

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

Lili Yu¹, Kening Gao², Xue Li², Anna L Hansell³, Athina Spiliopoulou⁴, Mark R Millar⁵, Evropi Theodoratou^{1 6}

¹ Centre for Global Health, Usher Institute, The University of Edinburgh. ² Department of Big Data in Health Science, School of Public Health, Zhejiang University.

³ Centre for Environmental Health and Sustainability, University of Leicester. ⁴ College of Medicine and Veterinary Medicine, Usher Institute, University of Edinburgh.

⁵ Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh.

⁶ Cancer Research UK Edinburgh Centre, The University of Edinburgh MRC Institute of Genetics and Cancer.



Background

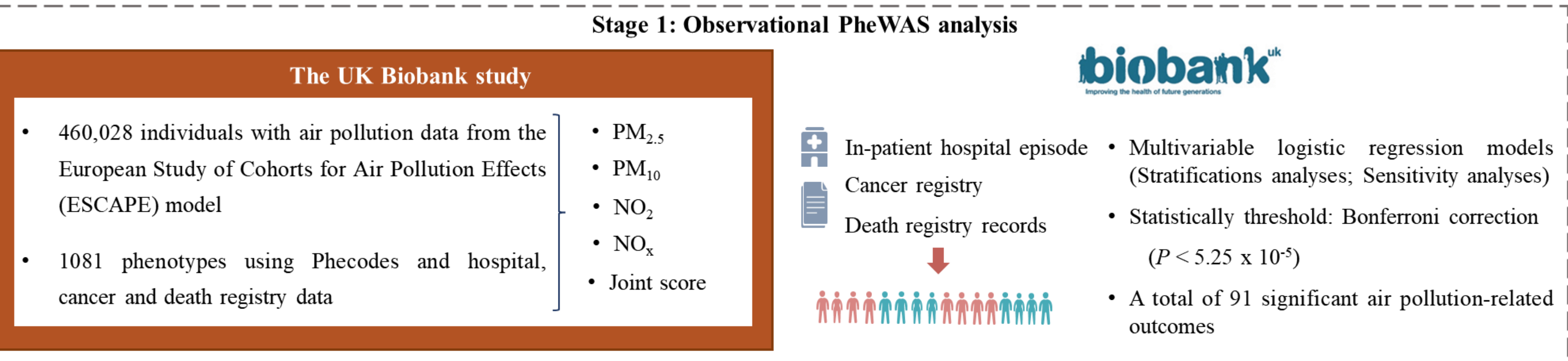
1. Ambient air pollution has been linked to respiratory and cardiovascular disease in observational studies. Nevertheless, considerable uncertainty remains regarding its causal role and underlying mechanisms in a wide range of disease outcomes.
2. The increasing availability of epigenome-wide association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

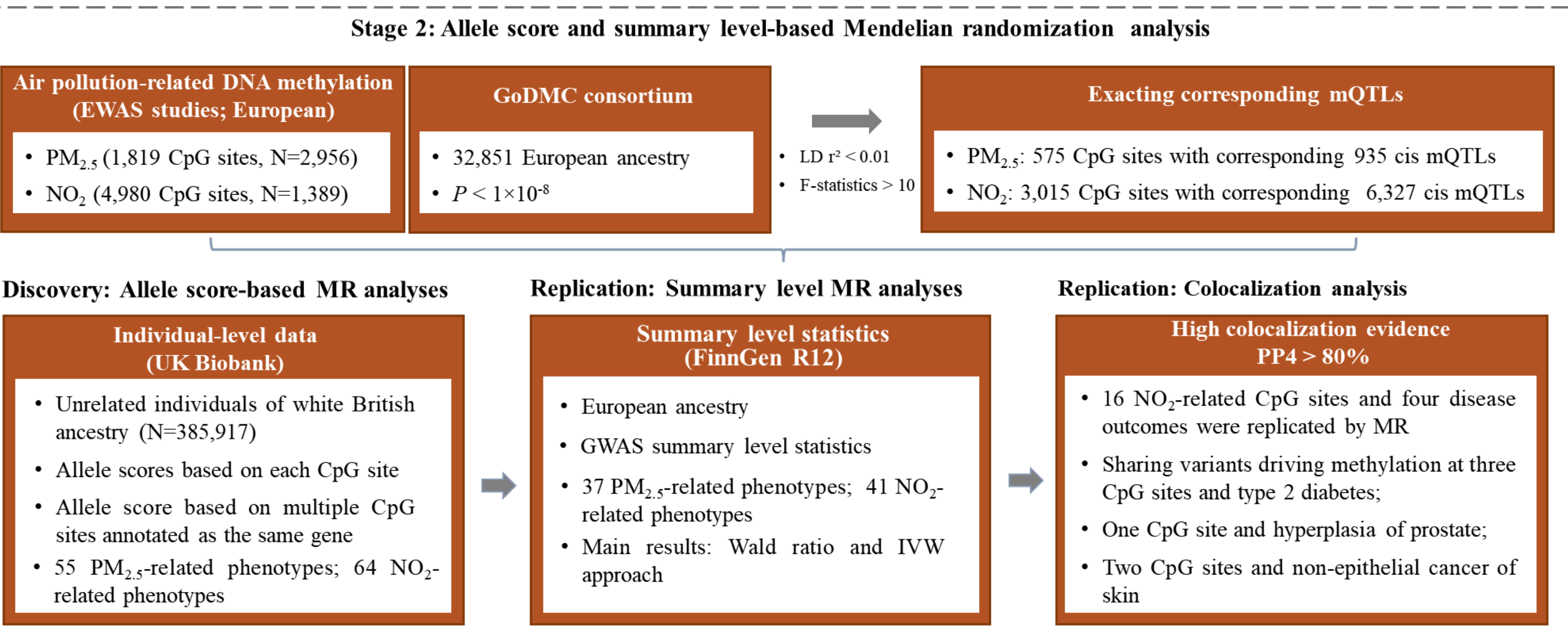
- We conducted a Phenome-wide association study and epigenetic Mendelian randomization analysis to comprehensively explore the associations between air pollution, DNA methylation, and the risk of multiple health-related conditions.

