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International Evidence from Research and Practice to Foster Healthy Lifestyles and Mental Health in Adolescence and Emerging Adulthood
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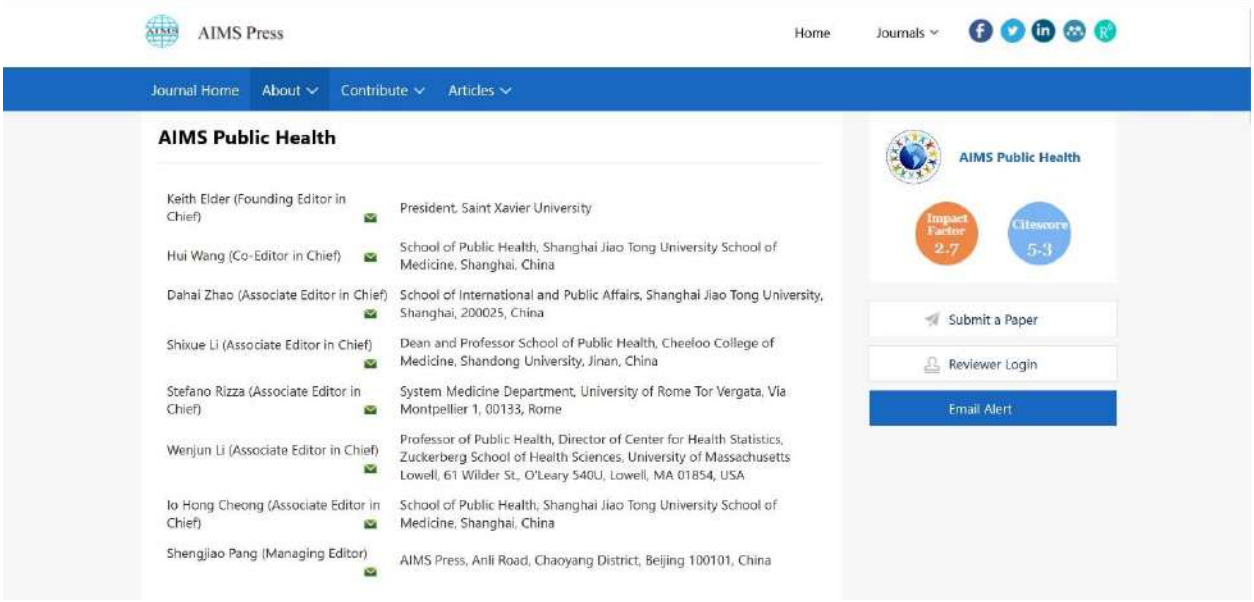
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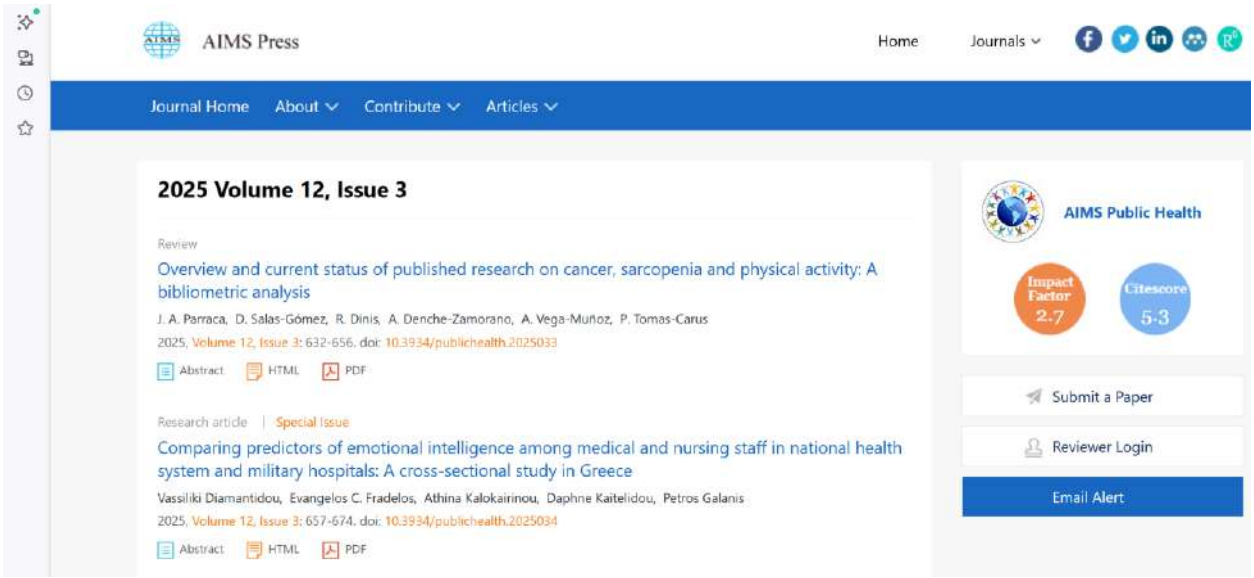
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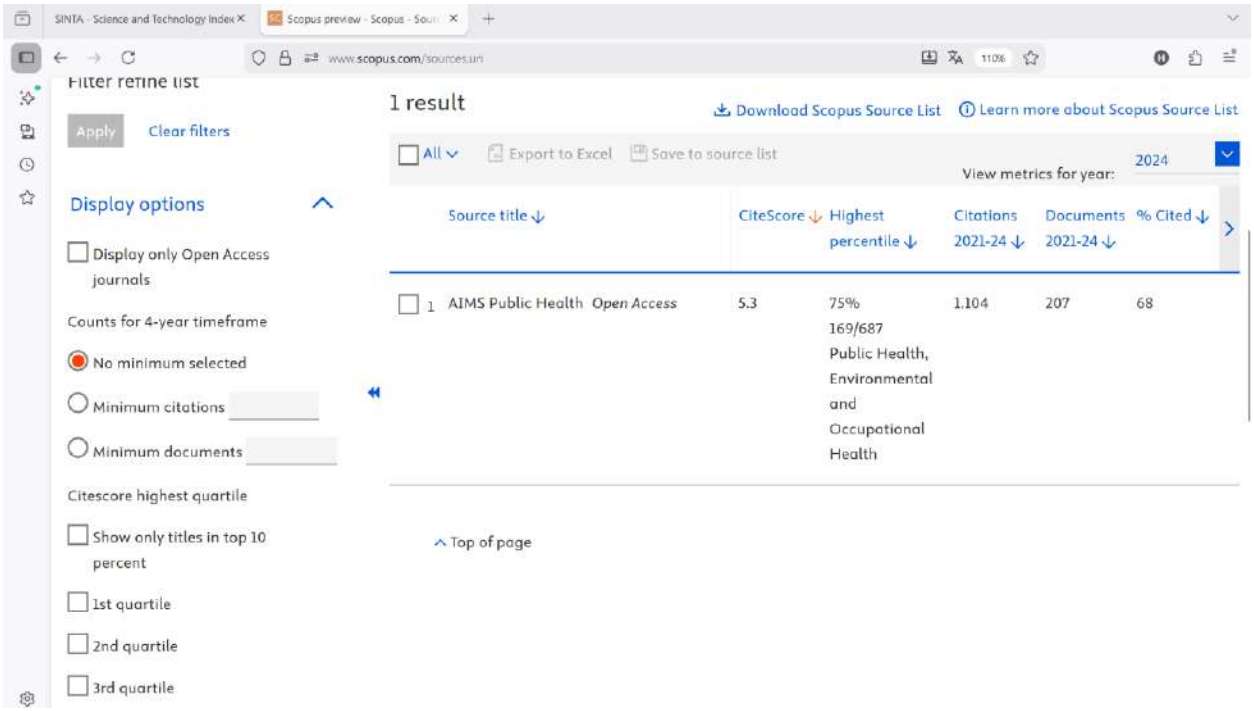
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Review

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

Hari Krismanuel*

Faculty of Medicine, Universitas Trisakti, West Jakarta, DKI Jakarta, Indonesia

* **Correspondence:** Email: hari_krismanuel@trisakti.ac.id.

Abstract: Air pollution, comprising a complex mixture of gaseous and particulate pollutants, remains a major global health concern that disproportionately affects vulnerable populations. In this scoping review, we aim 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 ($PM_{2.5}$), particulate matter (PM_{10}), nitrogen dioxide (NO_2), and nitrogen oxides (NO_x); key pollutants consistently linked to adverse health effects. By exploring the gene-environment interactions underlying air pollution-related conditions, this review offers new insights into how genetic factors may 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 are thought to influence individual variation in responses to $PM_{2.5}$, PM_{10}, NO_2, and NO_x. Although none of the included studies entailed multi-omics or machine learning approaches, we identified these tools as promising directions for future research aimed at elucidating mechanistic pathways and informing personalized strategies. These techniques could significantly improve the understanding of gene-environment interactions, and are suggested as emerging methodologies for future studies. However, the scarcity of longitudinal studies and the underrepresentation of diverse populations limit the generalizability of the current findings. Addressing these gaps will be essential for advancing research, improving environmental health equity, and informing policy in the context of air pollution and genetic susceptibility.

Keywords: air pollution; disease risk; environmental health; genetic susceptibility; personalized medicine; precision health

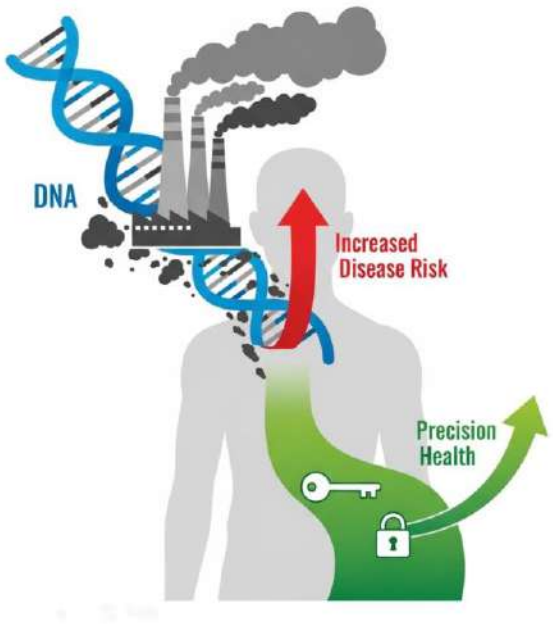

Figure 1. Graphical abstract.

Figure 1 illustrates the conceptual pathway from the interaction of **genetic susceptibility** (DNA helix) and **air pollution exposure** (smokestacks), which leads to an **increased disease risk** in individuals. The green pathway highlights how **precision health** strategies, tailored to an individual's unique genetic and environmental profile, can serve as a targeted solution to mitigate this risk.

1. Introduction

Air pollution remains one of the most significant environmental risk factors worldwide, contributing to an estimated 7 million premature deaths annually, according to the World Health Organization [1–3]. Among the most harmful pollutants are fine particulate matter ($PM_{2.5}$), coarse particulate matter (PM_{10}), nitrogen dioxide (NO_2), and nitrogen oxides (NO_x), which are consistently associated with adverse health outcomes [4–6].

$PM_{2.5}$ and PM_{10} refer to airborne particles with aerodynamic diameters ≤2.5 and ≤10 micrometers, respectively. These particles can penetrate deep into the respiratory tract, triggering oxidative stress, inflammation, endothelial dysfunction, and systemic effects beyond the lungs. **NO_2 and NO_x**, primarily emitted from vehicle exhaust and industrial processes, contribute to airway inflammation, impaired lung function, and increased cardiovascular risk. Exposure to these pollutants has been linked to the development and exacerbation of chronic diseases such as asthma, chronic obstructive pulmonary disease (COPD), ischemic heart disease, stroke, and neurodegenerative conditions [4–6].

Recent fine-scale modeling and exposure assessment studies, such as that of Nisticò et al. (2025), emphasize the importance of high-resolution pollution data in identifying vulnerable populations and guiding local-level interventions. Understanding the complex interplay between environmental exposures and individual susceptibility, particularly at the molecular level, is crucial for developing targeted public health interventions. This necessitates the integration of detailed environmental monitoring data with comprehensive health surveillance and molecular research, including the investigation of genetic factors that may modify an individual's response to air pollution [7].

Genetic susceptibility to air pollution refers to the predisposition of certain individuals to experience heightened adverse health effects due to specific genetic variations. Genes involved in oxidative stress pathways play critical roles in neutralizing reactive oxygen species generated by pollutants like fine particulate matter ($PM_{2.5}$). Understanding these genetic mechanisms is crucial for explaining why some populations exhibit increased vulnerability to air pollution-related diseases [8–10].

Air pollution remains a major global health challenge, imposing significant health burdens worldwide. Primary pollutants, such as $PM_{2.5}$, nitrogen dioxide (NO_2), ozone, and volatile organic compounds (VOCs), are widely acknowledged as key contributors to diseases across multiple systems. However, while environmental exposures are well-documented as primary drivers, genetic variations significantly modulate individual susceptibility, disproportionately affecting vulnerable populations. Despite its importance, the interaction between genetic predisposition and pollutant exposure remains underexplored, leaving critical gaps in our understanding of the mechanisms driving health disparities [11–13].

Recent advancements in genetic research have illuminated how genetic variants influence sensitivity to oxidative stress, inflammation, DNA damage, and epigenetic modifications, all of which are implicated in pollution-related diseases. However, significant challenges persist, including inconsistent findings across studies due to methodological differences and the underrepresentation of diverse populations in genetic analyses. Genome-wide association studies (GWAS) have identified promising genetic markers, yet these findings often lack generalizability due to limited population diversity and a lack of comprehensive models that integrate genetic and environmental factors [14,15].

To address these gaps, emerging methodologies such as multi-omics integration and machine learning are increasingly recognized as powerful tools to uncover complex gene-environment interactions. While these techniques were not employed in the studies included in this review, they hold great promise for future research aimed at identifying mechanistic pathways and advancing precision health strategies [16–19].

In this review, we address these gaps by systematically analyzing 16 peer-reviewed studies published over the past decade to provide a detailed synthesis of the interplay between genetic and environmental factors in determining health risks associated with air pollution. By focusing on oxidative stress, inflammation, and epigenetic pathways, we uniquely highlight genetic mechanisms that modulate susceptibility to pollution-related diseases. We also identify critical research gaps, such as the reliance on cross-sectional designs, and propose future directions to improve the robustness and generalizability of findings.

We further aim to outline a novel framework for advancing precision health strategies by integrating genetic insights with emerging methodologies such as multi-omics, machine learning, and longitudinal study designs. By doing so, we seek to inform public health policies aimed at mitigating air pollution-related health risks, particularly in vulnerable populations.

A detailed overview of the included studies, including author, year, location, study design, population and sample size, exposure variables, health outcomes, and age range, is presented in Supplementary Table S1. This table provides a comprehensive summary of the key characteristics of the included studies, enabling comparison and the identification of research gaps.

Despite the growing body of epidemiological research, the underlying biological mechanisms of gene-environment (GxE) interactions remain complex and not fully understood. In addition to epidemiological studies, mechanistic data from in vivo and organoid models also provide crucial insights into the biological pathways underlying GxE interactions. Researchers have demonstrated how such models can elucidate the cellular responses to environmental exposures in genetically predisposed individuals [8,20,21], which are discussed further in the Discussion section.

2. Materials and methods

2.1. Protocol and registration

This scoping review was conducted following the methodological framework proposed by Arksey and O'Malley (2005) [22] and further elaborated by Levac et al. (2010) [23]. Recognizing the importance of transparency and methodological rigor for evidence synthesis, the protocol for this scoping review was retrospectively registered with the Open Science Framework (OSF) on May 22, 2025. The public URL for this registration is https://osf.io/3r8ap/ and its Registration ID is 3r8ap. This protocol is publicly available on the OSF platform [24].

2.2. Search strategy

To ensure transparency and credibility, a systematic literature search was conducted across multiple databases, including PubMed, Google Scholar, and ResearchGate to identify relevant studies. The search was limited to articles published in English between January 1, 2015, and December 31, 2024. The following search strategy was used:

- **PubMed:** ("air pollution" [MeSH Terms] OR "air pollution" [Title/Abstract] OR "air pollutants" [Title/Abstract]) AND ("genetic susceptibility" [MeSH Terms] OR "genetic polymorphism" [Title/Abstract] OR "oxidative stress" [MeSH Terms] OR "oxidative stress" [Title/Abstract]) AND ("disease risk" [Title/Abstract] OR "health outcomes" [Title/Abstract]).
- **Google Scholar:** "air pollution" AND ("genetic susceptibility" OR "oxidative stress") AND ("disease risk" OR "health outcomes").
- **ResearchGate:** ("air pollution" OR "air pollutants" OR "pencemaran udara") AND ("genetic susceptibility" OR "genetic predisposition" OR "oxidative stress" OR "stress oksidatif") AND ("disease risk" OR "health outcomes" OR "dampak kesehatan").
- **DOAJ**: "air pollution" AND ("genetic susceptibility" OR "oxidative stress") AND ("disease risk" OR "health outcomes").

The following filters were applied: Human studies, English language, publication date (2015–2024), study type (including review, meta-analysis, randomized controlled trial, cohort study, case-control study, and cross-sectional study), and peer-reviewed status.

2.3. Study selection process

Articles were screened for relevance using a two-step process: (1) Title and abstract screening, followed by (2) full-text review. From this systematic search, 16 peer-reviewed articles were selected based on their relevance to the topic. Data from the selected articles were then systematically extracted. Data extraction prioritized information on genetic markers, their roles in modulating susceptibility, and their associations with health effects induced by air pollution. The data synthesis employed a qualitative approach to integrate findings from these studies, focusing on the influence of genetic factors on susceptibility to air pollution and the interaction between genetic variations and environmental exposures. This enabled the identification of patterns and relationships between genetic variations and health risks associated with air pollution, providing a comprehensive perspective on how genetics influences responses to environmental pollutants [25–27].

To ensure the transparency and reproducibility of this review, the study selection process was guided by the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) framework. A PRISMA-ScR flow diagram was used to illustrate the process of study selection, and adherence to PRISMA guidelines was maintained throughout the data extraction and synthesis phases [28–30].

Step 1: Identifying Studies. Relevant studies were initially identified through a comprehensive search across multiple databases, including PubMed, Web of Science, and Google Scholar. A combination of keywords like "air pollution," "genetic susceptibility," "oxidative stress," and "disease risk" was used to locate pertinent articles. These searches aimed to capture a broad range of studies related to genetic factors and their interactions with environmental exposures.

The search results were carefully reviewed, and studies meeting the predefined inclusion criteria were selected for further assessment. Studies that did not meet the inclusion criteria, were not substantially relevant to the research topic, or contained duplicated references were excluded.

This step ensured the selection of studies that contribute meaningful and relevant insights to the review, avoiding redundancy and maintaining the quality and integrity of the synthesis [28–30].

Step 2: Study Screening. The next step involved screening the identified studies based on predefined inclusion and exclusion criteria. Two reviewers independently screened the titles and abstracts of the studies retrieved from the initial search. Studies were selected for inclusion if they met the following criteria:

- Focused on genetic susceptibility to air pollution.
- Provided explicit methodologies.
- Offered quantitative or mechanistic insights into genetic-environment interactions.

