

High-Impact Cilia-Related Rare Variant Burden Modifies the Association Between PM2.5 Exposure and Lung Cancer Risk, Especially in Never-Smokers

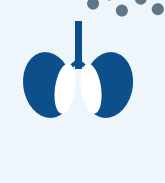
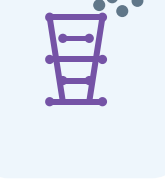
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Higher cilia-related rare variant burden may increase susceptibility to PM2.5-related lung carcinogenesis, with a stronger effect in never-smokers.



Background

-  Air pollution is an established risk factor for lung cancer, particularly in never-smokers.
-  Cilia are central to mucociliary clearance and airway defense against inhaled particles.
-  Inherited cilia-related defects may plausibly increase susceptibility to PM2.5-associated lung injury and carcinogenesis.

Objective

-  To investigate whether **cilia-related rare variant burden** modifies the association between **PM2.5** exposure and lung cancer risk in the UK Biobank, and whether this effect is more pronounced in **never-smokers**.

Methods

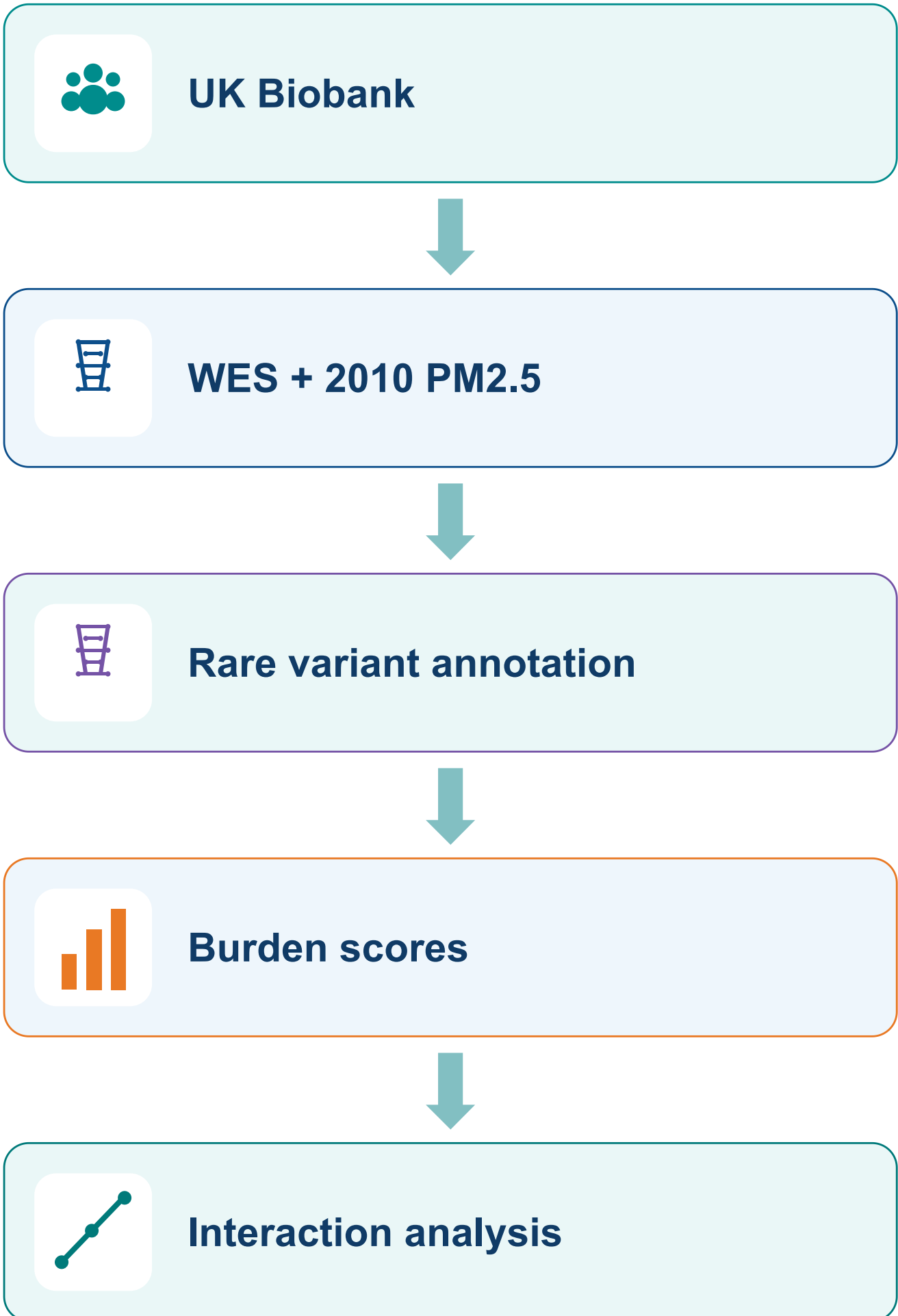
- UK Biobank participants with whole-exome sequencing data and 2010 PM2.5 estimates
- Cilia-related gene set curated from a 2025 Cell resource
- Rare variants extracted at allele frequency <1% and annotated for predicted functional impact
- Primary exposure: standardized HIGH-impact cilia-related rare variant burden score
- Secondary analyses: weighted HIGH + MODERATE burden and binary carrier definitions
- Outcome: lung cancer case status
- Logistic regression

