SUPPLEMENTARY MATERIALS

Exploring Genetic Susceptibility to Air Pollution and Its Implication for Disease Risk and Precision Health

Hari Krismanuel[1]

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

*** Correspondence:**
Hari Krismanuel
hari_krismanuel@trisakti.ac.id

Content

Table S1: Characteristics of Studies Examining the Association Between Air Pollution and Health Outcomes

Author & year	Location	Study Design	Population and Sample size	Exposure/ Variables	Health Outcome	Age range
Gruzieva et al., 2016	European and North American	Meta-analysis of cohort studies	Newborns, children aged 4 and 8 from European and North American cohorts (n=1,508 newborns, n=733 at age 4, n=786 at age 8)	NO2 exposure at residential addresses during pregnancy	DNA methylation in mitochondria-related genes; methylation and expression of antioxidant and anti-inflammatory genes (CAT, TPO)	aged 4 and 8
Huang et al., 2021	UK Biobank/ UK	Case control study (using UK Biobank data)	455,974 participants in UK Biobank (53% women) with no previous history of cancer	Concentrations of PM (PM2.5, PMcoarse, PM10), NO2, and NOx estimated using land-use regression models	Incidence of lung cancer	40 - 69 years
Ma et al., 2024	UK Biobank/ 22 centres across the UK	Cohort study (using UK Biobank data)	449,463 participants from the UK Biobank	Long-term exposure to PM2.5, PM10, NO2, and NOx measured over time	Incidence of Abdominal Aortic Aneurysm (AAA)	37 - 73 years
Li et al., 2023	UK Biobank/ 22 centers in urban areas of England, Wales, and Scotland	Prospective cohort study (using UK Biobank data)	354,897 participants aged 37-73 years from the UK Biobank	Annual average concentrations of PM2.5 PM10, NO2, and NOx estimated using a Land Use Regression model	Incidence of Major Depressive Disorder (MDD)	37 - 73 years
Fu et al., 2023	UK Biobank (approximately 487,507 participants recruited across the UK . at baseline from 2006	Prospective cohort study.	407,470 participants were investigated the relationship Of PM, genetic factors, and CAD, and 438,736 in the NO group. These participants	Long-term exposure to air pollutants, including: (PM2.5), (PM10), Nitrogen dioxide (NO2), Nitrogen oxides (NOx). Genetic Variable: Polygenic risk score	The incidence of coronary artery disease (CAD).	40 to 69 years at recruitment (baseline).

	to 2010.		were free of CAD at baseline (the start of the study).	(PRS) for CAD, representing an individual's genetic susceptibility to the disease.		
Ma et al., 2024	UK Biobank/ UK	Prospective cohort study.	The analytical sample consisted of 452,196 participants from the UK Biobank.	The study examined long-term exposure to: PM2.5, PM10, Nitrogen dioxide (NO2), Nitrogen oxides (NOx)	The primary health outcome was the incidence of stroke, further categorized into ischemic and hemorrhagic stroke.	30 to 73 years at baseline (recruitment).
Liu et al., 2024	UK Biobank/ UK	Prospective cohort study.	Large sample size (485,288 participants) from the UK Biobank.	Long-term exposure to air pollutants, including: Nitrogen dioxide (NO2), Nitrogen oxides (NOx), Particulate matter with a diameter of 2.5 micrometers or less (PM2.5), Particulate matter with a diameter of 10 micrometers or less (PM10)	The primary health outcome of interest was the incidence of schizophrenia, which was identified through hospital records and self-reported diagnoses in the UK Biobank.	37 to 73 years at the time of recruitment (baseline).
Huang et al., 2024	Qingdao, China.	Prospective cohort study.	Large sample size of over 312,000 participants.	Long-term exposure to air pollutants, particularly: - Fine particulate matter (PM2.5) - Nitrogen dioxide (NO2) - Nitrogen oxides (NOx) **Genetic Variable:** Polygenic risk score (PRS) for PD	The primary health outcome of interest was Parkinson's disease (PD) diagnosed by neurologists.	Average age of the participants was 57 years old
Wang et al., 2022	UK Biobank/ UK	Prospective cohort study.	approximately 452,762 participants across the UK. (UK Biobank)	Long-term exposure to air pollution, particularly PM2.5. Genetic Variable: Not directly measured, but genetic susceptibility for COPD was estimated based on the	The primary health outcome of interest was chronic obstructive pulmonary disease (COPD).	37 to 73 years

				participants' region of residence (a proxy). Lifestyle Variables: Smoking status, alcohol consumption, diet, and physical activity level.		
Rhee et al., 2024	UK Biobank, which genetically unrelated White British participants without CVD.	Prospective cohort study.	A total of 249 082 participants	Long-term exposure to air pollutants, primarily PM2.5. Other pollutants were likely considered, but PM2.5 was the focus. Genetic Variable: Polygenic risk score (GRS) for CVD, representing an individual's genetic predisposition to the disease.	The primary health outcome was the incidence of cardiovascular diseases (CVD). This included various conditions such as coronary heart disease, stroke, and heart failure.	Aged 40 to 69 Years (2006 - 2010).
Li et al., 2022	United Kingdom (UK Biobank)	Prospective cohort study.	41,149 participants recruited from the project of Prediction for Atherosclerotic Cardiovascular Disease Risk in China (China-PAR) were included.	Long-term exposure to fine particulate matter (PM2.5). Genetic Variables: Genetic risk scores for coronary artery disease. Residential PM2.5 concentrations.	The primary health outcome investigated was coronary artery disease (CAD), focusing on how long-term exposure to fine particulate matter (PM2.5) and genetic predisposition influence the risk of developing CAD.	40 to 69 years at recruitment.
Chen et al., 2024	The data primarily comes from the UK Biobank	Prospective cohort study.	The observational analyses involved a large sample size of 453,919 individuals. The genetic analyses focused on individuals of White European descent.	Air Pollution: This was the main exposure of interest. The study examined several air pollutants: Nitrogen oxides (NOx), Nitrogen dioxide (NO2) Particulate matter with a diameter of 2.5 micrometers or less (PM2.5)	The primary health outcome studied was the incidence of ulcerative colitis (UC).	between 40 and 69 years at recruitment.

