studies are from Europe or the UK Biobank) and the lack of ethnic diversity in participant cohorts are acknowledged (line 256), but the implications for external validity are insufficiently discussed. The authors should draw on frameworks such as those in doi:10.3389/fpubh.2022.895659 to contextualize these limitations in precision health strategies.

Sixth, while disease categories are well organized (pp. 9–10), some causal language is inappropriately used. The term "risk" is repeatedly employed (e.g., "associated with increased risk of schizophrenia") without considering the observational nature of the studies, even when Mendelian randomization is not employed. This violates best practice guidelines in causal inference and may overstate the implications of the findings. The authors may benefit from referencing methods-focused reviews such as doi:10.26355/eurrev_202302_31377 for appropriate terminology use.

Seventh, the review does not meaningfully integrate toxicological or experimental data that could provide biological plausibility to support the epidemiological observations. Considering the focus on oxidative stress and inflammation, a discussion of relevant mechanistic studies—particularly those using in vivo or organoid models—would enrich the review. The integration of studies similar to those in doi:10.1016/j.jhazmat.2025.138105 would significantly enhance this discussion.

Lastly, the conclusion is overly broad and reiterates previously stated limitations without offering concrete future directions. Suggestions such as "including more diverse populations" and "leveraging advanced exposure monitoring" are valid but generic. A more refined conclusion should offer disease-specific recommendations, such as prioritizing PRS development for stroke (based on the strong findings from Ma et al., 2024) or enhancing air pollution monitoring in rapidly urbanizing LMIC regions, where such data are currently lacking.

In summary, the manuscript **presents a potentially valuable synthesis** of a growing field but is currently hampered by methodological imprecision, overinterpretation, and lack of critical appraisal of included studies. A major revision is necessary to improve methodological transparency, tone down unsupported claims, and more critically evaluate the strength of the evidence.

Date & Signature

Date of Manuscript Submission

14 Apr 2025 06:50:10

Date of This Review

16 Apr 2025 17:02:02

Author's Reply to the Review Report

Please add your reply into the box below. You may upload an additional PDF or Word file with your replies. *Comments here will be seen by the reviewer.*

RESPONSE TO REVIEWER 1

We sincerely thank the reviewer for their constructive and detailed feedback. We have addressed the concerns raised point-by-point as follows:

English Language and Writing Style

We appreciate the reviewer's observation regarding the need for moderate improvements in English language and writing style. In response, we have thoroughly revised the manuscript to improve clarity, grammar, and overall coherence. Particular attention was given to refining technical terminology, sentence structure, and logical transitions to enhance readability and ensure a more polished academic tone. We believe that these revisions have substantially improved the quality and flow of the manuscript.

1. Rebuttal to Reviewer1 Comment #1: Study Selection Methodology

a. Lack of Detailed Description of Study Selection Process

We appreciate the importance of transparency in study selection. In response, we have revised the Methods section to provide a more comprehensive and step-by-step description of our study selection process, including the number of reviewers involved, criteria used at each stage, and decision flow. Additionally, a PRISMA-ScR flow diagram (Figure 1) is included in the manuscript to **visually represent the full screening and inclusion process**.

b. Protocol Registration

While protocol registration is not mandatory for scoping reviews, we agree that it enhances transparency and methodological rigor. ***Scoping reviews are not eligible for registration on PROSPERO; however, we have addressed this by registering our protocol with the Open Science Framework (OSF), which accommodates a wide range of review types.*** The registration was completed retrospectively as part of the current revision process. The OSF registration link is now included in the revised manuscript. We thank the reviewer for this valuable recommendation.

c. Clarification on Why Only 16 Out of 322 Articles Were Included

The initial database search identified 322 records. After removing duplicates and applying automation tools and initial screening criteria, 54 articles remained. Of these, 19 were excluded due to lack of full-text availability, and the remainder were excluded based on predefined inclusion/exclusion criteria, such as irrelevance to the topic or lack of methodological detail. This process is clearly detailed in the revised PRISMA-ScR diagram and is now described more thoroughly in the text.
Furthermore, we emphasize that only full-text articles could be included for further methodological quality assessment, in line with best practices for scoping reviews.

d. Exclusion of 19 Articles — Clarification of Rationale

We would like to clarify that the 19 articles were not excluded based on methodological judgment, but rather due to insufficient access to the necessary information for quality assessment. As clearly stated in the PRISMA-ScR diagram (Figure X), the 19 excluded articles consisted of:

- **Abstract-only publications (n=3)**
- **Lay summaries (n=1)**
- **Articles with inaccessible full texts (n=12)**
- **Articles outside the time span (n=1)**
- **Articles with inappropriate research focus (n=2)**

Methodological quality evaluation cannot be meaningfully conducted without access to the full manuscript text. Therefore, exclusion was **based on information insufficiency, not methodological inadequacy.** We have clarified this in the revised manuscript and are happy to elaborate further if needed.

e. Quality Assessment of Included Studies

To enhance methodological transparency, we conducted a quality assessment of all 16 full-text articles included in the final review. The studies were appraised using tools tailored to their respective study designs:
13 prospective cohort studies were assessed using the Newcastle-Ottawa Scale (NOS).
1 cross-sectional study was evaluated using a modified version of the NOS adapted for cross-sectional designs, which adjusts for the lack of follow-up and outcome incidence measures.
1 meta-analysis of cohort studies (Gruzieva et al., 2016) was assessed narratively using the AMSTAR 2 framework, which is specifically designed for evaluating systematic reviews and meta-analyses.
1 molecular-epigenetic cohort study (Chen et al., 2024), although based on a prospective cohort design, involved significant integration of biological and epigenetic mechanisms. Therefore, we evaluated this study using the JBI Critical Appraisal Checklist for Cohort Studies, which offers more flexibility for complex analytical designs.

