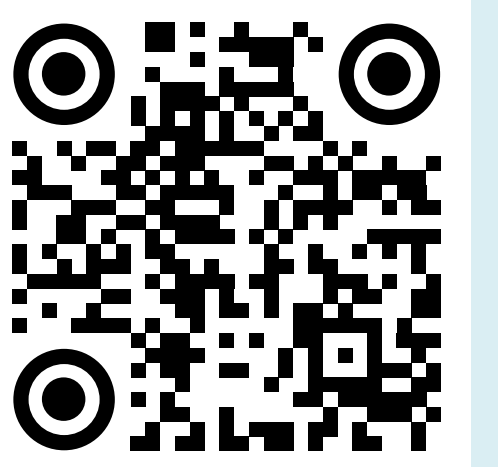


An estimate of the causal influence of body mass index on gut microbiome variation

David A Hughes^{1,2}, Charlie Hatcher^{1,2}, Kaitlin H Wade^{1,2}, Jeroen Raes^{3,4}, Nicholas J Timpson^{1,2}
¹MRC Integrative Epidemiology Unit at the University of Bristol, UK, ²Population Health Science, Bristol Medical School, University of Bristol, UK, ³Department of Microbiology and Immunology, Rega Instituut, KU Leuven–University of Leuven, Leuven, Belgium, ⁴Center for Microbiology, VIB, Leuven, Belgium

Poster link



SCAN ME

Introduction

Variation in the accumulation of body fat, body composition, and obesity can all be proxied by body mass index (BMI) which itself is a recognized risk factor for numerous health outcomes including life expectancy, various cancers, and cardiometabolic diseases. What remains unclear is the complete picture of factors influencing BMI. One possible factor is gut microbiome variation, which previous research has demonstrated to be strongly correlated with BMI. Critically, whilst it may be the case that human gut flora variation influences BMI, it remains at least equally – if not more – likely that the opposite effect is true. Here, we use both BMI and fecal 16S rRNA sequencing data from the Flemish Gut Flora Project to estimate causal effect estimates between BMI (exposure) and gut flora (outcome).

Abbreviation Key

MR: Mendelian Randomization
MT: microbial traits
AB: abundance MT
PA: presence | absence MT
PGS: polygenic score