Model adjustment

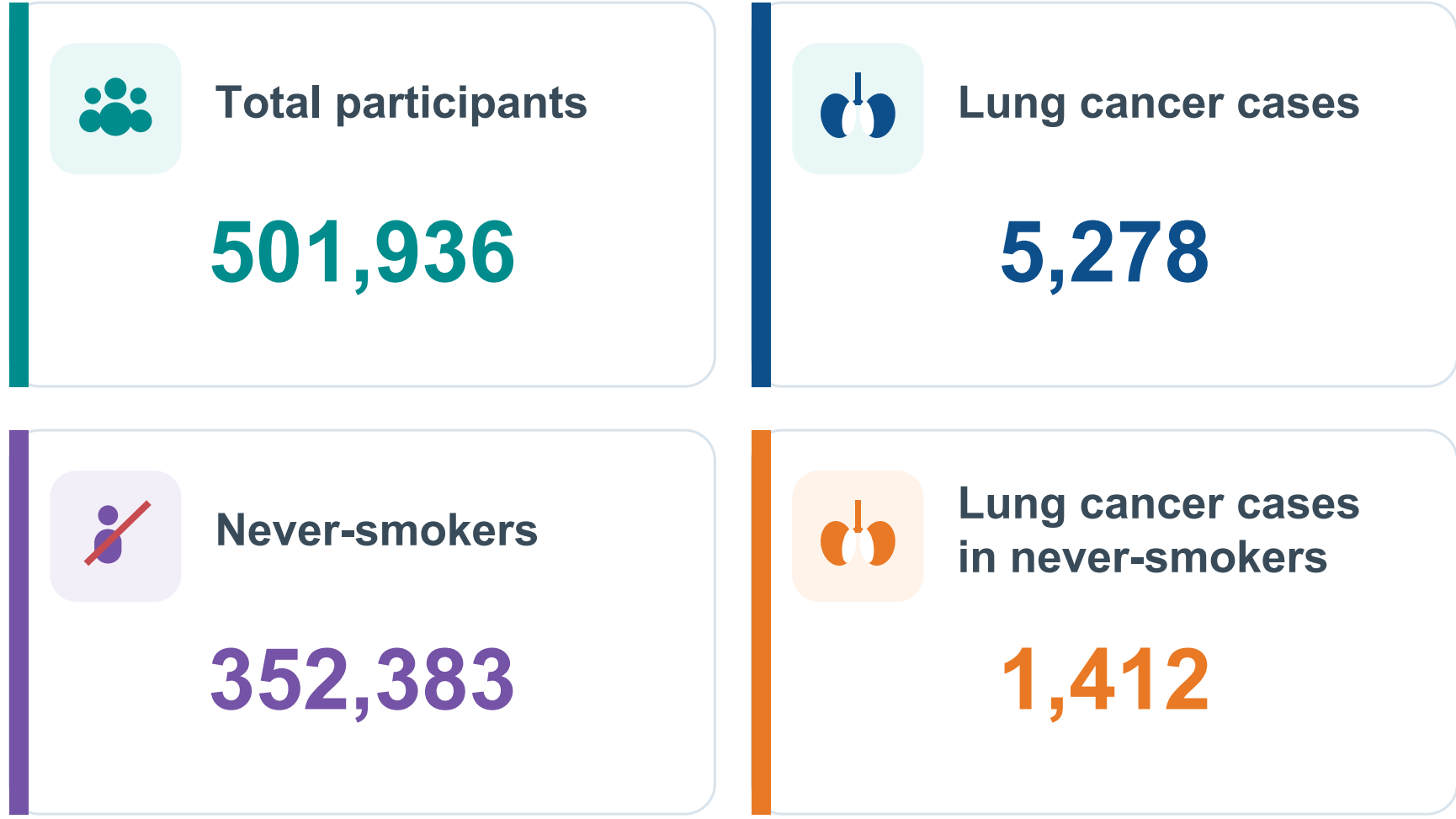
Overall population:
age, sex, pack-years

