BMI and low serum vitamin D are independent causal risk factors for MS: *A Mendelian Randomisation study*

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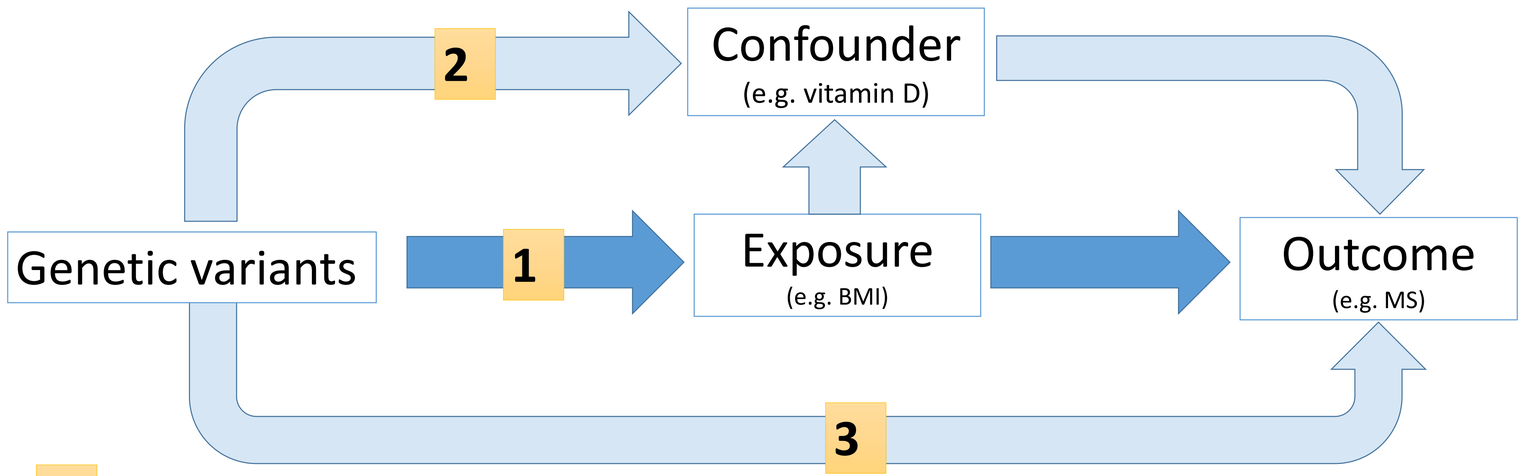
Background

- Observational studies have shown that low serum vitamin D and elevated BMI (especially during adolescence) increase MS risk.
- These associations could be due to a causal relationship, confounding, or reverse causation.
- Mendelian Randomisation (MR) uses genetic variants which are associated with an exposure (e.g. vitamin D level) as proxy instruments .
- MR can be used to determine whether associations observed in cohort and case-control settings are due to a **causal** relationship.
- This approach will help to inform MS prevention studies by distinguishing causal risk factors from exposures associated with the disease.