Methods

1. Estimate linear effect estimates

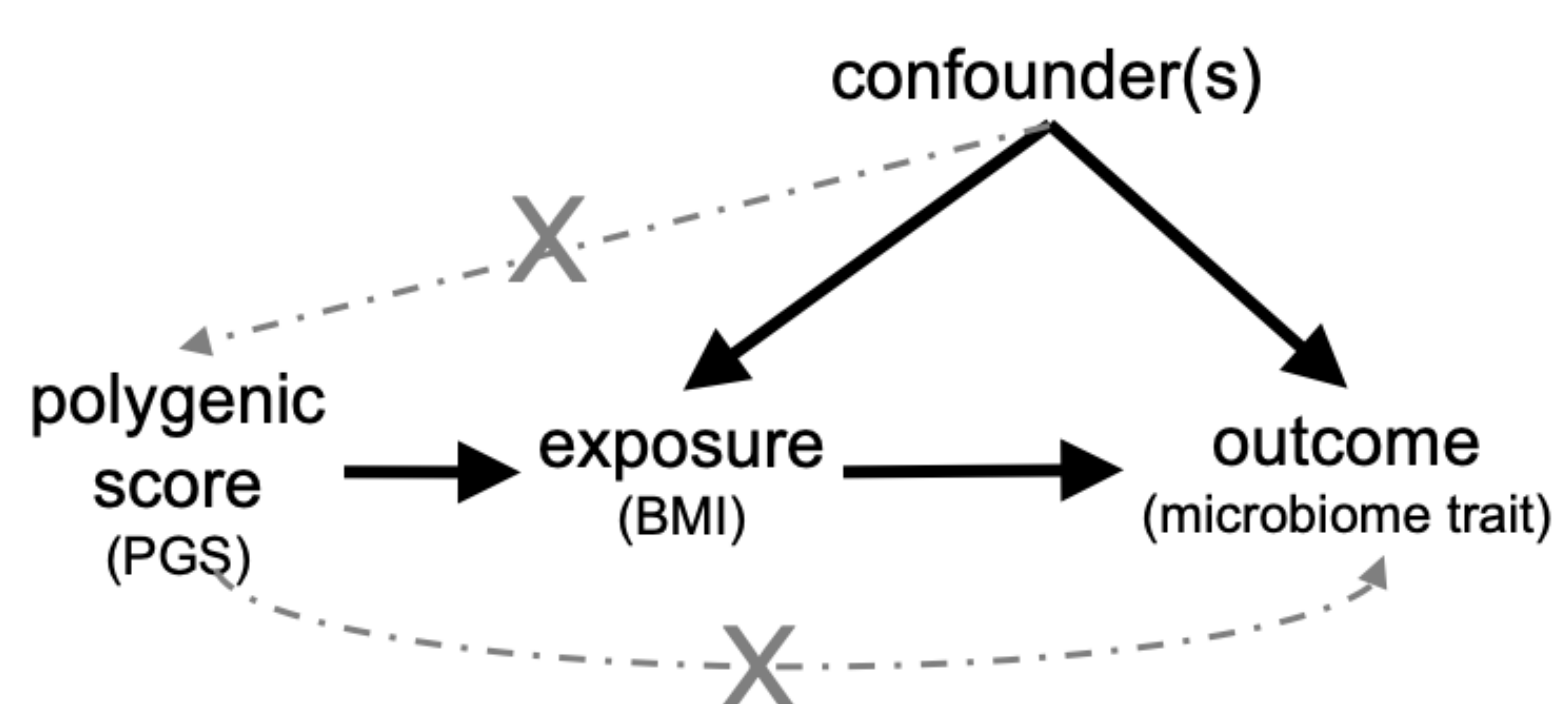
- (generalized) multivariable linear model
- exposure = BMI
- outcome = MT (AB: rank normal transformed)

2. Estimate the causal effect by one-sample MR (see Figure below)

- exposure = BMI
- outcome = MT (AB: rank normal transformed)
- instrumental variable or genetic proxy was a PGS composed of 670 SNPs associated to BMI by Pulit et al HMG 2019.

