Health as an asset: estimating the causal effects of health conditions and health behaviours on social and economic outcomes using Mendelian randomization

Laura D Howe

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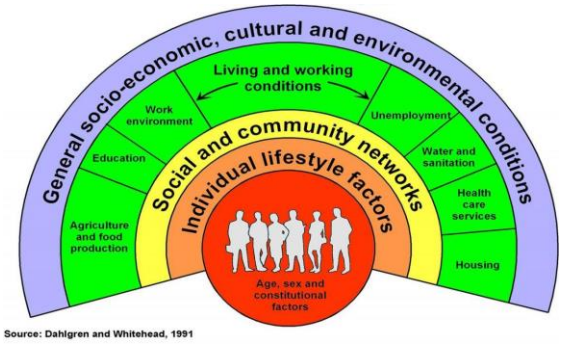
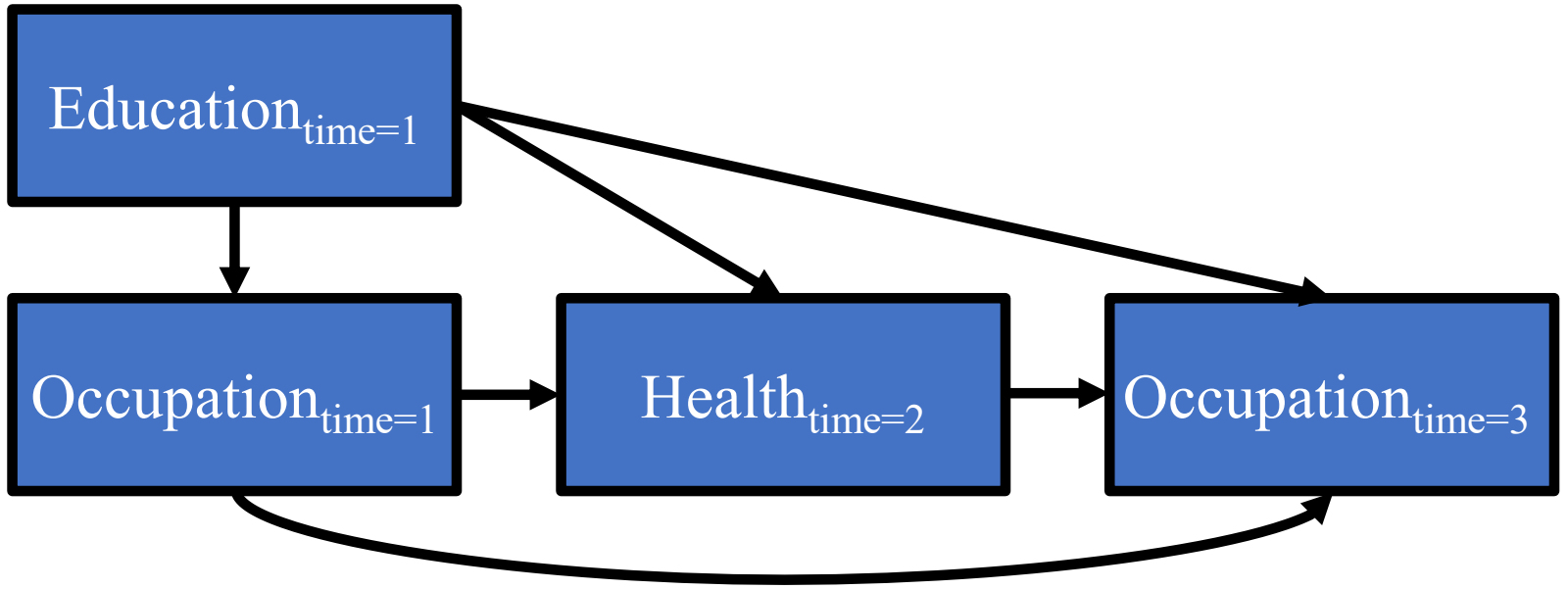
15 September 2020


General socio-economic, cultural and environmental conditions
Living and working conditions
Work environment
Unemployment
Education
Water and sanitation
Social and community networks
Individual lifestyle factors
Health care services
Agriculture and food production
Housing
Age, sex and constitutional factors
Source: Dahlgren and Whitehead, 1991


GLUE
INK


£20
Bank of England
Twenty Pounds


Education time=1
Occupation time=1
Health time=2
Occupation time=3


time

Mendelian randomization: using genetic information to strengthen causal inference

- Genetics are determined at conception, and cannot be influenced by the social environment

- Genetics are assigned randomly*

  **conditional on parent's genotypes. More on this later!*

- Hence, not vulnerable to either reverse causation or classical sources of confounding common in epidemiology

- This quasi-random assignment of genetics can be considered a kind of natural experiment, and is sometimes compared with RCTs

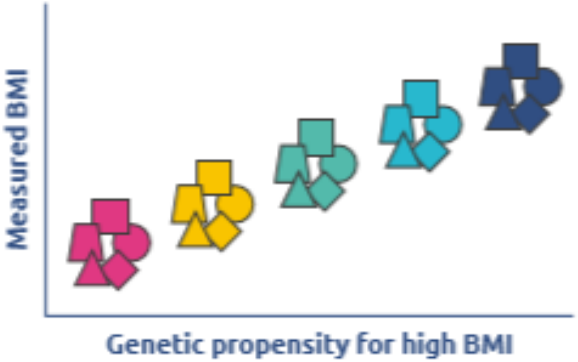
Figure 2. Illustration of using Mendelian randomisation to show BMI increases systolic blood pressure

General Population

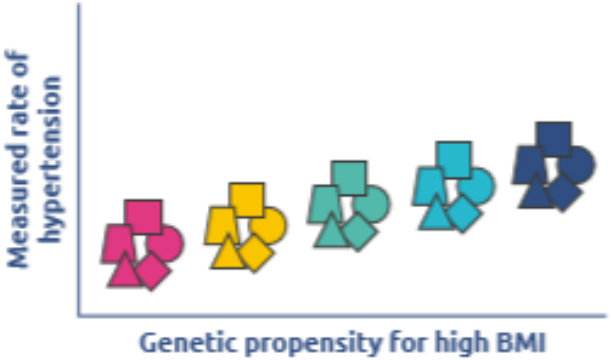
1. People in the general population have many differences that could confound the relationship between BMI and hypertension (shown here as different shapes).

Genetic propensity for high BMI

2. However, these differences should not affect their genetic propensity for having a high or low BMI (shown here as different colours).



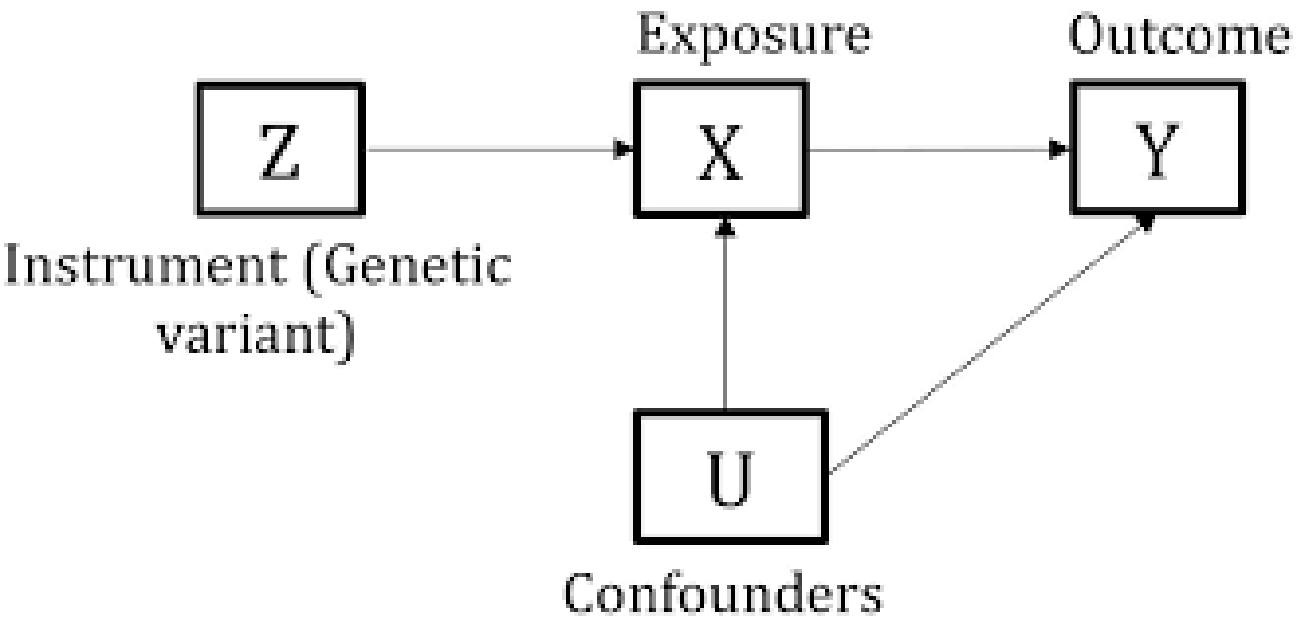
3. On average, people with a higher genetic propensity towards a high BMI will have higher measured BMI values



4. If, on average, people with higher genetic propensities towards a high BMI also have a higher rate of hypertension, then we have evidence that BMI causally increases hypertension risk, as genetic propensity can't be affected by confounders or hypertension itself.