Wu et al., 2024	UK Biobank (United Kingdom)	Prospective cohort using data from the UK Biobank.	The study used data from the UK Biobank. The sample size for the observational analyses included over 400,000 participants. The genetic analyses were conducted on a subset of participants of European ancestry.	Primary Exposures: Nitrogen dioxide (NO2), particulate matter ≤2.5 µm (PM2.5) Particulate matter ≤10 µm (PM10) Other Variables: Polygenic risk score (PRS) for psoriasis (measuring genetic predisposition)	The primary health outcome was incident psoriasis, defined as a first diagnosis of psoriasis during the follow-up period in the UK Biobank.	aged between 40 and 69 years at the time of recruitment (between 2006 and 2010).
Zhang et al., 2024	Beijing, China	Cross-sectional study using data from the UK Bio-Bank.	522 healthy participants living in Beijing from January 2014 to July 2016	Primary Exposure: Particulate matter ≤2.5 µm (PM2.5) Other Variables: Polygenic risk score (PRS) for depression (measuring genetic predisposition) Processing speed (cognitive outcome) Resting-state functional connectivity of the occipitoparietal network and spontaneous activity in the precuneus (neuroimaging measures) Covariates: age, sex, education, smoking status, body mass index, and socioeconomic status	The primary health outcome was processing speed, a measure of cognitive function.	aged between 40 and 69 years at recruitment.
Gao et al., 2023	UK Biobank (United Kingdom)	Prospective cohort study.	The study included 502,536 participants from the UK Biobank, recruited in 2006–2010.	Researchers estimated participants' long-term exposure to air pollutants: Fine particulate matter (PM2.5)	Researchers assessed depression and anxiety using: #NAME? for mental disorders.	Age of 37–73 years old (baseline survey)

				Coarse particulate matter (PM10) Nitrogen oxides (NOx) Nitrogen dioxide (NO2)	#NAME? completed by participants during a follow-up survey.	
Zhang et al., 2024	UK (UK Biobank participants)	Prospective cohort study.	Data from the UK Biobank was used. The study included 401,244 participants.	Primary Exposures: Fine particulate matter (PM2.5) Nitrogen dioxide (NO2) Nitrogen oxides (NOx) Joint exposure to these pollutants (analyzed using a weighted quantile sum (WQS) regression) Genetic Susceptibility: APOE ε4 allele (a genetic variant associated with increased dementia risk)	Outcome: Incident dementia	aged between 40 and 69 years at recruitment.

Footnote: Abbreviations: AAA, Abdominal Aortic Aneurysm; AF, Atrial Fibrillation; CAD, Coronary Artery Disease; CAT, Catalase; COPD, Chronic Obstructive Pulmonary Disease; CVD, Cardiovascular Disease; FT3, Free Triiodothyronine; FT4, Free Thyroxine; MDA, Malondialdehyde; MDD, Major Depressive Disorder; NO2, Nitrogen Dioxide; NOx, Nitrogen Oxides; PM10, Particulate Matter ≤ 10 µm; PM2.5, Particulate Matter ≤ 2.5 µm; PRS, Polygenic Risk Score; SLE, Systemic Lupus Erythematosus; TAA, Total Antioxidant Activity; TPO, Thyroid Peroxidase; TSH, Thyroid-Stimulating Hormone.

Table S2: Summary of Key Findings, Conclusions, and Limitations of Included Studies

Author & year	Key Findings	Conclusion	Limitations
Gruzieva et al., 2016	Epigenome-wide significant associations between maternal NO2 exposure during pregnancy and DNA methylation in newborns for 3 CpG sites in mitochondria related genes (LONP1, HIBADH, SLC25A28). Association with SLC25A28	This study conducted an epigenome-wide meta-analysis to identify DNA methylation sites in newborns potentially associated with prenatal exposure to nitrogen dioxide (NO2), a traffic-related air pollutant. They found no statistically significant associations between NO2 exposure and DNA methylation across the entire genome.	This study was limited by potential insufficient statistical power (due to sample size), its focus on cord blood DNA methylation (which may not reflect all relevant changes), incomplete understanding of the link be - tween DNA methylation and health, the exclusive focus on NO2 (other pollutants may have stronger effects), and the assessment being limited to newborns. Despite finding epigenome -wide significant associations at three CpG sites, no genome-wide significant associations were observed.
Huang et al., 2021	Significant associations between lung cancer risk and PM2.5, PM10, NO2, and NOx. Additive interactions between air pollutants and genetic risk; Highest risk observed in participants with combined high exposure and high genetic risk.	This study provides strong evidence that long-term exposure to air pollutants, particularly PM2.5, NO2, and NOx, significantly increases the risk of lung cancer. It demonstrates a combined effect of genetic predisposition and air pollution, with individuals at high genetic risk and high pollution exposure facing the greatest risk.	This study was limited by the difficulty in isolating individual pollutant effects, the use of a single baseline pollution measurement, the lack of occupational exposure data, simplified smoking data, the lack of oxidative damage biomarkers, and the use of multiple imputation for missing data.
Ma et al.,	Long-term exposure to PM2.5, PM10,	Long-term exposure to air pollu-	As an observational study, it demonstra-

2024	NO2, and NOx associated with an increased AAA risk; highest risk in in participants with combined high exposure and high genetic risk.	tants, particularly NO2, NOx, PM2.5, and PM10, is associated with an increased risk of abdominal aortic aneurysm (AAA). This risk is compounded in AAA.	tes association but cannot prove causation. The findings require confirmation in other populations.
Li et al., 2023	Long-term exposure to PM2.5, NO2, and NOx) associated with increased Major Depressive Disorder (MDD) risk; interaction observed between air pollution exposure and genetic predisposition (PRS) to MDD.	The study concluded that both genetic susceptibility and lifestyle factors modify the association between long-term air pollution exposure and MDD. Individuals with a higher genetic risk for MDD are more vulnerable to the effects of air pollution.	This study was limited by reliance on self-reported data (potential recall bias), self-reported MDD diagnoses, the predominantly European ancestry of the study population, and potential residual confounding.
Fu et al., 2023	Exposure to PM2.5, PM10, NO2, and NOx associated with increased CAD risk; higher genetic risk (PRS) increases susceptibility to air pollution's negative effects; additive gene-environment interaction observed.	both air pollution exposure and genetic predisposition play a role in CAD development. However, the impact of air pollution is more pronounced for individuals with a higher genetic risk. This highlights the importance of considering both factors for preventing and managing CAD.	As an observational design, it limits causal inference. Unmeasured confounding factors may be present.
Ma et al., 2024	Long-term exposure to PM2.5, PM10, NO2, and NOx, associated with increased stroke risk; gene-environment Interaction observed; higher genetic predisposition (PRS) increases suscep-	The study concludes that genetic susceptibility modifies the relationship between air pollution exposure and stroke risk. People with a higher genetic	As an observational design, it limits causal inference. The primarily East Asian study population may limit generalizability. Residual confounding is possible.