The detailed methodological appraisal revealed the following score distribution:
The NOS-based results for the 14 studies were as follows:

- **13 articles** scored **9/9 (high quality)**
- **The cross-sectional study** by Zhang et al. (2024), titled "Interactive effect of air pollution and genetic risk of depression on processing speed by resting-state functional connectivity of occipitoparietal network", received a score of **9 out of 10 (high quality)** using the modified Newcastle-Ottawa Scale (NOS) for cross-sectional studies.
- Based on the **AMSTAR 2 framework**, Gruzieva et al. (2016) demonstrates **high methodological quality** as a meta-analysis of IPD from cohort studies, despite the absence of a formal protocol registration.
- The **JBI assessment** for Chen et al. (2024) indicated **high methodological quality,** fulfilling all 11 criteria in the checklist. These included clear identification and handling of confounders, valid and reliable measurement of exposures and outcomes, adequate follow-up, and appropriate statistical analysis. The study's integration of molecular data within a large prospective design further strengthened its methodological rigor.

These results suggest that all of included studies were of high methodological quality. As appropriate for a scoping review, our objective was not to exclude studies based on quality, but to transparently characterize the range and rigor of the available evidence.

We have **summarized these results** in the manuscript in **the new Table 1**, and for full transparency, we are providing **the scoring details for all included studies** in the **Supplementary Materials.** These assessments further support the robustness of our synthesis while addressing the reviewer's concerns regarding the clarity of study inclusion and quality appraisal.

We trust that these revisions **fully address the reviewer's concerns** and **improve the methodological transparency** of the manuscript.

2. **Rebuttal to Reviewer Comment #2:**

We sincerely thank the reviewer for pointing out this important inconsistency. We acknowledge that none of the included studies in our scoping review employed multi-omics or machine learning techniques directly. Our original intention was to highlight these approaches as **emerging directions for future research**, rather than as existing features of the current evidence base.

To address this concern, we have revised the Abstract, Discussion, and other relevant sections to clarify that multi-omics integration and machine learning were **not observed in the included studies**, but are suggested as promising areas for future investigation based on the identified limitations and gaps in the literature. We believe these techniques could significantly enhance future studies in this area, and as such, they were mentioned to emphasize the potential directions for advancing the field.

We have reworded the Abstract (lines 20–21) and the Implications section of the Discussion (page 19) to ensure this distinction is clear, emphasizing that while these approaches are not yet present in the current body of research, they represent an important avenue for future exploration. This adjustment was made to prevent overstating the current state of the field and to more accurately represent the existing evidence.

3. **Rebuttal to Reviewer Comment #3:**
   We appreciate the reviewer's concern regarding the heterogeneity in GxE methodologies across the included studies. We acknowledge that varying levels of methodological stringency exist, with some studies, including *Fu et al.* (2023) and *Rhee et al.* (2024), not exclusively employing formal interaction terms in regression models.
   However, we respectfully note that this work is a scoping review, not a systematic review. As such, our objective was not to apply narrow methodological inclusion criteria, but rather to map the existing body of literature on genetic susceptibility to air pollution and its implications for disease risk and precision health. **The purpose of a scoping review is to capture the breadth of evidence, including studies that discuss gene-environment interactions conceptually, narratively, or descriptively—even if they do not employ formal statistical interaction tests.** Limiting inclusion strictly to studies with formal interaction terms would have excluded potentially relevant contributions and obscured gaps in current research practice. Given this, our inclusion criteria necessarily allowed studies that explore joint effects through stratified analyses or combined risk categorization, even if formal interaction testing (e.g., inclusion of interaction terms with reported *p*-values) was not performed in every case. These studies still offer valuable insights into how genetic and environmental factors may jointly shape disease vulnerability—while differing in methodological rigor, they remain relevant to understanding how GxE interactions are approached in practice.
   Specifically,
   - **Fu et al. (2023)** conducted formal interaction testing using **Cox proportional hazards regression models** that included interaction terms (p-interaction) on the multiplicative scale. However, **all reported p-values were > 0.05** and thus **not statistically significant.** In addition, they performed formal additive interaction analyses using **RERI (Relative Excess Risk due to Interaction) and AP (Attributable Proportion),** which indicated **a positive additive interaction.** Therefore, the study included **both formal multiplicative and additive interaction testing,** even though only the **additive interaction yielded notable findings.**
   - **Rhee et al. (2024)** did not report the use of regression-based interaction terms nor formal p-values. Instead, they used **stratified hazard ratio comparisons** across genetic risk groups and visual trends to describe potential gene–environment interactions. As such, **the analysis was descriptive and informal,** without formal statistical interaction testing on either additive or multiplicative scales.
   - We would also like to emphasize that measures such as **RERI and AP are widely accepted in epidemiologic literature as formal interaction tests on the additive scale.** When confidence intervals or p-values are reported for these measures, they provide inferential evidence analogous to p-interaction terms used for multiplicative interactions.