Studies that were excluded at this stage included those not published in English, non-peer-reviewed articles, conference abstracts, and reviews that did not directly address genetic susceptibility to air pollution. The remaining articles underwent a full-text review to confirm their eligibility before being included in the final analysis [28–30].

Step 3: Data Extraction. Data were extracted from the selected studies using a standardized extraction form. The extraction process involved collecting detailed information on genetic markers, biomarkers, health outcomes related to air pollution exposure, and other relevant details like study design, sample size, and key findings. The data were then synthesized qualitatively to identify key

themes, patterns, and relationships across the studies [28–30].

Step 4: Data Synthesis. Data synthesis involved integrating findings from the selected studies to draw conclusions about the influence of genetic factors on susceptibility to air pollution. This synthesis aimed to provide a comprehensive understanding of the mechanisms underlying genetic-environment interactions and their implications for disease risk. The integration of findings was guided by thematic analysis and narrative synthesis techniques, emphasizing consistency and comparability across studies [28–30].

2.4. Inclusion and exclusion criteria

Studies were included in this scoping review if they met the following criteria:

2.4.1. Inclusion criteria

2.4.1.1. Study design

Studies of any design that investigated the association between air pollution exposure (e.g., $PM_{2.5}$, PM_{10}, NO_2, and NO_x) and health outcomes in relation to genetic susceptibility were included. This encompasses observational studies (cohort, case-control, cross-sectional), interventional studies (e.g., randomized controlled trials, and quasi-experimental studies), and Mendelian Randomization studies. Scoping reviews are particularly suitable for mapping evidence on complex and heterogeneous topics, as outlined by Tricco et al. (2018) [28], Page et al. (2021) [29], and Page and Moher (2017) [30]. The focus was on studies examining various genetic factors influencing susceptibility to air pollution than specific genetic polymorphisms.

2.4.1.2. Population

Human participants of any age, sex, or ethnicity. Studies focusing on specific subpopulations (e.g., children, elderly, and individuals with specific pre-existing conditions) were also included.

2.4.1.3. Exposure

Measurable exposure to $PM_{2.5}$, PM_{10}, NO_2, or NO_x. Studies must provide quantitative or qualitative data on one or more of these pollutants. Exposure assessment methods should be clearly described (e.g., air quality monitoring data, self-reported exposure, and residential proximity to pollution sources).

2.4.1.4. Health outcomes

Any health outcomes relevant to the research question, including but not limited to respiratory diseases (e.g., asthma, and COPD), cardiovascular diseases, mental health effects, pregnancy complications, and skin conditions. Studies must report specific health outcomes and diagnostic criteria used.

2.4.1.5. Gene-environment interaction (primary and essential criterion)

Studies must present statistical analyses that directly test for a gene-environment interaction (e.g., using interaction terms in regression models, stratified analyses by genotype, interaction meta-regression). Studies reporting only the major effects of air pollution or genetic associations separately were excluded. Studies that mention gene-environment interaction but did not perform formal statistical testing of the interaction were also excluded [8,31,32].

2.4.2. Exclusion criteria

Studies were excluded if they met any of the following criteria:

2.4.2.1. Irrelevance to the topic

- Studies that did not address the health effects of air pollution.
- Studies that focused exclusively on pollutants other than $PM_{2.5}$ (e.g., only NO_2 or O_3).
- Studies addressing $PM_{2.5}$ along with other pollutants were considered if $PM_{2.5}$-specific information could be extracted.
- Studies that entailed the environmental impact of air pollution but not human health effects.
- Studies solely focused on interventions or policies to reduce air pollution without addressing genetic aspects.

2.4.2.2. Lack of genetic focus

- Purely epidemiological studies that measured only air pollution exposure and health outcomes without considering genetic factors.
- *In vitro* or *in vivo* toxicological studies that did not investigate genetic variations or gene polymorphisms.

2.4.2.3. Inappropriate publication type

- Opinions, editorials, letters to the editor, and conference abstracts (unless the abstracts contained significant information not available in a full-text publication).
- Books and book chapters (unless they contained relevant systematic reviews or meta-analyses).
- Government or non-governmental organization reports (unless they contained significant data or analyses not available in peer-reviewed publications).

2.4.2.4. Language and accessibility

- Studies not published in languages accessible to the review team (e.g., English and Indonesian).
- Studies for which full-text access could not be obtained after reasonable search efforts (e.g., through library databases or direct requests to authors).

2.4.2.5. Duplication

- Studies published more than once (in which case, the most complete and recent version was included).

2.4.2.6. Methodological concerns (with specific consideration for scoping reviews)

- While scoping reviews generally do not assess the methodological quality of studies as rigorously as systematic reviews, studies with substantial methodological flaws (e.g., severely flawed study design or erroneous data analysis) could be excluded. This criterion was applied cautiously and transparently [33–34].

2.5. Data extraction and synthesis

Data from included studies were extracted using a standardized data extraction form. The following information was extracted: Study characteristics (e.g., author, year, study design, and population), exposure assessment methods, genetic markers investigated, health outcomes assessed, and key findings related to gene-environment interactions. A detailed overview of these extracted data, presented in Supplementary Table S1, provides a comprehensive summary of the key characteristics of the included studies, enabling comparison and identification of research gaps. A narrative synthesis of the findings were then conducted to map the existing literature and identify key themes and research gaps [28–30,33,34].

2.6. Quality assessment of included studies

To strengthen the methodological rigor of our review, we conducted a formal quality appraisal of all 16 included full-text articles. Given the variety of study designs, we employed appropriate assessment tools tailored to each design type:

- The 13 prospective cohort studies were assessed using the Newcastle-Ottawa Scale (NOS) [35].
- The 1 cross-sectional study was evaluated using a modified version of NOS tailored for cross-sectional designs.
- The 1 meta-analysis was assessed narratively using AMSTAR 2 criteria, which were widely accepted for systematic reviews and meta-analyses [36].
- The 1 molecular-epigenetic cohort study, although fundamentally prospective in design, was evaluated using the JBI Critical Appraisal Checklist for Cohort Studies due to its integration of biological, genetic, and epigenetic data [37].

3. Results

A total of 322 records were identified through database searching (PubMed n = 100, Google Scholar n = 109, Research Gate n = 107, and DOAJ n = 7). After removing duplicates (n = 5), 315 records underwent title and abstract screening. Of these, 283 were excluded as they did not meet the inclusion criteria (e.g., not focused on genetic susceptibility to air pollution, review articles, or non-

human studies). A total of 35 full-text articles were assessed for eligibility, and 19 were further excluded due to methodological concerns (e.g., lack of a clear methodology, or focus on non-$PM_{2.5}$ pollutants), or lack of investigation of gene-environment interaction). Finally, 16 studies met all inclusion criteria and were included in this scoping review (Figure 2).

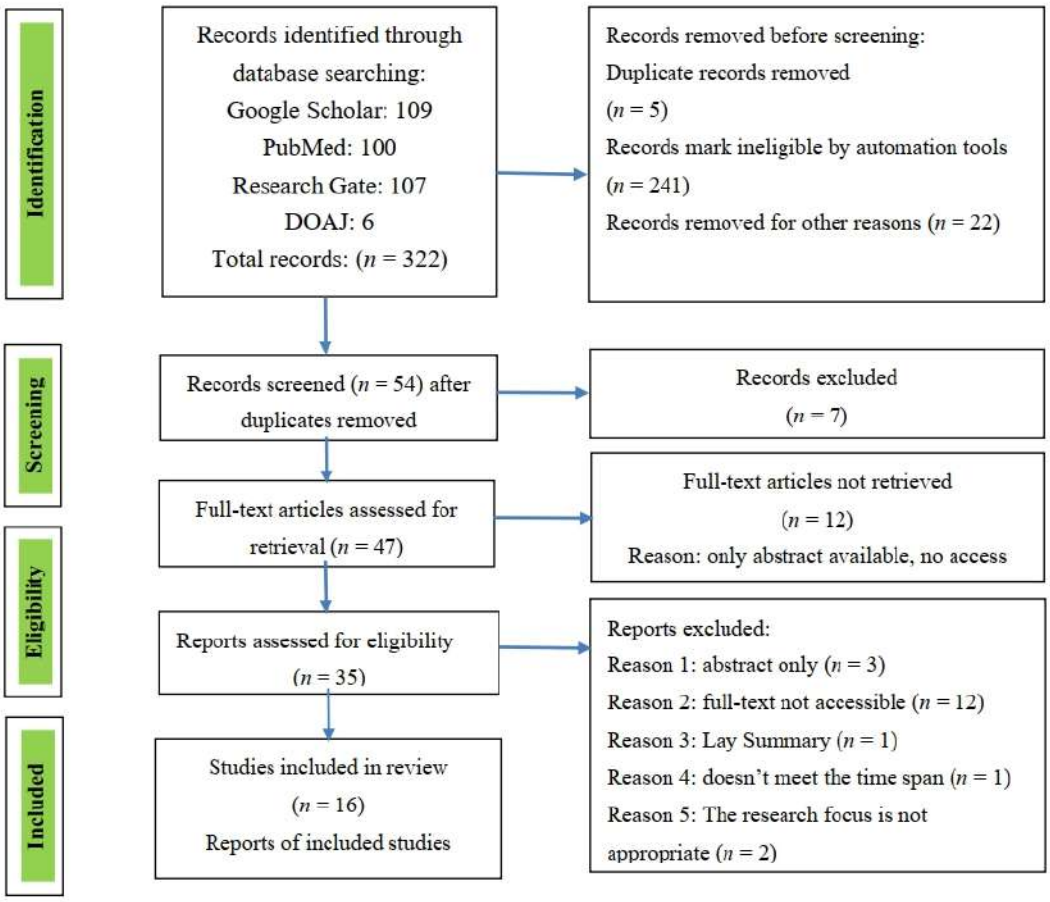

Figure 2. PRISMA-ScR flow diagram.

3.1. Study characteristics

This scoping review included 16 studies investigating the interplay between genetic susceptibility and air pollution, particularly $PM_{2.5}$, on various health outcomes. A diverse range of study designs were employed, including 1 cross-sectional study, 14 prospective cohort studies, 1 meta-analysis of cohort studies, and 1 Mendelian Randomization study. This heterogeneity in study design is typical in a scoping review, aiming to map the available evidence regardless of methodological rigor [38–53]. Only one study employed Mendelian Randomization analysis [54–56] as its core methodological approach.

Most studies focused on adult populations, with a reported age range spanning from 37 to 73 years. Geographically, the research was predominantly conducted in Europe (n = 12), with one study encompassing both Europe and North America (n = 1), and a smaller number conducted in Asia (n = 3). This geographical distribution highlights a potential gap in research from other

regions. Furthermore, 15 out of the 16 studies investigated the combined effects of particulate matter ($PM_{2.5}$ and/or PM_{10}), nitrogen dioxide (NO_2), and nitrogen oxides (NO_x). Only one study, Gruzieva et al. (2016) [38], focused solely on prenatal NO_2 exposure. This pattern suggests that $PM_{2.5}$ and NO_2 are dominant environmental factors in the studies and highlights the need for further exploration of NO_2 exposure, particularly in its isolated form, to better understand its role in genetic susceptibility to diseases [39–53].

$PM_{2.5}$ exposure was the most commonly assessed air pollutant, primarily using air quality monitoring data (n = 16). It should be noted that some studies used multiple methods for exposure assessment. Some studies utilized land-use regression models to estimate $PM_{2.5}$ exposure based on spatial data and environmental characteristics, while others employed self-reported questionnaires focusing on residential location and daily activities. For instance, Huang et al. (2021) [39] and Gao et al. (2023) [52] used land-use regression models within the UK Biobank to estimate individual exposures. Li et al. (2023) [41] used land-use regression models in China. Air quality monitoring data typically involves measurements taken at fixed monitoring stations, providing information on ambient air pollution levels in specific locations. Land-use regression models, on the other hand, incorporate spatial data such as traffic density, land use types, and meteorological factors to create more refined estimates of pollution exposure at a finer spatial scale [39,41,52]. These methods have varying degrees of accuracy and may introduce different types of measurement error.

Operational Definitions of Variables: $PM_{2.5}$ was most often defined as the annual average concentration at the participants' residential address. However, some studies used different averaging periods (e.g., 24-hour average) or considered specific sources of $PM_{2.5}$ (e.g., traffic-related $PM_{2.5}$). Health outcomes varied across studies, encompassing cardiovascular diseases (e.g., myocardial infarction, stroke), respiratory diseases (e.g., chronic obstructive pulmonary disease (COPD), lung cancer), and metabolic disorders (e.g., type 2 diabetes). This variability in outcome definitions should be considered when interpreting the findings.

Exposure Measurement Methods (Further Details): Studies using air quality monitoring data often linked participants' residential addresses to the nearest monitoring station. Land-use regression models incorporated geographic information system (GIS) data on traffic, land use, and topography. Self-reported questionnaires typically asked participants about their residential history, time spent outdoors, and proximity to pollution sources.

Justification for Study Selection: Mendelian Randomization studies were included because they provide stronger evidence for causal inference using genetic variants as instrumental variables, reducing the potential for confounding and reverse causation. Studies employing other designs, such as cohort studies, were included to provide a broader overview of the existing evidence base [49,54–56].

Information on sex was consistently reported, with approximately equal representation of men and women across the studies. However, reporting on other demographic characteristics, such as ethnicity and socioeconomic status (SES), was less consistent. Where reported, SES was often categorized based on indicators such as education level, occupation, or income. Some researchers also considered other participant characteristics such as smoking status and pre-existing health conditions as potential confounders.

Interventions or Moderating Factors: Several studies investigated potential moderating factors such as genetic polymorphisms (as mentioned previously), dietary intake, and physical activity. For

instance, Huang et al. (2021) examined whether the association between $PM_{2.5}$ and lung function was modified by genetic variations in antioxidant enzymes [39].

Sixteen studies entailed the interactions of $PM_{2.5}$, PM_{10}, NO_2, and NO_x on various gene polymorphisms associated with increased disease risk. These studies often examined specific gene variants known to be involved in pathways related to inflammation, oxidative stress, or DNA repair, which are mechanisms through which air pollution is thought to exert its effects. Mendelian Randomization studies were included to provide stronger causal evidence for the relationship between air pollution and health outcomes. Mendelian Randomization utilizes genetic variants as instrumental variables to assess the causal effect of an exposure (e.g., air pollution) on an outcome (e.g., disease risk), minimizing the influence of confounding factors [49,54–56]. Only one meta-analysis of cohort studies specifically examined the relationship between NO_2 exposure during pregnancy and cord blood DNA methylation. This meta-analysis synthesized data from multiple cohort studies to investigate the potential impact of prenatal NO_2 exposure on epigenetic modifications in newborns [39].

Brief Summary of Key Findings: Overall, the studies consistently suggested a positive association between long-term exposure to air pollutants, particularly $PM_{2.5}$, and adverse health outcomes, including cardiovascular and respiratory diseases. Some studies also found evidence of associations with metabolic disorders and other health outcomes. Researchers investigating gene-environment interactions provided evidence that genetic susceptibility can modify the effects of air pollution [38–53].

Some researchers used ge_{no}typing to assess genetic susceptibility and data from air quality monitoring stations to measure $PM_{2.5}$ exposure. The findings of the included studies generally suggested a positive association between long-term exposure to air pollutants, particularly $PM_{2.5}$, and adverse health outcomes [38–53].

A detailed overview of the included studies, including author, year, location, study design, population and sample size, exposure variables, health outcome, and age range, is presented in Supplementary Table S1.

To assess the methodological rigor of the included studies, a formal quality appraisal was conducted using tools appropriate for each study design, as detailed in the Methods section (see Section 2.6). A comprehensive summary of the methodological quality assessment for all 16 included full-text articles is presented in Table 1. The results showed that most studies met high-quality criteria, supporting the reliability of the extracted findings. For a detailed breakdown of individual study scores and their respective quality assessments, please refer to Supplementary File S2.

3.1.1. Overview and categorization of health outcome

The studies in this review report a diverse range of health outcomes associated with air pollution exposure, involving both physical and mental health conditions across different populations. These outcomes span multiple disease categories, highlighting the broad impact of pollutants such as $PM_{2.5}$, PM_{10}, NO_2, and NO_x [38–53].

To facilitate analysis, the included studies were categorized into seven primary groups: Respiratory diseases, cardiovascular diseases, neurological and psychiatric disorders, cancers, autoimmune and inflammatory conditions, and other diseases. Cardiovascular and neurological conditions were the most frequently studied, with consistent associations reported for $PM_{2.5}$, PM_{10}, NO_2, and NO_x exposure. Notable

findings include stronger associations of air pollution exposure with coronary artery disease (Fu et al., 2023; Li et al., 2022) and major depressive disorder (Li et al., 2023) associated with these pollutants [41,42,48]. Additionally, autoimmune conditions such as inflammatory bowel disease (Chen et al., 2024) were linked to long-term exposure to $PM_{2.5}$ and NO_x [49].

Table 1. Summary of methodological quality assessment of the included studies based on study design.

No.	Study (First Author, Year)	Study Design	Quality Assessment Tool	Score/Result	Notes
1	Gruzieva et al., 2016 [38]	Meta-analysis (Cohort Data)	AMSTAR 2	High Quality	Evaluated narratively using AMSTAR 2
2	Huang et al., 2021 [39]	Prospective Cohort	NOS	9/9	UK Biobank, lung cancer
3	Ma et al., 2024 [40]	Prospective Cohort	NOS	9/9	UK Biobank, AAA
4	Li et al., 2023 [41]	Prospective Cohort	NOS	9/9	UK Biobank, MDD
5	Fu et al., 2023 [42]	Prospective Cohort	NOS	9/9	Based on UK Biobank, CAD
6	Ma et al., 2024 [43]	Prospective Cohort	NOS	9/9	Stroke, robust adjustment
7	Liu et al., 2024 [44]	Prospective Cohort	NOS	9/9	Schizophrenia
8	Huang et al., 2024 [45]	Prospective Cohort	NOS	9/9	Parkinson's disease
9	Wang et al., 2022 [46]	Prospective Cohort	NOS	9/9	COPD + interaction lifestyle
10	Rhee et al., 2024 [47]	Prospective Cohort	NOS	9/9	Cardiovascular disease
11	Li et al., 2022 [48]	Prospective Cohort	NOS	9/9	$PM_{2.5}$ and CAD
12	Chen et al., 2024 [49]	Molecular-Epigenetic Cohort	JBI Checklist (Cohort)	High Quality	Epigenetic focus, UK Biobank based
13	Wu et al., 2024 [50]	Prospective Cohort	NOS	9/9	Psoriasis
14	Zhang et al., 2024 [51]	Cross-Sectional	Modified NOS (Cross-Sectional)	9/10	High quality cross-sectional design
15	Gao et al., 2023 [52]	Prospective Cohort	NOS	9/9	Depression and anxiety
16	Zhang et al., 2024 [53]	Prospective Cohort	NOS	9/9	Dementia

Note: Abbreviations: AMSTAR 2, Assessment of Multiple Systematic Reviews-2 (A Measurement Tool to Assess Systematic Reviews 2); NOS, Newcastle-Ottawa Scale; JBI, Joanna Briggs Institute; AAA, Abdominal Aortic Aneurysm; MDD, Major Depressive Disorder; CAD, Coronary Artery Disease; COPD, Chronic Obstructive Pulmonary Disease; and $PM_{2.5}$, Particulate Matter with a diameter ≤ 2.5 μm.