	tibility.	risk are more vulnerable to the adverse effects of air pollution, especially regarding ischemic stroke.	
Liu et al., 2024	Long-term exposure to NO2, NOx, PM2.5, and PM10 associated with Increased schizophrenia risk; significant interaction between genetic susceptibility (PRS) and air pollution; highest risk in individuals with combined high risk and high exposure.	The study concludes that both air pollution exposure and genetic predisposition play a role in the development of schizophrenia. However, the impact of air pollution is more pronounced for individuals with a higher genetic risk. This highlights the importance of considering both factors for risk assessment, prevention, and potentially developing targeted interventions for those at greatest risk.	As an observational design, it limits causal inference. The primarily European ancestry of the study population limits generalizability. Residual con - founding is possible.
Huang et al., 2024	- No significant association between Air pollution and PD risk in general population; interaction found be - tween genetic susceptibility and air pollution; higher genetic risk increases susceptibility; high genetic risk + exposure to PM2.5, NO2, and NOx associated with increased PD risk.	The study suggests that air pollution might be a risk factor for PD, but its impact is limited to individuals with a preexisting genetic vulnerability. People with a high genetic risk for PD should be more aware of their environmental exposures and consider measures to reduce	As an observational design, it limits causal inference. Other factors could be influencing PD development. Specific genetic markers associated with PD risk are not specified. The study population was recruited from a single city in China, limiting generalizability.

		air pollution intake.	
Wang et al., 2022	Interaction between air pollution, genetic susceptibility,and lifestyle factors for COPD risk; highest risk observed in individuals with com - bined high air pollution, high gene- tic risk, and unhealthy lifestyle.	Air pollution exposure is a risk factor for COPD, but its impact is more pronounced for indivi- duals with a higher genetic pre- disposition to the disease or those with unhealthy lifestyles. This highlights the importance of considering these combined factors for COPD prevention and risk management.	As an observational design, it limits causal inference. Other factors might influence COPD development. Reliance on self-reported lifestyle data may be prone to bias. The study population was primarily from China, limiting generalizability.
Rhee et al., 2024	Long-term PM2.5 exposure associated with increased CVD risk; significant interaction between genetic risk (GRS) and air pollution; combined high risk and high expo- sure resulted in substantially higher CVD risk.	Both genetic predisposition and long-term exposure to air pollution contribute to the development of CVD. The impact of air pollution is amplified in individuals with a higher genetic risk, emphasizing the importance of considering gene-environment interactions in CVD prevention and risk management.	As an observational design, it limits causal inference. The study population consisted primarily of individuals of East Asian descent, limiting generalizability. Air pollution exposure assessment was based on residential address. Genetic risk assessment was based on a polygenic risk score (GRS), which may not fully represent all genetic contributions to to CVD risk.
Li et al., 2022	Long-term PM2.5 exposure associ - ated with increased CAD risk; high genetic risk for CAD exacerbates PM2.5's adverse effects.	The findings indicate that genetic risk modifies the effect of long- term PM2.5 exposure on coronary artery disease. Individuals with higher genetic susceptibility to CAD are more	This study was limited by its observati- onal nature (cannot establish causality), potential residual confounding factors, and PM2.5 exposure assessment based on residential addresses.

		vulnerable to the detrimental effects of PM2.5. This underscores the importance of considering both environmental and genetic factors in assessing cardiovascular disease risk.	
Chen et al., 2024	Air pollution increases UC risk by altering DNA methylation, of CXCR2 (involved in immune cell movement) and MHC class III region genes (like AGPAT1). These changes, validated by multiple analyses, affect gene expression in colon tissue and are more pronounced in UC patients' epithelial cells, suggesting a key mechanism linking air pollution to UC development.	The study provides evidence for exposure and the development of ulcerative colitis (UC). This link is mediated, at least in part, by epigenetic alterations, specifically DNA methylation changes, affecting genes like CXCR2 and loci within the MHC class III region. These epigenetic changes influence gene expression in tissue and are more pronounced in UC patients. The findings highlight a potential mechanism by which environmental factors like air pollution can contribute to the pathogenesis of UC.	The observational nature of some analyses limits causal inference. The study population was primarily of White European descent, limiting generalizability. Residual confounding is possible. While Mendelian randomization strengthens causal inference, it relies on certain assumptions. The study focused primarily on UC, with limited analysis of Crohn's disease (CD). The colocalization analysis for cg16689962 could not be performed due to a limited number of mQTLs.
Wu et al., 2024	Long-term exposure to air pollutants (NO2, PM2.5, PM10) is associated with an increased risk of psoriasis. Genetic susceptibility exacerbates this risk. Mendelian randomization analyses suggest a potential causal role of NO2 and PM2.5 in psoriasis development.	Long-term exposure to air pollution, particularly NO2 and PM2.5, isassociated with an increased risk of psoriasis. Genetic susceptibility to psoriasis interacts with air pollution exposure, exacerbating the risk. This suggests that air pollution may be a trigger for psoriasis in	The study population was predominantly White British, limiting generalizability to other ethnicities. Psoriasis diagnosis was based on self-report or hospital records, which may introduce misclassification. Residual confounding factor is possible. MR analyses rely on assumptions (e.g., no pleiotropy). The study did not inves -