Mendelian randomisation: assumptions



1 Variants are associated with the exposure.

2 Variants are not associated with confounders of the exposure-outcome association.

3 Variants are only associated with the outcome ***via*** effects on the exposure.

Methods

SNP associations with trait
- Childhood BMI
- Adult BMI
- Vitamin D

From EGG consortium, GIANT, and SUNLIGHT GWAS

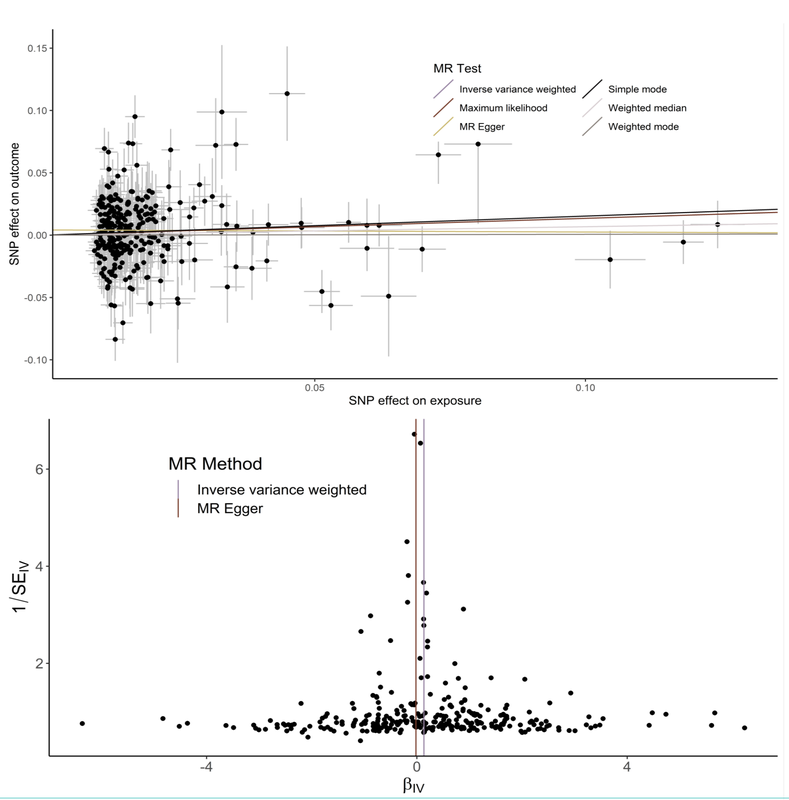
→ SNP associations with outcome (MS)
From IMSGC discovery phase MS Chip

→ Univariate MR to test for trait-outcome association
Inverse-variance weighted meta-analysis as primary, followed by secondary sensitivity analyses.

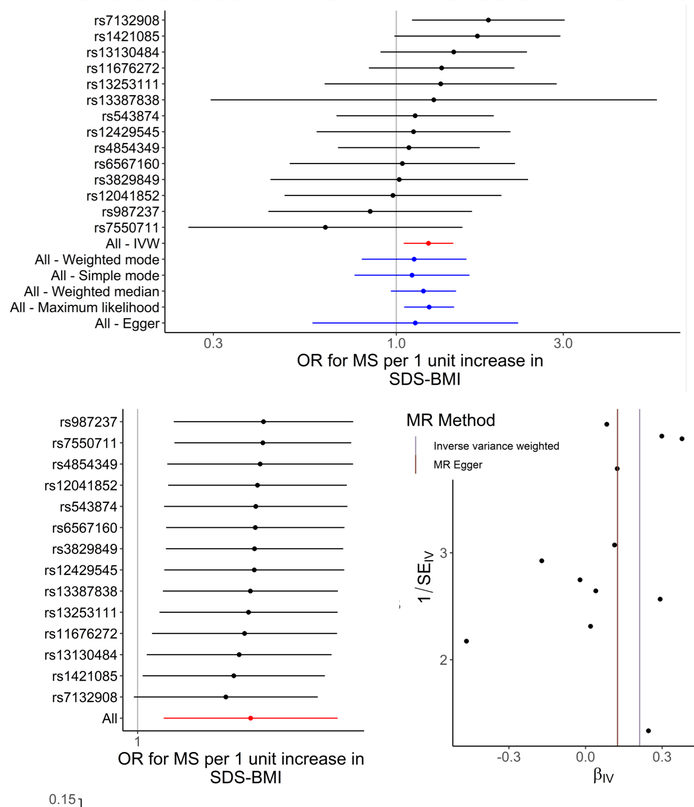
→ Multivariate MR to test for trait-outcome association ***correcting for confounding***
Regression of outcome on confounder, followed by regression of residuals from regression 1 on exposure of interest.