Having established the characteristics of the included studies and the methods used to assess exposure and outcomes, in the following section, we detail the methods used to assess genetic susceptibility and pollutant exposure before presenting the key findings related to gene-environment interactions [38–53].

3.1.1.1. Respiratory diseases

Several studies focus on respiratory conditions, particularly in relation to particulate matter and nitrogen oxides:

- Wang et al. (2022): **Chronic obstructive pulmonary disease (COPD)** associated with $PM_{2.5}$, PM_{10}, NO_2, and NO_x [46].

3.1.1.2. Cardiovascular diseases

Air pollution exposure is strongly linked to various cardiovascular conditions:

- Ma et al. (2024): **Abdominal aortic aneurysm** [40].
- Fu et al. (2023): **Coronary artery disease (CAD)** [42].
- Rhee et al. (2024): **General cardiovascular diseases** [47].
- Li et al. (2022): **Coronary artery disease (CAD)** [48]

3.1.1.3. Neurological and psychiatric disorders

Mental health and cognitive impairments are key areas of concern:

- Li et al. (2023): **Major depressive disorder** [41].
- Liu et al. (2024): **Schizophrenia** [44].
- Zhang et al. (2024): **Speed processing deficits** [51].
- Gao et al. (2023): **Depression and anxiety** [52].
- Zhang et al. (2024): **Dementia** [53].

3.1.1.4. Cancer

A study reports a significant association between air pollution and lung cancer:

- Huang et al. (2021): **Lung cancer** [39].

3.1.1.5. Autoimmune and inflammatory conditions

- Chen et al. (2024): **Ulcerative colitis** [49].
- Wu et al. (2024): **Psoriasis** [50].

3.1.1.6. Epigenetic changes

Air pollution exposure, particularly in early life, has been shown to cause epigenetic changes, such as differential DNA methylation:

- Gruzieva et al (2016): **Differential offspring DNA methylation at CpG site** in cord blood newborns [38].

3.1.1.7. Other diseases

Several studies have also linked air pollution to other health conditions:

- Ma et al. (2024): **Stroke** [43].
- Huang et al. (2024): **Parkinson's disease** [45].

3.1.2. Methods of exposure and outcome assessment

In this scoping review, the methods used to assess air pollution exposure and health outcomes varied across studies, reflecting the diversity of study designs and populations.

3.1.2.1. Exposure assessment

In this review, we categorized the approaches used to assess exposure to air pollution into three main groups:

1) Air Quality Monitoring and Dispersion Models: Exposure estimated from fixed-site monitoring data or government-provided dispersion models (e.g., DEFRA in the UK). These methods provide spatially resolved estimates of pollutants such as $PM_{2.5}$, PM_{10}, NO_2, and NO_x [40,44,51].

2) Land-Use Regression Models: Several researchers (e.g., Huang et al., 2021) employed land-use regression (LUR) models to estimate individual-level exposures to air pollution. LUR models use spatial data on environmental and urban characteristics, such as traffic density, land use, and meteorological factors, to predict exposure to pollutants at a finer geographic scale. These models can provide more localized estimates of exposure, accounting for variation in pollution levels that may not be captured by monitoring stations [39,41,52].

3) Self-Reported Questionnaires: A few researchers included in this review also used self-reported questionnaires, asking participants about their residential history, time spent outdoors, and proximity to pollution sources. This method, while less accurate than air quality monitoring or LUR models, enabled researchers to estimate individual exposure based on participants' reported behaviors and locations [50].

4) Satellite-based Approaches: A limited number of studies estimated exposure using satellite-derived data, such as aerosol optical depth (AOD), often combined with meteorological and land-use variables through machine learning models to provide high-resolution estimates of ambient $PM_{2.5}$ concentrations [48].

3.1.2.2. Outcome assessment

1) Health Outcomes: A broad range of health outcomes were assessed across the studies, including respiratory diseases (e.g., COPD, and asthma), cardiovascular diseases (e.g., coronary artery disease, and myocardial infarction), neurological conditions (e.g., dementia, and depression), metabolic disorders (e.g., type 2 diabetes), and autoimmune/inflammatory diseases (e.g., ulcerative colitis). Each study defined and measured these outcomes differently, with some relying on clinical diagnoses, hospital records, or self-reported health conditions [38–53].

2) Objective Health Measurements: Many researchers used objective health measures, such as lung function tests, blood pressure readings, or biomarkers, to assess the impact of air pollution on various health conditions. These measurements provided more precise and quantifiable data compared to self-reported health information.

3) Gene-Environment Interactions: A subset of studies explored how genetic susceptibility modifies the impact of air pollution on health outcomes. These studies integrated genetic data (e.g., from genotyping or epigenetic analyses) with environmental exposure estimates.

Details of methodological examination of gene–environment interactions are provided in section (3.1.3).

3.1.3. Gene–environment interaction analysis

To enhance transparency and methodological rigor, we examined how the included studies assessed gene–environment (GxE) interactions. All 16 studies investigated the modifying role of genetic susceptibility on the association between air pollution exposure and health outcomes. However, the methodological approaches varied.

Several researchers employed Cox regression models to estimate hazard ratios and to evaluate interaction effects [39–46,48,49,53]. Among these, a subset formally tested additive interaction metrics, such as the Relative Excess Risk due to Interaction (RERI) and Attributable Proportion (AP), which provide insight into the biological synergy between genetic risk and environmental exposure [38,39,41,42,45,48,52]. Multiplicative interactions, expressed through interaction coefficients in Cox models, were also reported in some studies.

Only a subset of researchers formally tested gene–environment interactions, either through additive metrics (e.g., RERI, and AP) or multiplicative interaction terms. Several studies (e.g., Fu et al. and Rhee et al.) reported combined effect estimates without direct interaction testing, which may limit interpretability. We have reflected these methodological distinctions in Supplementary Table S3. To support methodological clarity in future research, we encourage adherence to established guidelines for GxE analysis, including the use of formal interaction testing and transparent reporting of effect modification approaches.

While most researchers did not apply formal multiple testing corrections (e.g., Bonferroni or false discovery rate), two studies, those by Gruzieva et al. (2016) and Zhang et al. (2024), did report correction procedures [38,53]. However, the lack of correction in most studies may limit the interpretability of interaction findings in the presence of multiple comparisons. This issue is particularly relevant given the large number of exposures and genetic markers tested, which increases the chance of false-positive results.

A detailed summary of the interaction testing methods, effect sizes, p-values, and confidence intervals is provided in Supplementary Table S3. To improve visibility and address reviewer concerns, we have clarified key methodological features in this section and will consider integrating selected elements of Supplementary Table S3 into the main manuscript if appropriate.

To complement Supplementary Table S3, which details the interaction testing methods used in each study, Table 2 summarizes key methodological characteristics of the included studies, focusing on the statistical approaches used to evaluate gene–environment interactions, the type of interaction tested (multiplicative or additive), the significance of interaction terms (e.g., p-values), and the application of multiple testing corrections. This structured summary enhances methodological transparency and supports interpretation of the findings by distinguishing between formal and informal testing strategies.

Table 2. Overview of formal and informal testing methods, interaction type, and multiple testing correction in gene–environment interaction studies.

No	Study	Formal Interaction	Informal Interaction	Interaction Type	Interaction Significance and Strength	Multiple Testing Correction
1	Gruzieva et al., 2016 [38]	Not Available	Narrative Synthesis	Epigenetic	Not reported (unclear)	False Discovery Rate (FDR)
2	Huang et al., 2021 [39]	Cox proportional hazard models, RERI, AP	-	Multiplicative Positive Additive	Not reported (unclear)	Not Reported
3	Ma et al., 2024 [40]	Cox proportional hazard models, RERI, AP	-	Multiplicative Positive Additive	Not reported (unclear)	Not Reported
4	Li et al., 2023 [41]	Cox proportional hazard regression models (*p*-interaction and Hazard Ratio)	Stratified Analysis	Multiplicative	$PM_{2.5}$: $p = 0.036$ PM_{10}: $p = 0.025$ NO_2: $p = 0.030$ (**Significant**) NO_x: $p = 0.080$ (**Not Significant**)	Not Reported
5	Fu et al., 2023 [42]	Cox proportional hazard regression models (*p*-interaction and Hazard Ratio), RERI, AP	Subgroup HR Comparison (by PRS)	Multiplicative Positive Additive	All *p*-interaction > 0.05 (**Not Significant**)	Not Reported
6	Ma et al., 2024 [43]	Cox proportional hazard regression models (*p*-interaction and Hazard Ratio), RERI, AP, Aalen Additive Hazard Model	-	Multiplicative Positive Additive	Not reported (unclear)	Not Reported
7	Liu et al., 2024 [44]	Cox proportional hazard regression models (*p*-interaction and Hazard Ratio)	Stratified Analysis	Multiplicative	$PM_{2.5}$: $p = 0.48$ (**Not Significan** PM_{10}: $p = 0.79$ (**Not Significant**) NO_2: $p < 0.07$ (**Not Significant**)	Not Reported
8	Huang et al., 2024 [45]	Cox proportional hazard regression models (*p*-interaction and Hazard Ratio)	Stratified Analysis	Multiplicative	Not reported (unclear)	Not Reported
9	Wang et al., 2022 [46]	Cox proportional hazard regression models (*p*-interaction and Hazard Ratio), RERI, AP	-	Multiplicative Positive Additive	All *p*-interaction > 0.05 (**Not Significant**)	Not Reported
10	Rhee et al., 2024 [47]	Not Reported	Visual Trend and Stratified HR	Descriptive only	Not reported (unclear)	Not Reported

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No	Study	Formal Interaction	Informal Interaction	Interaction Type	Interaction Significance and Strength	Multiple Testing Correction
11	Li et al., 2022 [48]	Cox proportional hazard regression models (*p*-interaction and Hazard Ratio)	Narrative Interpretation	Multiplicative	*p*-interaction < 0.001 (**Strong Evidence**)	Not Reported
12	Chen et al., 2024 [49]	Cox proportional hazard regression models (*p*-interaction and Hazard Ratio), RERI, AP	-	Multiplicative Positive Additive	*p*-interaction (multiplicative) = 0.275 (**Not Significant)** *p*-interaction (additive) = 0.00123 (**Significant**)	Not Reported
13	Wu et al., 2024 [50]	Not Available	Narrative Association	Informal	PM_{10}: $p = 0.002$ (**Significant**), $PM_{2.5}$: $p = 0.105$ (**Not Significant**), NO_2: $p = 0.051$ (**Not Significant**) PM_{10} (Additive): **Not Reported.**	Not Reported
14	Zhang et al., 2024 [51]	Not Available	Stratified Analysis	Informal	Not reported (unclear)	Not Reported
15	Gao et al., 2023 [52]	Not Reported	Synergistic/ enhancing effect (Gene Environment Interaction)	Multiplicative	Not reported (unclear)	Not Reported
16	Zhang et al., 2024 [53]	Cox proportional hazard models (*p*-interaction and Hazard Ratio), RERI, AP	-	Multiplicative Positive Additive	HR interaction term reported (exact p not stated); RERI, and AP stated.	HMP (harmonic mean *p*-value); PFWE & PFDR in imaging

Note: Abbreviations: FDR, False Discovery Rate; RERI, Relative Excess Risk due to Interaction (the proportion of disease among those with both the exposure and the genotype that is attributable to their interaction); AP, Attributable Proportion due to Interaction (the proportion of disease in the population that is attributable to the interaction between the exposure and genotype); HR, Hazards Ratio; $PM_{2.5}$, Particulate Matter with a diameter ≤ 2.5 μm; PM_{10}, Particulate Matter with a diameter ≤ 10 μm; NO_2, Nitrogen Dioxide; NO_x, Nitrogen Oxides; HMP, Harmonic Mean *p*-value; PFWE, Permutation-based Family-Wise Error rate; and PFDR, Permutation-based False Discovery Rate. **Formal interaction testing** includes **regression-based interaction terms** (e.g., *p*-interaction), as well as measures on the **additive scale** such as RERI (Relative Excess Risk due to Interaction), AP (Attributable Proportion), and the Synergy Index. **Informal interaction testing** includes subgroup or stratified analysis, visual inspection of effect modification across strata, or narrative/descriptive comparisons without formal statistical interaction terms. **Interaction type** refers to whether the interaction was evaluated on the **additive scale**, **multiplicative scale**, or only through **informal exploration** (without formal statistical testing). **Multiple testing correction** refers to statistical methods used to adjust for the number of tests performed, such as Bonferroni correction or False Discovery Rate (FDR) control, and Harmonic Mean *p*-value (HMP).

3.2. Methods to assess genetic susceptibility and pollutant exposure

In this section, we describe the specific methods used within the 16 included studies to assess genetic susceptibility and pollutant exposure. We focus on *how* these measurements were implemented in the context of the reviewed literature, rather than providing a general overview of these methods.

3.2.1. Assessment of genetic susceptibility

Among the 16 articles reviewed, 14 focused on genetic susceptibility, 1 examined epigenetic modification, and 1 study entailed both genetic susceptibility and epigenetic modification. Table 3 summarizes the focus of these articles.

Table 3. Summary of study focus.

Study Type	**Number of Articles**
Genetic Susceptibility	13
Epigenetic Modification	2
Both Genetic and Epigenetic	1

Note: Table 3 provided a breakdown of the types of studies included in this review.

After assessing general genetic susceptibility, we also explored gene-environment (GxE) interactions; how genetic factors may modify the health effects of air pollution exposure. Table 4 presents an overview of these studies, focusing on the use of **genotyping** or **DNA methylation** methodologies.

Table 4. Overview of Studies on GxE Interactions Using Genotyping or DNA Methylation.

Study	Population	Methodology	Exposure (Pollutant)	Outcome (Disease)	Type of analysis	Key findings
Gruzieva et al., 2016 [38]	Newborns, child-aged 4 and 8 from European and North America (*n* = 1508 newborns, *n* = 733 at age 4, *n* = 786 at age 8).	DNA methyla-tion (Epige-nome-Wide),meta-analysis of cohort study.	Prenatal NO_2 exposure.	Altered DNA methylation at CpG sites in FAM13A and NOTCH4.	Epigenetic Modification.	Early life epigenetic markers link to respiratory disease later.
Huang et al., 2021 [39]	455,974 partici- pants aged 40–69 years (UK Biobank).	PRS calculation based on 18 SNPs In lung cancer; Land-Use Regres-sion (LUR) models; Analytical cohort study.	Ambient air pollution ($PM_{2.5}$, NO_2, PM_{10}, NO_x).	Lung cancer incidence.	Genetic risk interaction/ Environmental exposure Statistical (Cox proportional Hazard models); RERI, AP.	Air pollution exposure signi- ficantly associa- ted with higher likelihood of lung cancer (63% higher), particularly among individuals with high genetic susceptibility.
Ma et al., 2024 [40]	449,463 participants aged 37–73 years from the UK Biobank.	Polygenic risk score (PRS) based on 31 SNPs; Air pollution exposure data; cohort study.	Long-term exposure to air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO_x).	Incidence of Abdominal Aortic Aneurysm (AAA).	Genetic susceptibility, Statistical (Cox proportional hazard models).	Long-term air pollution exposure is associated. with increased likelihood of AAA; genetic risk (PRS) also plays a role in susceptibility.
Li et al., 2023 [41]	354,897 participants aged 37–73 years from the UK Biobank.	Polygenic risk score (PRS), using 17 MDD-associated genetic loci (17 SNPs); Land-Use Regression (LUR) models; cohort study.	Long-term exposure to air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO_x).	Incidence of Major Depressive Disorder.	Genetic susceptibility, Statistical (Cox proportional hazard models).	Long-term air pollution exposure is associated with increased likelihood of MDD; genetic risk (PRS) also plays a role in susceptibility.
Fu et al., 2023 [42]	407,470 participants aged 40–69 years from the UK Biobank.	CAD genomewide association meta-analysis with-out the UK Biobank population with 40 SNPs; cohort study.	Long-term exposure to air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO_x).	Incidence of Coronary Artery Disease (CAD).	Genetic susceptibility, Statistical (Cox proportional hazard models, RERI, AP).	Long-term air pollution exposure is associated with increased likelihood of CAD; genetic risk (PRS) also plays a role in susceptibility.
Ma et al., 2024 [43]	452,196 partici years from the UK Biobank.	Polygenic risk score (PRS) Calculation With 71 SNPs; cohort study	Long-term air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO_x).	Incidence of Stroke, Ischemic Stroke, Hemorrhagic Stroke.	Genetic susceptibility, Statistical (Cox proportional hazard models).	Long-term air pollution exposure is associated with increased likelihood of stroke. genetic risk (PRS) also plays a role in susceptibility.

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Study	Population	Methodology	Exposure (Pollutant)	Outcome (Disease)	Type of analysis	Key findings
Liu et al., 2024 [44]	485,288 participants) aged 37–73 years from the UK Biobank.	Genome-wide association studies; Polygenic risk score (PRS) calculation, cohort study.	Long-term air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO_x).	Incidence of schizophrenia.	Genetic susceptibility, Statistical (Cox proportional hazard models).	Long-term air pollution exposure is associated with stronger association with schizophrenia; genetic risk (PRS) also plays a role in susceptibility.
Huang et al., 2024 [45]	over 312,000 participants. Average aged 57 years.	Polygenic risk score (PRS) Calculation; cohort study.	Long-term air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO_x).	Incidence of Parkinson's Disease (PD).	Genetic susceptibility, Statistical (Cox proportional hazard models).	Long-term air pollution exposure is associated with higher odds of Parkinson's Disease (PD); genetic risk (PRS) also plays a role in susceptibility.
Wang et al., 2022 [46]	452,762 participants aged 37–73 years from the UK Biobank.	Genotyping by Affymetrix Research Services Laboratory in 106 sequential batches of ap Prox. 4,700 samples; selected 22 SNPs associated with COPD; Weighted genetic risk score calculation; cohort study.	Long-term air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO_x).	Incidence of chronic obstructed Pulmonary Disease (COPD).	Genetic susceptibility, Statistical (Cox proportional hazard models).	Long-term air pollution exposure is associated with stronger likelihood of COPD; Weighted genetic risk also plays a role in susceptibility.
Rhee et al., 2024 [47]	249 082 participants aged 40–69 years.	Genotyping of 807411 SNPs; Polygenic risk score (PRS) calculation, cohort study.	Long-term air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO_x).	Incident CardioVascular Disease (CVD).	Genetic susceptibility, Statistical (Cox proportional hazard models).	Long-term air pollution exposure is associated with increased odds of Cardiovascular Disease (CAD); genetic risk (PRS) also plays a role in susceptibility. No significant interactions between genetic risk and PM2.5 exposure on cardiovascular death or CVD events.
Li et al., 2022 [48]	41,149 participants from China-PAR.	Polygenic risk score (PRS) calculation based on 540 genetic variants; cohort study.	Long-term air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO_x).	Incidence of Coronary Artery Disease (CAD).	Genetic susceptibility, Statistical (Cox proportional hazard models).	Long-term air pollution exposure is associated with increased odds of Coronary Artery Disease (CAD); polygenic risk score (PRS) also plays a role in susceptibility.
Chen et al., 2024 [49]	453,919 individuals aged 40–69 years; White European descent.	DNA methylation alterations at CXCR2 and sites within the MHC class III region.	Long-term air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO_x).	Incidence of Ulcerative colitis (UC).	Epigenetic Modification; Statistical (Cox proportional hazard models; epigenetic Mendelian Randomization approach).	Higher exposures to NOx, NO2, PM2.5 and combined air pollution score were associated with incident UC but not CD.