		genetically predisposed individuals.	gate the effects of specific types of psoriasis. Air pollution exposure was estimated based on residential address.
Zhang et al., 2024	Higher PM2.5 exposure was associated with reduced processing speed and precuneus activity (a brain region) in individuals with a high genetic risk for depression.	The study suggests that air pollution may be associated with an increased likelihood of cognitive impairment (specifically reduced processing speed in individuals who are genetically predisposed to depression. This effect may be mediated by alterations in the resting-state function of the occipitoparietal network and the precuneus. These findings highlight the importance of considering gene-environment interactions in understanding the impact of air pollution on brain health.	As a cross-sectional study, it cannot establish causality. It shows associations, but it doesn't prove that air pollution causes reduced processing speed or that the observed brain changes are a direct result of air pollution. The study population is predominantly White British, limiting generalizability. Air pollution exposure was estimated based on residential address, which may not perfectly reflect individual exposure levels. Other potential confounders may not have been fully accounted for.
Gao et al., 2023	Higher air pollution levels were associated with increased risk of depression and anxiety, both at baseline and during follow-up. This effect may be stronger in individuals with higher genetic risk for depression.	This study suggests a link between long-term air pollution exposure and an increased risk of developing depression and anxiety. Genetic predisposition may play a role in how air pollution affects mental health.	The study relies on estimations of air pollution exposure based on residential address, which may not reflect individual variations. The study design can't definitively prove that air pollution causes depression or anxiety. The focus on genetic predisposition was general, not looking at specific genes. The study population is predominantly White British, limiting generalizability to

			other ethnicities.
Zhang et al., 2024	Combined exposure to air pollutants (PM2.5, NO2, NOx) increased dementia risk, especially in individuals carrying the APOE ε4 allele (a genetic risk rfactor for dementia).	Joint exposure to multiple air pollutants increases the risk of dementia. Genetic susceptibility, particularly carrying the APOE ε4 allele, enhances the detrimental effects of air pollution on dementia risk. This highlights a gene-environment interaction.	Exposure to air pollution was estimated based on residential address at baseline, which may not accurately reflect individual exposure over time. Dementia diagnoses were based on administrative data (hospital records and death certificates), which may not capture all cases. The study population is predominantly White British, limiting generalizability to other ethnicities. Residual confounding (influence of other unmeasured factors) is possible.

Footnote: Abbreviations: AAA, Abdominal Aortic Aneurysm; AF, Atrial Fibrillation; CAD, Coronary Artery Disease; COPD, Chronic Obstructive Pulmonary Disease; CpG sites, Cytosine-phosphate-guanine sites; CVD, Cardiovascular Disease; FT3, Free Triiodothyronine; FT4, Free Thyroxine; GRS, Genetic Risk Score; HIBADH, 3-Hydroxyisobutyrate dehydrogenase; LONP1, Lon peptidase 1, mitochondrial; MDA, Malondialdehyde; MDD, Major Depressive Disorder; NO₂, Nitrogen Dioxide; NOx, Nitrogen Oxides; PM₁₀, Particulate Matter ≤ 10 µm; PM_{2.5}, Particulate Matter ≤ 2.5 µm; PRS, Polygenic Risk Score; mQTLs, methylation Quantitative Trait Loci; SLC25A28, Solute carrier family 25 member 28; SLE, Systemic Lupus Erythematosus; TAA, Total Antioxidant Activity; TSH, Thyroid-Stimulating Hormone; T3, Triiodothyronine; APOE ε4 allele, Apolipoprotein E ε4 allele.

Table 3. Summary of Gene-Environment Interactions for Environmental Exposure and Health Outcomes

Author & year	Genetic Variable	Environmental Variable	GxE interaction /Genetic Susceptibility reported	Direction of Interpretation	Health outcome	p-value of Interaction	Effect Size (Interaction/ Main) with (95% CI)	Study Participants	Notes
Ma et Al., 2024	Polygenic Risk Score (PRS) for Abdominal Aortic Aneurysm (AAA)	PM2.5, PM10, NO2, NOx	No, G × E interaction not assessed. Genetic risk categories (low, intermediate, high) significantly associated with AAA risk ($p < 0.001$).	High levels of air pollutants exposure and high genetic risk had a higher risk of developing AAA.	**Abdominal aortic aneurysm**	Not reported	**Interaction HR: - Main HR:** PM 2.5, per SDa increase: HR = 1.21 (1.16, 1.27), p<.001 PM 10 , per SD b increase: HR = 1.21 (1.16, 1.27), p<.001 NO2, per SDc increase: HR = 1.16 (1.11, 1.22), p<.001 NOx, per SDd increase: HR = 1.10 (1.05, 1.15), p<.001	UK Biobank participants	PRS constructed from 31 independent SNPs associated with AAA in individuals of European ancestry (MAF > 0.05, $P < 1 \times 10^{-5}$) from two GWASs. Details of PRS construction and SNP information in Supplementary Materials (Text S1, Table S1). Participants categorized into tertiles based on PRS. Significant interactions were reported on an additive

									scale, but exact p-values were not provided. See Table S8 for further details.
Rhee et al., 2024	**Coronary Artery Disease:** PRS for Coronary Artery Disease. **Myocardial Infarction:** PRS for Myocardial Infarction. **Any Stroke:** PRS for Any Stroke. **Ischemic Stroke:** PRS for Ischemic Stroke. **Heart Failure:** PRS for Heart Failure. **Atrial Fibrillation:** PRS for Atrial Fibrillation.	Data on both PM2.5 and PM10 were collected; however, the main analysis focused on PM2.5.	Because we lack p-interaction values, we will use "Suspected," Potential, or Possible to indicate that an interaction is suggested but not statistically confirmed. A crucial footnote is necessary to explain this.	The effect of PM2.5 exposure appears stronger in individuals with high genetic risk for [CVD Type].	Incident **Cardiovascular disease.**	Not Available (NA) The p-interaction value was not reported explicitly in this study. Interactions were inferred based on differences in Hazard Ratio (HR) between genetic risk groups, but without formal statistical testing for interactions.	Difference in HR at highest exposure level: 1.0. This is *not* a formal interaction effect size, but rather the difference in HRs at the highest exposure level, as a p-interaction value is not available. This provides a rough estimate of the difference in effect between genetic risk groups, but does not account for data variability. Therefore, this value should be interpreted with caution	249,082 participants. Individuals aged 40 to 69 years (2006–2010).	The *p-interaction* was not reported. The difference in HRs at the highest exposure level is presented as a rough estimate of the interaction effect, but statistical significance can not be determined. PRS calculated using continuous shrinkage method (PRScs) based on Bayesian regression and continuous shrinkage priors (Ge et al.). SNPs coded 0, 1, or 2 based on risk allele count. Posterior effect sizes