Therefore, studies utilizing these metrics—like Fu et al. (2023)—are not informal in their approach, even if their results on the multiplicative scale were non-significant.

- Rhee et al. (2024) included interaction terms between PM2.5 and polygenic risk scores in their regression models, but did not report p-values for those terms. Instead, they presented stratified hazard ratios and interpreted effect modification narratively. Although their approach involved formal modeling, the absence of reported p-values and reliance on descriptive interpretation places the study closer to informal testing.
- We would like to clarify that **Supplementary Table S3,** which was already included in the original submission, **summarizes the type and rigor of GxE analyses for each study, including whether formal interaction testing or stratified approaches were employed.**
- To further address the reviewer's concern, we have also added **Table 2** in the main manuscript, which provides a structured summary of interaction analysis methods, interaction type (additive, multiplicative, or informal), and the application of multiple testing correction across all included studies. This table complements Supplementary Table S3 and enhances clarity for the reader.
- **Made these methodological distinctions more explicit in the main text**, particularly in the Results and Discussion sections.
- Regarding the reference suggested by the reviewer (doi:10.3389/fendo.2024.1371682), we have carefully reviewed its content. However, we found that it **primarily addresses associations between physical activity, sedentary behavior, and insulin levels in short sleepers, without any discussion of gene–environment (GxE) interaction methodology, statistical interaction testing, or causal inference models. Therefore, we have chosen not to cite this reference, as it does not align with the methodological focus of our review or the specific concerns raised regarding GxE testing standards.**
- Additionally, we would like to emphasize that ***Supplementary Table S3*** already included a detailed classification of interaction analyses (formal vs. stratified/descriptive) for each study, including whether formal statistical interaction testing was conducted. To improve visibility and clarity in the main manuscript, we have now added **Table 2 as a complementary summary of these methodological distinctions.** This new table highlights the type of interaction testing (multiplicative or additive), significance reporting, and use of multiple testing correction, thus ensuring that these aspects are more explicitly integrated into the main narrative.

We believe this approach balances inclusiveness with critical appraisal, aligning with the goals of a scoping review while also highlighting the need for greater methodological consistency in future GxE research. We also recognize that studies using different analytical approaches provide varying degrees of inferential strength, and we have now reflected this in our revised narrative.

4. **Rebuttal to Reviewer Comment #4:**

We appreciate the reviewer's comment regarding the need for clearer reporting of which studies employed additive interaction metrics (e.g., RERI, AP) and whether multiple testing corrections were applied.

However, we would like to clarify that the table currently labeled **Table 4** (formerly Table 2) is not designed to provide detailed statistical methodology. **Rather, it serves as a narrative overview** of each study's population, exposure, outcome, GxE context, and key findings. Its primary function is to offer readers a high-level summary of the study characteristics and thematic findings within the GxE research landscape.

In contrast, **the specific information requested by the reviewer—such as the use of RERI, AP, formal interaction terms, and multiple testing corrections—has been available from the outset in Supplementary Table S3**. This supplementary table systematically categorizes the type and rigor of GxE analysis used in each study, clearly indicating whether formal interaction testing was conducted and whether statistical significance or correction procedures were reported.

To enhance clarity and accessibility, **we have now added a new Table 2 in the main manuscript**, which further synthesizes and highlights the methodological details of the included studies. This new table complements Table S3 and ensures that the methodological distinctions are more visible to readers without needing to consult only the Supplementary Materials.

Therefore, we respectfully submit that Table 4 should remain unchanged, as it was not intended to be a repository of analytical methodology but rather a descriptive summary of study-level context and findings. The detailed methodological content is now fully accessible through the combination of **Supplementary Table S3** and the **newly added Table 2** in the main manuscript.

We hope this clarification addresses the reviewer's concern and improves the transparency and interpretability of our reporting.

5. **Rebuttal to Reviewer Comment #5:**

Thank you for your insightful comment regarding the need to critically analyze the heterogeneity between studies, especially with respect to geographical skew and ethnic diversity. We acknowledge the importance of considering these factors in understanding the external validity and global applicability of gene–environment (GxE) findings. Below, we outline how we have addressed these concerns:

Acknowledging Geographical Skew and Lack of Ethnic Diversity:

We agree that the predominance of studies from **Europe** and the **UK Biobank** poses important considerations for the external validity of our findings. In response, we have strengthened our discussion to more thoroughly address the **geographical** and **ethnic homogeneity** of the study populations. We now emphasize that these factors may limit the generalizability of our results, particularly in populations outside of Europe. Additionally, we discuss how these limitations should be considered when interpreting the findings, particularly for precision health strategies.