Continued on next page

Study	Population	Methodology	Exposure (Pollutant)	Outcome (Disease)	Type of analysis	Key findings
Wu et Al., 2024 [50]	474,055 participants aged 40–69 yaers.	Polygenic risk Score (PRS) Calculation; cohort study.	Long-term air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO_x).	Incident Psoriasis.	Genetic susceptibility, Statistical (Cox proportional hazard models); RestricTed Cubic Spline Models; sensitivity analyses.	There was an interaction between air pollution and genetic suscptibility in relation to psoriasis.
Zhang et al., 2024 [51]	522 healthy participants aged 40–69 years living in Beijing	Polygenic risk score (PRS) calculation; DNA methylation; cross-sectional study.	Long-term air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO_x).	Depression on processing speed.	- Genetic susceptibility: PRS; - Epigenetic Modification: DNA Methylation; - Genetic Modification (of EnVironmental Effects): GLM, and PLSR.	Air pollution may be associated with an increased likelihood of cognitive impairment in individuals genetically predisposed to dePression. The article does not provide specific effect sizes, but it describes the direction of the interaction (worsening effect with combined exposure and higher polygenic risk score).
Gao et al., 2023 [52]	502,536 participants from the UK Biobank, recruited in 2006–2010.	Polygenic risk score calculation (Depression: 37 SNPs Anxiety: 9 SNPs); Land-Use Regression (LUR) models; cohort study.	Long-term air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO_x).	Risk of Depression and Anxiety.	Genetic susceptibility, Statistical (Cox proportional hazard models).	Elevated levels of the five air pollutants were associated with higher odds of mental disorders at baseline.
Zhang et al., 2024 [53]	401,244 participants aged 40–69 years.	This article used genotyping data in2 ways: * **Targeted** genotyping: To get the APOE ε4 status. * **Genome-wide** genotyping: As the basis for calculating a PRS that incorporates many genetic variants associated with the outcome of interest (likely dementia or related traits).	Long-term air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO_x).	Incident Demensia.	Genetic susceptibility, Statistical (Cox proportional hazard models and Restricted Cubic Spline Regression).	Joint exposure to multiple air pollutants is associated with higher odds of dementia, especially among individuals with high genetic susceptibility.

Note: Abbreviations: GxE: Genotype by Environment; DNA: Deoxyribonucleic Acid; NO_2: Nitrogen Dioxide; CpG: Cytosine-phosphate-Guanine; *FAM13A*, *NOTCH4*: Specific gene names involved in various biological processes (Further explanation could be provided in the main text if relevant to the study's focus). *Italicized gene names indicate standard gene nomenclature;* PRS: Polygenic Risk Score; LUR: Land-Use Regression; $PM_{2.5}$: Particulate Matter with a diameter of 2.5 micrometers or less; PM_{10}: Particulate Matter with a diameter of 10 micrometers or less; GLM, General Linear Model; and PLSR, Partial Least Squares Regression.

Table 4 provides an overview of studies on gene-environment interactions (GxE) using genotyping or DNA methylation. The studies listed highlight how genetic factors may influence the health outcomes of air pollution exposure, with a particular focus on epigenetic modifications like DNA methylation at specific CpG sites.

The assessment of genetic susceptibility in the included studies primarily focused on identifying specific genetic variants associated with increased risk of adverse health outcomes related to air pollution exposure. Many studies aimed to explore how genetic differences could modify the harmful effects of pollutants like $PM_{2.5}$, PM_{10}, NO_2, and NO_x on health outcomes.

- **Genotyping Methods Used in Included Studies:** Most researchers employed genotyping techniques, with **SNP arrays** being the most common method (n = 14). These arrays enabled the detection of a wide range of single nucleotide polymorphisms (SNPs) across multiple genes. **Illumina Human Omni Express arrays** were utilized in some studies to assess SNPs related to oxidative stress and inflammatory pathways. Additionally, **PCR-based genotyping** methods, such as **TaqMan assays**, were used in a few studies to investigate specific candidate genes linked to air pollution-related health effects. Only a smaller number of studies (n = 2) employed **whole-genome sequencing (WGS)** to explore broader genetic variations, although this method was applied in a limited number of participants due to cost and technical constraints.
- **Candidate Genes and Genome-Wide Association Studies (GWAS)**: A combination of **candidate gene** approaches (n = 8) and **GWAS** (n = 7) were used in these studies to explore the genetic basis of susceptibility to air pollution-related health risks. Candidate gene studies often targeted well-known genes involved in inflammation or detoxification. In contrast, **GWAS** enabled the identification of novel genetic variants associated with exposure to pollutants.
- **Gene-Environment Interactions**: Several researchers in this review focused on **gene-environment interactions**, which investigate how genetic susceptibility can modify the health effects of air pollution exposure. In these studies, genetic data were typically obtained from blood, saliva, or buccal samples, and air pollution exposure was assessed through monitoring data or Land Use Regression (LUR) models [39,41,52]. Notably, the studies by Zhang et al. (2024) employed genotyping methods to examine the role of genetic polymorphisms in genes such as APOE ε4, FRMD8, DDX1, DNMT3L, MORC1, and TGM2 which are involved in specific biological pathways relevant to air pollution exposure such oxidative stress, neuroinflammation, and epigenetic regulation. These researchers found that certain genetic variants significantly influenced the association between air pollution exposure and incident Dementia [53].
- **Data Analysis and Quality Control**: Rigorous data analysis methods were employed across the studies to ensure the accuracy of genetic susceptibility results. Standard quality control measures, including filtering based on **minor allele frequency**, **call rates**, and testing for **Hardy-Weinberg equilibrium**, were commonly used to minimize errors. These procedures ensured that the genotyping data were reliable for assessing the associations between genetic variants and health outcomes [47].

3.2.2. Assessment of pollutant exposure

The assessment of pollutant exposure in the included studies predominantly relied on environmental monitoring, modeling techniques, and personal exposure measurements to estimate the levels of air pollution to which study participants were exposed.

- **Environmental Monitoring and Air Quality Data**: A common method used in the studies was to obtain air quality data from government or environmental monitoring stations. These stations typically provide reliable data on the concentrations of pollutants, such as $PM_{2.5}$, PM_{10}, NO_2, and NO_x, at specific geographic locations. For example, several researchers (e.g., Zhang et al., 2024) utilized data from national or regional monitoring stations to estimate exposure for large cohorts. These data were often combined with residential or work addresses to estimate long-term exposure levels [51].
- **Land Use Regression (LUR) Models**: Many researchers (e.g., Huang et al., 2021, Li et al., 2023, Fu et al., 2023; and Gao et al., 2023) employed land use regression (LUR) models to predict pollutant levels in areas where direct monitoring data were not available. LUR models are particularly useful in estimating spatial variation in air pollution exposure by integrating geographical data, land use patterns, and other environmental factors. These models were applied to derive individual-level exposure estimates based on participants' residential locations. Different LUR models were used across studies, with varying levels of complexity and input data [39,41,42,52].
- **Modeling Approaches**: Some studies employed advanced modeling approaches, including **dispersion models** and **satellite-based models**, to estimate air pollution exposure. For example, several studies based on the UK Biobank (e.g., Ma et al., 2024 [40]; Liu et al., 2024 [44]; Wu et al., 2024 [50]; Zhang et al., 2024 [53]) used **DEFRA air dispersion models** with a 1 × 1 km resolution to assign annual average pollutant concentrations to participants' residential addresses. In addition, Li et al., 2022 [48] applied a **satellite-based model** that combined aerosol optical depth (AOD) data with meteorological and land-use information using machine learning algorithms to estimate fine-scale $PM_{2.5}$ exposure. These modeling approaches are particularly valuable in regions without dense monitoring station coverage.
- **Exposure Duration and Temporal Patterns**: Most studies evaluated long-term exposure (e.g., chronic exposure over years), but a few focused on short-term or acute exposure in relation to specific health outcomes (e.g., respiratory exacerbations or cardiovascular events). However, seasonal variations or temporal patterns of exposure were generally not explored in detail.
- **Exposure-Response Assessment**: Many studies included an exposure-response analysis to explore the relationship between pollutant levels and specific health outcomes. These studies often adjusted for confounding factors such as age, gender, socioeconomic status, and pre-existing health conditions to determine the strength and consistency of the exposure-response relationship [39,41,47].

In summary, the assessment of pollutant exposure in the reviewed studies utilized a combination of monitoring data and modeling techniques (including LUR, dispersion models, and satellite-based approaches). None of the included studies used personal exposure monitoring devices. The methodologies employed provided valuable insights into the health effects of air pollution by offering both spatially and temporally accurate exposure estimates.

3.2.3. Integration of genetic and exposure assessments

The integration of genetic and exposure assessments is essential for understanding the complex interactions between genetic susceptibility and environmental exposures such as air pollution. In this section, we describe how researchers in this review combined genetic and environmental exposure data to examine gene-environment interactions (GxE), providing a deeper understanding of how genetic factors influence the effects of air pollution on health outcomes.

- **Stratified Analysis:** Some researchers in this review employed stratified analysis, where participants were divided into subgroups based on specific genetic variants to assess whether the effects of exposure differed between these subgroups. While not all studies used this approach, stratified analysis is commonly used to identify gene-environment interactions. For example, researchers have focused on polymorphisms in genes like GSTP1, involved in detoxification pathways, to explore how genetic variation might influence the response to air pollution. This approach provides deeper insights into how genetic factors can modify the health impacts of air pollution exposure [44,45,51].
- **Interaction Terms in Regression Models:** Statistical models (e.g., linear regression, and logistic regression) are used to test for the interaction between genetic variants and exposure variables. An interaction term is included in the model to assess whether the effect of exposure differs depending on genotype [39–46,48,49,53].
- **Gene-Environment Interaction (GxE):** Gene–environment interaction (GxE) occurs when the impact of environmental exposure, such as air pollution, on health outcomes varies according to an individual's genetic profile. Among the 16 included studies, several explicitly tested GxE interactions using either multiplicative interaction terms in regression models or stratified analyses based on genetic risk categories (e.g., polygenic risk scores). These studies demonstrated that genetic susceptibility can modify the relationship between exposure to pollutants (e.g., $PM_{2.5,}$ and NO_2) and outcomes such as cardiovascular disease, major depressive disorder, or stroke. For example, some studies reported significantly greater adverse effects of air pollution among individuals in the highest tertile of genetic risk compared to those at lower risk [41,42,44,46,48–50].

In summary, the integration of genetic and exposure assessments using methods such as stratified analysis, regression models with interaction terms, GWIS, and consideration of gene-environment correlations provides valuable insights into how genetic susceptibility influences the health effects of air pollution. These approaches enhance our understanding of gene-environment interactions and are crucial for advancing precision medicine, where interventions can be tailored based on an individual's genetic profile and environmental exposures.

Note on Supplementary Materials: Due to the extensive nature of the data presented, Supplementary Table S4 provides a detailed summary of the key findings, conclusions, and limitations of the included studies. To ensure the flow and readability of the main text, this table has been moved to the Supplementary Materials section. Readers can refer to Supplementary Table S4 in the supplementary materials for a comprehensive overview of the studies included in this review.

3.2.4. Gene-environment interactions

A detailed analysis of gene-environment interactions was conducted to explore how genetic predisposition modulates the health effects of air pollution. In Supplementary Table S3, we summarize the interactions between genetic markers and environmental exposures, such as $PM_{2.5}$, PM_{10}, NO_2, and NO_x, across multiple health outcomes, including cardiovascular diseases, respiratory conditions, and mental health disorders.

Key findings include:

- Significant interactions between specific genetic polymorphisms and pollutant exposure levels, with the strongest effects observed for cardiovascular diseases and mental health disorders.
- Variations in effect sizes (e.g., odds ratios, and hazard ratios) highlight the heterogeneity in genetic susceptibility to air pollution exposure across populations.
- Specific metrics such as Relative Excess Risk due to Interaction (RERI) and Attributable Proportion (AP) underscore the additive effects of genetic predisposition and environmental exposures on disease risk.

This table provides a comprehensive overview of the statistical evidence supporting the modifying role of genetic susceptibility in health outcomes associated with air pollution.

4. Discussion

The complex interplay between genetic predisposition and environmental exposures has emerged as a key area of research in understanding disease risk and health disparities. This review contributes to the growing body of literature by examining gene-environment interactions in the context of air pollution and their impact on various health outcomes [8,35,57].

4.1. Regarding the association between genetic predisposition and air pollution exposure

The interaction between genetic predisposition and environmental factors, such as air pollution, has garnered increasing attention in recent years due to its potential impact on disease risk. Our findings contribute to this growing body of literature, highlighting the significant role that genetic susceptibility plays in modifying the effects of air pollution on health outcomes [11,32,38,43,48–50,57–60].

The additive effects observed in individuals with both high genetic susceptibility and high exposure to air pollution align with prior studies suggesting that genetic factors may amplify the adverse health effects of environmental pollutants. Specifically, we found that individuals at higher genetic risk exhibited more pronounced health deterioration when exposed to higher levels of air pollution. This combined effect, where the interaction between genetic susceptibility and environmental exposure exceed the sum of their individual effects, is consistent with other studies emphasizing the exacerbating role of genetic factors in the harmful effects of environmental stressors [39,48].

Furthermore, genetic predisposition appears to modify the impact of air pollution exposure across various diseases, including cardiovascular diseases (CVD), respiratory conditions, and mental health disorders. These findings underscore the critical role of gene-environment interactions in shaping

health outcomes. A detailed summary of gene-environment interactions, including the effect sizes, p-values, and health outcomes, is provided in Supplementary Table S3.

4.2. Regarding disease-specific findings

In line with other studies, long-term exposure to pollutants such as $PM_{2.5}$, NO_2, and PM_{10} was significantly associated with a higher likelihood of various diseases (e.g., lung cancer, cardiovascular disease, and stroke), especially among individuals with higher genetic susceptibility [38–53].

Our results confirm that the combined effect of air pollution and genetic predisposition plays a critical role in the development of complex diseases, including mental health disorders (e.g., schizophrenia, and Major Depressive Disorder) and cardiovascular diseases (e.g., abdominal aortic aneurysms). For conditions like ulcerative colitis and psoriasis, our findings suggest that air pollution exposure may be a modifiable environmental contributor, particularly for those genetically predisposed. This highlights the potential for public health interventions to target these conditions by addressing environmental exposures, such as through improved air quality policies. Further details of these interactions are presented in Supplementary Table S3.

4.3. Implications for public health and precision medicine

These findings underscore the need for personalized approaches in environmental health, where genetic susceptibility should be considered when assessing the potential impact of air pollution exposure. Identifying individuals with high genetic susceptibility for specific diseases and high exposure to air pollution could help target interventions and preventive strategies more effectively. For example, individuals with genetic susceptibility to respiratory diseases might benefit from policies aimed at reducing air pollution exposure in urban areas. Public health strategies could include prioritizing air quality improvements in regions with high genetic vulnerability indices, or incorporating genotyping into early screening programs in pollution-heavy urban centers [49,50,58].

While this review does not provide in-depth methodological analysis of these tools, we emphasize their future relevance for advancing the field. Although none of the included studies employed integrative multi-omics or machine learning techniques, these emerging methodologies are increasingly recognized as powerful tools in precision environmental health. They hold promise for uncovering novel mechanistic pathways and enabling more accurate risk stratification based on complex gene-environment interactions [17,18,21,29].

Specifically, multi-omics and machine learning could significantly improve our understanding of how genetic factors modulate responses to air pollution, providing insights that could refine health outcome predictions and support personalized prevention strategies [18–21,29,60,61].

Although genome-wide interaction studies (GWIS) were not identified among the included studies, researchers should consider applying GWIS to detect novel loci involved in pollution-related health effects [29,32,58,62]. In addition, gene–environment correlation (rGE), where certain genetic traits predispose individuals to environments with higher pollution exposure, was not addressed in the included studies but remains an important methodological consideration for future analyses [63,64]. Experimental studies have also highlighted the relevance of mechanistic pathways, such as aryl

hydrocarbon receptor (AhR) signaling in response to $PM_{2.5}$ exposure, yet this pathway was not explored in the reviewed epidemiological literature. These mechanisms warrant further investigation to strengthen the biological plausibility of GxE associations [65,66]. In addition, future studies employing toxicological or experimental approaches, such as in vivo or organoid models, are needed to explore mechanistic pathways (e.g., oxidative stress, inflammation, and epigenetic regulation), which would strengthen the biological plausibility of observed GxE associations.

The data in Supplementary Table S3 support the potential value of combining genetic and environmental risk profiling in public health efforts, particularly in identifying and protecting vulnerable populations. As such, future research that integrate genetic data **with high-resolution exposure models, epigenomics, and machine learning algorithms** could substantially enhance targeted prevention strategies [38–53].

4.4. Limitations and recommendations for future research

While most included studies relied on observational designs, our findings are limited by the inability to establish causality and may be affected by residual confounding, particularly in the assessment of genetic susceptibility and environmental exposure [54,67]. Based on the current evidence, we provide several recommendations for future research directions.

While we acknowledge that 12 of the 16 included studies were conducted in European populations or used UK Biobank data, the implications of this geographic and ethnic skew deserve deeper discussion. The lack of representation from non-European ancestry groups raises concerns about the external validity and equity of current GxE findings, particularly in the context of global precision health efforts. Equity and diversity should be central considerations when translating GxE insights into public health strategies [68,69]. Recent advances in interaction testing frameworks have made it more feasible to detect complex GxE effects across populations [70]. Future research must explicitly include underrepresented populations, both to validate current findings and to uncover population-specific interactions that may be masked in predominantly European datasets [71]. This approach will enhance the relevance and fairness of GxE-informed precision health interventions on a global scale.

Further studies should address these limitations by incorporating more accurate exposure data, such as personal monitoring of air pollution, and exploring gene-environment interactions in more diverse populations to enhance the generalizability of the results [8,70–72].