Never-smokers:
age, sex

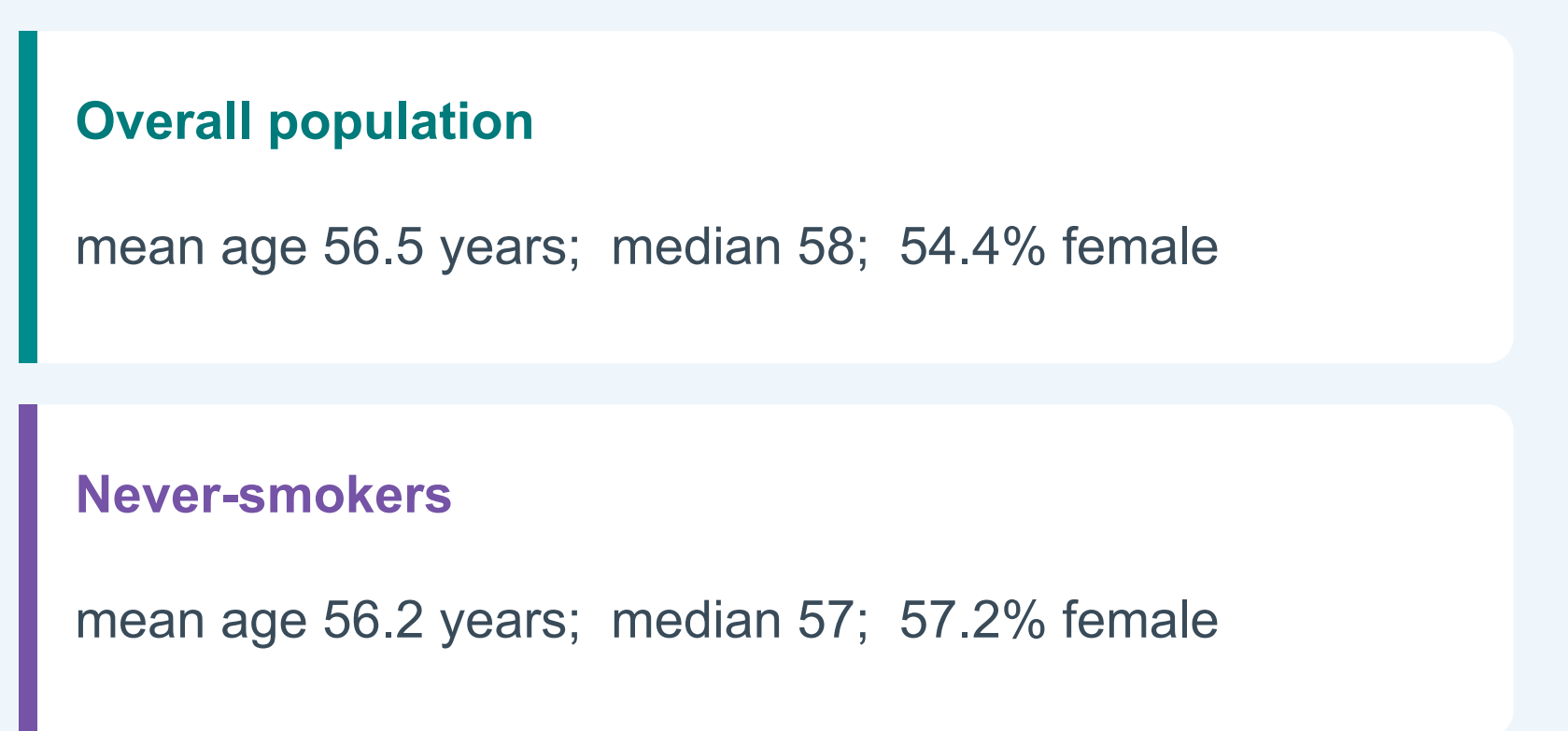
Analysis Workflow



Study Population