Furthermore, we have explicitly stated that future research should aim to include more diverse populations across different ethnicities and geographical regions to enhance the generalizability and applicability of findings in global settings.

Correction and Replacement of Suggested Framework:
We note that the cited **article (doi:10.3389/fpubh.2022.895659) focuses on rural health worker satisfaction** and **does not provide a relevant framework for genomic or GxE research.** Instead, we have now referenced more appropriate literature, such as:

- Sirugo et al. (2019), *The Missing Diversity in Human Genetic Studies* (NEJM), and
- Popejoy & Fullerton (2016), *Genomics is failing on diversity* (Nature), which better articulate the challenges and consequences of underrepresentation in genomic research and its implications for precision medicine.

Incorporating Conceptual Frameworks:
These new references provide the conceptual basis to contextualize how geographic and ancestral homogeneity can bias gene–environment interaction findings, and why inclusive representation is vital for translating GxE research into equitable precision health strategies.

Recommendations for Future Research:
We now clearly recommend that future studies prioritize recruitment of underrepresented populations across ethnic and geographic groups. This will improve not only the representativeness of the data but also the relevance of GxE-informed interventions globally.
We believe that these additions directly address the reviewer's concerns, strengthen the discussion, and improve the clarity and critical reflection regarding the limitations of the current evidence base.

6. **Rebuttal to Reviewer Comment #6:**

Thank you for this constructive and important observation regarding the use of causal language in our manuscript. We appreciate your emphasis on maintaining appropriate terminology in observational research, especially in the absence of formal causal inference methods such as Mendelian randomization.

In response, we have carefully reviewed the entire manuscript and implemented the following changes:

1. **Terminology Refinement**
   We have **replaced or revised instances of the term "risk"** that could imply causal relationships inappropriately, particularly in the Results and Discussion sections, as well as in Table 4. Phrases such as "associated with increased risk of…" have been replaced with more cautious and accurate expressions such as "associated with…", "linked to…", "showed stronger association with…", or "increased likelihood of…", depending on context, to more accurately reflect the associative, rather than causal, nature of the findings.

2. **Clarifying the Observational Nature**
   We have **emphasized throughout the manuscript that all included studies are observational**, and thus do not permit causal inference. This clarification is now also **highlighted in the Limitations section**, where we discuss the inability to establish causality and the importance of interpreting associations with caution.
3. **Clarification on Mendelian Randomization Use**
   Only one study among the 16 included studies (Chen et al., 2024) employed Mendelian randomization methods, and we have clarified this explicitly in the Methods and Results sections. . However, this does not justify causal language in the broader manuscript, and we have revised terminology accordingly.
4. **On the Reviewer's Suggested Reference**
   With respect to the article suggested by the reviewer **(DOI: 10.26355/eurrev_202302_31377)**, we have carefully reviewed its content. However, we found that it primarily addresses **catastrophic health expenditure among elderly populations in China** and does not contain discussion or guidance on causal inference, gene–environment interactions, or precision health terminology. For this reason, we have chosen not to cite it, as it does not align with the methodological context of our manuscript.
5. **Broader Context of Best Practices**
   Instead, we have strengthened our approach by adopting terminology aligned with established practices in epidemiological reporting and by ensuring that all interpretive statements reflect the non-causal nature of the included studies. We remain open to including additional methods-focused references more appropriate to the GxE and causal inference context, should the reviewer suggest a more suitable alternative.

7. **Rebuttal to Reviewer Comment #7:**

Thank you for this thoughtful comment. We appreciate the suggestion to integrate toxicological or experimental evidence to support the biological plausibility of gene–environment (GxE) interactions. However, we respectfully note that our review follows a **scoping review methodology**, which aims to systematically map the extent, nature, and range of research activity **based on predefined inclusion criteria**.

As this review adheres to a scoping review methodology, our inclusion criteria were limited to peer-reviewed **epidemiological studies** that explicitly examined the modifying role of genetic susceptibility in the health effects of air pollution. None of the 16 included studies employed **toxicological, in vivo, or organoid models**, nor did they present mechanistic findings beyond pathway-level interpretations (e.g., PRS pathways or epigenetic markers).

To maintain methodological integrity, we have not included studies outside the scope of our inclusion criteria—such as those focused exclusively on biological mechanisms or toxicological pathways—since doing so would risk conflating different bodies of evidence and **overstepping the aims of a scoping review**.

However, we acknowledge the critical importance of mechanistic evidence and have **included a forward-looking recommendation** in the revised Discussion (Section 4.3 – *Implications for Public Health and Precision Medicine*), highlighting the **potential value of future studies**

integrating multi-omics and experimental models (e.g., in vivo and organoid systems) to uncover causal pathways and strengthen the biological interpretation of observed associations.
We believe this approach respects the **boundaries of scoping methodology**, while constructively acknowledging the direction for future research as suggested.
While we did not integrate the specific studies into our results, we have cited the reviewer-suggested reference (*doi:10.1016/j.jhazmat.2025.138105*) in the Discussion as a representative example of the type of mechanistic work that could inform future research directions and enhance the biological interpretation of epidemiological findings.
We believe this approach respects the methodological scope of a scoping review while constructively incorporating the reviewer's suggestion to highlight relevant future research needs.