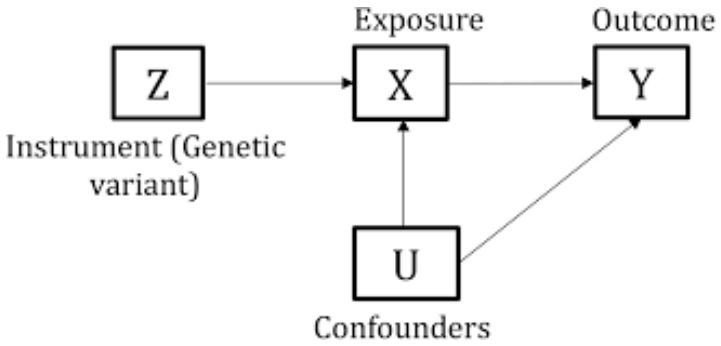
Making sense of Mendelian randomisation and its use in health research: A short overview
S Harrison, L Howe, A Davies
http://www.bristol.ac.uk/integrative-epidemiology/mr-methods/

The basic idea:



Mendelian Randomization

- **Some key assumptions:**
  - **No horizontal pleiotropy:** SNPs are associated with your outcome *only* via the exposure
    A range of methods developed to test for the influence of pleiotropy
  - **SNPs are truly randomly** assigned across a whole population
    Recent work has shown that this assumption can be violated, with important consequences.
    Novel family methods for MR, which require data on multiple members of the same family, are robust to violations of the second assumption. More on this later.



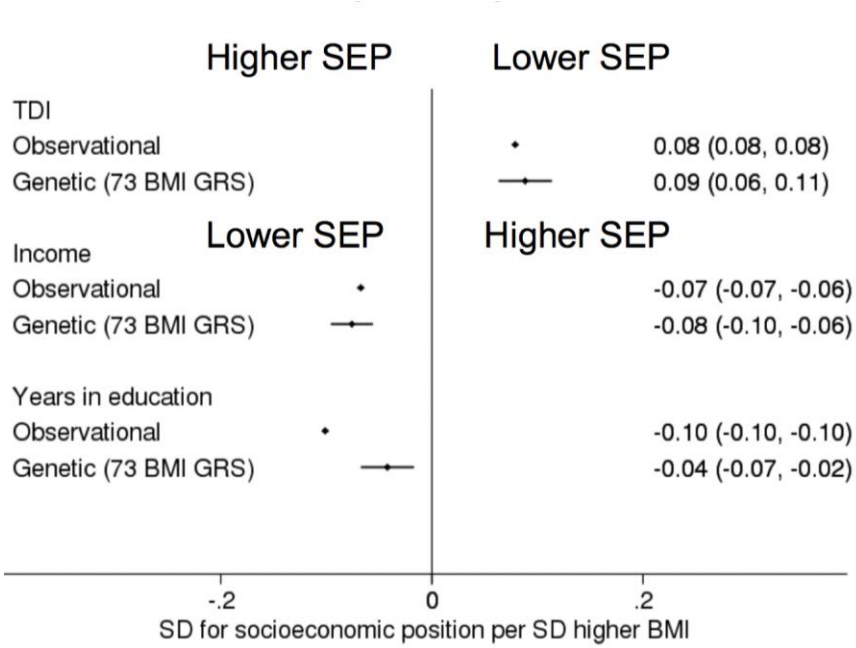
Obesity and social and socioeconomic outcomes

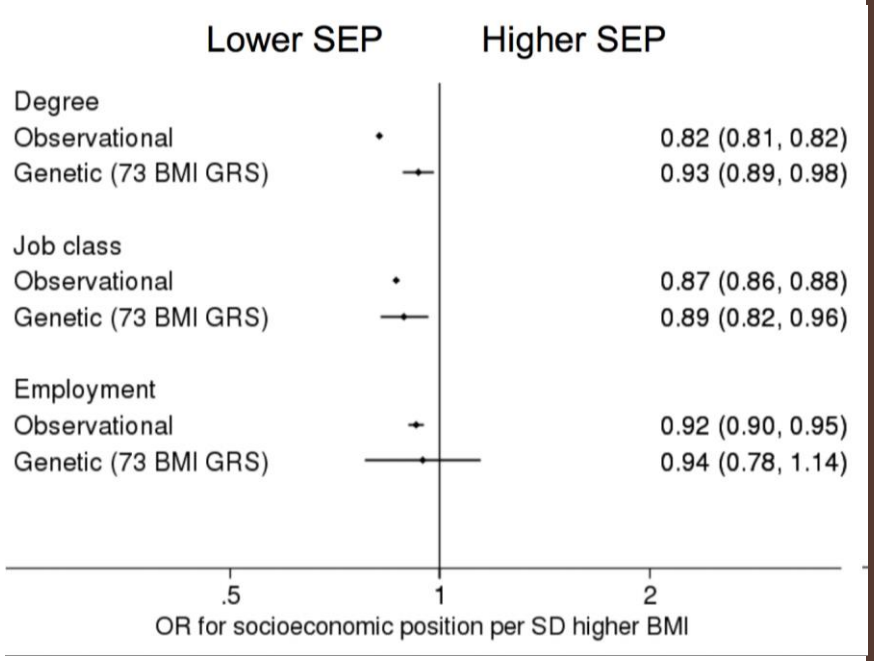
Methods

- UK Biobank
  - N=350,000
  - white British ancestry
  - 40-69 years

- 6 measures of SEP:
  - Townsend Deprivation Index
  - Annual household income
  - Job class (skilled vs unskilled)
  - Employed or self-employed vs unemployed
  - Years in education
  - Degree-level education or lower

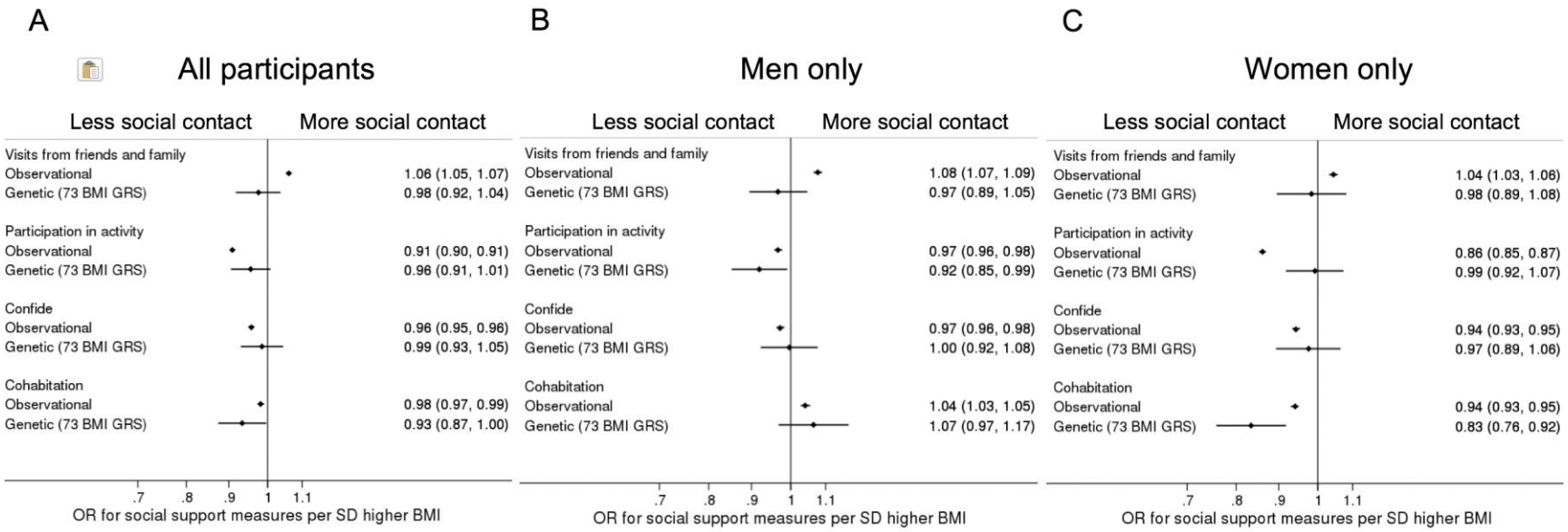
- 4 measures of social connectedness:
  - In a cohabiting relationship
  - Less than weekly vs weekly or more visits from friends/family
  - No participation in leisure or social activity vs any participation
  - Less than weekly vs weekly or more confiding in others