3. Compare linear sex-specific estimates

4. Compare linear and MR estimates

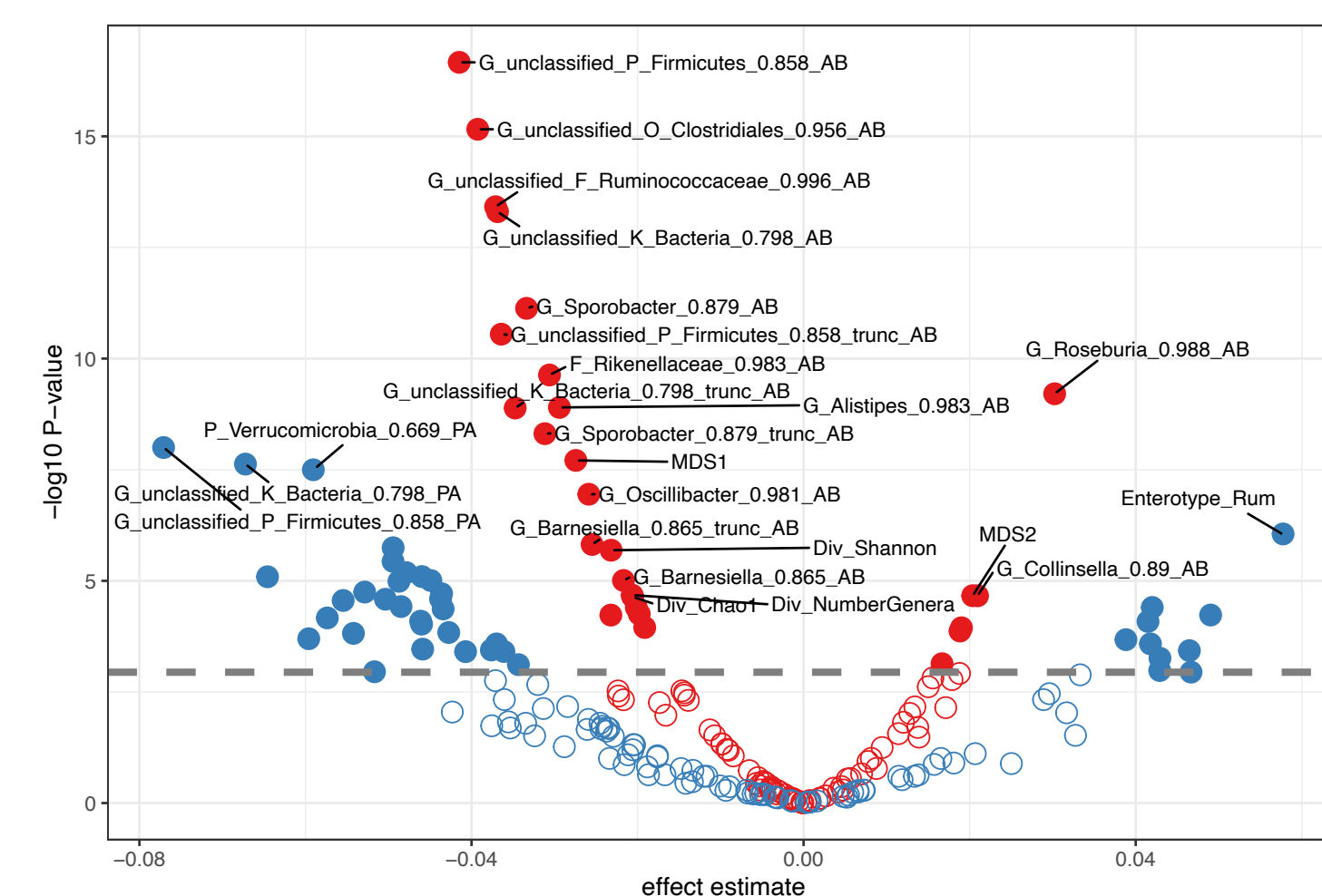