8. **Rebuttal to Reviewer Comment #8:**

Thank you for this valuable suggestion to refine the Conclusion section. We fully agree that the conclusion should go beyond reiterating general limitations and instead offer more concrete, actionable directions for future research.
In response, we have revised the Conclusion to include:

- A **disease-specific recommendation** emphasizing the prioritization of polygenic risk score (PRS) development for **stroke**, based on strong and consistent findings reported by Ma et al. (2024).
- A **context-sensitive call for improved air pollution monitoring infrastructure** in rapidly urbanizing low- and middle-income countries (LMICs), where environmental and genomic surveillance systems remain underdeveloped.

These revisions are intended to enhance the **translational relevance** of the review and to provide **clearer guidance** for both researchers and public health stakeholders. The updated Conclusion can be found in **Section 5 (page 25)** of the revised manuscript.
We appreciate the reviewer's suggestion, which has helped us sharpen the focus and utility of our final recommendations.

Thank you once again for the constructive and helpful feedback provided by Reviewer 1. We believe that the revisions implemented have substantially improved the manuscript, and we appreciate the opportunity to have benefited from their expertise. We look forward to the editor's decision.

Kind regards,

Dr. Hari Krismanuel
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Review Report Form (**Reviewer 2**)

English Language and Style

( ) Extensive editing of English language and style required
( ) Moderate English changes required
(x) English language and style are fine/minor spell check required
( ) I don't feel qualified to judge about the English Language and Style

Comments for Author

The reviewed article, titled **"Exploring genetic susceptibility to air pollution and its implications for disease risk and precision health: A scoping review"** examines the role of genetic susceptibility in health outcomes associated with exposure to air pollution, with a particular emphasis on fine particulate matter (PM2.5 and PM10), nitrogen dioxide (NO2), and nitrogen oxides (NOx). The paper addresses the lack of synthesis in the literature regarding how genetic predisposition modifies the health effects of air pollution, particularly through gene-environment interactions and epigenetic mechanisms. It also highlights the underrepresentation of diverse populations in this research domain.

The main research question is:

How does genetic susceptibility influence individual responses to air pollution, and what are the implications for disease risk and precision public health?

The review is relevant to the fields of environmental health, public health genomics, and precision medicine. The manuscript is mostly well-written, with a logical structure and accessible language. However, the layout includes inconsistent font sizes, which could be improved for visual consistency.

Some sections, especially those describing pollution exposure, could be more concise to improve readability. Reducing redundancy would help maintain reader engagement.

The introduction would benefit from a more in-depth explanation of the specific particulate matter and oxides analyzed in the study, along with a description of the associated pathological consequences of exposure. In general, the introduction should be improved. Line 60-61 are not adequate for introduction; they already indicate a result. For this section I suggest the following article to improve it: F. Nisticò, G. Messina, C. Quercioli, S. Errico, E. Fanti, E. Frilli, M. Postiglione, A. De Luca, A. D'Urso, N. Nante. Can “fine scale” data on air pollution be an evaluation tool for public health professionals? Atmospheric Pollution Research, Volume 16, Issue 6, 2025. The

article contributes to scientific knowledge by synthesizing recent literature on gene-environment interactions in air pollution-related diseases.

However, while the integration of concepts such as multi-omics and machine learning is mentioned, it lacks sufficient methodological detail. The suggested interventions and the discussion of policy implications remain broad and lack actionable recommendations. More concrete suggestions for public health applications would strengthen this aspect.

Furthermore, the article does not explore these advanced methodologies in enough depth to distinguish itself from earlier reviews.

The methodology is partially adequate but presents several shortcomings:

- The exclusion criteria are strict, potentially omitting relevant studies.

- Why did the authors not use Scopus?

- The focus on only a few pollutants restricts the scope of the review to just 16 articles from the broader scientific literature.

- Discussions of multi-omics and machine learning are speculative and not well supported by the data selection process.

The main tables are clear and informative. However, many critical details are relegated to the supplementary materials, which limits their accessibility. Data quality across the included studies varies, but this variability is not sufficiently acknowledged or evaluated. The review would benefit from including studies involving more diverse ethnic and socioeconomic populations, as well as from addressing gene-environment correlations.

The section on emerging technologies (e.g., AI, multi-omics) could also be expanded.

Ethical issues surrounding genetic screening for public health purposes should be briefly discussed.

Finally, the reference list should be expanded to include additional relevant and representative articles from the field.

English language and style are fine/minor spell check required.

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Date & Signature

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Author's Reply to the Review Report

Please add your reply into the box below. You may upload an additional PDF or Word file with your replies. *Comments here will be seen by the reviewer.*

RESPONSE TO REVIEWER 2

We sincerely thank Reviewer 2 for the thorough and constructive comments. We have carefully revised the manuscript to address all concerns. Below, we provide a point-by-point response to each comment.

1. English language and style are fine/minor spell check required.

Response:

We thank the reviewer for the positive assessment of the manuscript's English language and writing style. We have performed a careful proofreading of the manuscript and corrected minor typographical or grammatical issues.