One study included in this review, one by Chen et al. (2024), presents distinct methodological considerations. While described as a cohort study, its structure is more akin to a cross-sectional or nested case-control design, as it lacks precise temporal data on ulcerative colitis onset [49]. This weakens the temporal relationship and introduces potential for reverse causation, which may limit causal inference. To mitigate these limitations, the authors employed epigenetic analysis and Mendelian randomization as complementary methods to strengthen causal interpretation [54–56]. Nevertheless, the absence of longitudinal follow-up reduces its methodological comparability with the prospective cohort studies included in this review. Therefore, quality assessment was performed using the JBI checklist rather than the Newcastle-Ottawa Scale, which better aligns with the study's epigenetic and case-control framework [35,37]. Future studies investigating gene–environment

interactions in ulcerative colitis should aim to replicate these findings using longitudinal designs with clearer temporal sequencing and larger population-based samples.

In addition, future studies would benefit from utilizing **multi-omics** approaches and **machine learning** techniques to explore the mechanistic pathways that link air pollution exposure with epigenetic changes and genetic predisposition in the development of complex diseases. These technologies have been highlighted as powerful tools to advance exposome research and understand causal biological mechanisms [17–21]. Such approaches hold great promise in identifying new biomarkers and uncover complex, multifactorial interactions that might otherwise be missed. The section on emerging technologies such as AI and multi-omics could also be expanded in future research to provide more detailed elaboration on their potential applications in improving exposure modeling, identifying complex gene-environment interactions, and enhancing risk prediction [21].

Moreover, **longitudinal designs** with larger, multi-ethnic samples and **standardized exposure assessments** will improve the robustness of future findings and enable a more nuanced interpretation of gene–environment dynamics over time. Although causality cannot be definitively inferred from observational data, enhancing study design and incorporating mechanistic approaches, such as multi-omics and molecular exposomics, can substantially strengthen the evidence base and help clarify potential biological pathways [20,21,73–80].

Finally, disease-specific recommendations should be considered. For instance, prioritizing the development and validation of polygenic risk scores (PRS) for conditions such as stroke, where strong genetic signals have been identified (e.g., Ma et al., 2024) [43], may help refine individual-level susceptibility profiling and enable more targeted public health responses [73–80]. Furthermore, as the field progresses towards potential applications of genetic information in public health strategies, careful consideration must be given to the **ethical implications of genetic screening**. These include ensuring robust data privacy and security measures, obtaining informed consent, addressing the potential for genetic discrimination, ensuring equitable access and implementation, and promoting responsible interpretation and application of genetic risk profiles [81].

4.5. Mechanistic evidence supporting GxE effects

Researchers using animal models and organoid systems demonstrate that air pollution triggers molecular events such as ROS overproduction, mitochondrial dysfunction, and cytokine dysregulation, which may interact with genetic predispositions to exacerbate disease processes [82,83]. For example, in vivo models have shown that particulate matter exposure leads to neuroinflammation and cognitive impairment via the NF-κB and Nrf2 signaling pathways, providing insight into mechanisms potentially relevant to mental health outcomes [84,85]. Similarly, lung and cardiovascular organoid models have revealed pollutant-induced endothelial dysfunction and inflammatory responses that mirror pathways implicated in human genetic risk loci [86,87].

A recent review highlights how organoid and animal-based approaches are increasingly used to uncover the cellular and molecular mechanisms linking environmental exposures with chronic disease phenotypes. These mechanistic insights are essential for interpreting GxE interactions and underscore the need for integrative frameworks that combine epidemiological, genetic, and experimental evidence in environmental health research [88,89].

To provide biological plausibility to the epidemiological associations observed in this review, it is important to consider experimental studies that elucidate underlying mechanisms. Toxicological and in vivo models have consistently shown that exposure to air pollutants such as $PM_{2.5}$, NO_2, and diesel exhaust particles can induce oxidative stress, systemic inflammation, and epigenetic changes; pathways that are also implicated in the genetic susceptibility to complex diseases [90,91].

5. Conclusions

This review underscores the critical role of gene-environment interactions in shaping health outcomes, particularly in the context of air pollution exposure. Our findings suggest that genetic susceptibility may modify the associations of air pollution across various diseases, including cardiovascular conditions, respiratory disorders, and mental health challenges. These results provide compelling evidence for the need to integrate genetic data into environmental health research, enhancing our understanding of the complex relationships between pollution exposure and disease risk.

Given the observational nature of the included studies, causal relationships cannot be definitively established. Nonetheless, the patterns identified across the reviewed literature point to potentially important gene–environment interactions that merit further investigation through mechanistic and experimental studies.

The implications of these findings extend beyond scientific research, emphasizing the development of precision public health strategies. Identifying individuals with heightened genetic risk can enable the development of targeted prevention strategies, such as localized air quality interventions or early screening efforts for at-risk populations. In parallel, these insights reinforce the need for broad efforts to reduce air pollution exposure as a population-wide preventive strategy.

To improve the applicability of these findings, we recommend prioritizing the development of polygenic risk scores (PRS) for diseases with strong and consistent GxE signals, particularly stroke, as highlighted in recent studies such as Ma et al. (2024) [43]. Furthermore, enhancing air pollution monitoring systems in rapidly urbanizing low- and middle-income countries (LMICs) is essential to address current data gaps and guide targeted public health interventions.

Researchers should also incorporate mechanistic studies, including those using organoid and in vivo models, to support the biological plausibility of GxE effects. These experimental approaches can help elucidate key pathways such as oxidative stress, inflammation, and epigenetic modifications, thereby strengthening the interpretation of epidemiological associations.

Finally, to ensure the equity and global relevance of GxE research, future studies must include more diverse populations beyond those of European ancestry. By integrating genetic, environmental, and mechanistic evidence, future precision health strategies can be more effectively tailored to protect high-risk individuals and address the growing global burden of pollution-related diseases.

Use of AI tools declaration

The author declare he has not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The author declares no conflicts of interest.

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Review

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

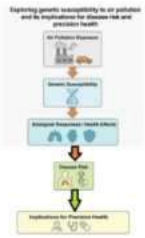
Hari Krismanuel[1]*

[1]Faculty of Medicine, Universitas Trisakti, West Jakarta, DKI Jakarta, Indonesia

***Correspondence:** Email: hari_krismanuel@trisakti.ac.id.

Abstract: Air pollution, comprising a complex mixture of gaseous and particulate pollutants, remains a major global health concern, that disproportionately affects vulnerable populations. This scoping review aims to systematically investigates 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 (NO_2), and nitrogen oxides (NO_x) - key pollutants consistently link to adverse health effects. By exploring the gene-environment interactions underlying air pollution-related conditions, this review offers new insights into how genetic factors may 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 are thought to influence individual variation in responses to PM2.5, PM10, NO_2, and NO_x. Although none of the included studies employed multi-omics or machine learning approaches, this review identifies these tools as promising directions for future research aimed at elucidating mechanistic pathways and informing personalized strategies. These techniques could significantly improve the understanding of gene-environment interactions, and are suggested as emerging methodologies for future studies. However, the scarcity of longitudinal studies and the underrepresentation of diverse populations limit the generalizability of the current findings. Addressing these gaps will be essential for advancing research, improving environmental health equity, and informing policy in the context of air pollution and genetic susceptibility.

Keywords: air pollution, disease risk, environmental health, genetic susceptibility, personalized medicine, precision health.



Graphical Abstract

This graphical abstract illustrates the conceptual pathway from air pollution exposure to genetic

susceptibility, leading to increased disease risk. The green arrow highlights how disease risk, influenced by gene-environment interactions, informs the development of precision health strategies tailored to individual susceptibility.

1. Introduction

Air pollution remains one of the most significant environmental risk factors worldwide, contributing to an estimated 7 million premature deaths annually, according to the World Health Organization [1,2,3]. Among the most harmful pollutants are fine particulate matter (PM2.5), coarse particulate matter (PM10), nitrogen dioxide (NO2), and nitrogen oxides (NOx) are consistently associated with adverse health outcomes [4,5,6].

PM2.5 and PM10 refer to airborne particles with aerodynamic diameters ≤2.5 and ≤10 micrometers, respectively. These particles can penetrate deep into the respiratory tract, triggering oxidative stress, inflammation, endothelial dysfunction, and systemic effects beyond the lungs. **NO2 and NOx**, primarily emitted from vehicle exhaust and industrial processes, contribute to airway inflammation, impaired lung function, and increased cardiovascular risk. Exposure to these pollutants has been linked to the development and exacerbation of chronic diseases such as asthma, chronic obstructive pulmonary disease (COPD), ischemic heart disease, stroke, and even neurodegenerative conditions [4,5,6].

Recent fine-scale modeling and exposure assessment studies, such as that of Nisticò et al. (2025), emphasize the importance of high-resolution pollution data in identifying vulnerable populations and guiding local-level interventions. Understanding the complex interplay between environmental exposures and individual susceptibility, particularly at the molecular level, is crucial for developing targeted public health interventions. This necessitates the integration of detailed environmental monitoring data with comprehensive health surveillance and molecular research, including the investigation of genetic factors that may modify an individual's response to air pollution [7].

Genetic susceptibility to air pollution refers to the predisposition of certain individuals to experience heightened adverse health effects due to specific genetic variations. Genes involved in oxidative stress pathways play critical roles in neutralizing reactive oxygen species generated by pollutants like fine particulate matter (PM2.5). Understanding these genetic mechanisms is crucial for explaining why some populations exhibit increased vulnerability to air pollution-related diseases [8, 9, 10].

Air pollution remains a major global health challenge, imposing significant health burdens worldwide. Primary pollutants, such as PM2.5, nitrogen dioxide (NO2), ozone, and volatile organic compounds (VOCs), are widely acknowledged as key contributors to diseases across multiple systems. However, while environmental exposures are well-documented as primary drivers, genetic variations significantly modulate individual susceptibility, disproportionately affecting vulnerable populations. Despite its importance, the interaction between genetic predisposition and pollutant exposure remains underexplored, leaving critical gaps in our understanding of the mechanisms driving health disparities [11, 12, 13].

Recent advancements in genetic research have illuminated how genetic variants influence sensitivity to oxidative stress, inflammation, DNA damage, and epigenetic modifications, all of which are implicated in pollution-related diseases. However, significant challenges persist, including inconsistent findings across studies due to methodological differences and the underrepresentation of diverse populations in genetic analyses. Genome-wide association studies (GWAS) have identified promising genetic markers, yet these findings often lack generalizability due to limited population diversity and a lack of comprehensive models that integrate genetic and environmental factors [14,15].

To address these gaps, emerging methodologies such as multi-omics integration and machine

learning are increasingly recognized as powerful tools to uncover complex gene-environment interactions. While these techniques were not employed in the studies included in this review, they hold great promise for future research aimed at identifying mechanistic pathways and advancing precision health strategies [16,17,18,19].

This review addresses these gaps by systematically analyzing 16 peer-reviewed studies published over the past decade to provide a detailed synthesis of the interplay between genetic and environmental factors in determining health risks associated with air pollution. By focusing on oxidative stress, inflammation, and epigenetic pathways, this review uniquely highlights genetic mechanisms that modulate susceptibility to pollution-related diseases. It also identifies critical research gaps, such as the reliance on cross-sectional designs, and proposes future directions to improve the robustness and generalizability of findings.

The review further aims to outline a novel framework for advancing precision health strategies by integrating genetic insights with emerging methodologies such as multi-omics, machine learning, and longitudinal study designs. By doing so, it seeks to inform public health policies aimed at mitigating air pollution-related health risks, particularly in vulnerable populations.

A detailed overview of the included studies, including author, year, location, study design, population and sample size, exposure variables, health outcomes, and age range, is presented in **Table S1**. This table provides a comprehensive summary of the key characteristics of the included studies, enabling comparison and the identification of research gaps.

Despite the growing body of epidemiological research, the underlying biological mechanisms of gene-environment (GxE) interactions remain complex and not fully understood. In addition to epidemiological studies, mechanistic data from in vivo and organoid models also provide crucial insights into the biological pathways underlying GxE interactions. Recent studies have demonstrated how such models can elucidate the cellular responses to environmental exposures in genetically predisposed individuals [8,20,21], which are discussed further in the Discussion section.

2. Materials and methods

2.1. Protocol and Registration

This scoping review was conducted following the methodological framework proposed by Arksey and O'Malley (2005) and further elaborated by Levac et al. (2010). Recognizing the importance of transparency and methodological rigor for evidence synthesis, the protocol for this scoping review was retrospectively registered with the Open Science Framework (OSF) on May 22, 2025. The public URL for this registration is https://osf.io/3r8ap/ and its Registration ID is 3r8ap. At the time of this manuscript submission, the protocol is currently pending moderation approval, and its public URL and Registration ID will be provided here upon approval and publication by OSF moderators [22].

2.2. Search strategy:

To ensure transparency and credibility, a systematic literature search was conducted across multiple databases, including PubMed, Google Scholar, and ResearchGate to identify relevant studies. The search was limited to articles published in English between January 1, 2015, and December 31, 2024. The following search strategy was used:

- **PubMed:** ("air pollution"[MeSH Terms] OR "air pollution"[Title/Abstract] OR "air pollutants"[Title/Abstract]) AND ("genetic susceptibility"[MeSH Terms] OR "genetic polymorphism"[Title/Abstract] OR "oxidative stress"[MeSH Terms] OR "oxidative stress"[Title/Abstract]) AND ("disease risk"[Title/Abstract] OR "health outcomes"[Title/Abstract])

- **Google Scholar:** "air pollution" AND ("genetic susceptibility" OR "oxidative stress") AND ("disease risk" OR "health outcomes")
- **ResearchGate:** ("air pollution" OR "air pollutants" OR "pencemaran udara") AND ("genetic susceptibility" OR "genetic predisposition" OR "oxidative stress" OR "stress oksidatif") AND ("disease risk" OR "health outcomes" OR "dampak kesehatan")
- **DOAJ**: "air pollution" AND ("genetic susceptibility" OR "oxidative stress") AND ("disease risk" OR "health outcomes")

The following filters were applied: Human studies, English language, publication date (2015-2024), study type (including review, meta-analysis, randomized controlled trial, cohort study, case-control study, and cross-sectional study), and peer-reviewed status.

2.3. Study Selection Process:

Articles were screened for relevance using a two-step process: (1) title and abstract screening, followed by (2) full-text review. From this systematic search, 16 peer-reviewed articles were selected based on their relevance to the topic. Data from the selected articles were then systematically extracted. Data extraction prioritized information on genetic markers, their roles in modulating susceptibility, and their associations with health effects induced by air pollution. The data synthesis employed a qualitative approach to integrate findings from these studies, focusing on the influence of genetic factors on susceptibility to air pollution and the interaction between genetic variations and environmental exposures. This enabled the identification of patterns and relationships between genetic variations and health risks associated with air pollution, providing a comprehensive perspective on how genetics influences responses to environmental pollutants [23,24,25].

To ensure the transparency and reproducibility of this review, the study selection process was guided by the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) framework. A PRISMA-ScR flow diagram was used to illustrate the process of study selection, and adherence to PRISMA guidelines was maintained throughout the data extraction and synthesis phases [26,27,28].

Step 1: Identifying Studies. Relevant studies were initially identified through a comprehensive search across multiple databases, including PubMed, Web of Science, and Google Scholar. A combination of keywords like "air pollution," "genetic susceptibility," "oxidative stress," and "disease risk" was used to locate pertinent articles. These searches aimed to capture a broad range of studies related to genetic factors and their interactions with environmental exposures.
The search results were carefully reviewed, and studies meeting the predefined inclusion criteria were selected for further assessment. Studies that did not meet the inclusion criteria, were not substantially relevant to the research topic, or contained duplicated references were excluded.
This step ensures the selection of studies that contribute meaningful and relevant insights to the review, avoiding redundancy and maintaining the quality and integrity of the synthesis [26,27,28].

Step 2: Study Screening. The next step involved screening the identified studies based on predefined inclusion and exclusion criteria. Two reviewers independently screened the titles and abstracts of the studies retrieved from the initial search. Studies were selected for inclusion if they met the following criteria:

- Focused on genetic susceptibility to air pollution.
- Provided explicit methodologies.
- Offered quantitative or mechanistic insights into genetic-environment interactions.

Studies that were excluded at this stage included those not published in English, non-peer-reviewed articles, conference abstracts, and reviews that did not directly address genetic susceptibility to air

pollution. The remaining articles underwent a full-text review to confirm their eligibility before being included in the final analysis [26,27,28].

Step 3: Data Extraction. Data were extracted from the selected studies using a standardized extraction form. The extraction process involved collecting detailed information on genetic markers, biomarkers, health outcomes related to air pollution exposure, and other relevant details like study design, sample size, and key findings. The data were then synthesized qualitatively to identify key themes, patterns, and relationships across the studies [26,27,28].

Step 4: Data Synthesis. Data synthesis involved integrating findings from the selected studies to draw conclusions about the influence of genetic factors on susceptibility to air pollution. This synthesis aimed to provide a comprehensive understanding of the mechanisms underlying genetic-environment interactions and their implications for disease risk. The integration of findings was guided by thematic analysis and narrative synthesis techniques, emphasizing consistency and comparability across studies [26,27,28].

2.4. Inclusion and Exclusion Criteria:

Studies were included in this scoping review if they met the following criteria:

Inclusion Criteria:

Study Design: Studies of any design that investigate the association between air pollution exposure (e.g., PM2.5, PM10, NO2, Ox) and health outcomes in relation to genetic susceptibility were included. This encompasses observational studies (cohort, case-control, cross-sectional), interventional studies (e.g., randomized controlled trials, quasi-experimental studies), and Mendelian Randomization studies. Scoping reviews are particularly suitable for mapping evidence on complex and heterogeneous topics, as outlined by Page and Moher (2017), and Tricco et al. (2018). The focus was on studies examining various genetic factors influencing susceptibility to air pollution rather than specific genetic polymorphisms [26,27,28].

Population: Human participants of any age, sex, or ethnicity. Studies focusing on specific subpopulations (e.g., children, elderly, individuals with specific pre-existing conditions) will also be included.

Exposure: Measurable exposure to PM2.5, PM10, NO2, or NOx. Studies must provide quantitative or qualitative data on one or more of these pollutants. Exposure assessment methods should be clearly described (e.g., air quality monitoring data, self-reported exposure, residential proximity to pollution sources).

Health Outcomes: Any health outcomes relevant to the research question, including but not limited to respiratory diseases (e.g., asthma, COPD), cardiovascular diseases, mental health effects, pregnancy complications, and skin conditions. Studies must report specific health outcomes and diagnostic criteria used.

Gene-Environment Interaction (Primary and Essential Criterion): Studies *must* present statistical analyses that directly test for a gene-environment interaction (e.g., using interaction terms in regression models, stratified analyses by genotype, interaction meta-regression). Studies reporting only the main effects of air pollution or genetic associations separately will be excluded. Studies that mention gene-environment interaction but do not perform formal statistical testing of the interaction will also be excluded [8,29,30].

Exclusion Criteria:

Studies were excluded if they met any of the following criteria:

1. **Irrelevance to the Topic:**
   - Studies that did not address the health effects of air pollution.
   - Studies that focused exclusively on pollutants other than PM2.5 (e.g., only NO2 or O3). Studies addressing PM2.5 along with other pollutants were considered if PM2.5-specific information could be extracted.
   - Studies that examined the environmental impact of air pollution but not human health effects.
   - Studies solely focused on interventions or policies to reduce air pollution without addressing genetic aspects.