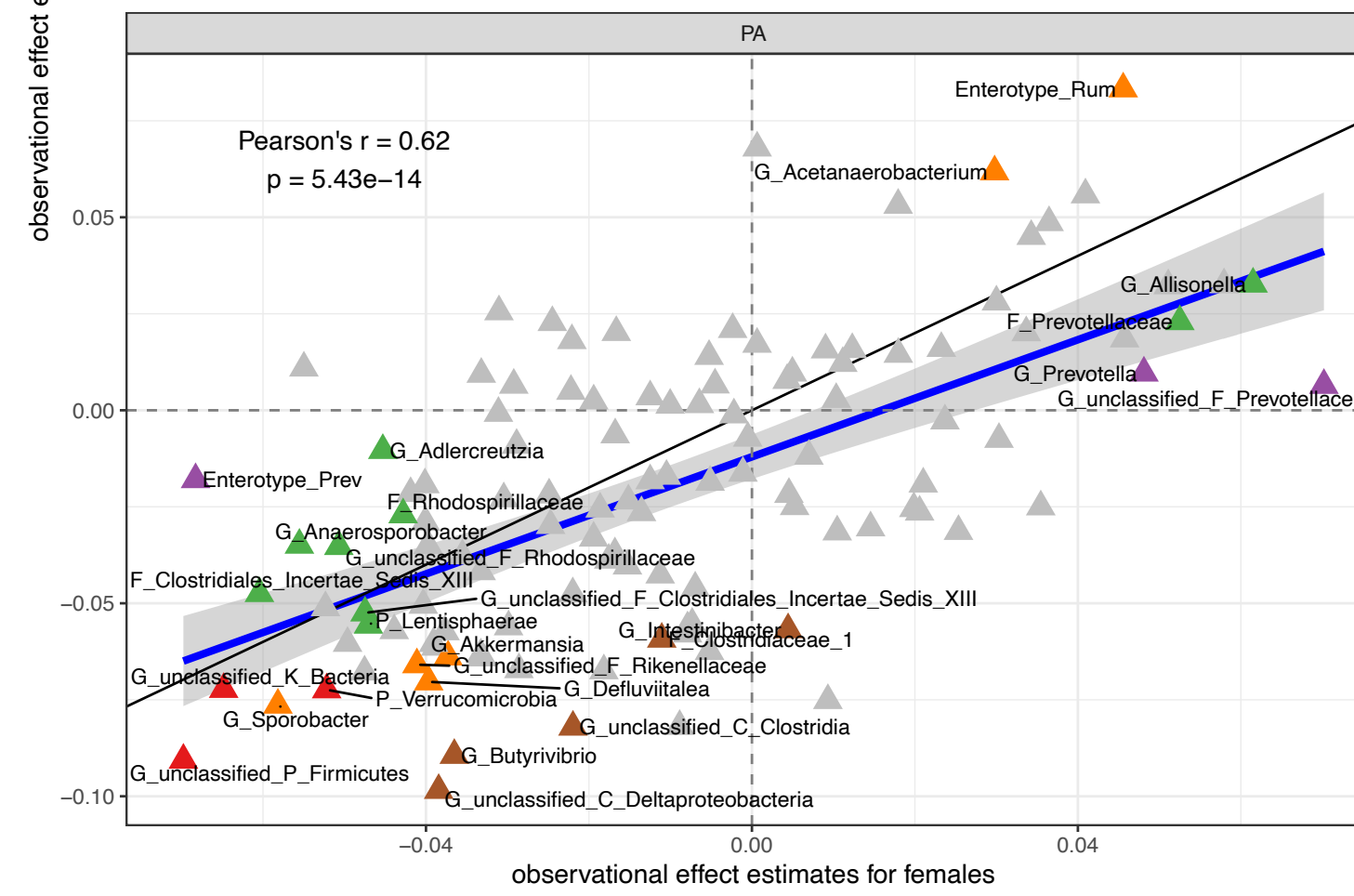
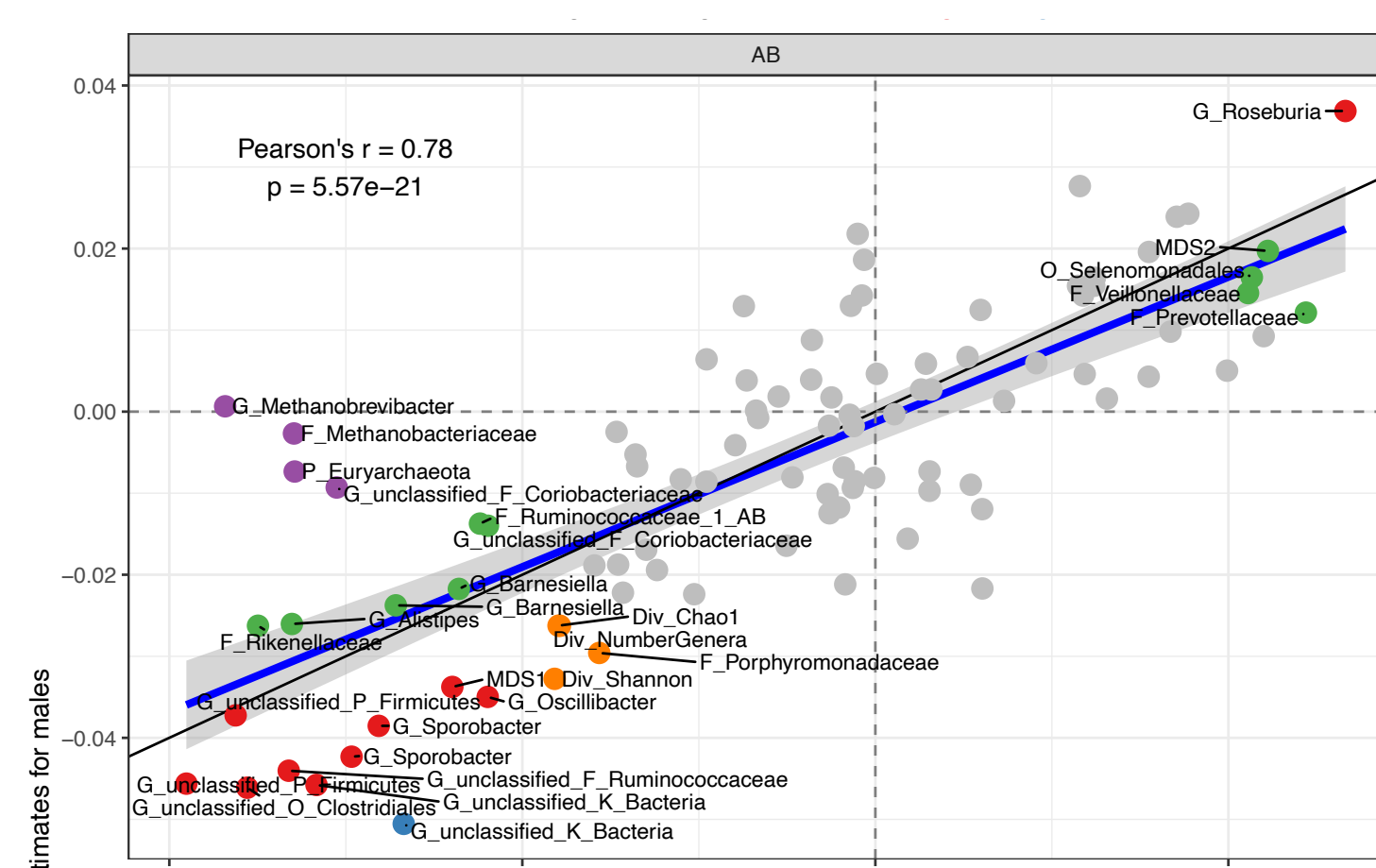