									from GWAS summary statistics and external LD reference panel data were used. Cox proportional hazards models were used to assess the relationship between PM2.5 exposure, genetic risk (PRS), and cardiovascular outcomes.
Wang et al., 2022	Weighted genetic risk score (GRS) for COPD derived from 22 SNPs associated with COPD in a previous GWAS, using UK Biobank data.	PM2.5, PM10, NO2, NOx	Although genetic susceptibility to COPD was considered, no statistically significant interaction between pollutants and genetic risk was found.	**PM2.5:** Although the interaction between PM2.5 and lifestyle was not statistically significant, there is a trend suggesting that the effect of PM2.5 on COPD risk may be slightly greater in	Incident **Chronic obstructive pulmonary disease (COPD).**	**PM2,5:** p-interaction= 0.101 **PM10:** p-interaction= 0.753 **NO2:** p-interaction= 0.123 **NOx** p-interaction= 0.258 The p-interaction values are all greater than	Effect modification observed, but not statistically significant (p-interaction > 0.05).	452,762 participants from UK Biobank. Aged from 37 to 73 years old.	This article performed statistical analyses of gene-environment interactions. However, results of these interaction analyses are reported as subgroup-specific HRs with p-interaction values, but not as interaction HRs from explicit

				individuals with an unfavorable lifestyle. Further research is needed to confirm these findings. **PM10, NOx, NO2:** There is no statistically significant evidence of interaction between these pollutants and lifestyle. Therefore, no interpretation of the direction of interaction can be provided.		0.05, meaning the differences in HRs between the subgroups are not statistically significant.			interaction models. The text and table confirms this focus. Based on the data, HR increases with increasing GRS, suggesting that higher genetic susceptibility generally increases the risk of COPD.
Fu et al., 2023	Polygenic Risk Score (PRS) for CAD based on 40 SNPs from a meta-analysis	PM2.5, PM10, NO2, NOx	No significant multiplicative interaction ($p > 0.05$). Significant additive interaction.	Increased CAD risk with higher PM2.5; highest risk in high genetic risk	Incident **coronary artery disease (CAD).**	**P-interaction:** 0.211	**Interaction effect: PM2.5: Low Genetic Risk:** Low PM2.5: Ref. High PM2.5: 1.06 [95% CI 1.00-1.12];	UK Biobank participants	RERI > 0: super-additive interaction (risk exceeds sum of individual effects);

excluding UK Biobank data.	& high PM2.5; synergistic effect; subgroups (female, overweight/ obese, smokers) more susceptible; effect attenuated after adjusting for race.		**Intermediate Risk:** Low PM2.5: 1.25 (95% CI 1.18 - 1.31). High PM2.5: 1.30 (95% CI 1.23 - 1.37). **High Genetic Risk:** Low PM2.5: 1.54 (95% CI 1.46 - 1.62). High PM2.5: 1.56 (95% CI 1.48 - 1.64).	AP: proportion of cases due to interaction. AP > 0: Proportion of cases attributed to interaction (higher AP indicates a larger
		P-interaction: 0.715	**PM10:** **Low Genetic Risk:** Low PM10: Ref. High PM10: 1.02 [95% CI 0.96-1.08]; **Intermediate Risk:** High PM10: 1.26 (95% CI 1.18 - 1.32). High PM10: 1.28 (95% CI 1.21 - 1.35). **High Genetic Risk:** High PM10: 1.48 (95% CI 1.41 - 1.56).	HRs from Cox models, adjusted for demographics, lifestyle, SES, study center, baseline health, and genetic covariates. (SES = Socioeconomic Status)

	High PM10:
	1.55 (95% CI
	1.48 - 1.63).
P-interaction:	**NO2:**
0.578	**Low Genetic Risk:**
	Low NO2: Ref.
	High NO2:
	1.05 [95%
	CI 0.99-1.11];
	Intermediate Risk:
	Low NO2:
	1.22 (95% CI
	1.16 - 1.28).
	High NO2:
	1.31 (95% CI
	1.24 - 1.38).
	High Genetic Risk:
	Low NO2:
	1.52 (95% CI
	1.45 - 1.59).
	High NO2:
	1.57 (95% CI
	1.49 - 1.65).
P-interaction:	**NOx:**
0.851	**Low Genetic Risk:**
	Low NOx: Ref.
	High NOx:
	1.03 [95%
	CI 0.98-1.09];
	Intermediate Risk:
	Low NOx:

							1.21 (95% CI 1.15 - 1.27). High NOx: 1.30 (95% CI 1.24 - 1.37). **High Genetic Risk:** Low NOx: 1.50 (95% CI 1.43 - 1.57). High NOx: 1.57 (95% CI 1.49 - 1.65).		
Li et al., 2022	PRS for CAD (540 variants).	Long-term PM2.5 exposure.	Yes (both additive and multiplicative).	Highest CAD risk observed in individuals with both high genetic risk and high PM2.5 exposure.	Incident **Coronary artery disease (CAD).**	p-interaction < 0.001.	The abstract provides the relative excess risk due to interaction (RERI): 2.75 (1.32–4.20). This is a specific measure of additive interaction. The HR (95% CI) for multiplicative interaction was 1.19 (1.10 - 1.28). p for interaction p < 0.001.	A total of 41,149 participants mainly Han Chinese were included in this analysis.	PRS calculated based on 540 variants. PM2.5 exposure categorized into tertiles. Cox proportional hazards regression models with sub-cohort stratum on a calendar year time scale were used to analyze the association between PM2.5, PRS, and CAD. PM2.5 was analyzed as