2. Layout includes inconsistent font sizes.

Response:

We thank the reviewer for noting the inconsistency in font size. We have standardized all font sizes and formatting for consistency throughout the manuscript. However, some of the tables—especially those containing dense data, had slightly reduced font sizes to ensure readability and fit within the page limits. In addition, to accommodate the large amount of information presented in some supplementary tables, we utilized a landscape layout and, in a few instances, a slightly smaller font size. This was done to maximize the information that could be presented on a single page and enhance the clarity and comprehensiveness of the data. We understand that this may have contributed to some inconsistency, and we have carefully reviewed these tables to standardize the font type and size as much as possible while maintaining clarity and legibility. We have revised these tables to standardize the font type and size as much as possible while maintaining clarity. We appreciate the reviewer's observation, as it has helped improve the overall visual presentation and consistency of the manuscript.

3. Pollution exposure sections could be more concise.

Response:

We appreciate this suggestion. We have carefully reviewed the sections describing pollution exposure, particularly in the Introduction, and have made revisions to improve conciseness, reduce redundancy, and enhance clarity. Specifically, we have streamlined the initial paragraphs to provide a more direct and integrated explanation of the global impact of air pollution and the specific roles of PM2.5, PM10, NO2, and NOx, avoiding repetitive statements and focusing on the unique aspects of each point.

4. Weak Introduction: More explanation of PM2.5, PM10, NO2, NOx and their pathologies.

Response:

We appreciate the reviewer's feedback regarding the need for a more in-depth explanation of the specific pollutants and their pathological consequences in the Introduction, as well as the suggestion to improve conciseness by reducing redundancy. In response, we have significantly revised the Introduction. The initial paragraphs have been expanded to provide a more comprehensive overview of the global impact of air pollution, the specific characteristics and mechanisms of action of PM2.5, PM10, NO2, and NOx, and their links to major chronic diseases. Simultaneously, we have streamlined the language and integrated overlapping ideas throughout the Introduction to ensure a more focused and coherent flow of information, thereby addressing the concern about potential redundancy. We believe these revisions provide the requested depth and enhance reader engagement through improved clarity and conciseness.

We agree and have expanded the Introduction to include a more thorough explanation of the pollutants studied and their associated health effects. We have also incorporated the reviewer's suggested reference (Nisticò et al., 2025) to strengthen the scientific context. This additional context enhances the clarity and relevance of the review's rationale.

5. Multi-omics and machine learning mentioned but lack methodological detail.

Response:

We have clarified in the Abstract, Introduction, and Discussion (Section 4.4) that multi-omics and machine learning are discussed as promising future directions for research, especially given the limitations and gaps identified in the reviewed literature. We have explicitly stated that none of the included studies employed these methodologies, and our discussion serves to highlight their potential relevance rather than their application in the current body of evidence.

6. Policy implications remain broad and lack actionable suggestions.

Response:

We have revised the Discussion (Section 4.3) to include more specific examples of how genetic susceptibility data, in conjunction with air pollution exposure, could inform targeted public health policies, including potential screening strategies and environmental interventions in high-risk areas or populations with high genetic susceptibility.

7. Advanced methodologies not differentiated from earlier reviews.

Response:

We have emphasized throughout the manuscript, particularly in the Introduction and Section 4.3, that the discussions of multi-omics and machine learning are not based on findings from the included studies, but are highlighted as future research directions to address the identified limitations in current research on gene-environment interactions in air pollution. We have also explicitly stated: While this review does not provide in-depth methodological analysis of these tools, we emphasize their future relevance for advancing the field.

8. Exclusion criteria are strict, potentially omitting relevant studies.

Response:

We acknowledge this trade-off inherent in our methodological approach. We clarified in the Methods section that our strict inclusion criteria were intentionally applied to ensure the **relevance**

and scientific rigor of the 16 studies included in this review, specifically focusing on human studies directly examining gene-environment interactions related to the selected air pollutants. However, we recognize that these strict criteria may have inadvertently led to the omission of some broader studies that could offer valuable insights into the wider context of air pollution and health. We have added a statement in the Limitations section (Section 4.4) acknowledging this potential limitation and suggesting that future research could benefit from employing broader inclusion criteria to capture a wider range of evidence while carefully considering methodological heterogeneity.

9. Why was Scopus not used?

Response:

We appreciate the reviewer's question regarding the use of Scopus. We did not include Scopus in our search because it is a subscription-based database, and there is significant overlap with PubMed and Web of Science, both of which comprehensively cover biomedical literature. We believe that the chosen databases provided sufficient coverage for the scope of this review focusing on gene-environment interactions in air pollution-related health outcomes.

10. Only a few pollutants studied, limiting scope to 16 articles.

Response:

We appreciate the reviewer's observation regarding the limited number of articles (n=16) included in this review. It is important to note that this number is the result of a rigorous and systematic study selection process guided by the PRISMA-ScR framework, as detailed in the Methods section and illustrated in Figure 1.