A directed acyclic graph (DAG) of Mendelian Randomization (MR) illustrating the assumptions of the methodology. Namely, the instrument or PGS here, is associated with the exposure, but independent of the outcome and of variables that are confounded with the exposure and outcome.

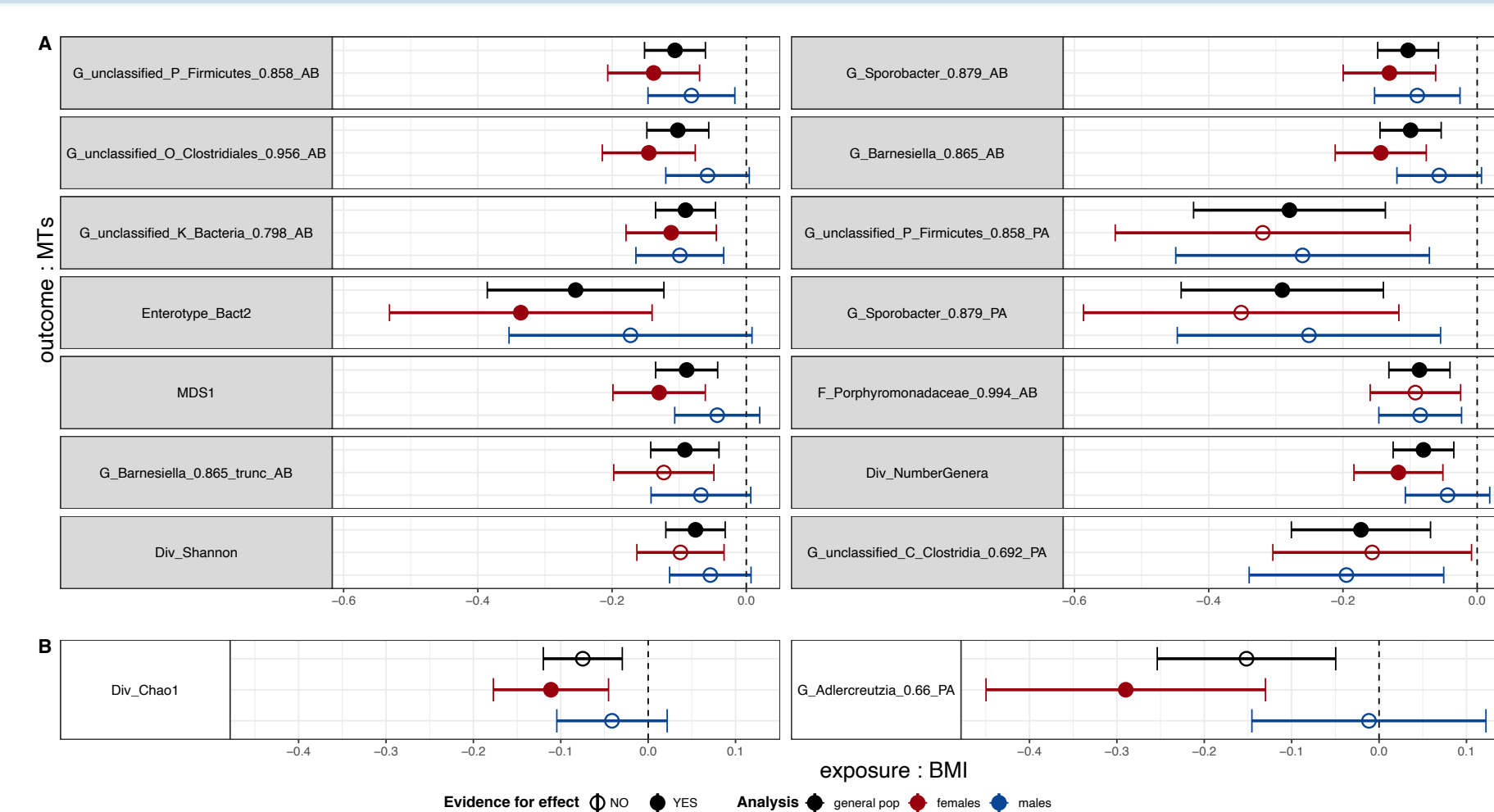
Population Description

	total pop.	females	males
N (obs. imputed)	2257	1330 1343	897 913
age in years (95 CI)	52.29 (24-73)	50.48 (23-71.77)	54.93 (27-74)
height in cm (95 CI)	170.1 (154-188)	165.49 (153-178)	176.91 (163-190)
weight in kg (95 CI)	72.72 (49.71-107)	66.85 (48.8-96.5)	81.39 (58.17-114)
BMI kg/cm^2 (95 CI)	25.06 (18.2-35.16)	24.42 (18-34.68)	25.99 (19.16-35.31)
smoking			
(Never Ever Current)	1040 803 172	700 409 90	327 387 79
PGS SNP count			
(study matched filtered)	670 665 656	281 281 279	221 104 103
BMI var. exp. by PGS (%)	4.40	1.79	3.00