									both continuous (per 10 µg/m³ increment) and categorical (tertiles) variable. Three models with increasing confounder adjustment were used. Schoenfeld residual test performed. Exposure-response modeled using restricted cubic splines.
Zhang et al., 2024	* Genetic Risk Score (PRS) * APOE ε4 APOE ε4 genotype (a well-known genetic risk factor for Alzheimer's disease, a common form of dementia)	Joint exposure to multiple air pollutants (PM2.5, PM10, NO2, and NOx).	Yes, interaction analysis conducted. The effect of air pollution on dementia appears to be modified by both a genetic risk score and APOE ε4 genotype, suggesting a synergistic/enhancing effect. However, the p-interaction and interaction effect size (e.g.,	Synergistic/ enhancing. The abstract concludes that joint exposure to air pollutants "substantially increases the risk of dementia, especially among individuals with high genetic susceptibility.	Incident **Dementia.**	**p-interaction: Not reported.**	**Interaction HR** (or other effect size for the interaction): The article does not provide a specific HR or other effect size for the interaction itself. It reports HRs for the main effect of the air pollution score (e.g., HR 1.13 for per IQR increase, HR 1.26 for Q4 vs.	Over half a million participants aged 40–69 years in the UK Biobank data recruited in 2006–2010.	* The study used a weighted air pollution score to represent joint exposure to multiple pollutants. * The authors assessed genetic susceptibility using both a PRS and APOE ε4 genotype. * While the article clearly indicates an interaction was investigated, it

			interaction HR) are not reported in the abstract.				Q1), but not a separate HR that quantifies the interaction.		lacks key statistical information (p-interaction and interaction HR) to fully evaluate its statistical significance and magnitude. Therefore, the conclusion of a synergistic effect is based on the observed pattern rather than a formal statistical test of interaction.
Gao et al.,2023	A polygenic risk score (PRS) approach, aggregating the effects of multiple genetic variants linked to mental health.	PM2.5, PM10, PM coarse, NO2, Nox.	Yes, interaction analysis conducted. The effect of air pollution on mental disorders appears to be modified by the genetic risk score for mental disorders, suggesting a synergistic/ enhancing effect. However, the p-interaction and interaction effect	Suggestive of synergistic/ enhancing interaction (effect of air pollution appears stronger in individuals with higher genetic risk).	**Depression and Anxiety** * Prevalent (at baseline) assessed by: o Hospital admission records. o Mental health questionnaires * Incident (during follow-up) assessed by:	**p-interaction: Not reported.**	The article reports HRs for the main effects of air pollutants but does not report an HR (or any other effect size measure) specifically for the interaction. An interaction HR would quantify how the effect of air pollution changes depending on the gene-	398,241 participants from the UK Biobank.	The abstract indicates that a gene-environment interaction was investigated, with findings suggesting that genetic predisposition to mental disorders may enhance the effects of air pollution. However, the abstract does not provide key information

size (e.g., interaction HR) are not reported in the abstract.	o Hospital admission records. o Mental health questionnaires	tic risk score. This is essential for understanding the magnitude of the interaction.	necessary for a full evaluation of the interaction: * **Specifics of the PRS:** Details regarding the SNPs included in the polygenic risk score (PRS) or its calculation method are not provided. * **p-interaction:** A p-value for the interaction term is not reported, precluding a definitive assessment of statistical significance. * **Interaction effect size:** No interaction HR (or other measure of effect size for the interaction) is reported, making it impossible to determine the magnitude of the interaction. * **Method of inter-**

									action analysis: The specific statistical method used to test the interaction is not described.
Gruzieva et al., 2016	-	NO2	No GxE interaction.	Effect NO2 exposure on DNA methylation in mitochondria related genes	**Differential DNA methylation** at specific CpG sites in cord blood of newborns.	The article does not report any p-interaction values.	Epigenome-wide significant associations [false discovery rate (FDR) $p < 0.05$] between maternal NO2 exposure during pregnancy and DNA methylation in newborns for 3 CpG sites. The associations they found were statistically significant after correcting for multiple comparisons. However, the abstract does not provide specific effect size measures like beta coefficients, odds ratios, or hazard ratios that would	1,508 newborn babies in four European and North American studies	These participants were newborn babies. They were assessed using cord blood DNA methylation. Cord blood is collected at the time of birth, so this sample represents newborns. This is the primary analysis group for the epigenome-wide association study (EWAS). **n = 733 (4 years old)** and **n = 786 (8 years old):** These were subsequent look-up analyses. Prenatal NO2

							quantify the magnitude of the change in methylation associated with NO2 exposure.		exposure and DNA methylation (an epigenetic modification) were assessed in newborns; no GxE interaction analyzed. Methylation was analyzed at specific CpG sites.
Huang et al., 2021	**18 SNPs:** Based on 18 single nucleotide polymorphisms (SNPs) reported in the largest lung cancer GWAS of European descent (International Lung Cancer Consortium). **Polygenic Risk** Score (PRS): A polygenic risk score (PRS) was	PM2.5, PM10, NO2, NOx	Yes, the article states that there are additive interactions between air pollutants and genetic risk.	Effect of PM2.5 on lung cancer risk stronger in individuals with high PRS	**Lung cancer**	NR (not reported)	**PM2.5:** Interm. PRS: RERI 0.36, AP 0.26; High PRS: RERI 0.37, AP 0.21. Positive additive interaction. **PM10:** Interm. PRS: RERI -0.03, AP -0.02; High PRS: RERI 0.11, AP 0.06. No significant additive interaction. **NO2:** Interm. PRS: RERI 0.07, AP 0.05; High PRS: RERI 0.26, AP 0.15. Positive additive interaction in	455,974 UK Biobank participants	PRS is likely calculated based on multiple SNPs; need to verify the details of the article. Analysis may be stratified by lung cancer type. Associations and interactions were assessed using Cox proportional hazards regression models, adjusted for relevant covariates.