Little evidence of sex differences in these results

Howe et al. IJE. 2019. dyz240



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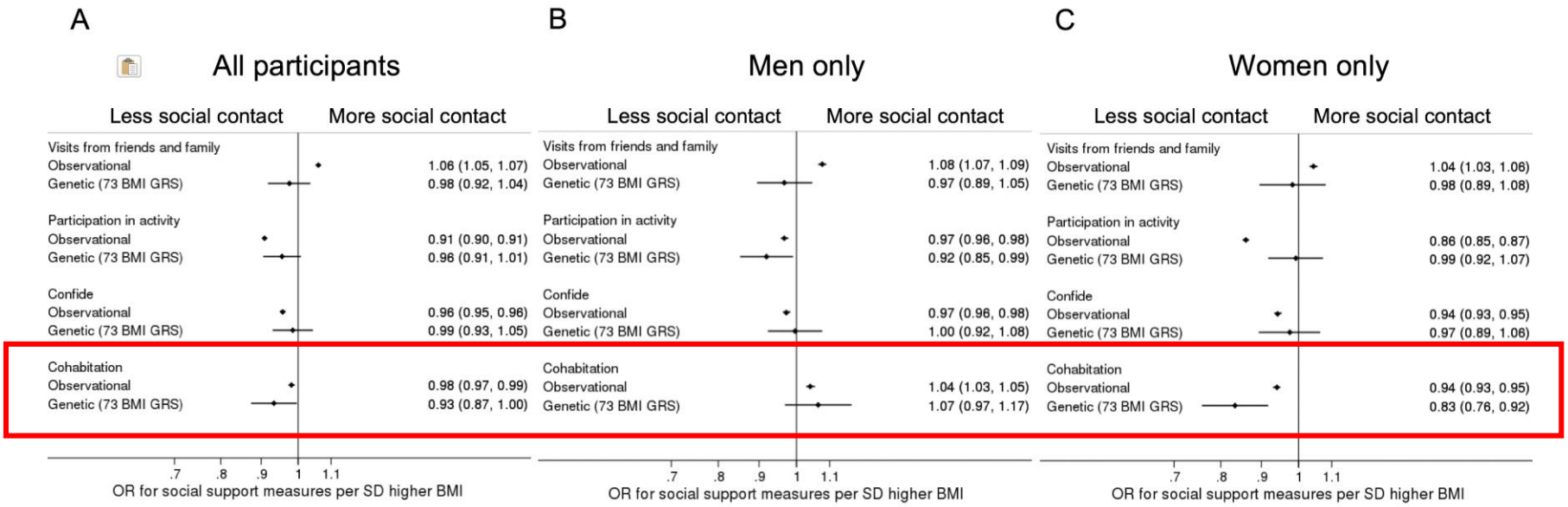
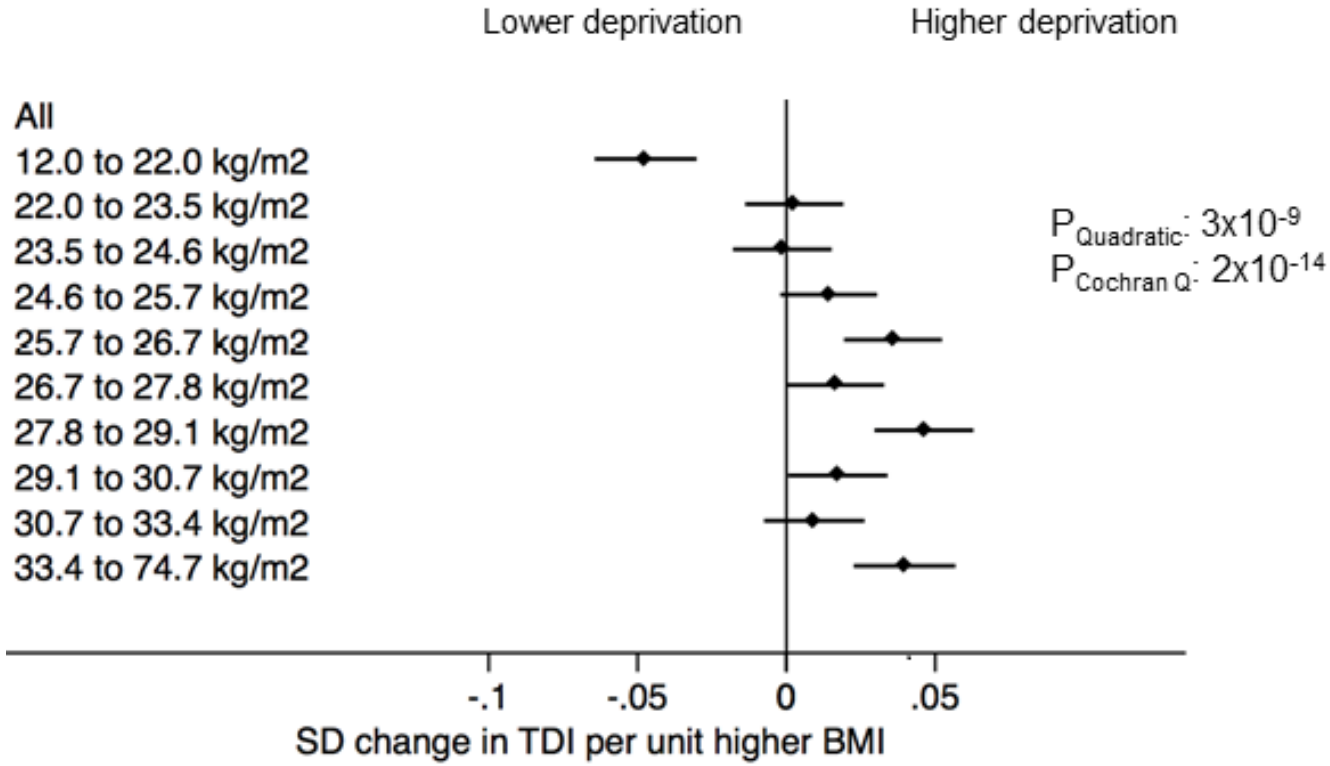


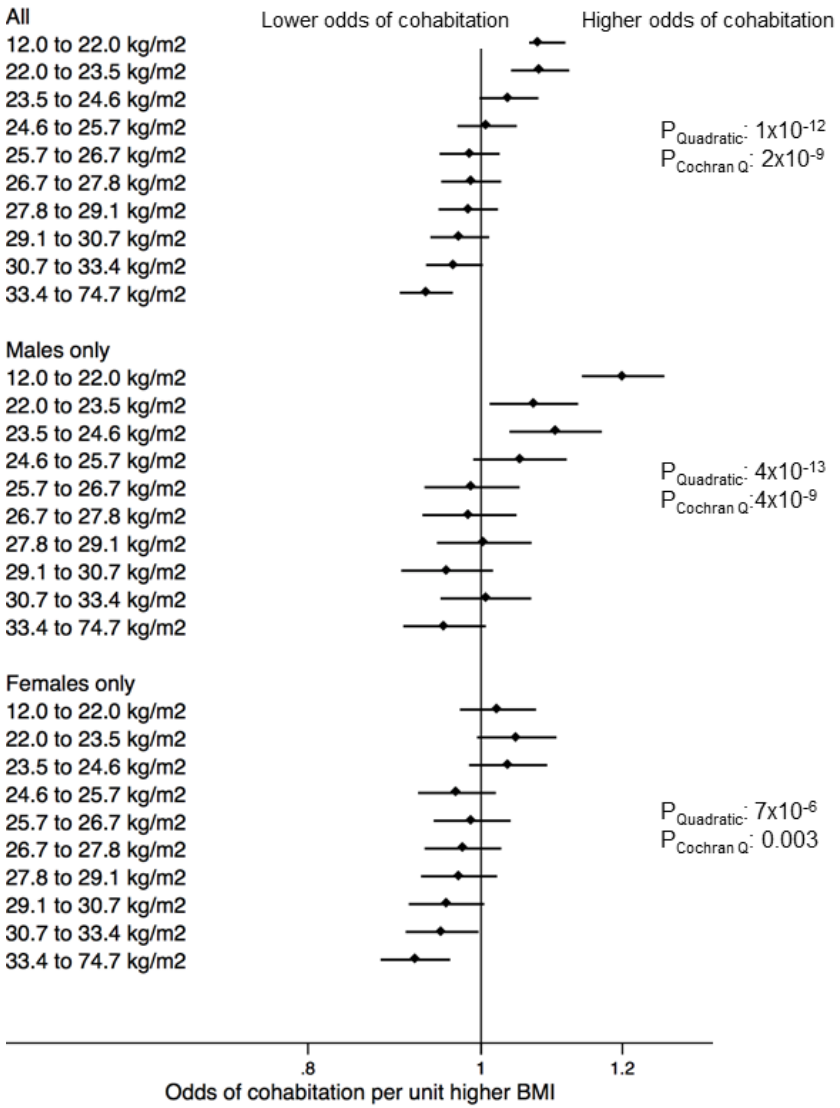
Points to sex-specific cultural expectations of body size? Large = strong for males? Consistent with other study designs showing greater weight stigma for women.