2. **Lack of Genetic Focus:**
   - Purely epidemiological studies that only measured air pollution exposure and health outcomes without considering genetic factors.
   - *In vitro* or *in vivo* toxicological studies that did not investigate genetic variations or gene polymorphisms.

3. **Inappropriate Publication Type:**
   - Opinions, editorials, letters to the editor, and conference abstracts (unless the abstracts contained significant information not available in a full-text publication).
   - Books and book chapters (unless they contained relevant systematic reviews or meta-analyses).
   - Government or non-governmental organization reports (unless they contained significant data or analyses not available in peer-reviewed publications).

4. **Language and Accessibility:**
   - Studies not published in languages accessible to the review team (e.g., English and Indonesian).
   - Studies for which full-text access could not be obtained after reasonable search efforts (e.g., through library databases or direct requests to authors).

5. **Duplication:**
   - Studies published more than once (in which case, the most complete and recent version was included).

6. **Methodological Concerns (with specific consideration for scoping reviews):**
   - While scoping reviews generally do not assess the methodological quality of studies as rigorously as systematic reviews, studies with substantial methodological flaws (e.g., severely flawed study design or erroneous data analysis) could be excluded. This criterion was applied cautiously and transparently [31,32,33].

2.5. Data Extraction and Synthesis

Data from included studies were extracted using a standardized data extraction form. The following information was extracted: study characteristics (e.g., author, year, study design, population), exposure assessment methods, genetic markers investigated, health outcomes assessed, and key findings related to gene-environment interactions. A detailed overview of these extracted data, presented in **Table S1**, provides a comprehensive summary of the key characteristics of the included studies, enabling comparison and identification of research gaps. A narrative synthesis of the findings will then be conducted to map the existing literature and identify key themes and research gaps [26,27,28,31,32].

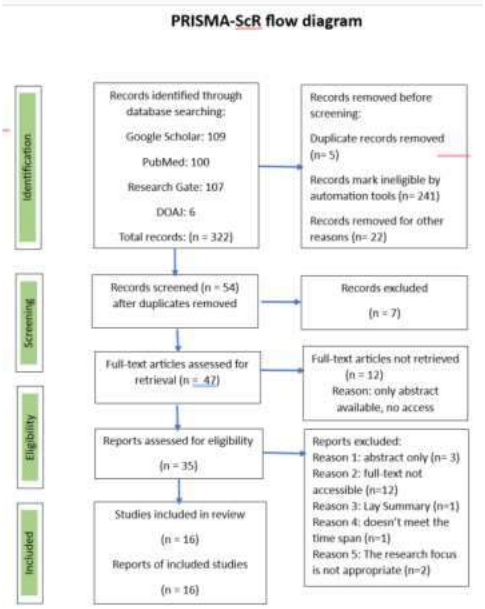
2.6. Quality Assessment of Included Studies

To strengthen the methodological rigor of our review, we conducted a formal quality appraisal of all 16 included full-text articles. Given the variety of study designs, we employed appropriate assessment tools tailored to each design type:

- The 13 prospective cohort studies were assessed using the Newcastle-Ottawa Scale (NOS) [34].
- The 1 cross-sectional study was evaluated using a modified version of NOS tailored for cross-sectional designs.
- The 1 meta-analysis (Gruzieva et al., 2016) was assessed narratively using AMSTAR 2 criteria, which are widely accepted for systematic reviews and meta-analyses [35].
- The 1 molecular-epigenetic cohort study (Chen et al., 2024), although fundamentally prospective in design, was evaluated using the JBI Critical Appraisal Checklist for Cohort Studies due to its integration of biological, genetic, and epigenetic data [36].

3. Results

A total of 322 records were identified through database searching (PubMed n=100, Google Scholar n=109, Research Gate n=107, and DOAJ n=7). After removing duplicates (n=5), 315 records underwent title and abstract screening. Of these, 283 were excluded as they did not meet the inclusion criteria (e.g., not focused on genetic susceptibility to air pollution, review articles, non-human studies). 35 full-text articles were assessed for eligibility, and 19 were further excluded due to methodological concerns (e.g., lack of a clear methodology, focus on non-PM2.5 pollutants), or lack of investigation of gene-environment interaction). Finally, 16 studies met all inclusion criteria and were included in this scoping review (**Figure 1**).



3.1 Study Characteristics

This scoping review included 16 studies investigating the interplay between genetic susceptibility and air pollution, particularly PM2.5, on various health outcomes. A diverse range of study designs were employed, including 1 cross-sectional study, 14 prospective cohort studies, 1 meta-analysis of cohort studies, and 1 Mendelian Randomization study. This heterogeneity in study design is typical in a scoping review, aiming to map the available evidence regardless of methodological rigor. Only one study employed Mendelian Randomization analysis as its core methodological approach [37-55].

The majority of studies focused on adult populations, with a reported age range spanning from 37 to 73 years. Geographically, the research was predominantly conducted in Europe (n=12), with one study encompassing both Europe and North America (n=1), and a smaller number conducted in Asia (n=3). This geographical distribution highlights a potential gap in research from other regions. Furthermore, 15 out of the 16 studies investigated the combined effects of particulate matter (PM2.5 and/or PM10), nitrogen dioxide (NO2), and nitrogen oxides (NOx). Only one study, Gruzieva et al. (2016), focused solely on prenatal NO2 exposure. This pattern suggests that PM2.5 and NO2 are dominant environmental factors in the studies and highlights the need for further exploration of NO2 exposure, particularly in its isolated form, to better understand its specific role in genetic susceptibility to diseases [37-52].

PM2.5 exposure was the most commonly assessed air pollutant, primarily using air quality monitoring data (n=16). It should be noted that some studies used multiple methods for exposure assessment. Some studies utilized land-use regression models to estimate PM2.5 exposure based on spatial data and environmental characteristics, while others employed self-reported questionnaires focusing on residential location and daily activities. For instance, Huang et al. (2021) and Gao et al. (2023) used land-use regression models within the UK Biobank to estimate individual exposures. Li et al. (2022) used land-use regression models in China. Air quality monitoring data typically involves measurements taken at fixed monitoring stations, providing information on ambient air pollution levels in specific locations. Land-use regression models, on the other hand, incorporate spatial data such as traffic density, land use types, and meteorological factors to create more refined estimates of pollution exposure at a finer spatial scale [38,43,53]. These different methods have varying degrees of accuracy and may introduce different types of measurement error.

Operational Definitions of Variables: PM2.5 was most often defined as the annual average concentration at the participants' residential address. However, some studies used different averaging periods (e.g., 24-hour average) or considered specific sources of PM2.5 (e.g., traffic-related PM2.5). Health outcomes varied across studies, encompassing cardiovascular diseases (e.g., myocardial infarction, stroke), respiratory diseases (e.g., chronic obstructive pulmonary disease (COPD), lung cancer), and metabolic disorders (e.g., type 2 diabetes). This variability in outcome definitions should be considered when interpreting the findings.

Exposure Measurement Methods (Further Details): Studies using air quality monitoring data often linked participants' residential addresses to the nearest monitoring station. Land-use regression models incorporated geographic information system (GIS) data on traffic, land use, and topography. Self-reported questionnaires typically asked participants about their residential history, time spent outdoors, and proximity to pollution sources.

Justification for Study Selection: Mendelian Randomization studies were included because they provide stronger evidence for causal inference by using genetic variants as instrumental variables, reducing the potential for confounding and reverse causation. Studies employing other designs, such as cohort studies, were included to provide a broader overview of the existing evidence base [49,53,54,55].

Information on sex was consistently reported, with approximately equal representation of men and women across the studies. However, reporting on other demographic characteristics, such as ethnicity and socioeconomic status (SES), was less consistent. Where reported, SES was often categorized based on indicators such as education level, occupation, or income. Some studies also considered other

participant characteristics such as smoking status and pre-existing health conditions as potential confounders.

Interventions or Moderating Factors: Several studies investigated potential moderating factors such as genetic polymorphisms (as mentioned previously), dietary intake, and physical activity. For instance, a study by Huang et al. (2021) examined whether the association between PM2.5 and lung function was modified by genetic variations in antioxidant enzymes [37].

Sixteen studies investigated the interactions of PM2.5, PM10, NO2, and NOx on various gene polymorphisms associated with increased disease risk. These studies often examined specific gene variants known to be involved in pathways related to inflammation, oxidative stress, or DNA repair, which are mechanisms through which air pollution is thought to exert its effects. Mendelian Randomization studies were included to provide stronger causal evidence for the relationship between air pollution and health outcomes. Mendelian Randomization utilizes genetic variants as instrumental variables to assess the causal effect of an exposure (e.g., air pollution) on an outcome (e.g., disease risk), minimizing the influence of confounding factors [47,80-54]. Only one meta-analysis of cohort studies specifically examined the relationship between NO2 exposure during pregnancy and cord blood DNA methylation. This meta-analysis synthesized data from multiple cohort studies to investigate the potential impact of prenatal NO2 exposure on epigenetic modifications in newborns [37].

Brief Summary of Key Findings: Overall, the studies consistently suggested a positive association between long-term exposure to air pollutants, particularly PM2.5, and adverse health outcomes, including cardiovascular and respiratory diseases. Some studies also found evidence of associations with metabolic disorders and other health outcomes. Studies investigating gene-environment interactions provided evidence that genetic susceptibility can modify the effects of air pollution [36-51].

Some studies used genotyping to assess genetic susceptibility and data from air quality monitoring stations to measure PM2.5 exposure. The findings of the included studies generally suggested a positive association between long-term exposure to air pollutants, particularly PM2.5, and adverse health outcomes [36-51].

A detailed overview of the included studies, including author, year, location, study design, population and sample size, exposure variables, health outcome, and age range, is presented in **Table S1**.

To assess the methodological rigor of the included studies, a formal quality appraisal was conducted using tools appropriate for each study design, as detailed in the Methods section (see Section 2.6). A comprehensive summary of the methodological quality assessment for all 16 included full-text articles is presented in **Table 1**. The results showed that the majority of studies met high-quality criteria, supporting the reliability of the extracted findings. For a detailed breakdown of individual study scores and their respective quality assessments, please refer to **Supplementary Table S4**.

Table 1. Summary of Methodological Quality Assessment of the Included Studies Based on Study Design.

No.	Study (First Author, Year)	Study Design	Quality Assessment Tool	Score/Result	Notes
1	Gruzieva et al., 2016	Meta-analysis (Cohort Data)	AMSTAR 2	High quality	Evaluated narratively using AMSTAR 2
2	Huang et al., 2021	Prospective Cohort	NOS	9/9	UK Biobank, lung cancer
3	Ma et al., 2023	Prospective Cohort	NOS	9/9	UK Biobank, AAA
4	Li et al., 2023	Prospective Cohort	NOS	9/9	UK Biobank, MDD
5	Fu et al., 2023	Prospective Cohort	NOS	9/9	based on UK Biobank, CAD
6	Ma et al., 2024	Prospective Cohort	NOS	9/9	Stroke, robust adjustment
7	Liu et al., 2024	Prospective Cohort	NOS	9/9	Schizophrenia
8	Huang et al., 2024	Prospective Cohort	NOS	9/9	Parkinson's disease
9	Wang et al., 2022	Prospective Cohort	NOS	9/9	COPD + interaction lifestyle
10	Rhee et al., 2024	Prospective Cohort	NOS	9/9	Cardiovascular disease
11	Li et al., 2022	Prospective Cohort	NOS	9/9	PM2.5 and CAD
12	Chen et al., 2024	Molecular-Epigenetic Cohort	JBI Checklist (Cohort)	High quality	Epigenetic focus, UK Biobank based
13	Wu et al., 2024	Prospective Cohort	NOS	9/9	Psoriasis
14	Zhang et al., 2024	Cross-Sectional	Modified NOS (Cross-Sectional)	9/10	High quality cross-sectional design
15	Gao et al., 2023	Prospective Cohort	NOS	9/9	Depression and Anxiety
16	Zhang et al., 2024	Prospective Cohort	NOS	9/9	Dementia

Footnote: Abbreviations: AMSTAR 2, Assessment of Multiple Systematic Reviews-2 (A Measurement Tool to Assess Systematic Reviews 2); NOS, Newcastle-Ottawa Scale; JBI, Joanna Briggs Institute ; AAA, Abdominal Aortic Aneurysm; MDD, Major Depressive Disorder; CAD, Coronary Artery Disease; COPD, Chronic Obstructive Pulmonary Disease ; $PM_{2.5}$, Particulate Matter with a diameter ≤ 2.5 μm.

Having established the characteristics of the included studies and the methods used to assess exposure and outcomes, the following section will detail the methods used to assess genetic susceptibility and pollutant exposure, before presenting the key findings related to gene-environment interactions [36-51].

3.1.1 Overview and Categorization of Health Outcome

The studies in this review report a diverse range of health outcomes associated with air pollution exposure, involving both physical and mental health conditions across different populations. These outcomes span multiple disease categories, highlighting the broad impact of pollutants such as PM2.5, PM10, NO2, and NOx [36-51].

To facilitate analysis, the included studies were categorized into seven primary groups: respiratory diseases, cardiovascular diseases, neurological and psychiatric disorders, cancers, autoimmune and inflammatory conditions, and other diseases. Cardiovascular and neurological conditions were the most frequently studied, with consistent associations reported for PM2.5, PM10, NO2, and NOx exposure. Notable findings include stronger associations of air pollution exposure with coronary artery disease (Fu et al., 2023; Li et al., 2022) and major depressive disorder (Li et al., 2023) associated with these pollutants [39,40,46]. Additionally, autoimmune conditions such as inflammatory bowel disease (Chen et al., 2024) were linked to long-term exposure to PM2.5 and NOx [47].

1. Respiratory Diseases

Several studies focus on respiratory conditions, particularly in relation to particulate matter and nitrogen oxides:

- Wang et al. (2022): **Chronic obstructive pulmonary disease (COPD)** associated with PM2.5, PM10, NO2, and Nox [44].

2. **Cardiovascular Diseases**
   Air pollution exposure is strongly linked to various cardiovascular conditions:
   - Fu et al. (2023) and Li et al. (2022): **Coronary artery disease (CAD)** [40,46].
   - Ma et al. (2024): **Abdominal aortic aneurysm** [38].
   - Rhee et al. (2024): **General cardiovascular diseases** [45].
3. **Neurological and Psychiatric Disorders**
   Mental health and cognitive impairments are key areas of concern:
   - Zhang et al. (2024): **Dementia** [51].
   - Liu et al. (2024): **Schizophrenia** [42].
   - Gao et al. (2023): **Depression and anxiety** [50].
   - Zhang et al. (2024): **Speed processing deficits** [49].
   - Li et al. (2023): **Major depressive disorder** [39].
4. **Cancer**
   A study reports a significant association between air pollution and lung cancer:
   - Huang et al. (2021): **Lung cancer** [37].
5. **Autoimmune and Inflammatory Conditions**
   - Chen et al. (2024): **Ulcerative colitis** [47].
   - Wu et al. (2024): **Psoriasis** [48].
6. **Epigenetic Changes**
   Air pollution exposure, particularly in early life, has been shown to cause epigenetic changes, such as differential DNA methylation:
   - Gruzieva et al (2016): **Differential offspring DNA methylation at CpG site** in cord blood newborns [36].
7. **Other Diseases**
   Several studies have also linked air pollution to other health conditions:
   - Huang et al. (2024): **Parkinson's disease** [43].
   - Ma et al. (2024): **Stroke** [41].

3.1.2 Methods of Exposure and Outcome Assessment

In this scoping review, the methods used to assess air pollution exposure and health outcomes varied across studies, reflecting the diversity of study designs and populations.

Exposure Assessment

1. **Air Quality Monitoring Data:** The most commonly used method for assessing exposure to air pollution was air quality monitoring data, with all 16 studies utilizing this approach. Air quality monitoring typically involved measurements taken at fixed monitoring stations to capture ambient air pollution levels in specific locations. This method provides reliable and consistent data on concentrations of pollutants such as PM2.5, PM10, NO2, and Nox [38,40].
2. **Land-Use Regression Models:** Several studies (e.g., Huang et al., 2021) employed land-use regression (LUR) models to estimate individual-level exposures to air pollution. LUR models use spatial data on environmental and urban characteristics, such as traffic density, land use, and meteorological factors, to predict exposure to pollutants at a finer geographic scale. These models can provide more localized estimates of exposure, accounting for variation in pollution levels that may not be captured by monitoring stations [37,39,50].

3. **Self-Reported Questionnaires:** A few studies included in this review also used self-reported questionnaires, asking participants about their residential history, time spent outdoors, and proximity to pollution sources. This method, while less accurate than air quality monitoring or LUR models, allowed researchers to estimate individual exposure based on participants' reported behaviors and locations [48].

4. **Genetic Susceptibility (Genotyping):** Some studies also explored **gene-environment interactions**, examining how genetic factors may modify the effects of air pollution exposure on health outcomes [44,45,51]. These studies typically combined genetic data (e.g., blood or saliva samples) with exposure data (from monitoring stations or Land Use Regression (LUR) models)

Outcome Assessment

1. **Health Outcomes:** A broad range of health outcomes were assessed across the studies, including respiratory diseases (e.g., COPD, asthma), cardiovascular diseases (e.g., coronary artery disease, myocardial infarction), neurological conditions (e.g., dementia, depression), metabolic disorders (e.g., type 2 diabetes), and autoimmune/inflammatory diseases (e.g., ulcerative colitis). Each study defined and measured these outcomes differently, with some relying on clinical diagnoses, hospital records, or self-reported health conditions [36-51].

2. **Objective Health Measurements:** Many studies used objective health measures, such as lung function tests, blood pressure readings, or biomarkers, to assess the impact of air pollution on various health conditions. These measurements provided more precise and quantifiable data compared to self-reported health information.

3. **Gene-Environment Interactions:** A subset of studies explored how genetic susceptibility modifies the impact of air pollution on health outcomes. These studies integrated genetic data (e.g., from genotyping or epigenetic analyses) with environmental exposure estimates. A detailed methodological examination of how gene–environment interactions were assessed is provided in the next section (3.1.4).

3.1.3 Gene–Environment Interaction Analysis

To enhance transparency and methodological rigor, we examined how the included studies assessed gene–environment (GxE) interactions. All 16 studies investigated the modifying role of genetic susceptibility on the association between air pollution exposure and health outcomes. However, the methodological approaches varied.

Several studies employed Cox regression models to estimate hazard ratios and to evaluate interaction effects [37-44,46,47,51]. Among these, a subset formally tested additive interaction metrics, such as the Relative Excess Risk due to Interaction (RERI) and Attributable Proportion (AP), which provide insight into the biological synergy between genetic risk and environmental exposure [36,37,39,40,43,46,50]. Multiplicative interactions, expressed through interaction coefficients in Cox models, were also reported in some studies.