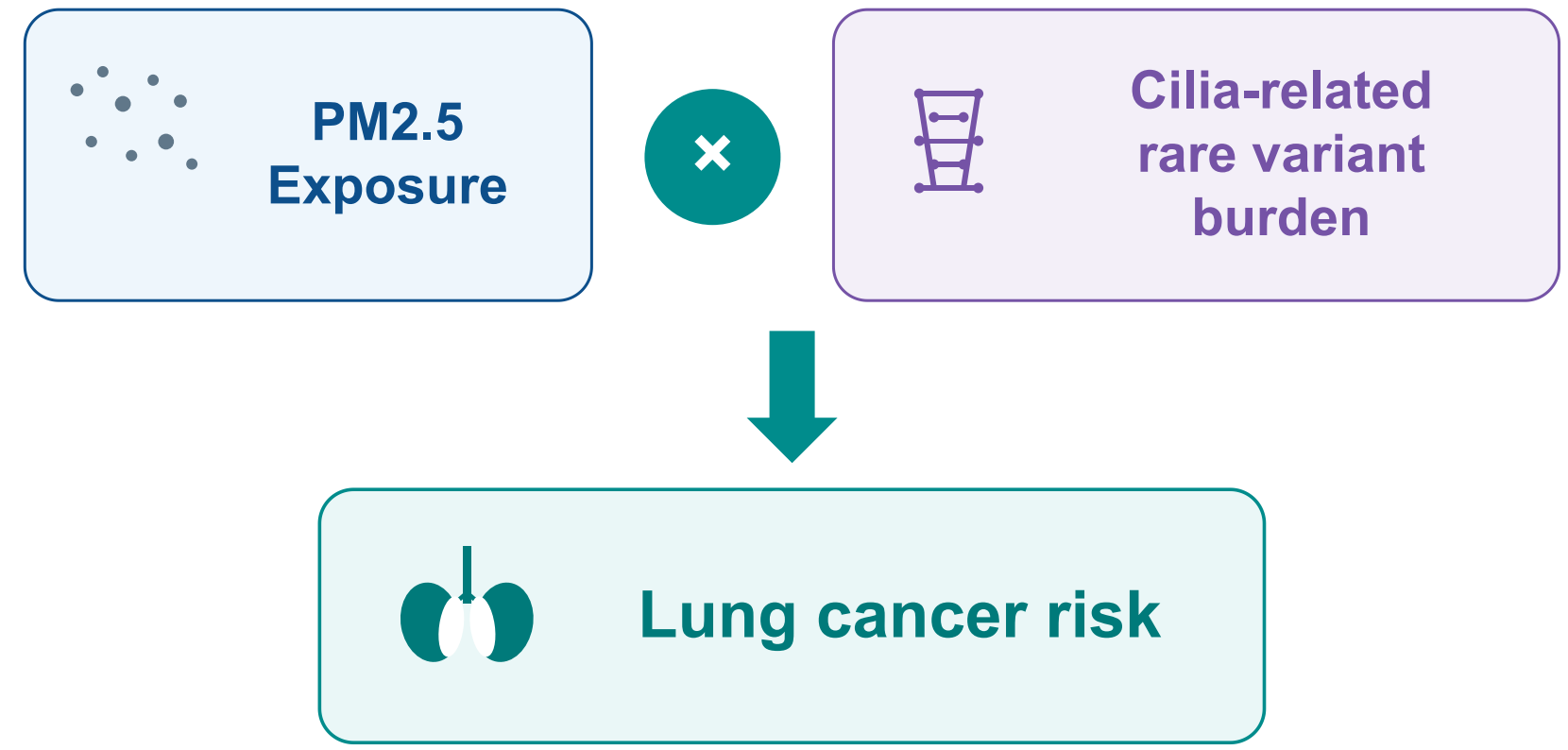


Demographics

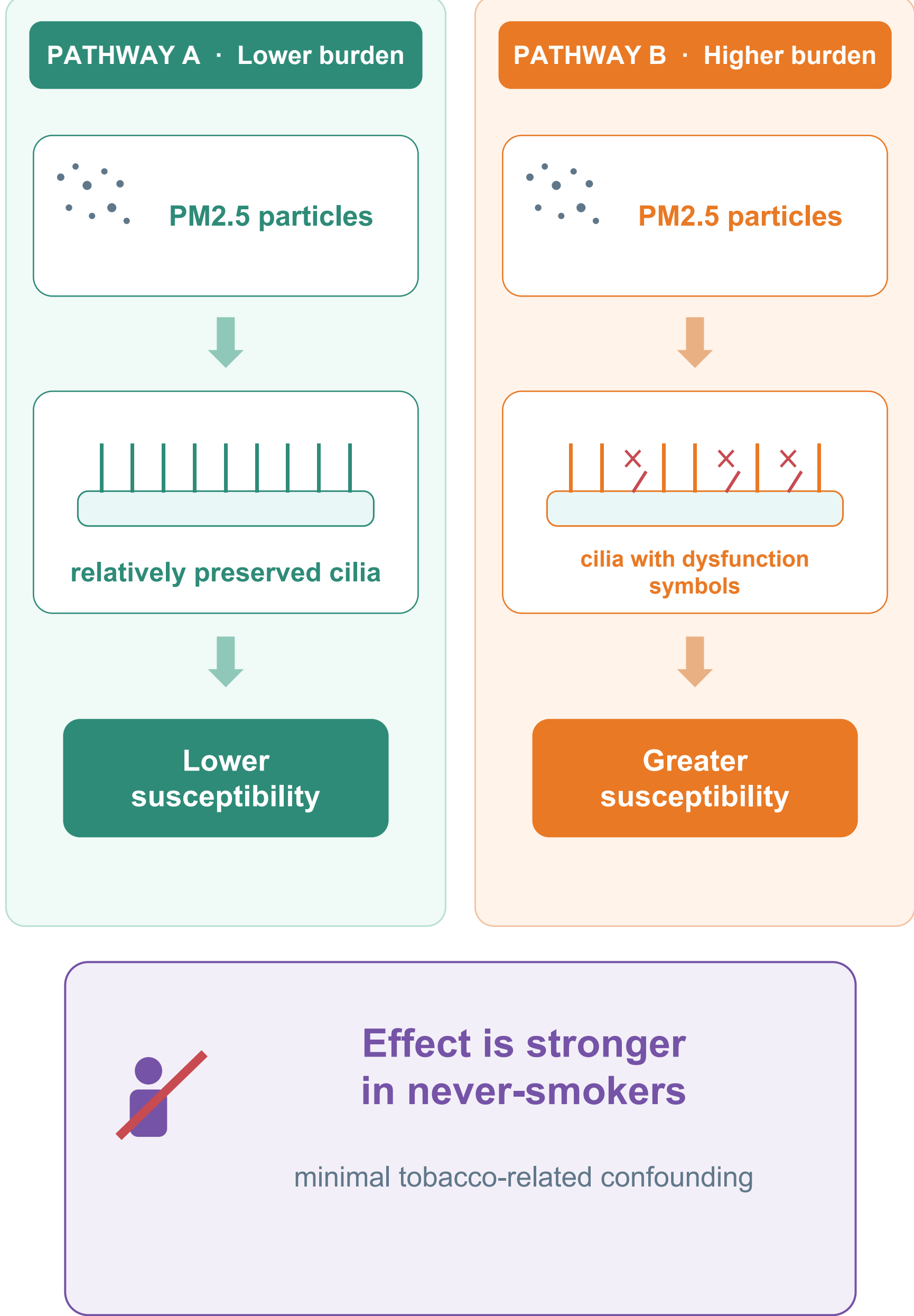


Key Hypothesis

PM2.5 exposure interacts with cilia-related rare variant burden to influence lung cancer risk.