Howe et al. IJE. 2019. dyz240



Similar non-linearities seen for income; no evidence of non-linearity for other SEP measures

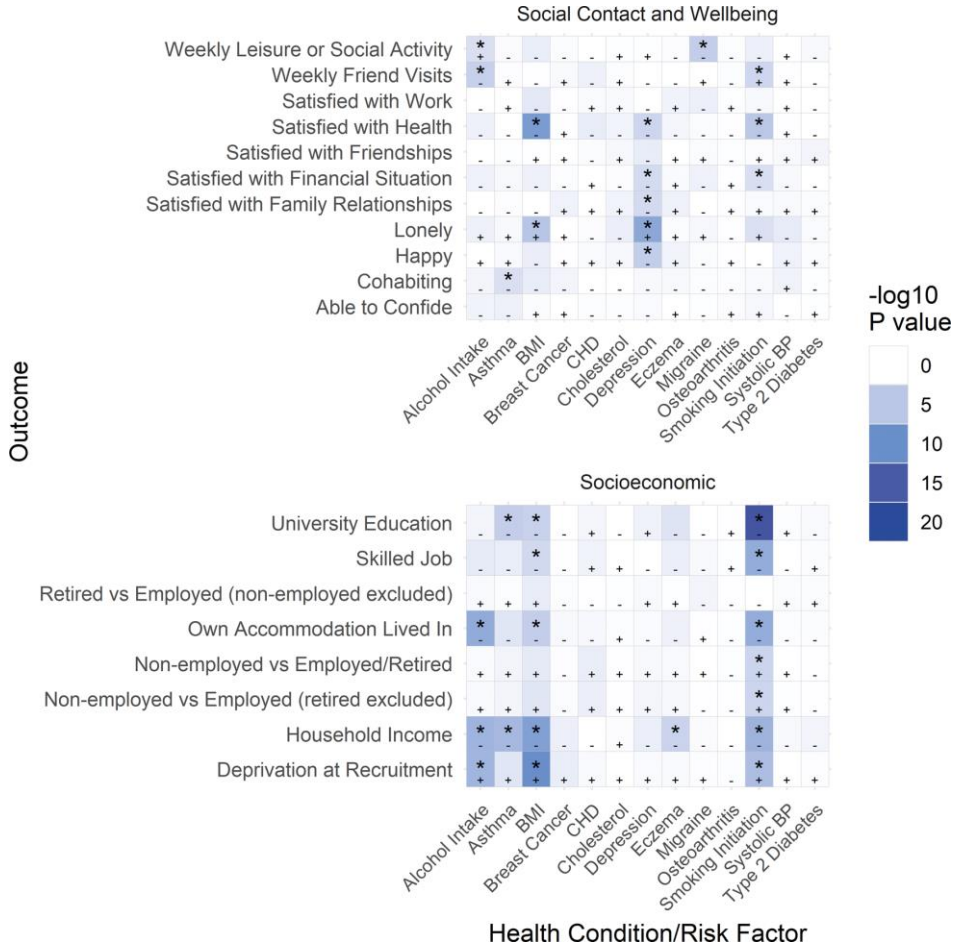
Howe et al. IJE. 2019. dyz240



Howe et al. IJE. 2019. dyz240

Social and socioeconomic consequences of health conditions and behaviours

Heat map of p values from the main analysis.



Harrison S et al. Int J Epidemiol, dyaa114, https://doi.org/10.1093/ije/dyaa114

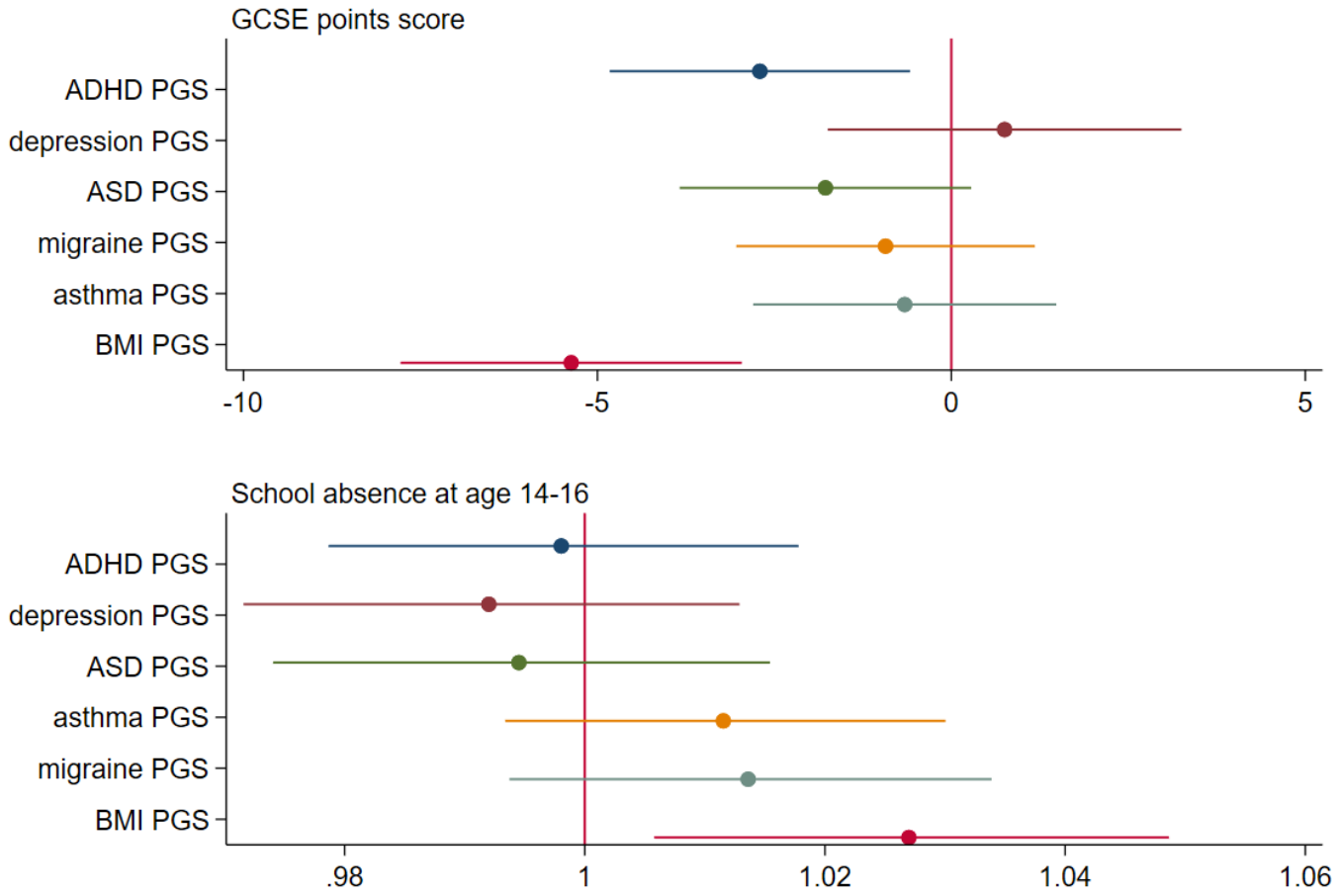
“Conclusions

Higher BMI, alcohol intake and smoking were all estimated to adversely affect multiple social and socioeconomic outcomes. Effects were not detected between health conditions and socioeconomic outcomes using Mendelian randomization, with the exceptions of depression, asthma and migraines. This may reflect true null associations, selection bias given the relative health and age of participants in UK Biobank, and/or lack of power to detect effects.”

Harrison S et al. Int J Epidemiol, dyaa114, https://doi.org/10.1093/ije/dyaa114

ALSPAC: polygenic scores, GCSEs and school absences

Figure 4: Association of polygenic scores with GCSEs and absenteeism age 14-16



Polygenic scores are standardized.

