Birth weight and Respiratory health:
2-Sample Mendelian Randomization Study

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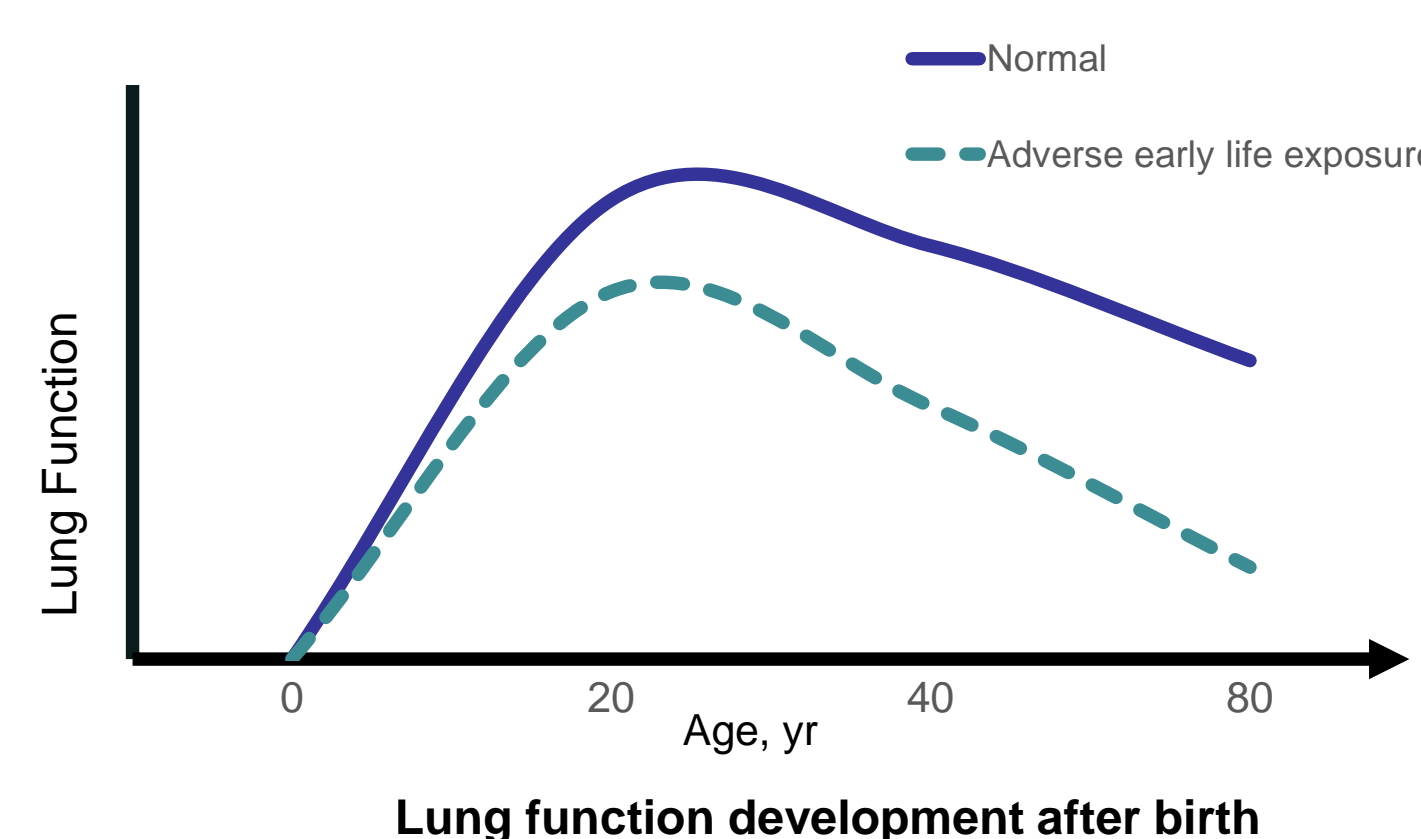
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BACKGROUND