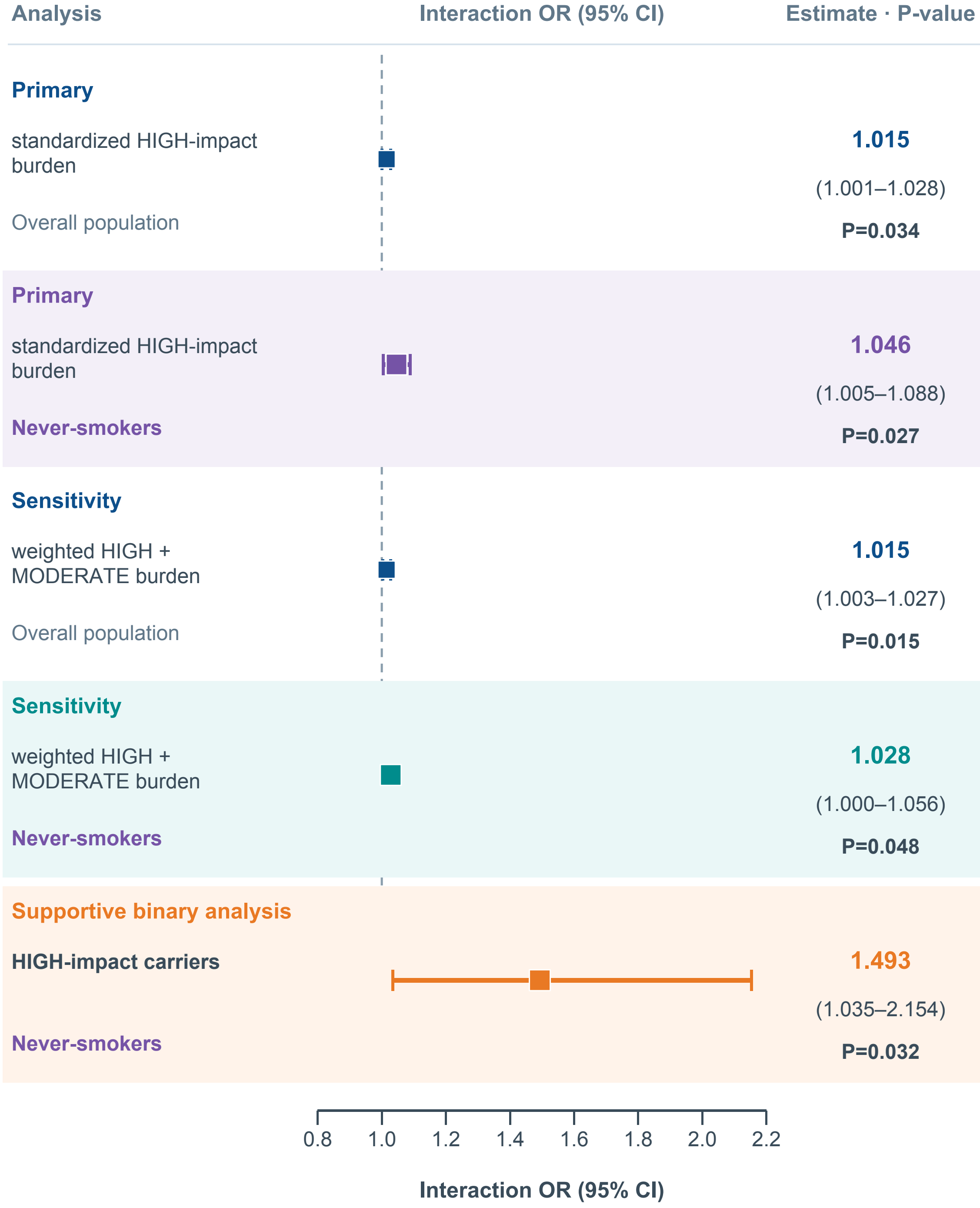


Biological interpretation



Results

Interaction effect estimates



Primary · Never-smokers

OR 1.046

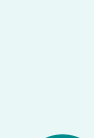
95% CI 1.005–1.088
P=0.027

Binary carriers · Never-smokers

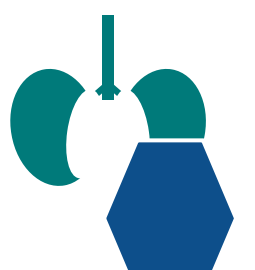
OR 1.493

95% CI 1.035–2.154
P=0.032

Key Findings

-  The PM2.5 × HIGH-impact burden interaction was significant in the overall population.
-  **The interaction effect was stronger in never-smokers.**
-  Sensitivity analyses showed the same direction of effect.
-  In a supportive binary analysis, HIGH-impact carriers showed greater PM2.5-associated vulnerability, particularly among never-smokers.
-  Exploratory protein- and gene-level decomposition suggested molecular heterogeneity within the cilia-related susceptibility signal.

Conclusion

 A higher cilia-related rare variant burden was associated with greater susceptibility to PM2.5-related lung carcinogenesis, with a stronger effect in never-smokers. These findings support cilia-related airway defense as a potential susceptibility axis in non-tobacco-associated lung carcinogenesis.