Coefficients for absences represent proportional increase (1=no change)

Hughes A et al. medrxiv https://www.medrxiv.org/content/10.1101/19012906v1

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However…

- New evidence suggests MR estimates with educational attainment as an outcome may be considerably biased by family-level processes

Within-family studies for Mendelian randomization: avoiding dynastic, assortative mating, and population stratification biases

Ben Brumpton* [1,2,3], Eleanor Sanderson[2,4], Fernando Hartwig[2,5], Sean Harrison[2,4], Gunnhild Åberge Vie[1], Yoonsu Cho[2,4], Laura D Howe[2,4], Amanda Hughes[2,4], Dorret I Boomsma[6], Alexandra Havdahl[2,7,8], John Hopper[9], Michael Neale[10], Michel G Nivard[6], Nancy L Pedersen[11], Chandra Renyolds[12], Elliot M Tucker-Drob[13], Andrew Grotzinger,[13] Laurence Howe[2,4], Tim Morris[2,4], Shuai Li[14,15], MR within-family Consortium, Wei-Min Chen[16], Johan Håkon Bjørngaard[1], Kristian Hveem[1], Cristen Willer[17,18,19], David M Evans[2,20], Jaakko Kaprio[21,22], George Davey Smith[2,4,^], Bjørn Olav Åsvold[1,23^], Gibran Hemani[2,4,^], Neil M Davies[2,4,^]

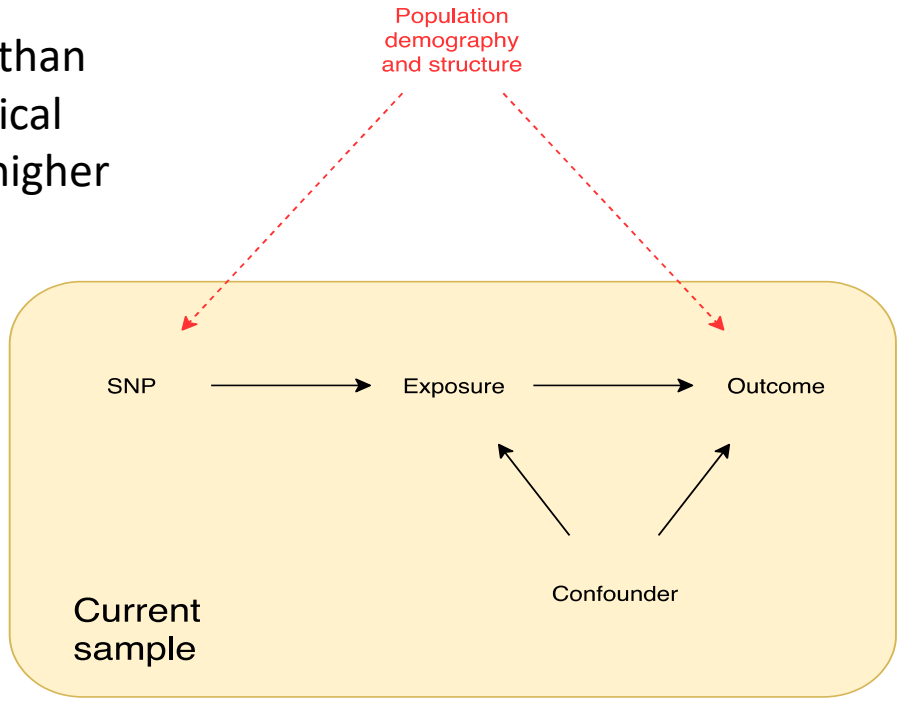
- These processes violate the assumption of MR

Processes leading to bias in MR

Population stratification: gene frequencies differ between ancestral populations, but so do environmental and cultural factors. This can produce spurious genetic associations

If certain SNPs are more common in richer than poorer areas of a country just due to historical reasons, those SNPs will appear to 'cause' higher income, education etc among individuals.

Adjustment in genetic models for PCAs (principal components of ancestry) corrects some of the bias, but not all of it.



Population stratification

Processes leading to bias in MR

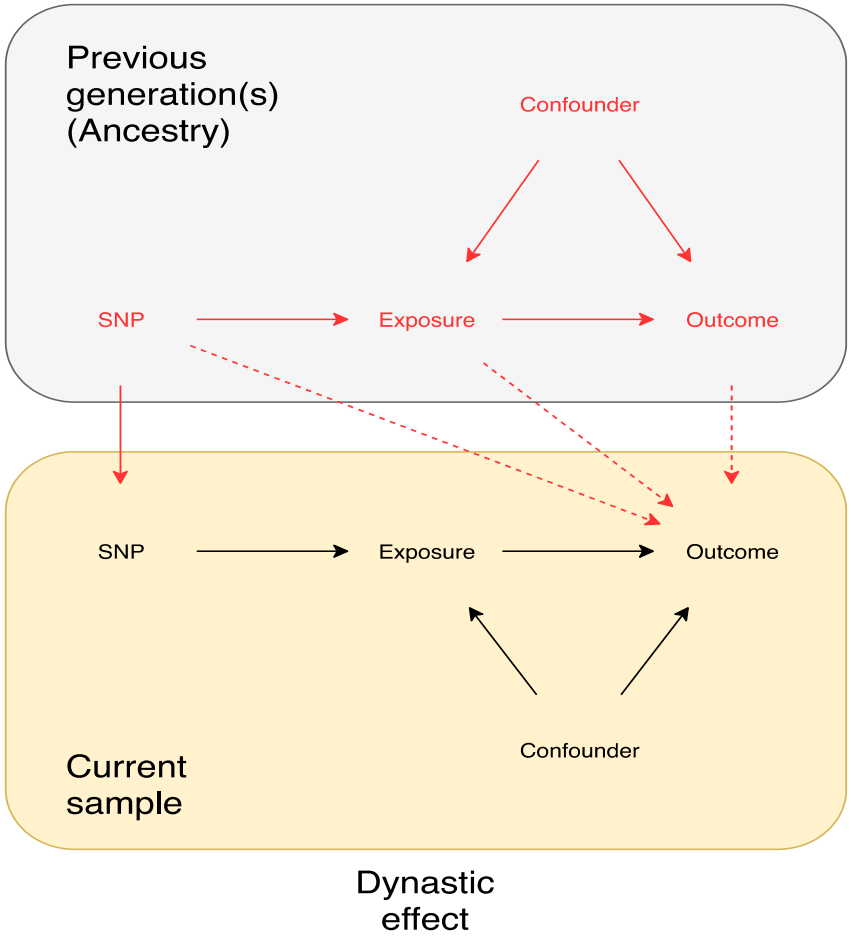
Dynastic effects: influence of parents' genes on offspring phenotype via *environmental* pathways

Kong et al 2018: 'The Nature of Nurture'

If a child has more BMI-increasing SNPs than the average person, so will the child's parents.

We find the child's polygenic score for BMI predicts lower educational attainment.

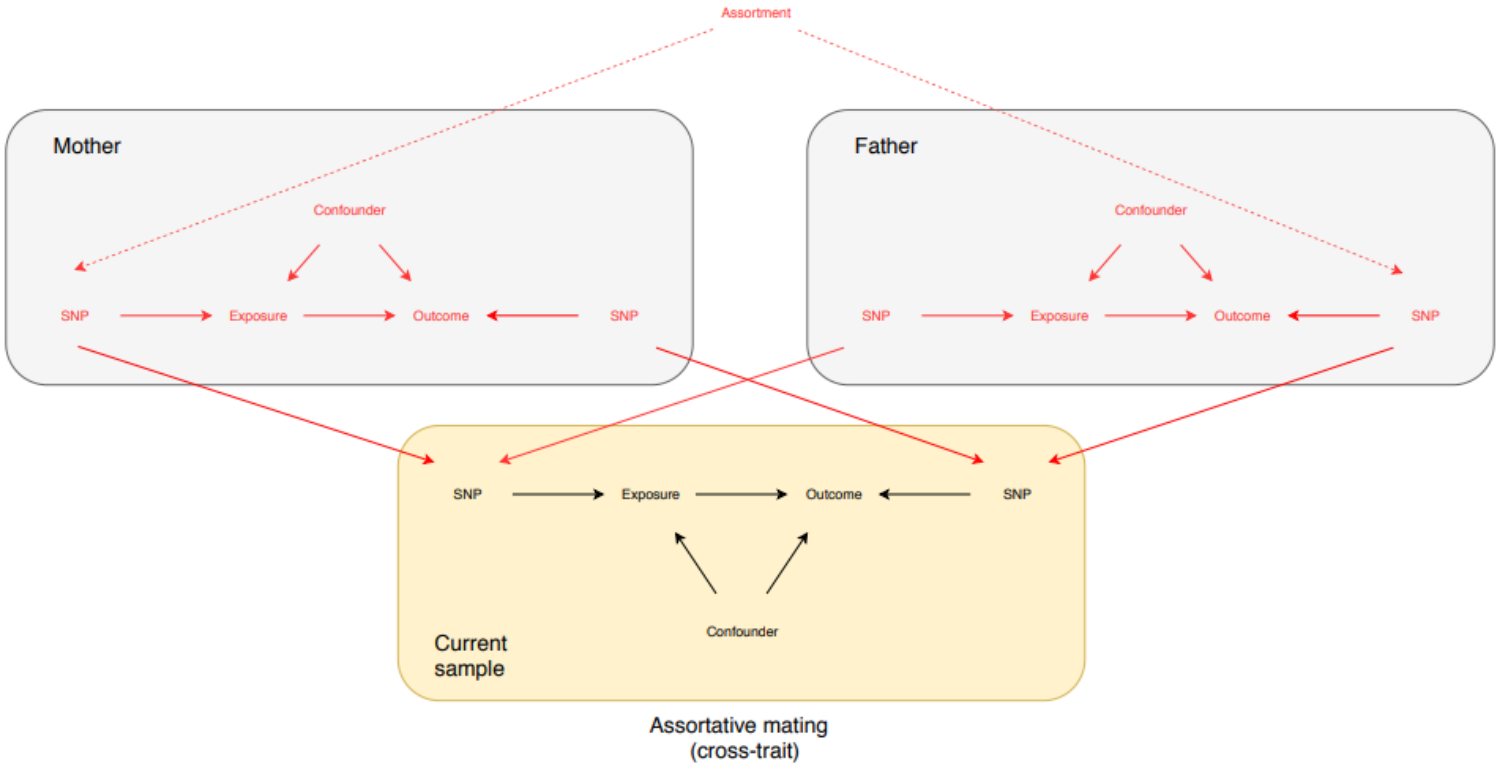
Is that caused by processes acting on the child (e.g., being bullied in school?) or through the parents (e.g., obesity-associated health problems caused the father to be unemployed, and lack of economic resources affects the child?)