The developmental origins of health and disease hypothesis highlights the fetal and early postnatal period as critical exposure windows for non-communicable diseases, particularly when a mismatch between predicted and actual adult environments occurs.
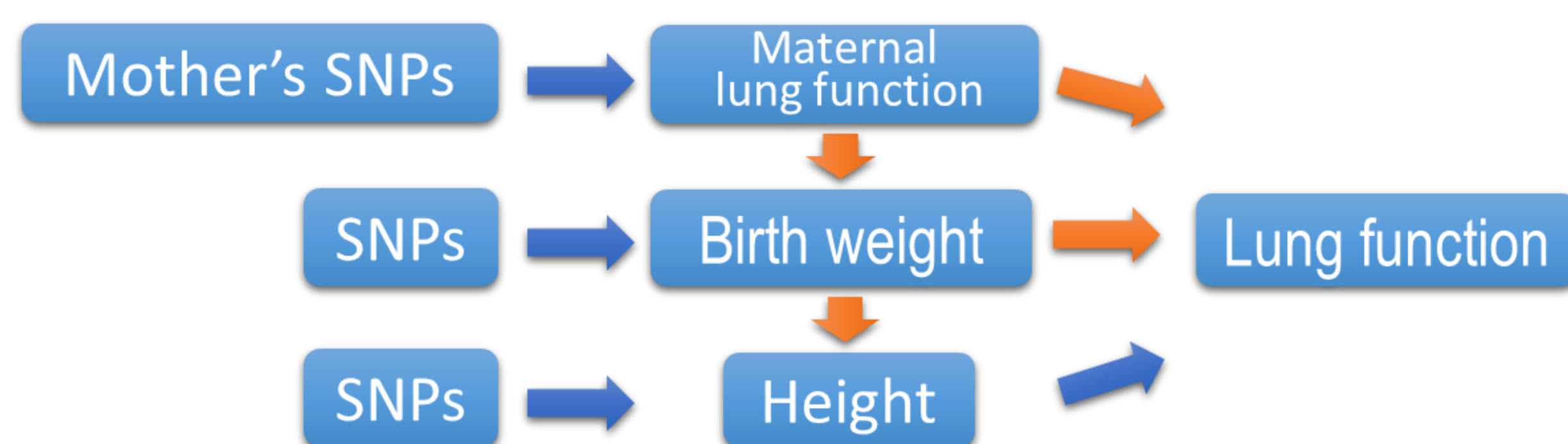
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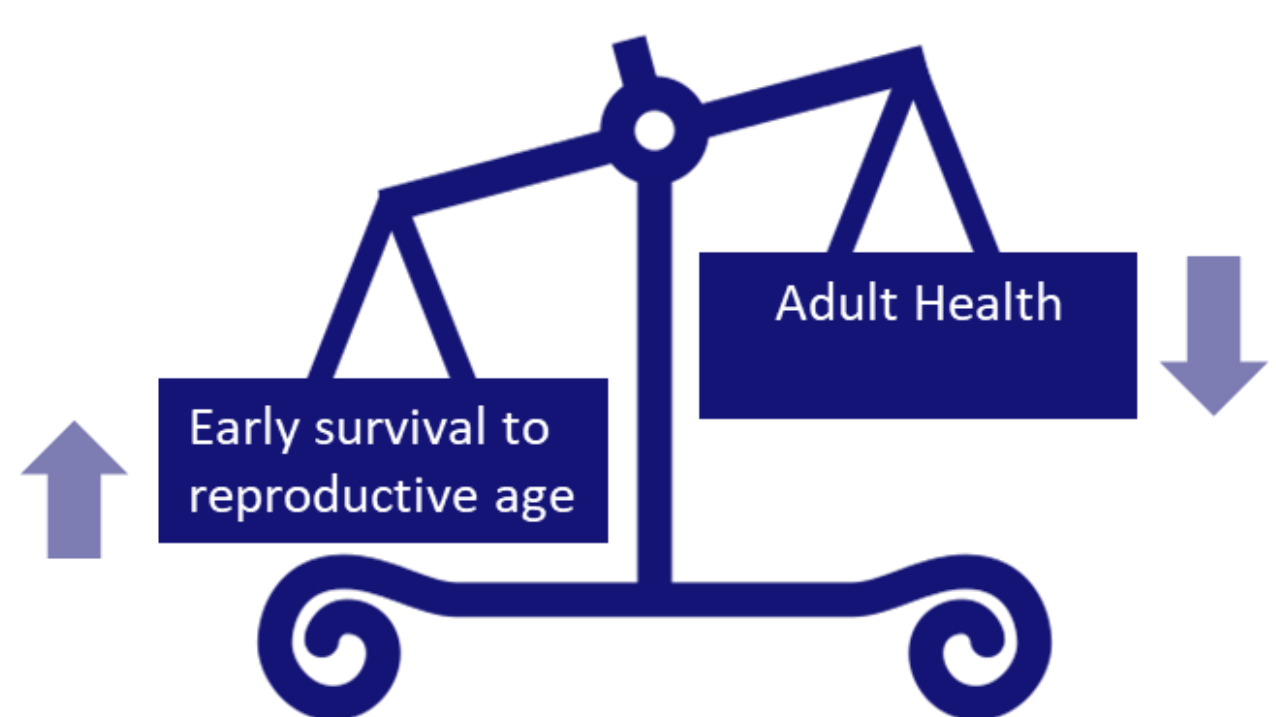
More broadly evolutionary biology suggests that growth (and reproduction) trade-off against longevity.