	constructed based on these 18 SNPs and categorized into low, intermediate, and high genetic risk based on tertiles of the PRS distribution among non-cases.						High PRS. **NOx:** Interm. PRS: RERI 0.33, AP 0.26; High PRS: RERI 0.53, AP 0.32. Positive additive interaction.		
Li et al., 2023	A polygenic risk score (PRS) was defined using 17 MDD-associated genetic loci.	PM2.5, PM10, NO2, NOx Annual average concentrations of pollutants were estimated using a Land Use Regression model.	Yes, participants were stratified into groups based on combinations of genetic risk (low, intermediate, high) and environmental exposure (e.g., high/low PM2.5) to assess combined effects	The effect of air pollution on MDD risk tends to be stronger in individuals with high genetic risk (synergistic interaction).	**Major depressive disorder (MDD)**	**PM2.5:** P-interaction = 0.036 (p-value < 0.05) **PM10:** P-interaction = 0.025 (p-value < 0.05)	**Interaction HR: - Main HR:** **PM2.5, per 5-µg/m³** increase: **Model 1**: HR = 1.92 (95% CI: 1.79–2.07) p < 0.001 **Model 2**: HR = 1.16 (95% CI: 1.07–1.26) p < 0.001 **PM10, per 10-µg/m3** increase: **Model 1**: HR = 1.30 (95% CI: 1.20 - 1.41) p < 0.001 **Model 2**: HR = 1.00	UK Biobank participants	Significant synergistic interaction (p < 0.05). Highlights the importanceof reducing PM2.5 exposure, especially for genetically susceptible individuals. Significant synergistic interaction (p < 0.05).further reinforces the link air pollution and MDD risk in genetically vulnerable individuals.

							(95% CI: 0.92 - 1.09) p = 0.610		Significant synergistic interaction ($p < 0.05$). Suggests a shared biological pathway involving genetic predisposition and NO2 exposure. No significant interaction detected ($p > 0.05$). Further research is needed to explore the potential role of NOx in MDD development.
						NO2: P-interaction = 0.030 (p-value < 0.05)	**NO2, per 10-µg/m3** increase: **Model 1**: HR = 1.15 (95% CI: 1.13 - 1.17) p < 0.001 **Model 2**: HR = 1.00 (95% CI: 0.98 - 1.02) p = 0.695		
						NOx: P-interaction = 0.080 (p-value > 0.05)	**NOX, per 20-µg/m3** increase: **Model 1**: HR = 1.15 (95% CI: 1.13 - 1.17) p < 0.001 **Model 2**: HR = 1.02 (95% CI: 1.02 - 1.05) p = 0.017		
Huang et al., 2024	**1. SNPs (Single Nucleotide Polymorphisms):** The specific SNPs used in the study, which in this case are 44 SNPs associated with	PM2.5, PM10, NO2, NOx The annual average air pollution concentration was intricately calculated using an advanced land	G x E interaction: Not Reported, but genetic susceptibility reported.	HR increases with increasing GRS, indicating that higher genetic susceptibility generally increases the risk of Parkinson's	Incident **Parkinson's disease (PD).**	p-interaction: not available. Figure 1 presents visual evidence of potential interaction; however, the p-value for the interaction term is necessary to determine	While Figure 1 displays hazard ratios (HRs) for each combination of pollution exposure and genetic risk group, it does not explicitly provide an "interaction HR. To quantify the	The population-based study involved 312,009 initially PD-free participants with complete genotyping data.	While the authors performed statistical analyses of gene-environment interactions using Cox proportional hazards models (including calculating p-interaction values), Figure 1 focuses on

Parkinson's disease (PD), derived from the PD GWAS.

2. β Coefficients: The log-odds ratio (β) per allele for each SNP, which represents the risk associated with the SNP for PD, obtained from the relevant GWAS study.

3, Number of Risk Alleles (SNPi): The count of risk alleles (0, 1, or 2) for each SNP in each individual.

4. Total Number of SNPs (n): The total number of

use regression (LUR) model.

disease.

statistical significance. This value is not shown in the article.

effect size of the interaction, a formal statistical analysis is needed. The figure suggests a modest effect modification, with the HR increasing more steeply across pollution quartiles in the high genetic risk group compared to the low genetic risk group.

visualizing main effects of genetic risk and stratifying participants by genetic risk level, rather than presenting interaction effects. Consequently, specific results of the interaction analyses (e.g., p-values, interaction HRs) are not reported in the context of Figure 1.

	SNPs used in the analysis, which is 44 in this study.								
Zhang et al., 2024	Polygenic Risk Score (PRS) of Major Depressive Disorder (MDD).	Fine particulate matter (PM2.5) exposure (average over 6 months).	Yes. The study investigated the interactive effect of air pollution (PM2.5) and genetic risk for MDD (PRS) on processing speed. They found that: * In individuals with high genetic risk for MDD, higher PM2.5 exposure was associated with reduced precuneus connectivity. * Genetic risk for MDD amplified the effect of PM2.5 on DMN connectivity, especially in frontal-parietal and frontal-limbic regions. * In genetically	The interaction suggests that genetic predisposition to MDD combined with higher PM2.5 exposure has a synergistic effect. It worsens the negative impact of air pollution on brain function (reduced local connectivity in precuneus, increased connectivity in DMN) and processing speed.	**Processing speed.**	The article mentions specific p-values for the interaction effects: * Precuneus local connectivity: PFWE=0.028 * Default mode network connectivity: PFDR<0.05.	The article doesn't provide specific effect sizes, but it describes the direction of the interaction (worsening effect with combined exposure and high genetic risk).	497 healthy adult volunteers (48.7% male, mean age 24.5 years) living in Beijing for at least 1 year.	The study investigated the interactive effect of air pollution (PM2.5) and genetic risk for MDD on processing speed and resting-state brain function using fMRI and cognitive tests. * The study suggests that air pollution may have a stronger negative impact on brain function and processing speed in individuals with a genetic predisposition to depression. * The study suggests that air pollution may have a stronger negative

			predisposed individuals, higher PM2.5 was linked to increased connectivity between the left angular and cuneus gyri, which in turn was associated with slower processing speed.						impact on brain function and processing speed in individuals with a genetic predisposition to depression. * The study also explored the potential role of DNA methylation and gene expression of the SLC30A3 gene in this interaction.
Wu et al., 2024	PRS for Psoriasis.	PM10, PM2.5, NO2, NOx	Yes (multiplicative interaction between PM10 and genetic predisposition).	A multiplicative interaction between PM10 and genetic predisposition (P for interaction = .002)	Incident **Psoriasis**	**PM10:** **P-interaction (Multiplicative):** 0.002 **P-interaction (Additive):** Not reported. **PM2.5:** **P-interaction:** 0.105 **P-interaction (Additive):** Not reported. **NO2:** **P-interaction:** 0.051	Multiplicative: HR 1.75 (1.25-2.45) The most substantial risk of psoriasis development was observed in participants exposed to elevated air pollution levels combined with high genetic risk.	474 055 individuals with a mean (SD) age of 56.54 (8.09) years.	Time-varying Cox proportional hazards models used. Adjusted for various confounders. Analysis restricted to White European ethnicity.