Dynastic effect

Processes leading to bias in MR

Assortative mating: if there is non-random partnership in the parents' generation on traits of interest, this can induce what looks like causal associations in the children's generation



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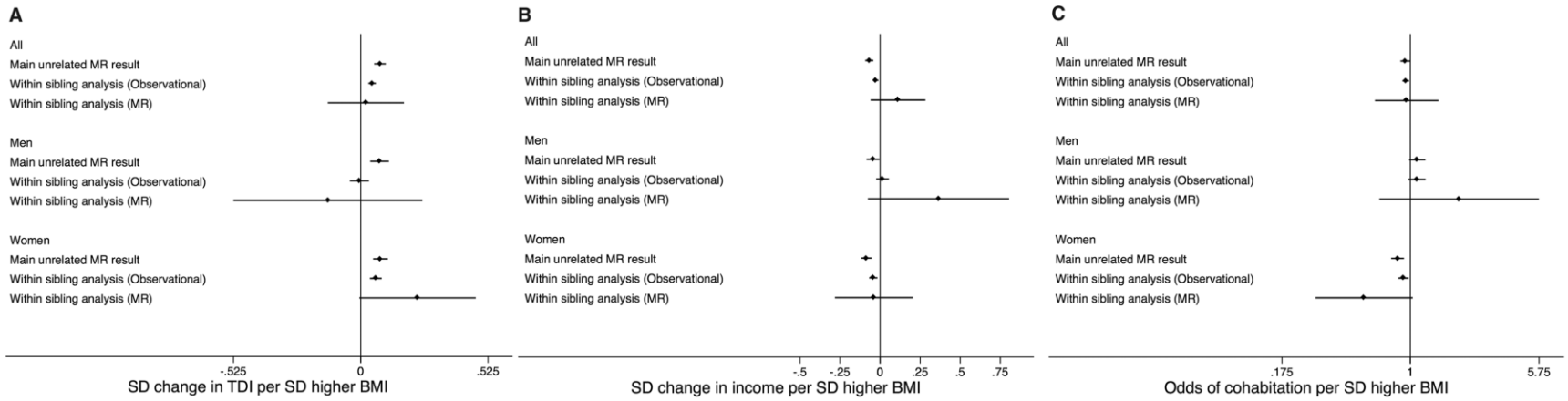
Within-family MR

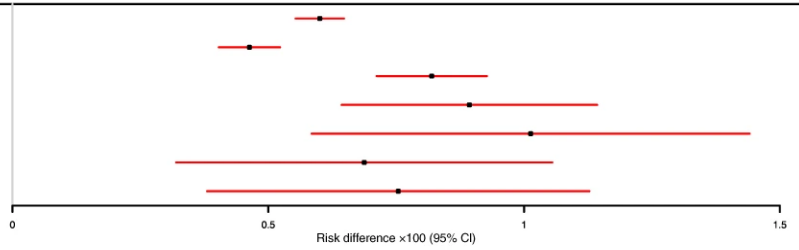
- **Within-family** genetic approaches - either within-siblings MR, or analysis within mother-father-child 'trios' - is not affected by these biases because *parental genotype is held constant*

39,000 siblings from 19,000 families in UK Biobank

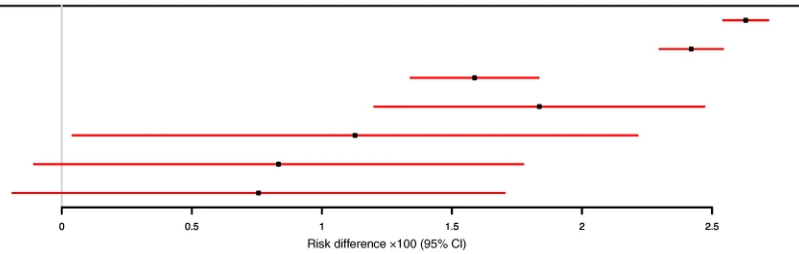


Howe et al. IJE. 2019. dyz240

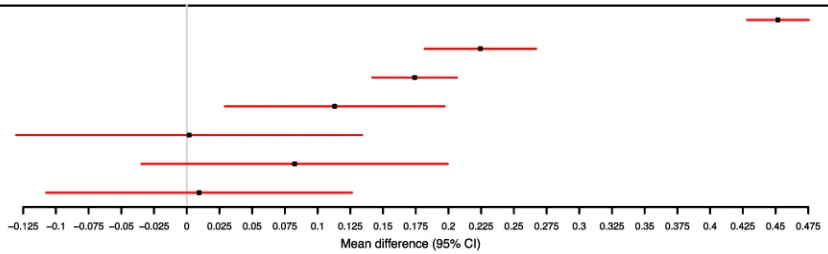
Effect of BMI on diabetes	*N*	Risk difference ×100 (95% CI)	*P*-value
IPD Ordinary least squares	61,008	0.60 (0.55 – 0.65)	1.07e–136
IPD OLS family FE	61,008	0.46 (0.40 – 0.52)	8.48e–52
IPD MR–PRS unrelateds	354,836	0.82 (0.71 – 0.93)	3.28e–50
IPD MR–PRS siblings	61,008	0.89 (0.64 – 1.14)	2.46e–12
IPD MR–PRS siblings family FE	61,008	1.01 (0.58 – 1.44)	3.53e–06
2SMR IVW siblings	61,008	0.69 (0.32 – 1.06)	2.47e–04
2SMR IVW siblings – split sample	61,008	0.75 (0.38 – 1.13)	7.62e–05



Effect of BMI on HBP	*N*	Risk difference ×100 (95% CI)	*P*-value
IPD Ordinary least squares	61,008	2.63 (2.54 – 2.72)	<1.00e–300
IPD OLS family FE	61,008	2.42 (2.30 – 2.54)	<1.00e–300
IPD MR–PRS unrelateds	354,836	1.59 (1.34 – 1.83)	1.26e–36
IPD MR–PRS siblings	61,008	1.84 (1.20 – 2.47)	1.44e–08
IPD MR–PRS siblings family FE	61,008	1.13 (0.04 – 2.21)	4.19e–02
2SMR IVW siblings	61,008	0.83 (–0.11 – 1.77)	8.25e–02
2SMR IVW siblings – split sample	61,008	0.76 (–0.19 – 1.70)	1.17e–01



Effect of height on education	*N*	Mean difference (95% CI)	*P*-value
IPD Ordinary least squares	61,008	0.45 (0.43 – 0.48)	9.05e–307
IPD OLS family FE	61,008	0.22 (0.18 – 0.27)	4.56e–25
IPD MR–PRS unrelateds	354,836	0.17 (0.14 – 0.21)	4.50e–26
IPD MR–PRS siblings	61,008	0.11 (0.03 – 0.20)	8.30e–03
IPD MR–PRS siblings family FE	61,008	0.00 (–0.13 – 0.13)	9.78e–01
2SMR IVW siblings	61,008	0.08 (–0.03 – 0.20)	1.67e–01
2SMR IVW siblings – split sample	61,008	0.01 (–0.11 – 0.13)	8.74e–01



Effect of BMI on education	*N*	Mean difference (95% CI)	*P*-value
IPD Ordinary least squares	61,008	–0.07 (–0.07 – –0.06)	8.38e–222
IPD OLS family FE	61,008	–0.02 (–0.02 – –0.01)	5.08e–13
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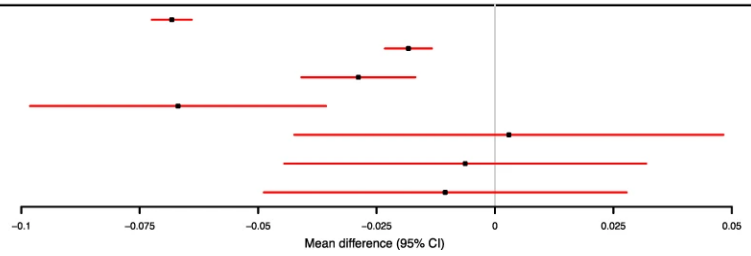