Linear Model Estimates

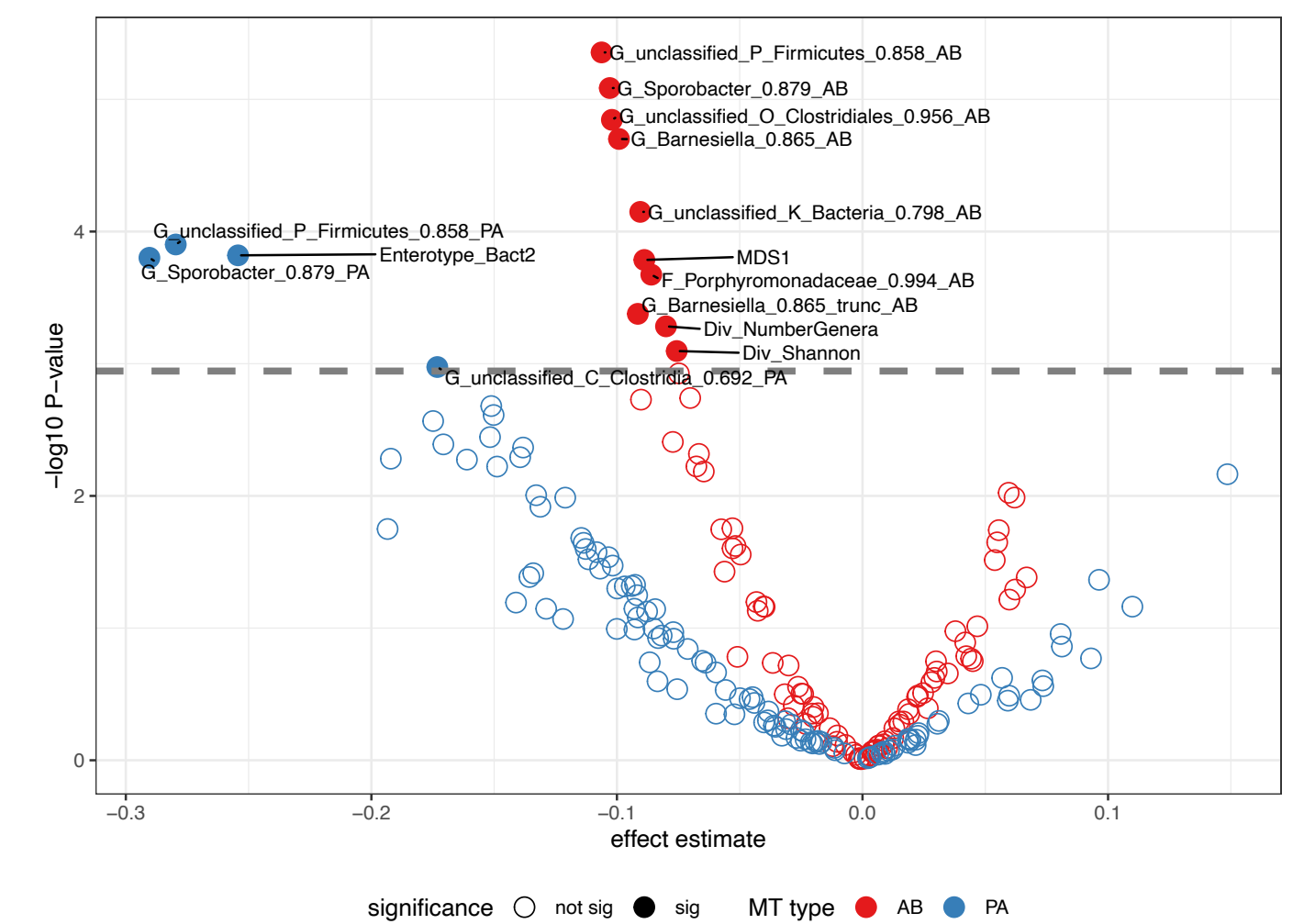
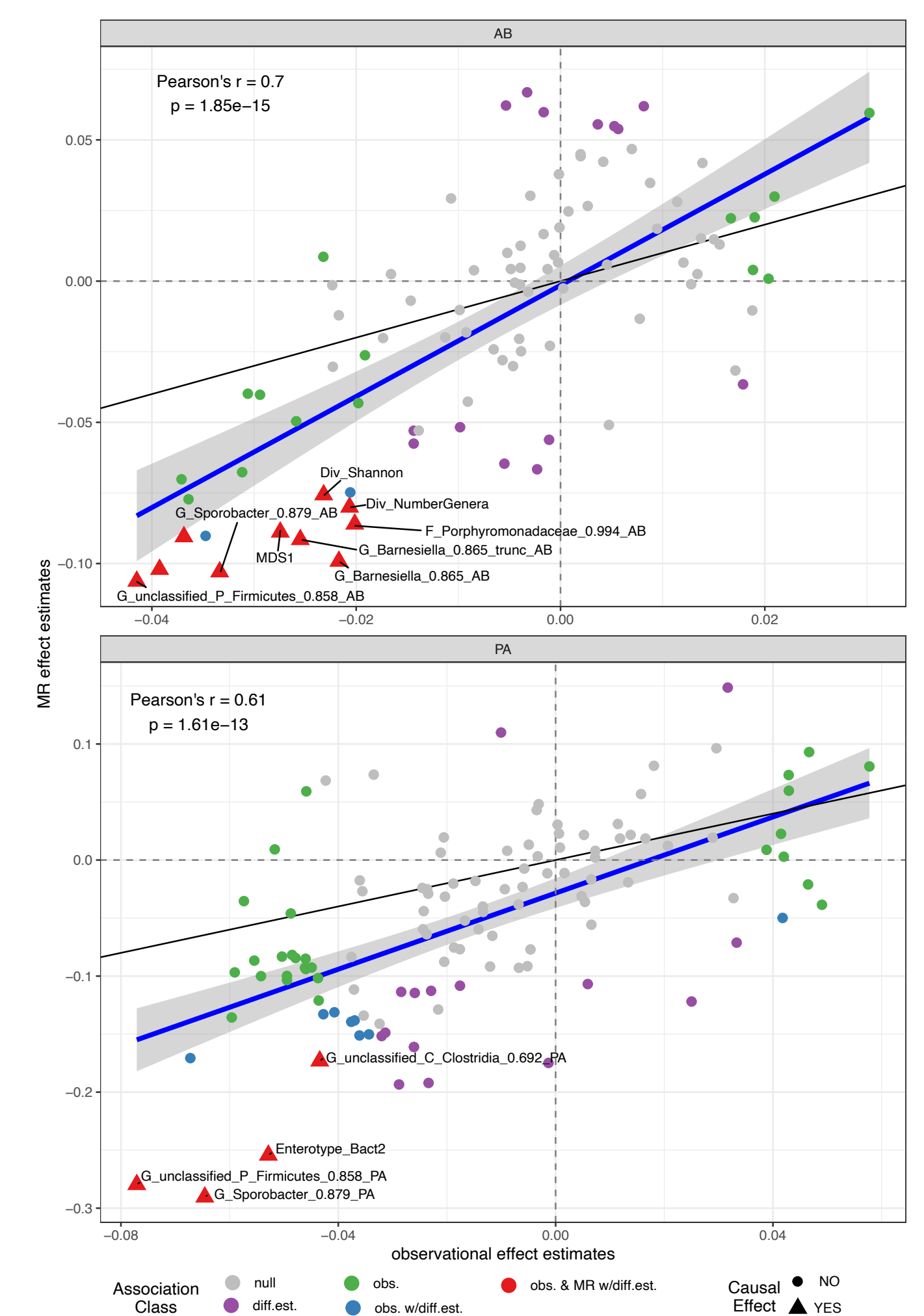
volcano plot of obs.
estimatesComparison of obs. effect
estimates between males and
females

Forest Plot of MTs with Evidence of a BMI Effect



(A) 14 MTs with evidence of being causally influenced by BMI in the general population (black points), alongside estimates in females (red) and males (blue).
(B) Two MTs with evidence of being causally influenced by BMI in females, but not in the general population or males.

MR Estimates

volcano plot of MR
estimatesComparison of MR and
conventional linear effect estimates

Results Summary & Conclusion

Overall, results support a conclusion that gut microbiome variation can be causally influenced by variation in BMI and that observational studies of the microbiome as a risk factor need to account for likely reverse causality as one source of association when analyzing BMI.

- 215 MTs tested
- 67 MTs associated with BMI in linear models
- 14 MTs causally affected by BMI in the general population
- 10 MTs causally affected by BMI in females
 - 2 of 10 are novel to females
 - including the phytoestrogen metabolizing genera *Adlercreutzia*
- Conventional linear estimates and MR estimates are correlated supporting:
 - linear est. are reasonable predictors of MR estimates
 - BMI has a broad effect on MTs

Acknowledgements

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Contact: <https://teamtimpson.github.io>