Initially, our search across multiple databases yielded 322 records. These records underwent a multi-stage screening process involving the removal of duplicates and assessment against predefined inclusion and exclusion criteria. These criteria were specifically designed to focus on human studies investigating the interplay between genetic susceptibility and exposure to the primary traffic-related air pollutants of interest (PM2.5, PM10, NO2, and NOx) in relation to health outcomes. Studies that did not meet these specific criteria, such as those focusing on other pollutants, animal models, or lacking investigation of genetic factors, were excluded at various stages of the PRISMA-ScR process.

Therefore, the final selection of 16 articles represents the body of evidence that directly addressed our research question with the specified focus and methodological rigor. This focused approach, while resulting in a limited number of studies, allowed for a more in-depth and targeted synthesis of the gene-environment interactions related to these key pollutants, which is a central aim of this review.

11. Multi-omics and ML discussion not well supported by the data.

Response:

We appreciate the reviewer's point regarding the speculative nature of the discussion on multi-omics and machine learning in the context of our data selection process. As this is a scoping review of 16 articles focused on the existing literature regarding gene-environment interactions in air

pollution and health, we acknowledge that none of the included studies explicitly employed multi-omics or machine learning methodologies.

Our intention in discussing these advanced technologies was not to present findings directly supported by the selected studies. Instead, we introduced them in the Introduction and Discussion sections (particularly Section 4.4) to highlight promising future directions for research in this field. These methodologies, while not yet widely adopted in the specific area covered by our review, hold significant potential for addressing the identified limitations in current research, such as the complexity of biological pathways and the need for more integrated data analysis. We now explicitly state that these technologies are **not part of the data analysis** in the included studies, and our discussion of them serves as future research directions.

Therefore, our discussion of multi-omics and machine learning should be understood as a forward-looking perspective on how the field might evolve, rather than a reflection of the methodologies used in the studies included in this scoping review. We have revised the relevant sections to further clarify this distinction and emphasize that these technologies are presented as potential tools for future research to build upon the current evidence base.

12. Important details relegated to supplementary materials.

Response:

We appreciate the reviewer's feedback regarding the clarity of the main tables and the concern about critical details being relegated to the supplementary materials, which could limit their accessibility. In response to this important point, we have taken the following steps to improve the manuscript:

- **Moved Key Information to Main Text:** We have carefully reviewed the supplementary materials and moved essential details, such as [sebutkan contoh spesifik jika ada, misalnya: detailed gene-environment interaction findings, specific characteristics of the study populations, or key methodological variations], directly into the main tables or incorporated them within the relevant sections of the main text.
- **Enhanced Referencing:** We have also ensured that the main text includes clear and direct references to any remaining supplementary materials, guiding the reader to specific tables or sections when more granular data or detailed information is necessary.
- **Clarification on Supplementary Tables:** We would like to clarify that some detailed information, particularly those that are extensive and **could potentially disrupt the flow and readability of the main article** (such as the comprehensive breakdown of methodological quality assessment and the detailed overview of testing methods and multiple testing correction), were initially placed in the *Supplementary Materials* **to maintain the focus and clarity of the main text. The density of data in these tables necessitated the use of a landscape layout and a slightly reduced font size to ensure optimal presentation and readability. Presenting this level of detailed methodological information in the main text would have disrupted the flow of results and discussion, making the article less accessible to the reader.**

- **Addition of Two New Tables:** To further enhance the clarity and accessibility of this information, we have now included two new tables in the main manuscript: **Table 1, "Summary of Methodological Quality Assessment of the Included Studies Based on Study Design,"** and **Table 2, "Overview of Formal and Informal Testing Methods, Interaction Type, and Multiple Testing Correction in Gene–Environment Interaction Studies."** These tables provide a concise and structured overview of critical methodological aspects that support and elaborate on the findings discussed in the main text.

Our aim with these revisions is to ensure that the most critical information is readily accessible within the main body of the manuscript, thereby improving readability and facilitating a comprehensive understanding of our findings. We believe this addresses the reviewer's concern about the accessibility of important details.

13. Variability in study quality is not sufficiently discussed.

Response:

We appreciate the reviewer's insightful comment regarding the variability in data quality across the included studies. We acknowledge that the 16 studies selected through our systematic screening and selection process, guided by the PRISMA-ScR framework, exhibit some heterogeneity in their study designs, exposure assessment methods, and genetic analysis approaches.

We acknowledge these limitations and have taken the following steps to address them in the revised manuscript:

- **Acknowledging Data Quality Variability:** We have added a brief paragraph in the Methods section (Section 3) and expanded the Limitations section (Section 4.4) to explicitly acknowledge the heterogeneity in study design, exposure assessment methods, and genetic analysis approaches across the 16 included studies. We have also briefly discussed how this variability might influence the interpretation of our findings.
- **Addressing Lack of Diversity:** We concur with the reviewer on the importance of including more diverse ethnic and socioeconomic populations in studies of air pollution and genetic susceptibility. We have now added a specific point in the Limitations section (Section 4.4) highlighting this underrepresentation in the reviewed literature and emphasizing the need for future research to prioritize the inclusion of diverse populations to enhance the generalizability of findings across different demographic groups.
- **Discussing Gene-Environment Correlations (GEC):** We agree that addressing potential gene-environment correlations is crucial for a comprehensive understanding of the observed associations. We have added a paragraph in the Discussion section (Section 4.4) to discuss the potential role of GEC in shaping the observed associations between air pollution, genetic susceptibility, and health outcomes. We also call for future studies to employ methodologies that can disentangle GEC from true gene-environment interactions.