Early survival to reproductive age — Adult Health

Observationally lower birth weight is associated with poorer lung function, but these associations may be confounded by social-economic position and infant or maternal attributes.

Genetic variants are randomly allocated at conception, making Mendelian Randomization (MR) estimates, with single nucleotide polymorphisms (SNPs) as genetic instruments, unconfounded.

Lung function development after birth
Normal — Adverse early life exposure

OBJECTIVES

Mother's SNPs → Maternal lung function
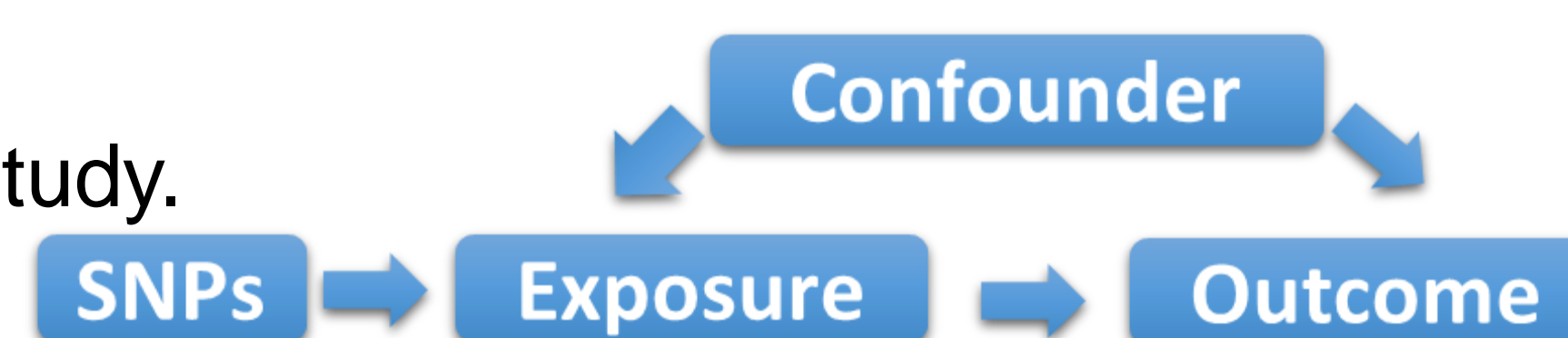SNPs → Birth weight → Lung function
SNPs → Height

- Assess potential confounding by maternal lung function and asthma.
- Obtain unconfounded estimates of birth weight on lung function and asthma.
- Allow for the effect of height using multivariable MR

METHODS

Study design
2 Sample MR study.

Confounder
SNPs → Exposure → Outcome

Genetic instrument selection
Genetic instruments need to fulfill three assumptions.
1. They are strongly associated with the exposure.
2. They are not confounded by exposure on outcome confounders.
3. They are only linked to the outcome by affecting the exposure.

Data Sources for independent genome wide significant genetic predictors of exposures
- Maternal Lung function: Large GWAS (Wain LV, et al. 2017)
- Maternal asthma: TAGC Consortium (Demenais F, et al. 2018)
- Birth weight: Early Growth Genetics (EGG) Consortium
- Height: Genetic Investigation of Anthropometric Traits (GIANT) Consortium

Genetic associations with outcomes (UK Biobank)
- Birth weight of first child
- Lung function
- Asthma

biobank uk — Improving the health of future generations

Main analysis
- Inverse-variance weighting (IVW) meta-analysis of SNP-specific Wald estimates, and multivariable IVW to adjust for height.