Methods

Study design



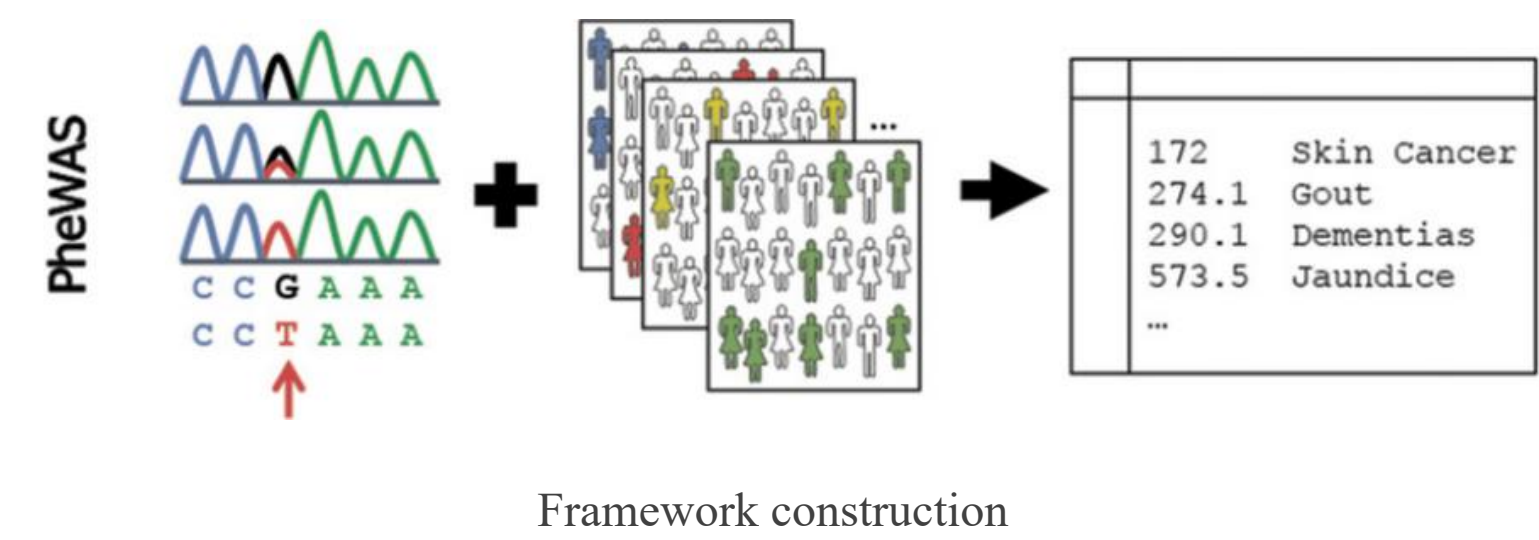
- An observational Phenome-wide association analysis was performed to examine the association between the modelled air pollutants concentration levels and a spectrum of disease outcomes in UK Biobank cohort.



