Role of linoleic acid in autoimmune disorders: a Mendelian randomisation study

I read with great interest the article by Zhao and Schooling[1] regarding the role of linoleic acid in autoimmune disorders. This Mendelian randomisation (MR) analysis suggests that linoleic acid protects against rheumatoid arthritis (RA). However, it has a methodological issue. The choice of the genetic instrumental variables (IV) is essential for a successful MR study. MR analyses using multiple genetic variants can be viewed as a meta-analysis of the causal estimates from each variant.[2] The availability of estimates of both the gene-risk factor and the gene-outcome associations for each of these variants is important. However, the authors used limited numbers of IVs (three single nucleotide polymorphisms (SNP) with top significance and seven SNPs on functionally relevant genes).[1] Genetic instruments tend to have weak power due to the limited availability of population-specific information on genetic associations.[3] Bias from weak instruments can result in misleading estimates of causal effects. If the variants in total explain a larger proportion of the variance in the exposure, this will lead to more precise estimates of causal effects, thus increasing the power for MR analysis.[3] Therefore, the approach of using multiple genetic variants in different gene regions is suitable for an MR study. I applied a two-sample MR analysis using the inverse-variance weighted (IVW), MR-Egger regression and weighted median methods to the data from a genome-wide association study (GWAS) of n-6 polyunsaturated fatty acid (PUFA) metabolism in 8631 adults[4] as an exposure variable and RA GWAS (14 361 cases and 43 923 controls)[5] as an outcome. I selected the independent association of 75 SNPs associated with PUFA metabolism based on a linkage disequilibrium R^2 of 0.001, clumping distance of 10 000 kb and a p value threshold of 5.00E-08 (genome-wide significance). The MR estimates determined using the IVW, weighted median and MR-Egger regression analyses were consistent and do not support a causal inverse association between linoleic acid and the occurrence of RA (beta=0.00008, SE=0.001, p=0.949). The MR-Egger regression revealed that directional pleiotropy was unlikely to have biased the results, and the funnel plot test revealed a symmetry, indicating no evidence of pleiotropy. Including more instruments, where each instrument explains an extra variation in the phenotype, should provide more information on the causal estimate. Thus, I believe that the findings of this MR study should be interpreted by taking the aforementioned methodological concerns into consideration.

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