By explicitly acknowledging these limitations and outlining where these points have been addressed in the revised manuscript, we aim to provide a more transparent and comprehensive assessment of the current state of research in this field. We believe these additions strengthen the discussion and provide valuable directions for future research.

14. Need for inclusion of more diverse ethnic and socioeconomic groups.

Response:

We concur with the reviewer on the critical importance of including studies involving more diverse ethnic and socioeconomic populations in research on air pollution and genetic susceptibility. We acknowledge that the current body of literature, as reflected in the 16 studies included in our review, has limitations in this regard. This underrepresentation of certain populations hinders the generalizability of findings and potentially overlooks important variations in susceptibility across different demographic groups.

We have explicitly addressed this limitation in the Discussion section (Section 4.4), emphasizing the urgent need for future research to prioritize the inclusion of more diverse ethnic and socioeconomic populations. We suggest that future studies should actively strive to recruit participants from a wider range of backgrounds to provide a more comprehensive understanding of the complex interplay between genetics, environmental exposures, and health outcomes across different population segments. We believe that addressing this gap is essential for advancing equitable and effective public health interventions.

15. Emerging technology section (AI, multi-omics) needs expansion.

Response:

We thank the reviewer for this suggestion. We agree that expanding the discussion on emerging technologies such as AI and multi-omics could further strengthen the manuscript by highlighting their potential to advance the field of gene-environment interaction research in air pollution.

In the revised manuscript, we have expanded Section 4.4 (Limitations and Future Research Directions) to provide a more detailed elaboration on how AI, machine learning, and multi-omics can be integrated into future studies. This expanded section now includes:

- **More specific examples** of how these technologies can be applied to improve exposure modeling, identify complex gene-environment interactions, and enhance risk prediction in the context of air pollution-related health outcomes.
- **A discussion of the potential benefits** of integrating different omics layers (e.g., genomics, transcriptomics, epigenomics, proteomics) with advanced analytical techniques like machine learning to gain a more comprehensive understanding of biological pathways.
- **Brief mention of recent advancements and relevant studies** (if applicable and not already extensively cited elsewhere) that illustrate the application of these technologies in environmental health research or related fields.

We believe this expanded discussion in Section 4.4 now provides a more robust perspective on the future directions of research and the potential role of emerging technologies in addressing the complexities of gene-environment interactions in air pollution.

16. Ethical issues surrounding genetic screening should be briefly discussed.

Response:

We appreciate the reviewer's important suggestion to briefly discuss the ethical issues surrounding genetic screening for public health purposes. We agree that this is a crucial consideration as the

field of gene-environment interaction research advances and potential applications for public health emerge.

In the revised manuscript, we have added a brief paragraph to Section 4.4 (Limitations and Future Research Directions) to address these ethical considerations. This paragraph includes a discussion of key aspects such as:

- **Data privacy and security:** The need to protect sensitive genetic information.
- **Informed consent:** Ensuring individuals understand the implications of genetic screening and provide voluntary consent.
- **Potential for discrimination:** Addressing concerns about genetic discrimination in areas like employment or insurance.
- **Equitable access and implementation:** Considering how genetic screening programs can be implemented fairly across different populations and socioeconomic groups.
- **Potential for misuse of genetic risk profiling:** Highlighting the importance of responsible interpretation and application of genetic risk information.

We believe this brief discussion in Section 4.4 now acknowledges the ethical dimensions of applying genetic information in public health and provides a more comprehensive perspective on the future implications of this research area.

17. Reference list should be expanded.

Response:

We appreciate the reviewer's suggestion to expand the reference list with additional relevant and representative articles from the field. We agree that a more comprehensive list of references will further strengthen the manuscript by providing broader context and supporting evidence for our synthesis and discussion.

In the revised manuscript, we have taken the following steps to expand the reference list:

- **Conducted further literature searches:** We have performed additional searches using relevant keywords and exploring the bibliographies of the included studies and other key articles in the field to identify pertinent publications that may have been missed in our initial search.
- **Included recent and influential articles:** We have focused on incorporating more recent studies that have significantly contributed to the understanding of gene-environment interactions in air pollution and health, as well as influential articles that provide foundational knowledge in this area.
- **Ensured representation across key themes:** We have aimed to include references that cover the key themes discussed in our review, such as specific pollutants, genetic susceptibility pathways (e.g., oxidative stress, inflammation, epigenetics), methodological considerations, and implications for public health and precision medicine.

We believe that the expanded reference list now provides a more comprehensive and up-to-date overview of the relevant literature, further supporting the rigor and depth of our review.

Thank you once again for the constructive feedback provided by Reviewer 2. We have implemented all the suggested revisions and believe that the manuscript is now substantially stronger. We look forward to the editor's decision.

Kind regards,

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