Brumpton et al. Nat Commun. 2020;11(1):3519

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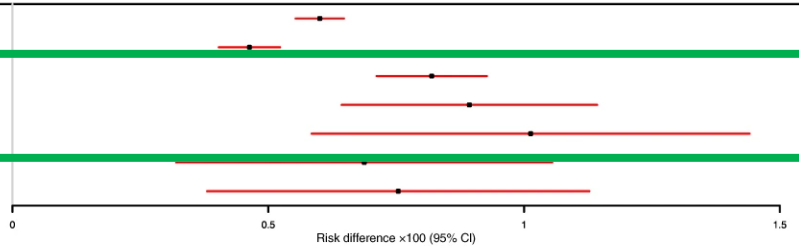

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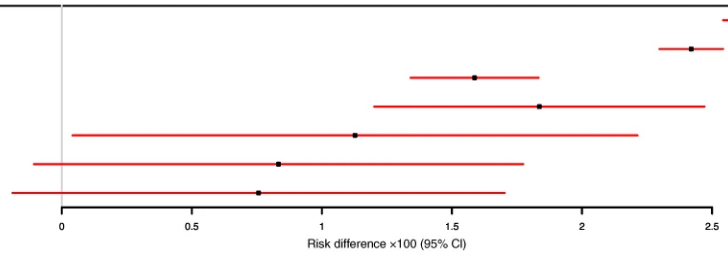

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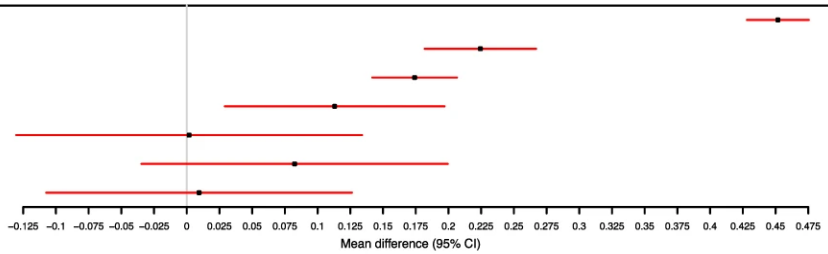

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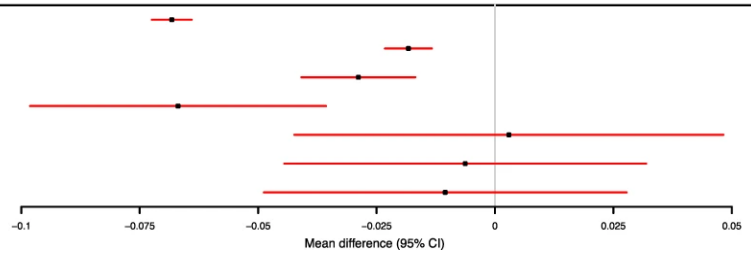

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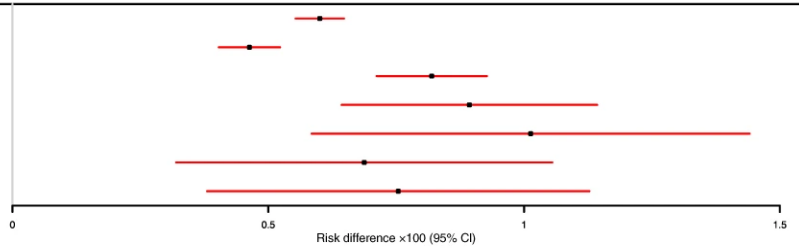
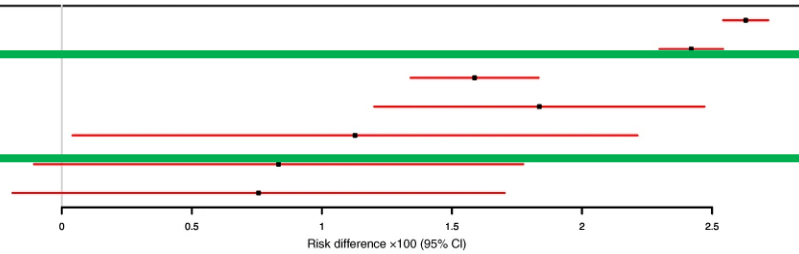
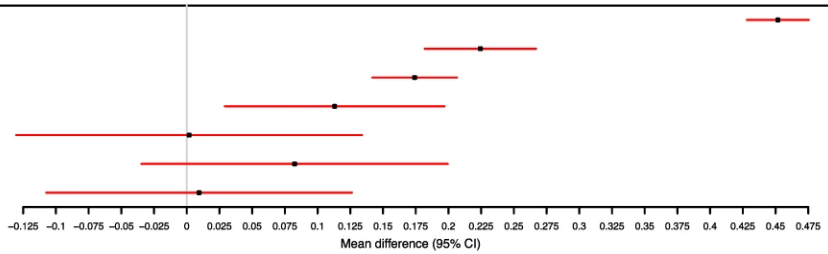
2SMR IVW siblings	61,008	0.69 (0.32 – 1.06)	2.47e–04
2SMR IVW siblings – split sample	61,008	0.75 (0.38 – 1.13)	7.62e–05



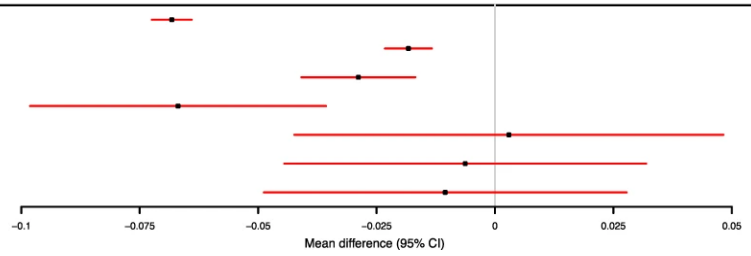
Effect of BMI on HBP	*N*	Risk difference ×100 (95% CI)	*P*-value
IPD Ordinary least squares	61,008	2.63 (2.54 – 2.72)	<1.00e–300
IPD OLS family FE	61,008	2.42 (2.30 – 2.54)	<1.00e–300
IPD MR–PRS unrelateds	354,836	1.59 (1.34 – 1.83)	1.26e–36
IPD MR–PRS siblings	61,008	1.84 (1.20 – 2.47)	1.44e–08
IPD MR–PRS siblings family FE	61,008	1.13 (0.04 – 2.21)	4.19e–02
2SMR IVW siblings	61,008	0.93 (–0.11 – 1.77)	8.25e–02
2SMR IVW siblings – split sample	61,008	0.76 (–0.19 – 1.70)	1.17e–01



Effect of height on education	*N*	Mean difference (95% CI)	*P*-value
IPD Ordinary least squares	61,008	0.45 (0.43 – 0.48)	9.05e–307
IPD OLS family FE	61,008	0.22 (0.18 – 0.27)	4.56e–25
IPD MR–PRS unrelateds	354,836	0.17 (0.14 – 0.21)	4.50e–26
IPD MR–PRS siblings	61,008	0.11 (0.03 – 0.20)	8.30e–03
IPD MR–PRS siblings family FE	61,008	0.00 (–0.13 – 0.13)	9.78e–01
2SMR IVW siblings	61,008	0.08 (–0.03 – 0.20)	1.67e–01
2SMR IVW siblings – split sample	61,008	0.01 (–0.11 – 0.13)	8.74e–01

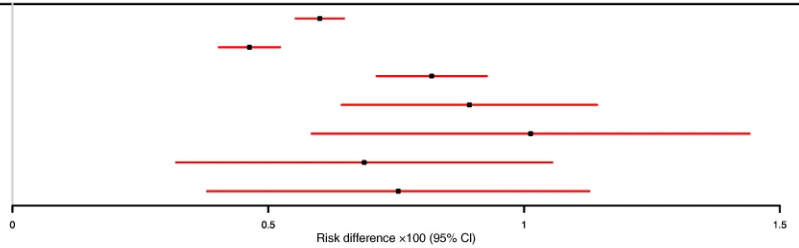


Effect of BMI on education	*N*	Mean difference (95% CI)	*P*-value
IPD Ordinary least squares	61,008	−0.07 (−0.07 – −0.06)	8.38e–222
IPD OLS family FE	61,008	−0.02 (−0.02 – −0.01)	5.08e–13
IPD MR–PRS unrelateds	354,836	−0.03 (−0.04 – −0.02)	2.59e–06
IPD MR–PRS siblings	61,008	−0.07 (−0.10 – −0.04)	2.70e–05
IPD MR–PRS siblings family FE	61,008	0.00 (−0.04 – 0.05)	8.99e–01
2SMR IVW siblings	61,008	−0.01 (−0.04 – 0.03)	7.47e–01
2SMR IVW siblings – split sample	61,008	−0.01 (−0.05 – 0.03)	5.91e–01