						P-interaction (Additive): Not reported. **PM10:** **P-interaction:** 0.053 **P-interaction (Additive):** Not reported.			
Liu et al., 2024	PRS for schizophrenia.	PM2.5, PM10, NO2, NOx	There was a significant interaction only for NO2 and NOx exposure, indicating that the effect of exposure on schizophrenia risk depends on the individual's level of genetic susceptibility. Individuals with high genetic risk for schizophrenia are more affected by NO2 and NOx exposure, highlighting the importance of	Synergistic (multiplicative), with higher genetic risk amplifies the impact of air pollution exposure (NO2 and NOx) on schizophrenia risk. The adverse effects of air pollution are more pronounced in individuals with greater genetic susceptibility.	Incident **shizo - phrenia.**	**PM2,5:** p-interaction= 0.48 **PM10:** p-interaction= 0.79 **NO2:** p-interaction= < 0.07 **NOx** p-interaction= < 0.01 This indicates the genetic risk for schizophrenia does not significantly modify the effect of PM2.5 and PM10 on schizophrenia risk.	The **Effect size** should represent the observed strength of the association between genetic risk, air pollution exposure, and schizophrenia risk. **1. Low genetic risk, T3 HR:** PM2.5: 2.33 (95% CI: 1.93–2.96). PM10: 2.69 (95% CI: 2.09 - 3.46). NO2: 2.40 (95% CI: 1.37 - 3.07). NOx: 2.60 (95% CI: 1.94 - 3.22). **2. High genetic risk, T3 HR:**	485,288 participants from UK Biobank.	Multiplicative interactions were assessed using Cox proportional ha - zards models with a product term for exposure and genetic risk. The reported p-interaction values represent the statistical significance of this interaction term. The proportional hazards assumption was checked and met. Hazard ratios (HR)

			gene-environment interactions in schizophrenia risk.				PM2.5: 6.25 (95% CI: 5.03 - 7.7). PM10: 7.36 (95% CI: 5.86 - 9.29). NO2: 6.31 (95% CI: 5.02 - 7.93). NOx: 6.62 (95% CI: 5.24 - 8.37). p-value for trends < 0.001 for 4 pollutants.		and 95% confidence intervals (95% CI) are provided for main effects and, where applicable, for the combined effect of exposure and genetic risk.
Ma et al., 2024	Polygenic Risk Score (PRS) for Stroke, using 71 independent SNPs associated with stroke in European ancestry populations.	PM2.5, PM10, NO2, NOx	While visual inspection of hazard ratios suggested a potential combined effect of air pollution and genetic risk on stroke, no statistically significant multiplicative interaction was found (all p-interaction > 0.05). However, some evidence of additive interaction was	direction of the interaction is synergistic or multiplicative.	Incident **stroke, ischemic stroke, and hemorrhagic stroke**	**PM2,5:** p-interaction= 0.11 **PM10:** p-interaction= 0.75 **NO2:** p-interaction= 0.02 **NOx** p-interaction= 0.87	Visually stronger exposure effect in high genetic risk group. Graph suggests increased exposure effect with higher genetic risk.	UK Biobank participants	Multiplicative interactions were assessed using Cox proportional hazards models with a product term for exposure and genetic risk. The reported p-interaction values represent the statistical significance of this interaction term. The proportional hazards assumption was checked

			observed.						and met. Hazard ratios (HR) and 95% confidence intervals (95% CI) are provided for main effects and, where applicable, for the combined effect of exposure and genetic risk.
Chen et al., 2024	For UC results: "UC GRS" (or Genetic Risk Score for UC). For CD results: "CD GRS" (or Genetic Risk Score for CD).	NOx exposure, NO2 exposure, PM2.5 exposure, Combined air pollution score.	Yes (Additive and Multiplicative).	Air pollution is associated with increased UC risk, with effects modified by lifestyle and genetic influences. Epigenetic alterations in CXCR2 and MHC class III region are implicated as potential mechanisms.	Incident **ulcerative colitis (UC).**	P-interaction for multiplicative model = 2.75E-01 P-interaction for additive model = 1.23E-03	**Multiplicative Interaction:** The effect size for the multiplicative interaction is represented by the Interaction HR (95% CI). However, the HRs presented in the "Subgroup analysis" section are not the interaction HRs directly. They are the HRs for the effect of air pollution within each genetic risk	A total of 452,012 (895 cases) and 453,199 (2082 cases) participants were eligible for CD and UC analysis, respectively.	GxE interaction observed, with epigenetic alterations in CXCR2 and MHC class III region implicated as potential mechanisms. Epigenetic Mendelian Randomization (MR) analysis was performed. Cox regression, Schoenfeld residuals test, Epigenetic MR analysis, Co-localization and gene expres-

	group. **Additive Interaction:** The effect size for additive interaction is given by the RERI: 0.95 (95% CI: 0.34-1.57)	sion analyses.; The main focus of the study was on Ulcerative Colitis, with no significant association found for CD.

Footnote: Abbreviations: OR, Odds Ratio (a measure of association between an exposure and an outcome); CI, Confidence Interval (a range of values that likely contains the true population parameter); 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); SNP, Single Nucleotide Polymorphism (a variation at a single nucleotide that occurs at a specific position in the genome); PRS, Polygenic Risk Score (a score that estimates an individual's risk of a disease based on their genetic variation); PM_{2.5}, Particulate Matter with a diameter ≤ 2.5 µm; PM₁₀, Particulate Matter with a diameter ≤ 10 µm; NO₂, Nitrogen Dioxide; NO_x, Nitrogen Oxides; GWAS, Genome-Wide Association Study; GxE, Gene-Environment Interaction.