Phenome-wide association and epigenetic Mendelian randomization study revealing health effects of air pollution altered DNA methylation

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Background

1. Ambient air pollution has been linked to respiratory and cardiovascular disease in observational studies. Nevertheless, considerable uncertainty remains regarding its causal role and underlying mechanisms in a wide range of disease outcomes.

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2. The increasing availability of epigenome-wide association studies (EWAS) has identified that air pollution exposure could alter epigenetic markers, specifically DNA methylation in blood samples and result to atypical DNA methylation near specific candidate genes.

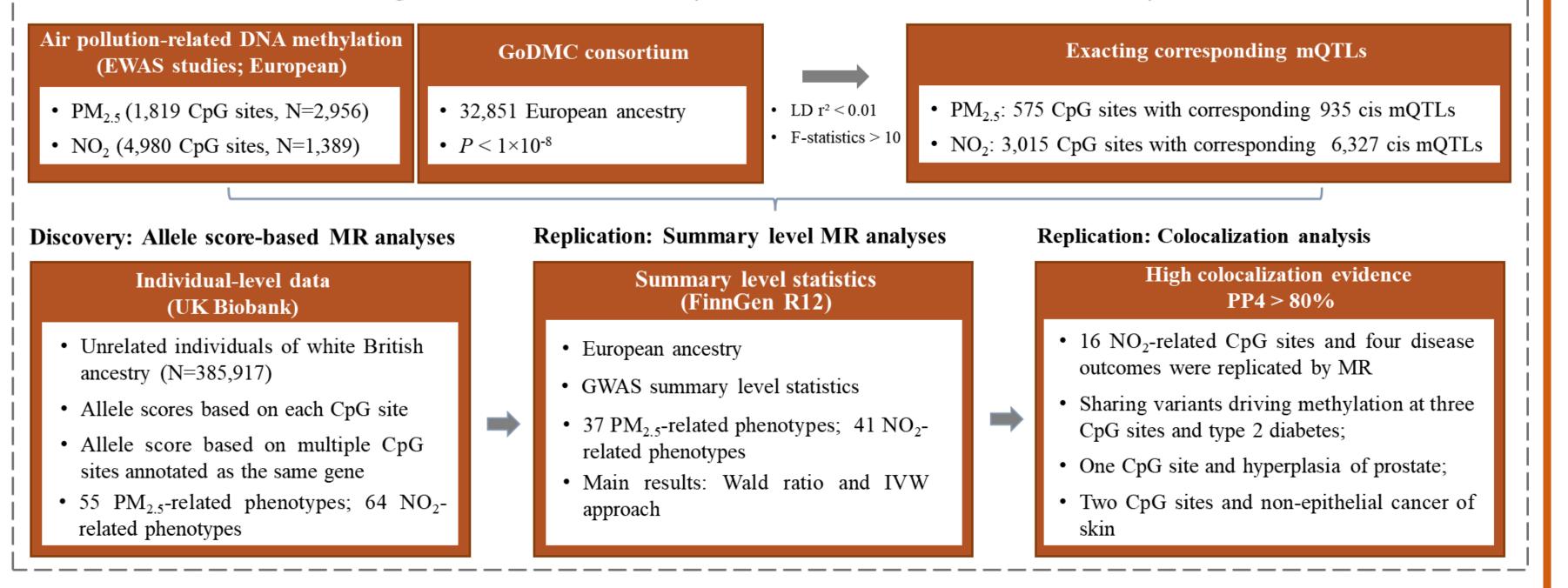
Aim

• We conducted a Phenome-wide association study and epigenetic Mendelian randomization analysis to comprehensively explore the associations between air pollution, DNA methylation, and the risk of multiple health-related conditions.