Brumpton et al. Nat Commun. 2020;11(1):3519

Effect of BMI on diabetes	*N*	Risk difference ×100 (95% CI)	*P*-value
IPD Ordinary least squares	61,008	0.60 (0.55 – 0.65)	1.07e–136
IPD OLS family FE	61,008	0.46 (0.40 – 0.52)	8.48e–52
IPD MR–PRS unrelateds	354,836	0.82 (0.71 – 0.93)	3.28e–50
IPD MR–PRS siblings	61,008	0.89 (0.64 – 1.14)	2.46e–12
IPD MR–PRS siblings family FE	61,008	1.01 (0.58 – 1.44)	3.53e–06
2SMR IVW siblings	61,008	0.69 (0.32 – 1.06)	2.47e–04
2SMR IVW siblings – split sample	61,008	0.75 (0.38 – 1.13)	7.62e–05



Effect of BMI on HBP	*N*	Risk difference ×100 (95% CI)	*P*-value
IPD Ordinary least squares	61,008	2.63 (2.54 – 2.72)	<1.00e–300
IPD OLS family FE	61,008	2.42 (2.30 – 2.54)	<1.00e–300
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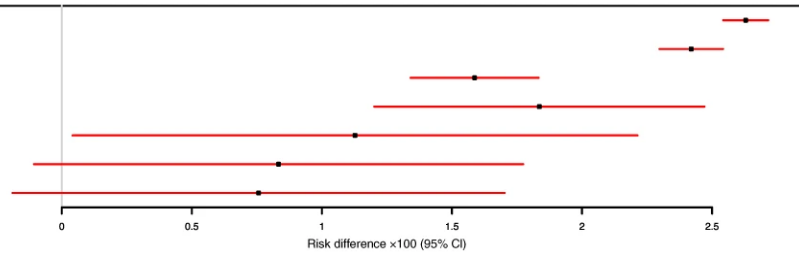
IPD MR–PRS siblings family FE	61,008	1.13 (0.04 – 2.21)	4.19e–02
2SMR IVW siblings	61,008	0.83 (–0.11 – 1.77)	8.25e–02
2SMR IVW siblings – split sample	61,008	0.76 (–0.19 – 1.70)	1.17e–01



Effect of height on education	*N*	Mean difference (95% CI)	*P*-value
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IPD OLS family FE	61,008	0.22 (0.18 – 0.27)	4.56e–25
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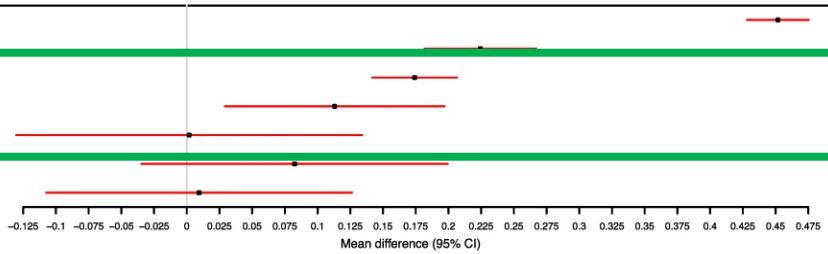
IPD MR–PRS siblings	61,008	0.11 (0.03 – 0.20)	8.30e–03
IPD MR–PRS siblings family FE	61,008	0.00 (–0.13 – 0.13)	9.78e–01
2SMR IVW siblings	61,008	0.08 (–0.03 – 0.20)	1.67e–01
2SMR IVW siblings – split sample	61,008	0.01 (–0.11 – 0.13)	8.74e–01



Effect of BMI on education	*N*	Mean difference (95% CI)	*P*-value
IPD Ordinary least squares	61,008	–0.07 (–0.07 – –0.06)	8.38e–222
IPD OLS family FE	61,008	–0.02 (–0.02 – –0.01)	5.08e–13
IPD MR–PRS unrelateds	354,836	–0.03 (–0.04 – –0.02)	2.59e–06
IPD MR–PRS siblings	61,008	–0.07 (–0.10 – –0.04)	2.70e–05
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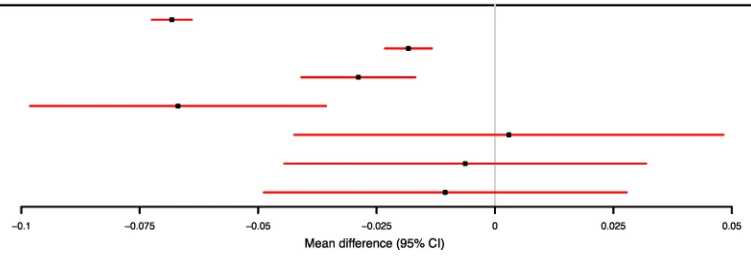

Brumpton et al. Nat Commun. 2020;11(1):3519

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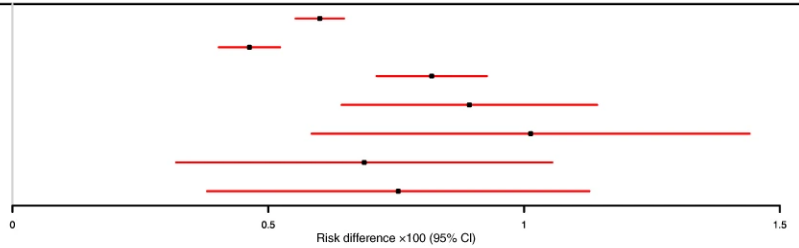

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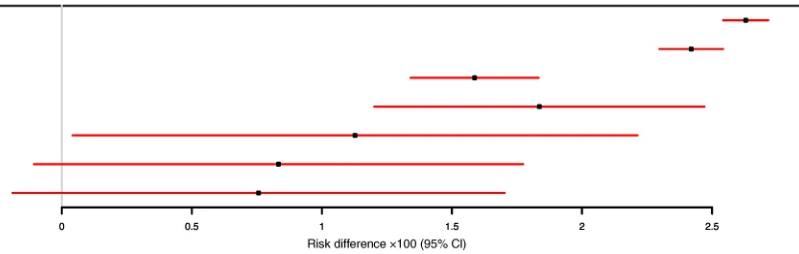
IPD MR–PRS siblings family FE	61,008	1.13 (0.04 – 2.21)	4.19e–02
2SMR IVW siblings	61,008	0.83 (–0.11 – 1.77)	8.25e–02
2SMR IVW siblings – split sample	61,008	0.76 (–0.19 – 1.70)	1.17e–01



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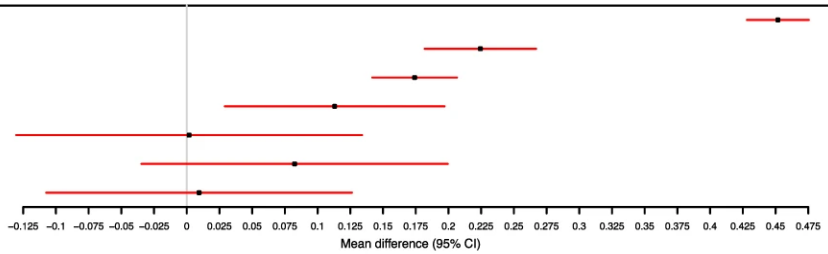
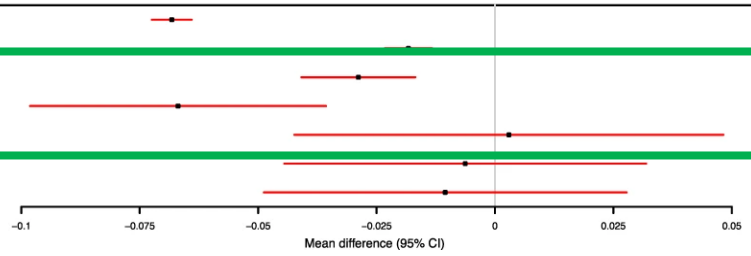


Effect of BMI on education	*N*	Mean difference (95% CI)	*P*-value
IPD Ordinary least squares	61,008	–0.07 (–0.07 – –0.06)	8.38e–222
IPD OLS family FE	61,008	0.02 (0.02 – 0.01)	5.08e–13
PD MR–PRS unrelateds	354,836	–0.03 (–0.04 – –0.02)	2.59e–06
PD MR–PRS siblings	61,008	–0.07 (–0.10 – –0.04)	2.70e–05
PD MR–PRS siblings family FE	61,008	0.00 (–0.04 – 0.05)	8.99e–01
2SMR IVW siblings	61,008	–0.01 (–0.04 – 0.03)	7.47e–01
2SMR IVW siblings – split sample	61,008	–0.01 (–0.05 – 0.03)	5.91e–01



Brumpton et al. Nat Commun. 2020;11(1):3519

Replication in 23andMe - >200,000 siblings:

- Height-education: 0.00 years education per 10cm (-0.01 to 0.002)
- BMI-education: 0.00 years education per 1kg/m2 (-0.02 to 0.02)

Brumpton et al. Nat Commun. 2020;11(1):3519

- **Next steps:**

- Norwegian MoBa cohort; mother-father-child trios
- BMI-depression
- BMI-education

Acknowledgements

Amanda Hughes

Sean Harrison

Neil Davies

Jess Tyrrell