Sensitivity analyses
- Weighted median, MR-Egger and MR-PRESSO
- Removal of potentially pleiotropic SNPs

LIMITATIONS

- MR is open to biases from violating the assumptions of instrumental variable analysis, specifically here unknown pleiotropy and selective survival before recruitment. However, the results were similar after excluding potentially pleiotropic SNPs, and the participants were relatively young.
- Genetically predicted adult asthma and lung function may differ from maternal lung function in pregnancy.
- Confounding by infant genetic is possible, if lung function and birth weight share genetic architecture, which may not be completely addressed by adjusting for height.
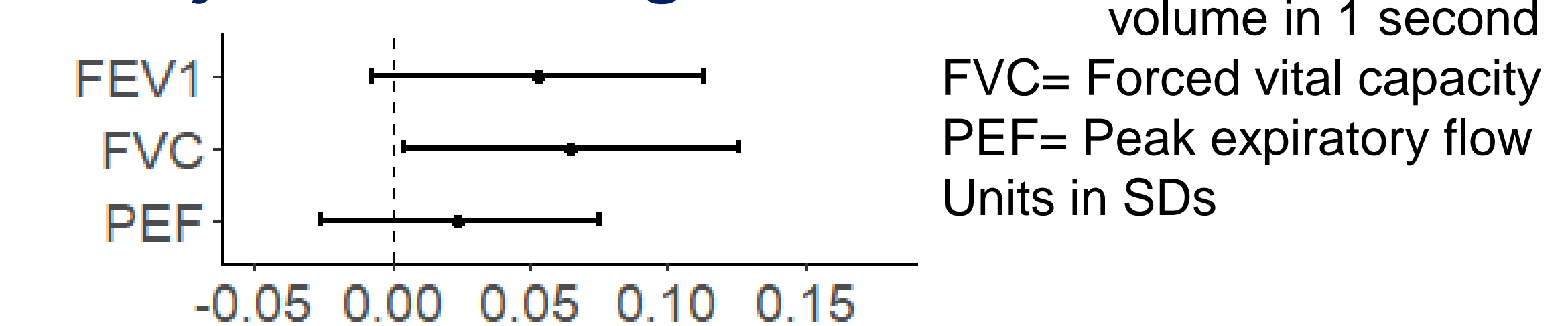
RESULTS