Results

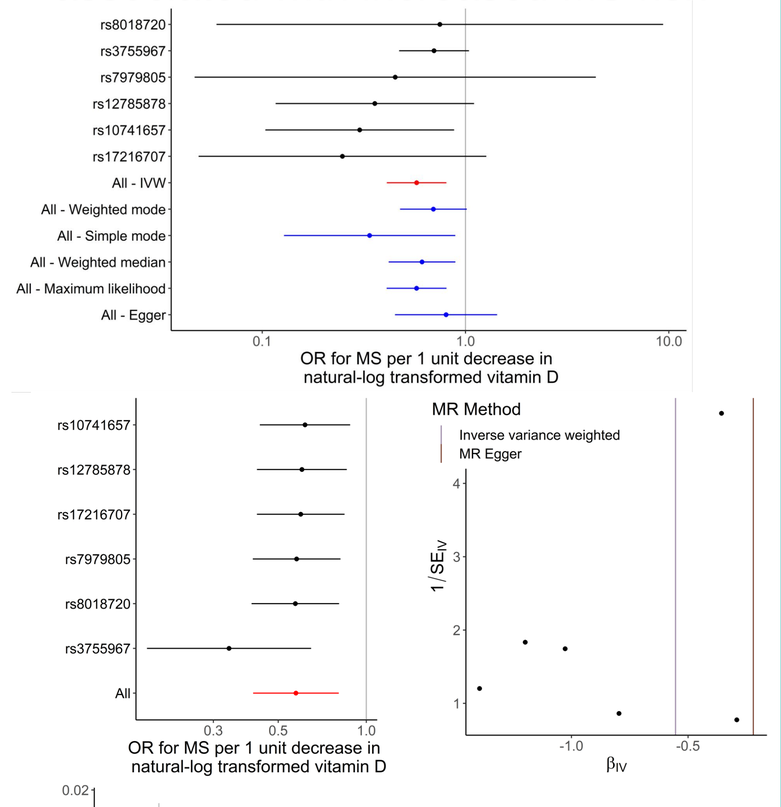
Genetically-increased adult BMI is associated with increased MS risk



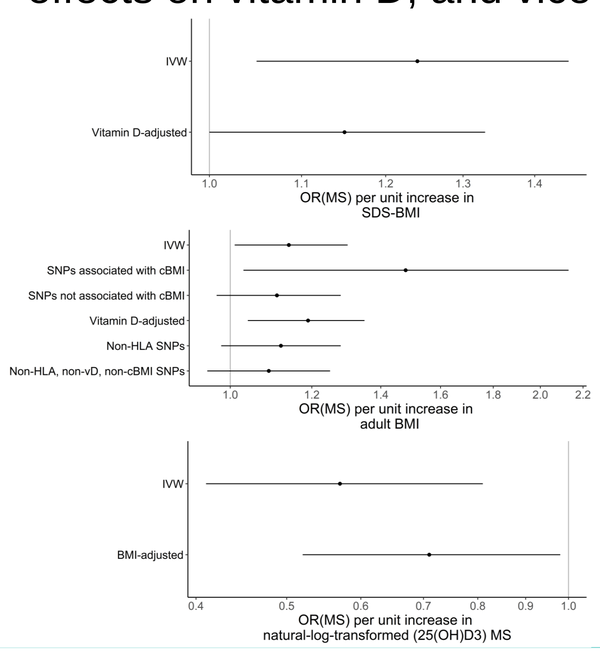
Genetically-increased childhood BMI is associated with increased MS risk



Genetically-decreased vitamin D is associated with increased MS risk

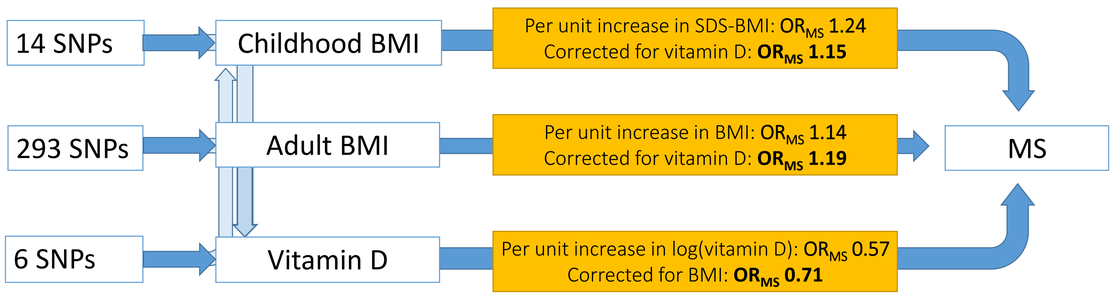


The causal effects of genetically-determined BMI on MS risk are not confounded by effects on vitamin D, and vice-versa



Conclusions

- Mendelian randomisation supports the hypothesis that BMI (especially during childhood) and lowered serum vitamin D are causal risk factors for MS.
- Multivariate MR, controlling for the effects of variants on possible confounding factors, confirms that the causal effects of vitamin D and BMI are independent of each other.
- These findings support targeting childhood obesity and avoiding vitamin D deficiency, especially in high-risk individuals, as measures to prevent MS.



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