- Allele score-based Mendelian randomization with individual-level genotypic data in UK Biobank, and summary level-based Mendelian randomization analysis in FinnGen study using summary statistics were conducted as replication.
- Bayesian colocalization analyses 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

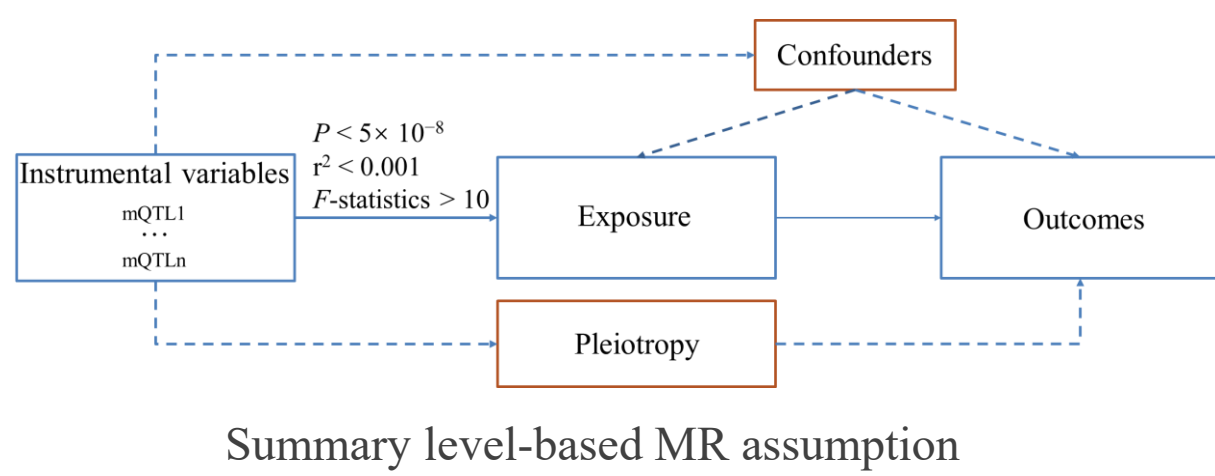
- Allele score-based

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

$$\sum_{i=1}^M \beta_j \times \text{dosage}_{ij}$$

- 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



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

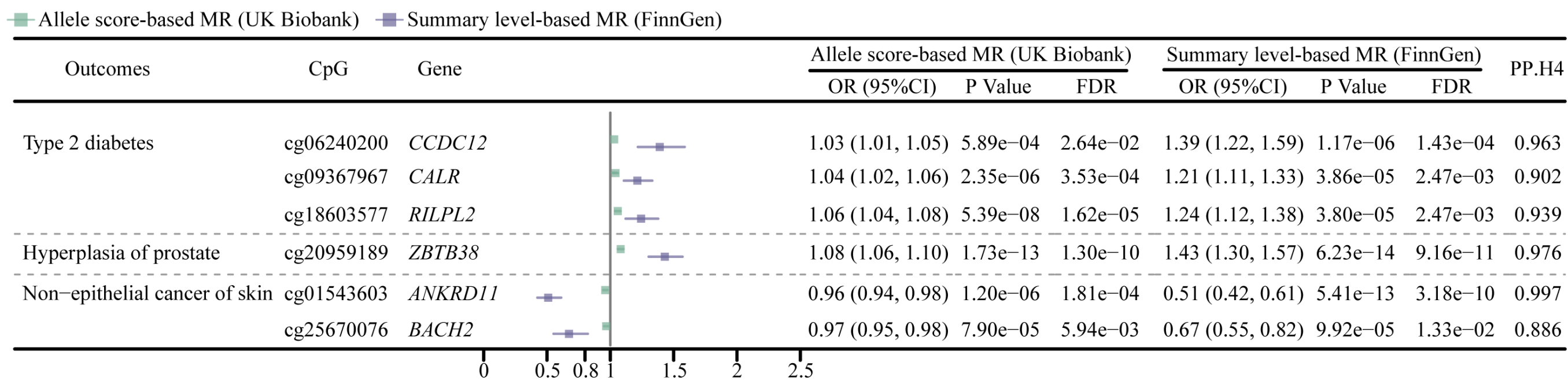


Figure 2 Forest plot showing evidence from Mendelian randomization and colocalization analysis between genetically predicted NO₂-related CpG sites and clinical outcomes.

Discussion and Conclusions

- Ambient air pollution exposures suggested significant associations with health outcomes of different human systems (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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- [2] Plusquin M, *et al.* DNA methylation and exposure to ambient air pollution in two prospective cohorts. Environ Int 2017; 108: 127-36.
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Acknowledgements

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