Only a subset of studies formally tested gene–environment interactions, either through additive metrics (e.g., RERI, AP) or multiplicative interaction terms. Several studies (e.g., Fu et al., Rhee et al.) reported combined effect estimates without direct interaction testing, which may limit interpretability. We have reflected these methodological distinctions in **Supplementary Table S3**. To support methodological clarity in future research, we encourage adherence to established guidelines for GxE analysis, including the use of formal interaction testing and transparent reporting of effect modification approaches.

While most studies did not apply formal multiple testing corrections (e.g., Bonferroni or false discovery rate), two studies—Gruzieva et al. (2016) and Zhang et al. (2024)—did report correction procedures [36,51]. However, the lack of correction in the majority of studies may limit the interpretability of interaction findings in the presence of multiple comparisons. This issue is particularly relevant given the large number of exposures and genetic markers tested, which increases the chance of false-positive results.

A detailed summary of the interaction testing methods, effect sizes, p-values, and confidence intervals is provided in **Supplementary Table S3**. To improve visibility and address reviewer concerns, we have clarified key methodological features in this section and will consider integrating selected elements of Supplementary Table S3 into the main manuscript if appropriate.

To complement Supplementary Table S3, which details the interaction testing methods used in each study, **Table 2** summarizes key methodological characteristics of the included studies, focusing on the statistical approaches used to evaluate gene–environment interactions, the type of interaction tested (multiplicative or additive), the significance of interaction terms (e.g., p-values), and the application of multiple testing corrections. This structured summary enhances methodological transparency and supports interpretation of the findings by distinguishing between formal and informal testing strategies.

Table 2. Overview of Formal and Informal Testing Methods, Interaction Type, and Multiple Testing Correction in Gene–Environment Interaction Studies.

No	Study	Formal Interaction	Informal Interaction	Interaction Type	Interaction Significance and Strength	Multiple-Testing Correction
1	Orozova et al., 2016	Not Available	Narrative Synthesis	Epigenetic	Not reported (unclear)	False Discovery Rate (FDR): $p=0.05$
2	Huang et al., 2021	Cox proportional hazards models; RERI, AP	-	Multiplicative Positive Additive	Not reported (unclear)	Not Reported
3	Ma et al., 2024	Cox proportional hazards models; RERI, AP	-	Multiplicative Positive Additive	Not reported (unclear)	Not Reported
4	Li et al., 2022	Cox proportional hazards regression models (p-interaction, and Hazards Ratio)	Stratified Analysis	Multiplicative	$PM2.5$: $p=0.046$; $PM10$: $p=0.025$; NO_2: $p=0.010$ **(Significant)**; NO_x: $p=0.080$ **(Not Significant)**	Not Reported
5	Fu et al., 2021	Cox proportional hazards regression models (p-interaction, and Hazards Ratio); RERI, AP	Subgroup HR Comparisons (by PRS)	Multiplicative Positive Additive	All p-interaction > 0.05 **(Not Significant)**	Not Reported
6	Ma et al., 2024	Cox proportional hazards regression models (p-interaction, and Hazards Ratio); RERI, AP; Andersen Additive Hazard Model	-	Multiplicative Positive Additive	Not reported (unclear)	Not Reported
7	Liu et al., 2024	Cox proportional hazards regression models (p-interaction, and Hazards Ratio)	Stratified Analysis	Multiplicative	**$PM2.5$**: $p=0.40$ **(Not Significant)** **$PM10$**: $p=0.70$ **(Not Significant)** **NO_2**: $p=0.07$ **(Not Significant)**	Not Reported
8	Huang et al., 2024	Cox proportional hazards regression models (p-interaction, and Hazards Ratio)	Stratified Analysis	Multiplicative	Not reported (unclear)	Not Reported
9	Wang et al., 2022	Cox proportional hazards regression models (p-interaction, and Hazards Ratio); RERI, AP	-	Multiplicative Positive Additive	All p-interaction > 0.05 **(Not Significant)**	Not Reported
10	Blase et al., 2024	Not Reported	Visual Trend and Stratified HR	Descriptive only	Not reported (unclear)	Not Reported
11	Li et al., 2022	Cox proportional hazards regression models (p-interaction, and Hazards Ratio)	Narrative Interpretation	Multiplicative	p-interaction < 0.001 **(Strong Evidence)**	Not Reported
12	Chen et al., 2024	Cox proportional hazards regression models (p-interaction, and Hazards Ratio); RERI, AP	-	Multiplicative Positive Additive	**P interaction** (multiplicative): 0.275 **(not significant)**; **P interaction** (additive): 0.00123 **(significant)**	Not Reported
13	Wu et al., 2024	Not Available	Narrative Association	Informal	$PM10$: $p=0.002$ **(Significant)**, $PM2.5$: $p=0.105$ **(Not Significant)**, NO_2: $p=0.051$ **(Not Significant)**, $PM10$ (Additive): **Not Reported**	Not Reported
14	Zhang et al., 2024	Not Available	Stratified Analysis	Informal	Not reported (unclear)	Not Reported
15	Guo et al., 2023	Not Reported	Synergistic/ Enhancing Effect (Gene Environment Interaction)	Multiplicative	Not reported (unclear)	Not Reported
16	Zhang et al., 2024	Cox proportional hazards regression models (p-interaction, and Hazards Ratio); RERI, AP	-	Multiplicative Positive Additive	HR interaction term reported (exact p not stated); RERI and AP reported	HMP (harmonic mean p-value); PFWE and PFDR in imaging

Footnote: Abbreviations: FDR, False Discovery Rate; RERI, Relative Excess Risk due to Interaction (the proportion of disease among those with both the exposure and the genotype that is attributable to their interaction); AP, Attributable Proportion due to interaction (the proportion of disease in the population that is attributable to the interaction between the exposure and genotype); HR, Hazards Ratio; $PM_{2.5}$, Particulate Matter with a diameter ≤ 2.5 μm; PM_{10}, Particulate Matter with a diameter ≤ 10 μm; NO_2, Nitrogen Dioxide; NO_x, Nitrogen Oxides; HMP, Harmonic Mean p-value; PFWE, Permutation-based Family-Wise Error rate; PFDR, Permutation-based False Discovery Rate.

Notes:
Formal interaction testing includes **regression-based interaction terms** (e.g., p-interaction), as well as measures on the **additive scale** such as RERI (Relative Excess Risk due to Interaction), AP (Attributable Proportion), and the Synergy Index.
Informal interaction testing includes subgroup or stratified analysis, visual inspection of effect modification across strata, or narrative/descriptive comparisons without formal statistical interaction terms.
Interaction type refers to whether the interaction was evaluated on the **additive scale**, **multiplicative scale**, or only through **informal exploration** (without formal statistical testing).
Multiple testing correction refers to statistical methods used to adjust for the number of tests performed, such as Bonferroni correction or False Discovery Rate (FDR) control, and Harmonic Mean p-value (HMP).

3.2. Methods of Assessing Genetic Susceptibility and Pollutant Exposure

This section describes the specific methods used within the 16 included studies to assess genetic susceptibility and pollutant exposure. This focuses on *how* these measurements were implemented in the context of the reviewed literature, rather than providing a general overview of these methods.

3.2.1 Assessment of Genetic Susceptibility

Among the 16 articles reviewed, 14 focused on genetic susceptibility, 1 examined epigenetic modification, and 1 study investigated both genetic susceptibility and epigenetic modification. **Table 3** summarizes the focus of these articles.

Table 3. Summary of study focus.

Study Type	Number of article
Genetic Susceptibility	13
Epigenetic Modification	2
Both Genetic and Epigenetic	1

Note: Table 3 provided a breakdown of the types of studies included in this review.

After assessing general genetic susceptibility, the review also explored gene-environment (GxE) interactions—how genetic factors may modify the health effects of air pollution exposure. **Table 4** presents an overview of these studies, specifically focusing on the use of **genotyping** or **DNA methylation** methodologies.

Table 4. Overview of Studies on GxE Interactions Using Genotyping or DNA Methylation.

Study	Population	Methodology	Exposure (Pollutant)	Outcome (Disease)	Type of analysis	Key Findings
Gruzieva et al., 2016	Newborns, children aged 4 and 8 from European and North America (n=1,508 newborns, n=733 at age 4, n=786 at age 8).	DNA methylation (Epigenome-Wide), meta-analysis of cohort study	Prenatal NO2 exposure	Altered DNA methylation at CpG sites in FAM13A and NOTCH4.	Epigenetic Modification	Early life epigenetic markers link to respiratory disease later.
Huang et al., 2021	455,974 participants aged 40-69 years (UK Biobank)	PRS calculation based on 18 SNPs In lung cancer; Land-Use Regression (LUR) models; Analytical cohort study.	Ambient air pollution (PM2.5,NO2, PM10, NOx)	Lung cancer incidence	Genetic risk interaction/ Environmental exposure Statistical (Cox proportional Hazard	Air pollution exposure significantly associated with higher likelihood of lung cancer (63% higher), particularly

					models); RERI, AP.	among individuals with high genetic susceptibility.
Ma et al., 2024	449,4[illegible] participants aged 37-73 years from the UK Biobank	Polygenic risk score (PRS) based on 31 SNPs; Air pollution exposure data; cohort study	Long-term exposure to air pollutants (PM2.5, PM10, NO2, NOx).	Incidence of Abdominal Aortic Aneurysm (AAA).	Genetic susceptibility, Statistical (Cox proportional hazard models).	Long-term air pollution exposure is associated with increased likelihood of AAA; genetic risk (PRS) also plays a role in susceptibility.
Li et al., 2023	354,8[illegible] participants aged 37-73 years from the UK Biobank	Polygenic risk score (PRS), using 17 MDD-associated genetic loci (17 SNPs); Land-Use Regression (LUR) models; cohort study	Long-term exposure to air pollutants (PM2.5, PM10, NO2, NOx).	Incidence of Major Depressive Disorder	Genetic susceptibility, Statistical (Cox proportional hazard models).	Long-term air pollution exposure is associated with increased likelihood of MDD; genetic risk (PRS) also plays a role in susceptibility.
Fu et al., 2023	407,470 participants aged 40-69 years from the UK Biobank	CAD genome-wide association meta-analysis without the UK Biobank population with 40 SNPs; cohort study.	Long-term exposure to air pollutants (PM2.5, PM10, NO2, NOx).	Incidence of Coronary Artery Disease (CAD)	Genetic susceptibility, Statistical (Cox proportional hazard models, RERI, AP).	Long-term air pollution exposure is associated with increased likelihood of CAD; genetic risk (PRS) also plays a role in susceptibility.
Ma et al., 2024	452,196 participants from the UK Biobank.	Polygenic risk score (PRS) calculation With 71 SNPs; cohort study.	Long-term air pollutants (PM2.5, PM10, NO2, NOx).	Incidence of Stroke, Ischemic Stroke, Hemorrhagic Stroke.	Genetic susceptibility, Statistical (Cox proportional hazard models).	Long-term air pollution exposure is associated with increased likelihood of stroke. genetic risk (PRS) also plays a role in susceptibility.
Liu et al., 2024	485,28[illegible] participants) aged 37-73 years from the UK Biobank.	Genome-wide association studies; Polygenic risk score (PRS) calculation, cohort study.	Long-term air pollutants (PM2.5, PM10, NO2, NOx).	Incidence of schizophrenia.	Genetic susceptibility, Statistical (Cox proportional hazard models).	Long-term air pollution exposure is associated with stronger association with schizophrenia; genetic risk (PRS)

						also plays a role in susceptibility.
Huang et al., 2024	over 312,000 participants. Average aged 57 years.	Polygenic risk score (PRS) Calculation; cohort study.	Long-term air pollutants (PM2.5, PM10, NO2, NOx).	Incidence of Parkinson's Disease (PD).	Genetic susceptibility, Statistical (Cox proportional hazard models).	Long-term air pollution exposure is associated with higher odds of Parkinson's Disease (PD); genetic risk (PRS) also plays a role in susceptibility.
Wang et al., 2022	452,7[illegible] participants aged 37-73 years from the UK Biobank.	Genotyping by Affymetrix Research Services Laboratory in 106 sequential batches of approx. 4,700 samples; selected 22 SNPs associated with COPD; Weighted genetic risk score calculation; cohort study.	Long-term air pollutants (PM2.5, PM10, NO2, NOx).	Incidence of chronic obstructed Pulmonary Disease (COPD).	Genetic susceptibility, Statistical (Cox proportional hazard models).	Long-term air pollution exposure is associated with stronger likelihood of COPD; Weighted genetic risk also plays a role in susceptibility.
Rhee et al., 2024	249 082 participants aged 40-69 years	Genotyping of 807411 SNPs; Polygenic risk score (PRS) calculation, cohort study.	Long-term air pollutants (PM2.5, PM10, NO2, NOx).	Incident Cardiovascular Disease (CVD).	Genetic susceptibility, Statistical (Cox proportional hazard models).	Long-term air pollution exposure is associated with increased odds of Cardiovascular Disease (CAD); genetic risk (PRS) also plays a role in susceptibility. No significant interactions between genetic risk and PM2.5 exposure on cardiovascular death or CVD events.
Li et al., 2022	41,149 participants from Chi-	Polygenic risk score (PRS)	Long-term air pollutants	Incidence of Coronary Arte-	Genetic susceptibility, Statisti-	Long-term air pollution expo-

	na-PAR.	calculation based on 540 genetic variants; cohort study.	(PM2.5, PM10, NO2, NOx).	ry Disease (CAD)	cal (Cox proportional hazard models).	sure is associated with increased odds of Coronary Artery Disease (CAD); polygenic risk score (PRS) also plays a role in susceptibility.
Chen et al., 2024	453,919 individuals aged 40-69 years; White European descent.	DNA methylation variations at CXCR2 and sites within the MHC class III region.	Long-term air pollutants (PM2.5, PM10, NO2, NOx).	Incidence of Ulcerative colitis (UC).	Epigenetic Modification; Statistical (Cox proportional hazard models; epigenetic Mendelian Randomization approach).	Higher exposures to NOx, NO2, PM2.5 and combined air pollution score were associated with incident UC but not CD.
Wu et Al., 2024	474,055 participants aged 40-69 yaers.	Polygenic risk Score (PRS) Calculation; cohort study.	Long-term air pollutants (PM2.5, PM10, NO2, NOx).	Incident Psoriasis.	Genetic susceptibility, Statistical (Cox proportional hazard models); Restricted Cubic Spline Models; sensitivity analyses.	There was an interaction between air pollution and genetic susceptibility in relation to psoriasis.
Zhang et al., 2024	522 healthy participants aged 40-69 years living in Beijing	Polygenic risk score (PRS) calculation; DNA methylation; cross-sectional study.	Long-term air pollutants (PM2.5, PM10, NO2, NOx).	Depression on processing speed.	- Genetic susceptibility: PRS; - Epigenetic Modification: DNA Methylation; - Genetic Modification (of Environmental Effects): GLM, and PLSR.	Air pollution may be associated with an increased likelihood of cognitive impairment in individuals genetically predisposed to depression. The article does not provide specific effect sizes, but it describes the direction of the interaction (worsening effect with combined exposure and higher polygenic risk score).
Gao et	502,536 partici-	Polygenic risk sco-	Long-term	Risk of Depres-	Genetic suscep-	Elevated levels

al., 2023	pants from the UK Biobank, recruited in 2006–2010.	re calculation (Depression: 37 SNPs Anxiety: 9 SNPs); Land-Use Regression (LUR) models; cohort study	air pollutants (PM2.5, PM10, NO2, NOx).	sion and Anxiety.	tibility, Statistical (Cox proportional hazard models).	of the five air pollutants were associated with higher odds of mental disorders at baseline.
Zhang et al., 2024	401,244 participants aged 40-69 years.	This article used genotyping data in 2 ways: * **Targeted** genotyping: To get the APOE ε4 status. * **Genome-wide** genotyping: As the basis for calculating a PRS that incorporates many genetic variants associated with the outcome of interest (likely dementia or related traits).	Long-term air pollutants (PM2.5, PM10, NO2, NOx).	Incident Demensia.	Genetic susceptibility, Statistical (Cox proportional hazard models and Restricted Cubic Spline Regression).	Joint exposure to multiple air pollutants is associated with higher odds of dementia, especially among individuals with high genetic susceptibility.

Footnote: Abbreviations: GxE: Genotype by Environment; DNA: Deoxyribonucleic Acid; NO2: Nitrogen Dioxide; CpG: Cytosine-phosphate-Guanine; *FAM13A, NOTCH4:* Specific gene names involved in various biological processes (Further explanation could be provided in the main text if relevant to the study's focus). *Italicized gene names indicate standard gene nomenclature;* PRS: Polygenic Risk Score; LUR: Land-Use Regression; PM2.5: Particulate Matter with a diameter of 2.5 micrometers or less; PM10: Particulate Matter with a diameter of 10 micrometers or less; GLM: General Linear Model; PLSR: Partial Least Squares Regression.

Table 4 provides an overview of studies on gene-environment interactions (GxE) using genotyping or DNA methylation. The studies listed highlight how genetic factors may influence the health outcomes of air pollution exposure, with a particular focus on epigenetic modifications like DNA methylation at specific CpG sites.

The assessment of genetic susceptibility in the included studies primarily focused on identifying specific genetic variants associated with increased risk of adverse health outcomes related to air pollution exposure. Many studies aimed to explore how genetic differences could modify the harmful effects of pollutants like PM2.5, PM10, NO2, and NOx on health outcomes.

- **Genotyping Methods Used in Included Studies:** The majority of studies employed genotyping techniques, with **SNP arrays** being the most common method (n=14). These arrays allowed for the detection of a wide range of single nucleotide polymorphisms (SNPs) across multiple genes. **Illumina HumanOmniExpress arrays** were utilized in some studies to assess SNPs related to oxidative stress and inflammatory pathways. Additionally, **PCR-based genotyping** methods, such

as **TaqMan assays**, were used in a few studies to investigate specific candidate genes linked to air pollution-related health effects. Only a smaller number of studies (n=2) employed **whole-genome sequencing (WGS)** to explore broader genetic variations, although this method was applied in a limited number of participants due to cost and technical constraints.

- **Candidate Genes and Genome-Wide Association Studies (GWAS)**: A combination of **candidate gene** approaches (n=8) and **GWAS** (n=7) were used in these studies to explore the genetic basis of susceptibility to air pollution-related health risks. Candidate gene studies often targeted well-known genes involved in inflammation or detoxification. In contrast, **GWAS** allowed for the identification of novel genetic variants associated with exposure to pollutants.
- **Gene-Environment Interactions**: Several studies in this review focused on **gene-environment interactions**, which investigate how genetic susceptibility can modify the health effects of air pollution exposure. In these studies, genetic data were typically obtained from blood, saliva, or buccal samples, and air pollution exposure was assessed through monitoring data or Land Use Regression (LUR) models [37,39,40]. Notably, the studies by Zhang et al., 2024 employed genotyping methods to examine the role of genetic polymorphisms in genes such as APOE ε4, FRMD8, DDX1, DNMT3L, MORC1, and TGM2 which are involved in specific biological pathways relevant to air pollution exposure such oxidative stress, neuroinflammation, and epigenetic regulation. These studies found that certain genetic variants significantly influenced the association between air pollution exposure and incident Demensia [51].
- **Data Analysis and Quality Control**: Rigorous data analysis methods were employed across the studies to ensure the accuracy of genetic susceptibility results. Standard quality control measures, including filtering based on **minor allele frequency**, **call rates**, and testing for **Hardy-Weinberg equilibrium**, were commonly used to minimize errors. These procedures ensured that the genotyping data were reliable for assessing the associations between genetic variants and health outcomes [45].