Maternal lung function and asthma on child birth weight
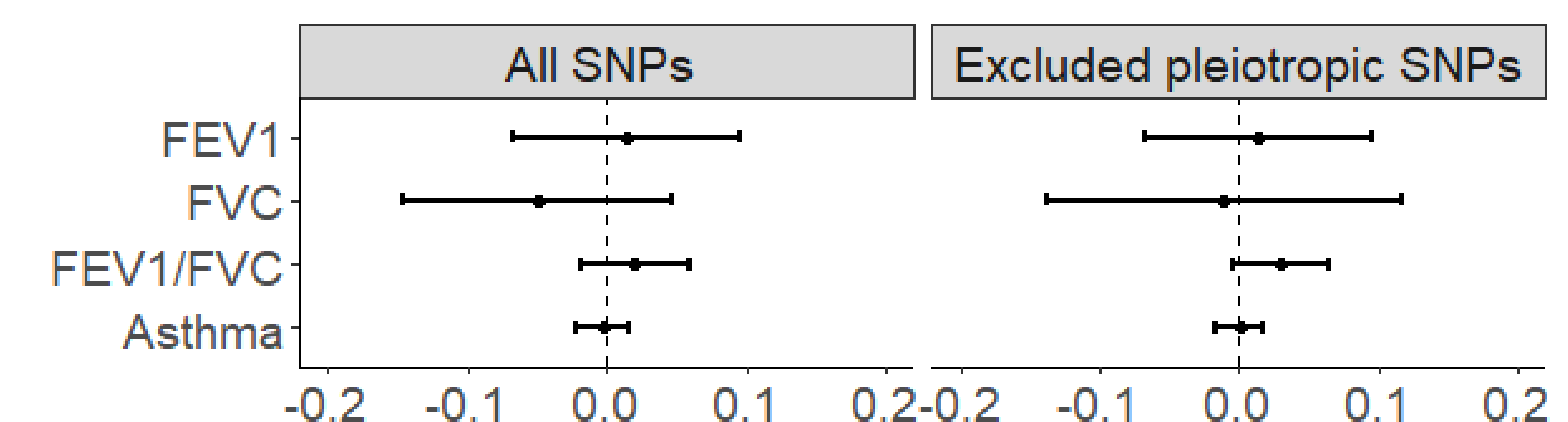
Birth weight on lung function and asthma
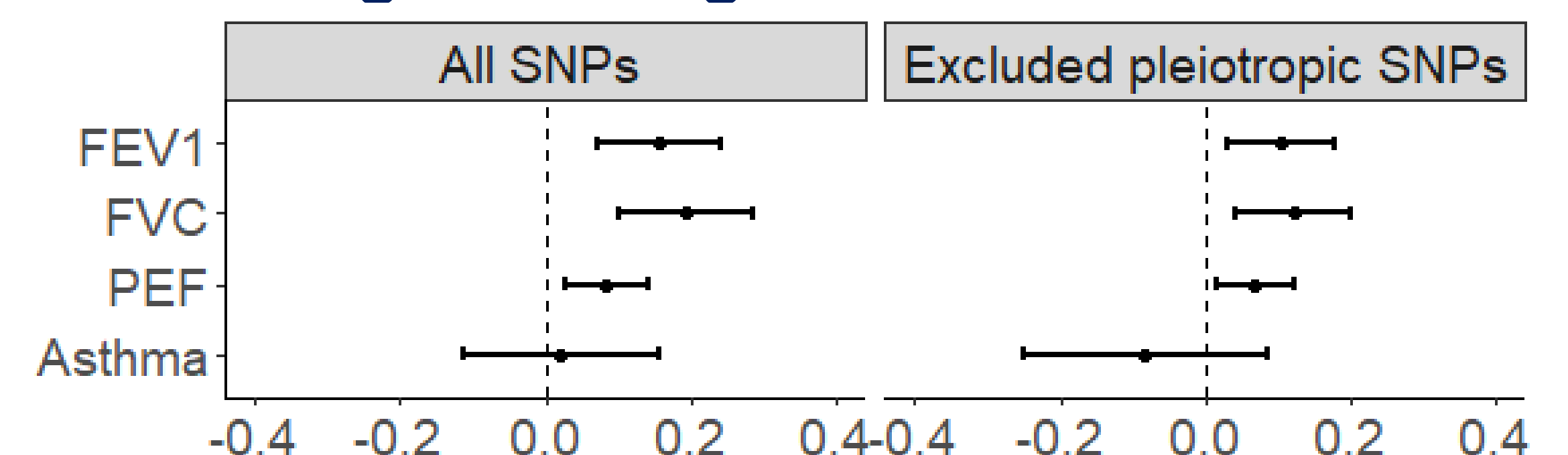
Birth weight on lung function adjusted for height

FEV1= Forced expiratory volume in 1 second
FVC= Forced vital capacity
PEF= Peak expiratory flow
Units in SDs

Maternal lung function was unrelated to offspring birth weight, suggesting it does not confound any associations of birth weight with lung function. Birth weight was positively associated with lung function, but only the association with FVC was evident after adjusting for height. Birth weight was not associated with asthma. Sensitivity analysis, using different methods, gave a similar interpretation to the IVW estimates shown.

CONCLUSIONS

Birth weight was only associated with FVC, but not with FEV1, FVC, PEF or asthma, after accounting for height. Birth weight could have some effect on lung function specifically FVC, perhaps operating via muscle mass which is also increased by higher birth weight.

REFERENCES

1. Haugen AC, et al. Evolution of DOHaD: the impact of environmental health sciences. *Journal of developmental origins of health and disease.*
2. Wells JCK, et al. Evolutionary public health: introducing the concept. *Lancet*
3. Wain LV, et al. Genome-wide association analyses for lung function and chronic obstructive pulmonary disease identify new loci and potential druggable targets. *Nature genetics.*
4. Sudlow C, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS medicine.*

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