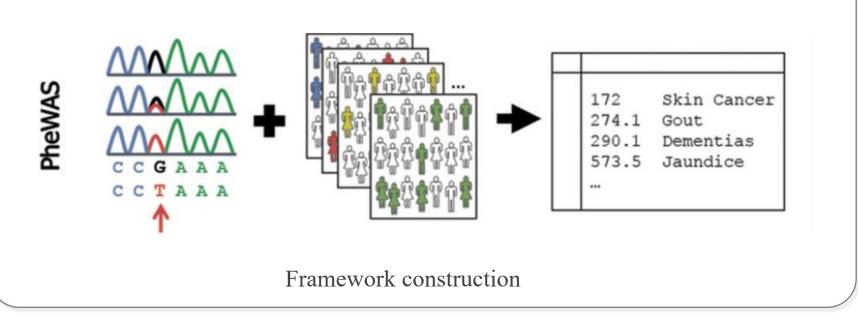
Methods Study design Stage 1: Observational PheWAS analysis biobank" The UK Biobank study 460,028 individuals with air pollution data from the • PM_{2.5} • Multivariable logistic regression models In-patient hospital episode European Study of Cohorts for Air Pollution Effects • PM₁₀ (Stratifications analyses; Sensitivity analyses) Cancer registry (ESCAPE) model • NO₂ • Statistically threshold: Bonferroni correction Death registry records • NO_x $(P \le 5.25 \times 10^{-5})$ 1081 phenotypes using Phecodes and hospital, Joint score cancer and death registry data • A total of 91 significant air pollution-related

• An <u>observational Phenome-wide association analysis</u> was performed to examine the association between the modelled air pollutants concentration levels and a spectrum of disease outcomes in UK Biobank cohort.

Stage 2: Allele score and summary level-based Mendelian randomization analysis

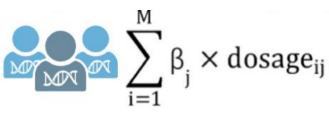


- <u>Allele score-based Mendelian randomization</u> with individual-level genotypic data in UK Biobank, and <u>summary level-based Mendelian randomization</u> analysis in FinnGen study using summary statistics were conducted as replication.
- <u>Bayesian colocalization analyses</u> was applied to further investigate the effect of biological pathway on blood DNA methylation related to air pollutants and susceptibility of specific disease.
- Phenome-wide association studies
- Air pollutants were modelled from a Land Use Regression Model.
- Multivariable regression model; Adjustment with age at recruitment, sex, BMI, education, Townsend deprivation index, ethnicity, smoking status, physical activity, alcohol drinking and current employment risk.



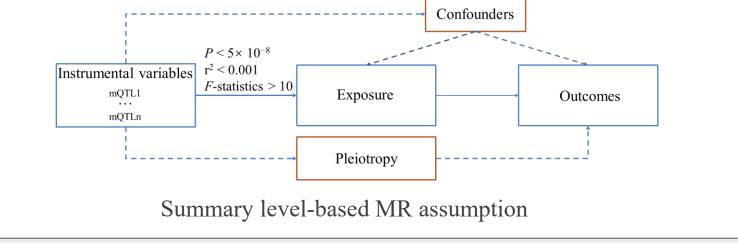
- Epigenetic Mendelian randomization
- Allele score-based

Adding up the number of air pollutant-risk alleles for corresponding mQTLs, using beta coefficients from GoDMC database.



Summary level-based

Main results: Wald ratio; Inverse variance weighted Heterogeneity: Cochran's Q statistic (P > 0.05) Horizontal pleiotropy: MR-Egger (P > 0.05)