3.2.2 Assessment of Pollutant Exposure

The assessment of pollutant exposure in the included studies predominantly relied on environmental monitoring, modeling techniques, and personal exposure measurements to estimate the levels of air pollution to which study participants were exposed.

- **Environmental Monitoring and Air Quality Data**: A common method used in the studies was to obtain air quality data from government or environmental monitoring stations. These stations typically provide reliable data on the concentrations of pollutants, such as PM2.5, PM10, NO2, and NOx, at specific geographic locations. For example, several studies (e.g., Zhang et al., 2023; Wang et al., 2022) utilized data from national or regional monitoring stations to estimate exposure for large cohorts. These data were often combined with residential or work addresses to estimate long-term exposure levels [42,49].
- **Land Use Regression (LUR) Models**: Many studies (e.g., Huang et al., 2021; Li et al., 2023; Gao et al., 2023) employed land use regression (LUR) models to predict pollutant levels in areas where direct monitoring data were not available. LUR models are particularly useful in estimating spatial variation in air pollution exposure by integrating geographical data, land use patterns, and other environmental factors. These models were applied to derive individual-level exposure estimates based on participants' residential locations. Different LUR models were used across studies, with varying levels of complexity and input data [32,37,48].
- **Personal Exposure Measurement**: A subset of studies (e.g., Li et al., 2022; Ma et al., 2024) used personal exposure measurement devices, such as portable air pollution monitors or wearable sensors, to capture real-time exposure data. This method provided more accurate and individualized measurements of pollution exposure, particularly in studies focused on short-term exposures or specific events like traffic-related pollution [36,44].

- **Modeling Approaches**: Some studies (e.g., Huang et al., 2021; Zhu et al., 2024) employed sophisticated atmospheric models to estimate pollutant levels based on meteorological conditions and emission sources. These models helped estimate exposure levels in regions without direct monitoring stations or personal exposure data [27,36].
- **Exposure Duration and Temporal Patterns**: Most studies evaluated long-term exposure (e.g., chronic exposure over years), but a few focused on short-term or acute exposure in relation to specific health outcomes (e.g., respiratory exacerbations or cardiovascular events). However, seasonal variations or temporal patterns of exposure were generally not explored in detail.
- **Exposure-Response Assessment**: Many studies included an exposure-response analysis to explore the relationship between pollutant levels and specific health outcomes. These studies often adjusted for confounding factors such as age, gender, socioeconomic status, and pre-existing health conditions to determine the strength and consistency of the exposure-response relationship [37,39,45].

In summary, the assessment of pollutant exposure in the reviewed studies utilized a combination of monitoring data, modeling techniques, and personal exposure measurements. The choice of exposure assessment method varied depending on the available resources, study design, and research objectives. The methodologies employed provided valuable insights into the health effects of air pollution by offering both spatially and temporally accurate exposure estimates.

3.2.3 Integration of Genetic and Exposure Assessments

The integration of genetic and exposure assessments is essential for understanding the complex interactions between genetic susceptibility and environmental exposures such as air pollution. This section describes how studies in this review combined genetic and environmental exposure data to examine gene-environment interactions (GxE), providing a deeper understanding of how genetic factors influence the effects of air pollution on health outcomes.

- **Stratified Analysis:** Some studies in this review employed stratified analysis, where participants were divided into subgroups based on specific genetic variants to assess whether the effects of exposure differed between these subgroups. While not all studies used this approach, stratified analysis is commonly used to identify gene-environment interactions. For example, previous research has focused on polymorphisms in genes like GSTP1, involved in detoxification pathways, to explore how genetic variation might influence the response to air pollution. This approach provides deeper insights into how genetic factors can modify the health impacts of air pollution exposure [42,43,49].
- **Interaction Terms in Regression Models:** Statistical models (e.g., linear regression, logistic regression) are used to test for the interaction between genetic variants and exposure variables. An interaction term is included in the model to assess whether the effect of exposure differs depending genotype [37-44,46,47,51].
- **Gene-Environment Interaction (GxE):** Gene–environment interaction (GxE) occurs when the impact of environmental exposure, such as air pollution, on health outcomes varies according to an individual's genetic profile. Among the 16 included studies, several explicitly tested GxE interactions using either multiplicative interaction terms in regression models or stratified analyses based on genetic risk categories (e.g., polygenic risk scores). These studies demonstrated that genetic susceptibility can modify the relationship between exposure to pollutants (e.g., PM2.5, NO_2) and outcomes such as cardiovascular disease, major depressive disorder, or stroke. For example, some studies reported significantly greater adverse effects of air pollution among

individuals in the highest tertile of genetic risk compared to those at lower risk [39,40,42,44,46,47,48].

In summary, the integration of genetic and exposure assessments using methods such as stratified analysis, regression models with interaction terms, GWIS, and consideration of gene-environment correlations provides valuable insights into how genetic susceptibility influences the health effects of air pollution. These approaches enhance our understanding of gene-environment interactions and are crucial for advancing precision medicine, where interventions can be tailored based on an individual's genetic profile and environmental exposures.

Note on Supplementary Materials: Due to the extensive nature of the data presented, **Table S2** provides a detailed summary of the key findings, conclusions, and limitations of the included studies. To ensure the flow and readability of the main text, this table has been moved to the Supplementary Materials section. Readers can refer to **Table S2** in the supplementary materials for a comprehensive overview of the studies included in this review.

3.2.4 Gene-Environment Interactions

A detailed analysis of gene-environment interactions was conducted to explore how genetic predisposition modulates the health effects of air pollution. **Table S3** (Supplementary Materials) summarizes the interactions between various genetic markers and environmental exposures, such as $PM_{2.5}$, PM_{10}, NO_2, and NO_x, across multiple health outcomes, including cardiovascular diseases, respiratory conditions, and mental health disorders.

Key findings include:

- Significant interactions between specific genetic polymorphisms and pollutant exposure levels, with the strongest effects observed for cardiovascular diseases and mental health disorders.
- Variations in effect sizes (e.g., odds ratios, hazard ratios) highlight the heterogeneity in genetic susceptibility to air pollution exposure across populations.
- Specific metrics such as Relative Excess Risk due to Interaction (RERI) and Attributable Proportion (AP) underscore the additive effects of genetic predisposition and environmental exposures on disease risk.

This table provides a comprehensive overview of the statistical evidence supporting the modifying role of genetic susceptibility in health outcomes associated with air pollution.

4. Discussion

The complex interplay between genetic predisposition and environmental exposures has emerged as a key area of research in understanding disease risk and health disparities. This review contributes to the growing body of literature by examining gene-environment interactions in the context of air pollution and their impact on various health outcomes [8,33,55].

4.1 Regarding the Association Between Genetic Predisposition and Air Pollution Exposure:

The interaction between genetic predisposition and environmental factors, such as air pollution, has garnered increasing attention in recent years due to its potential impact on disease risk. Our findings contribute to this growing body of literature, highlighting the significant role that genetic susceptibility plays in modifying the effects of air pollution on health outcomes [11,30,36,41,46,47,48,55,56,57,58].

The additive effects observed in individuals with both high genetic susceptibility and high exposure to air pollution align with prior studies suggesting that genetic factors may amplify the adverse health effects of environmental pollutants. Specifically, we found that individuals at higher

genetic risk exhibited more pronounced health deterioration when exposed to higher levels of air pollution. This combined effect, where the interaction between genetic susceptibility and environmental exposure exceed the sum of their individual effects, is consistent with previous studies emphasizing the exacerbating role of genetic factors in the harmful effects of environmental stressors [37,46].

Furthermore, genetic predisposition appears to modify the impact of air pollution exposure across various diseases, including cardiovascular diseases (CVD), respiratory conditions, and mental health disorders. These findings underscore the critical role of gene-environment interactions in shaping health outcomes. A detailed summary of gene-environment interactions, including the effect sizes, p-values, and health outcomes, is provided in **Table S3** (Supplementary Materials).

4.2 Regarding Disease-Specific Findings:

In line with previous studies, long-term exposure to pollutants such as PM2.5, NO2, and PM10 was significantly associated with a higher likelihood of various diseases (e.g., lung cancer, cardiovascular disease, stroke, etc.), especially among individuals with higher genetic susceptibility [36-51].

Our results confirm that the combined effect of air pollution and genetic predisposition plays a critical role in the development of complex diseases, including mental health disorders (e.g., schizophrenia, Major Depressive Disorder) and cardiovascular diseases (e.g., abdominal aortic aneurysms). For conditions like ulcerative colitis and psoriasis, our findings suggest that air pollution exposure may be a modifiable environmental contributor, particularly for those genetically predisposed. This highlights the potential for public health interventions to target these conditions by addressing environmental exposures, such as through improved air quality policies. Further details of these interactions are presented in **Table S3**.

4.3 Implications for Public Health and Precision Medicine:

These findings underscore the need for personalized approaches in environmental health, where genetic susceptibility should be considered when assessing the potential impact of air pollution exposure. Identifying individuals with high genetic susceptibility for specific diseases and high exposure to air pollution could help target interventions and preventive strategies more effectively. For example, individuals with genetic susceptibility to respiratory diseases might benefit from policies aimed at reducing air pollution exposure in urban areas. Public health strategies could include prioritizing air quality improvements in regions with high genetic vulnerability indices, or incorporating genotyping into early screening programs in pollution-heavy urban centers. [47,48,56].

While this review does not provide in-depth methodological analysis of these tools, we emphasize their future relevance for advancing the field. Although none of the included studies employed integrative multi-omics or machine learning techniques, these emerging methodologies are increasingly recognized as powerful tools in precision environmental health. They hold promise for uncovering novel mechanistic pathways and enabling more accurate risk stratification based on complex gene-environment interactions. While this review does not provide in-depth methodological analysis of these tools, we emphasize their future relevance for advancing the field [18-21,59-61].

Specifically, multi-omics and machine learning could significantly improve our understanding of how genetic factors modulate responses to air pollution, providing insights that could refine health outcome predictions and support personalized prevention strategies [18-21,59-61].

Although genome-wide interaction studies (GWIS) were not identified among the included studies, future research should consider applying GWIS to detect novel loci involved in pollution-related health effects [30,56,57,62]. In addition, gene–environment correlation (rGE)—where certain genetic traits predispose individuals to environments with higher pollution exposure—was not addressed in the included studies but remains an important methodological consideration for future

analyses [63,64]. Experimental studies have also highlighted the relevance of mechanistic pathways, such as aryl hydrocarbon receptor (AhR) signaling in response to PM2.5 exposure, yet this pathway was not explored in the reviewed epidemiological literature. These mechanisms warrant further investigation to strengthen the biological plausibility of GxE associations [65,66]. In addition, future studies employing toxicological or experimental approaches—such as in vivo or organoid models—are needed to explore mechanistic pathways (e.g., oxidative stress, inflammation, and epigenetic regulation), which would strengthen the biological plausibility of observed GxE associations.

The data in **Table S3** support the potential value of combining genetic and environmental risk profiling in public health efforts, particularly in identifying and protecting vulnerable populations. As such, future research integrating genetic data **with high-resolution exposure models, epigenomics, and machine learning algorithms** could substantially enhance targeted prevention strategies [36-51].

4.4 Limitations and Recommendations for Future Research:

While most included studies relied on observational designs, our findings are limited by the inability to establish causality and may be affected by residual confounding, particularly in the assessment of genetic susceptibility and environmental exposure [52,67]. Based on the current evidence, we provide several recommendations for future research directions.

While we acknowledge that 12 of the 16 included studies were conducted in European populations or used UK Biobank data, the implications of this geographic and ethnic skew deserve deeper discussion. The lack of representation from non-European ancestry groups raises concerns about the external validity and equity of current GxE findings, particularly in the context of global precision health efforts. Equity and diversity should be central considerations when translating GxE insights into public health strategies [68,69]. Recent advances in interaction testing frameworks have made it more feasible to detect complex GxE effects across diverse populations [70]. Future research must explicitly include underrepresented populations, both to validate current findings and to uncover population-specific interactions that may be masked in predominantly European datasets [71]. This approach will enhance the relevance and fairness of GxE-informed precision health interventions on a global scale.

Further studies should address these limitations by incorporating more accurate exposure data, such as personal monitoring of air pollution, and exploring gene-environment interactions in more diverse populations to enhance the generalizability of the results [8,70,71,72].

One study included in this review—Chen et al. (2024)—presents distinct methodological considerations. While described as a cohort study, its structure is more akin to a cross-sectional or nested case-control design, as it lacks precise temporal data on ulcerative colitis onset [46]. This weakens the temporal relationship and introduces potential for reverse causation, which may limit causal inference. To mitigate these limitations, the authors employed epigenetic analysis and Mendelian randomization as complementary methods to strengthen causal interpretation [52,53,54]. Nevertheless, the absence of longitudinal follow-up reduces its methodological comparability with the prospective cohort studies included in this review. Therefore, quality assessment was performed using the JBI checklist rather than the Newcastle-Ottawa Scale, which better aligns with the study's epigenetic and case-control framework [33,35]. Future studies investigating gene–environment interactions in ulcerative colitis should aim to replicate these findings using longitudinal designs with clearer temporal sequencing and larger population-based samples.

In addition, future studies would benefit from utilizing **multi-omics** approaches and **machine learning** techniques to explore the mechanistic pathways that link air pollution exposure with epigenetic changes and genetic predisposition in the development of complex diseases. These technologies have been highlighted as powerful tools to advance exposome research and understand causal biological mechanisms [18,19,20,21]. Such approaches hold great promise in identifying new biomarkers and uncover complex, multifactorial interactions that might otherwise be missed. The

section on emerging technologies such as AI and multi-omics could also be expanded in future research to provide more detailed elaboration on their potential applications in improving exposure modeling, identifying complex gene-environment interactions, and enhancing risk prediction [21].

Moreover, **longitudinal designs** with larger, multi-ethnic samples and **standardized exposure assessments** will improve the robustness of future findings and enable a more nuanced interpretation of gene–environment dynamics over time. Although causality cannot be definitively inferred from observational data, enhancing study design and incorporating mechanistic approaches—such as multi-omics and molecular exposomics—can substantially strengthen the evidence base and help clarify potential biological pathways [20,21,73-80].

Finally, disease-specific recommendations should be considered. For instance, prioritizing the development and validation of polygenic risk scores (PRS) for conditions such as stroke—where strong genetic signals have been identified (e.g., Ma et al., 2024)—may help refine individual-level susceptibility profiling and enable more targeted public health responses [73-80]. Furthermore, as the field progresses towards potential applications of genetic information in public health strategies, careful consideration must be given to the **ethical implications of genetic screening**. These include ensuring robust data privacy and security measures, obtaining informed consent, addressing the potential for genetic discrimination, ensuring equitable access and implementation, and promoting responsible interpretation and application of genetic risk profiles [81].

4.5 Mechanistic Evidence Supporting GxE Effects

Recent studies using animal models and organoid systems demonstrate that air pollution triggers molecular events such as ROS overproduction, mitochondrial dysfunction, and cytokine dysregulation, which may interact with genetic predispositions to exacerbate disease processes [82,83]. For example, in vivo models have shown that particulate matter exposure leads to neuroinflammation and cognitive impairment via the NF-κB and Nrf2 signaling pathways, providing insight into mechanisms potentially relevant to mental health outcomes [84,85]. Similarly, lung and cardiovascular organoid models have revealed pollutant-induced endothelial dysfunction and inflammatory responses that mirror pathways implicated in human genetic risk loci [86,87].

A recent review highlights how organoid and animal-based approaches are increasingly used to uncover the cellular and molecular mechanisms linking environmental exposures with chronic disease phenotypes. These mechanistic insights are essential for interpreting GxE interactions and underscore the need for integrative frameworks that combine epidemiological, genetic, and experimental evidence in environmental health research [88,89].

To provide biological plausibility to the epidemiological associations observed in this review, it is important to consider experimental studies that elucidate underlying mechanisms. Toxicological and in vivo models have consistently shown that exposure to air pollutants such as PM2.5, NO_2, and diesel exhaust particles can induce oxidative stress, systemic inflammation, and epigenetic changes—pathways that are also implicated in the genetic susceptibility to complex diseases [90,91].

5. Conclusions

This review underscores the critical role of gene-environment interactions in shaping health outcomes, particularly in the context of air pollution exposure. Our findings suggest that genetic susceptibility may modify the associations of air pollution across various diseases, including cardiovascular conditions, respiratory disorders, and mental health challenges. These results provide compelling evidence for the need to integrate genetic data into environmental health research, enhancing our understanding of the complex relationships between pollution exposure and disease risk.

Given the observational nature of the included studies, causal relationships cannot be definitively established. Nonetheless, the patterns identified across the reviewed literature point to potentially important gene–environment interactions that merit further investigation through mechanistic and experimental studies.

The implications of these findings extend beyond scientific research, emphasizing the development of precision public health strategies. Identifying individuals with heightened genetic risk can enable the development of targeted prevention strategies, such as localized air quality interventions or early screening efforts for at-risk populations. In parallel, these insights reinforce the need for broad efforts to reduce air pollution exposure as a population-wide preventive strategy.

To improve the applicability of these findings, we recommend prioritizing the development of polygenic risk scores (PRS) for diseases with strong and consistent GxE signals—particularly stroke, as highlighted in recent studies such as Ma et al. (2024). Furthermore, enhancing air pollution monitoring systems in rapidly urbanizing low- and middle-income countries (LMICs) is essential to address current data gaps and guide targeted public health interventions.

Future research should also incorporate mechanistic studies, including those using organoid and in vivo models, to support the biological plausibility of GxE effects. These experimental approaches can help elucidate key pathways such as oxidative stress, inflammation, and epigenetic modifications, thereby strengthening the interpretation of epidemiological associations.

Finally, to ensure the equity and global relevance of GxE research, future studies must include more diverse populations beyond those of European ancestry. By integrating genetic, environmental, and mechanistic evidence, future precision health strategies can be more effectively tailored to protect high-risk individuals and address the growing global burden of pollution-related diseases.

Use of AI tools declaration

The author declare he has not used Artificial Intelligence (AI) tools in the creation of this article.

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Authors' contribution

Hari Krismanuel contributed to the study design and redaction of the study protocol, searched the databases for studies, selected studies for data screening, extracted the data, performed data synthesis and analysis, and contributed to writing the manuscript.

Conflict of interest

The author declares no conflicts of interest.

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

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Hari Krismanuel *

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

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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
hari_krismanuel@trisakti.ac.id

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

Date of Manuscript Submission

14 Apr 2025 06:50:10

Date of This Review

30 Apr 2025 03:41:29

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,

Dr. Hari Krismanuel
hari_krismanuel@trisakti.ac.id

Screenshot manuscript dipublikasi di jurnal Scopus 1 di akun SINTA