

**Title:** Body Mass Index and reduced serum vitamin D levels are independent causal risk factors for Multiple Sclerosis: a Mendelian Randomisation study

**Authors:**

Main author: **Benjamin Meir Jacobs (BM BCh)**<sup>1,2</sup>

Co-authors: Alastair J Noyce (PhD, MRCP)<sup>1,2</sup>, Gavin Giovannoni (PhD)<sup>1,2</sup>, Ruth Dobson (PhD)<sup>1,2</sup>

**Affiliations:** 1: Preventive Neurology Unit, Wolfson Institute of Preventive Medicine, Barts and Queen Mary University of London. 2: Royal London Hospital, Barts Health NHS Trust.

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**Abstract:**

*Importance:*

Observational studies have reproducibly demonstrated associations for several environmental risk factors and Multiple Sclerosis (MS). Interpretation of these associations is limited by confounding and reverse causation. Mendelian randomisation (MR) can be used to mitigate these sources of bias.

*Objective:*

To update the causal estimates for the effects of adult BMI, childhood BMI, and vitamin D status on MS risk.

*Design:*

We used two-sample MR to determine causal estimates. Summary statistics for SNP associations with traits of interest were obtained from the relevant consortia. Primary analyses consisted of random-effects inverse-variance-weighted meta-analysis, followed by secondary sensitivity analyses.

*Results:*

Genetically-determined increased childhood BMI ( $OR_{MS}$  1.24, 95% CI 1.05-1.45,  $p=0.011$ ) and adult BMI ( $OR_{MS}$  1.14, 95% CI 1.01-1.30,  $p=0.042$ ) were associated with increased MS risk. The effect of genetically-determined adult BMI on MS risk lessened after exclusion of sixteen variants associated with childhood BMI ( $OR_{MS}$  1.11, 95% CI 0.97-1.28,  $p=0.121$ ). Correcting for effects of serum vitamin D in a multivariate analysis did not alter the direction or significance of these estimates. Each genetically-determined unit increase in natural-log-transformed vitamin D level was associated with a 43% decrease in the odds of MS ( $OR$  0.57, 95% CI 0.41-0.81,  $p=0.001$ ).

*Conclusions and Relevance:*

We provide novel evidence that BMI before the age of 10 is an independent causal risk factor for MS and strengthen evidence for the causal role of vitamin D in the pathogenesis of MS. This study argues for the importance of targeting obesity in early childhood to prevent MS.