Results Nonrheumatic tricuspid valve disorders Rheumatic disease of the heart valves Iron deficiency anemia secondary to blood loss (chronic) Disease of tricuspid valve Effects radiation NOS Orthostatic hypotension Cerebral ischemia Other mental disorder Peripheral vascular disease, unspecified Delirium due to conditions classified elsewhere Nonrheumatic mitral valve disorders Alcohol-related disorders Other forms of chronic heart disease Alzheimer's disease Angina pectoris Anxiety disorder Hypotension NOS Symptoms involving head and neck hlebitis and thrombophlebitis of lower extremities - Atopic/contact dermatitis due to other or unspecified Polyneuropathy due to drugs Gastritis and duodenitis Spondylosis without myelopathy Other chronic nonalcoholic liver disease Osteoporosis NOS Other specified gastritis Degeneration of intervertebral disc Nonspecific abnormal findings in stool contents Osteoarthrosis, localized, primary Esophagitis, GERD and related diseases Osteoarthrosis, generalized Other disorders of soft tissues Personal history of diseases of digestive system Osteoarthritis; localized Kyphoscoliosis and scoliosis Gastric ulcer Melanomas of skin Diseases of the oral soft tissues Other non-epithelial cancer of skin Malignant neoplasm, other Pulmonary collapse; interstitial and compensatory emphysema Vitamin D deficiency Chronic airway obstruction Respiratory failure Disorders of calcium/phosphorus metabolism Pulmonary congestion and hypostasis Disorders of phosphorus metabolism Pleurisy; pleural effusion Hyposmolality and/or hyponatremia Disorders of magnesium metabolism Type 2 diabetes Aphakia and other disorders of lens Other disorders of bladder Urinary tract infection Sensorineural hearing loss Disorders of refraction and accommodation; blindness and low vision Polyp of corpus uteri Disorders of vitreous body Dizziness and giddiness (Light-headedness and vertigo) Hyperplasia of prostate Chorioretinal scars Cyst of kidney, acquired Disorders of optic nerve and visual pathways Chronic prostatitis Swelling of limb Viral hepatitis B Abdominal pain Other abnormal blood chemistry

Figure 1 Overview of disease outcomes associated with air pollution in PheWAS analysis.

Outcomes	CpG	Gene		Allele score-based MR (UK Biobank)			Summary level-based MR (FinnGen)			PP.H4
				OR (95%CI)	P Value	FDR	OR (95%CI)	P Value	FDR	11,114
	cg06240200	CCDC12	-	1.03 (1.01, 1.05)	5.89e-04	2.64e-02	1.39 (1.22, 1.59)	1.17e-06	1.43e-04	0.96
	cg09367967	CALR	*	1.04 (1.02, 1.06)	2.35e-06	3.53e-04	1.21 (1.11, 1.33)	3.86e-05	2.47e-03	0.90
	cg18603577	RILPL2	*	1.06 (1.04, 1.08)	5.39e-08	1.62e-05	1.24 (1.12, 1.38)	3.80e-05	2.47e-03	0.93
Hyperplasia of prostate	cg20959189	ZBTB38	•	1.08 (1.06, 1.10)	1.73e-13	1.30e-10	1.43 (1.30, 1.57)	6.23e-14	9.16e-11	0.97
Non-epithelial cancer of skin	cg01543603	ANKRD11	+ *	0.96 (0.94, 0.98)	1.20e-06	1.81e-04	0.51 (0.42, 0.61)	5.41e-13	3.18e-10	0.99
	cg25670076	BACH2		0.97 (0.95, 0.98)	7.90e-05	5.94e-03	0.67 (0.55, 0.82)	9.92e-05	1.33e-02	0.88

Figure 2 Forest plot showing evidence from Mendelian randomization and colocalization analysis between genetically predicted NO₂-related CpG sites and clinical outcomes.

Discussion and Conclusions

- Ambient air pollution exposures suggested significant associations with health outcomes of <u>different human systems</u> (e.g., cardiometabolic diseases and genitourinary diseases).
- ➤ Our results indicated the evidence linking higher genetically predicted NO₂-related DNA methylation at cg06240200 [CCDC12], cg09367967 [CALR], cg18603577 [RILPL2] and increased risk of type 2 diabetes; cg20959189 [ZBTB38] and increased risk of hyperplasia of prostate; and cg01543603 [ANKRD11] and cg25670076 [BACH2] and decreased risk of non-epithelial cancer of skin.
- ❖ To summarise, this study suggests that NO₂ exposure is associated with health-related conditions, e.g., type 2 diabetes, hyperplasia of prostate, and non-epithelial cancer of skin via DNAm of specific genetic loci.
- Future studies could investigate the underlying biological mechanisms of the identified associations.

References

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Acknowledgements