Mendelian randomisation shows diverticular disease and irritable bowel syndrome increase the risk of haemorrhoidal disease

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Recently in *Gut*, Zhu and colleagues[1] investigated causality of genetic risk effects across three genetically correlated conditions: haemorrhoidal disease (HEM), diverticular disease (DIV) and IBS. Using genome-wide association study (GWAS) summary statistics from our previous HEM GWAS[2] and other studies,[3–5] they conducted unidirectional two-sample Mendelian randomisation (MR) and concluded 'HEM might not be a trigger for developing diverticular disease or IBS, providing novel insights into a modest genetic correlation in conditions. Simultaneously, the observed causal (protective, ed.) effects of HEM on diverticular disease and IBS requires further exploration'. Although we did not originally make any claims of causality from the observed genetic correlations, the findings of Zhu *et al* are surprising and not in line with previous results,[2] hence we set out to investigate further the relationship between HEM, DIV and IBS. Here, we briefly report an analysis that differs from Zhu *et al* in that: (1) we used best practice two-sample MR analysis,[6] (2) causality was studied bi-directionally (testing HEM both as exposure (cause) and outcome (effect) versus DIV and IBS risk) and (3) summary statistics from the largest, recent GWAS meta-analysis including >53 000 IBS cases were used to test genetic risk effects of HEM relative to IBS (online supplemental material).[7] By these means, we obtained results different from Zhu *et al* and new evidence of causative effects of DIV and (to a lesser extent) IBS towards the risk of HEM. Figure 1, online supplemental figure S1 and S2 illustrate the outcome of our analyses, outlined below.

We first optimised the instrument variable (IV) selection for MR by using consensus thresholds and methods[6] to select genetic variants that are: associated with the exposure ($p<5\times10^{-8}$ or $p<5\times10^{-5}$); not in linkage disequilibrium (LD) ($r^2<0.001$ across a 1 Mb window); and not horizontally pleiotropic (having no direct association with the outcome) ($p_{MR\text{-}PRESSO}<0.05$). Then, using the selected variants as IVs, we performed bi-directional two-sample MR analyses[8 9] using inverse variance weighted (IVW), MR Egger, weighted median, simple mode, weighted mode and CAUSE methods. Additionally, to ensure the robustness of the causal effects, we performed leave-one-out IVW regression analysis, which shows that causal effects are not driven by a few outlying genetic variants (online supplemental material).

Hence, this pipeline was first applied to testing HEM as exposure towards the risk of developing DIV or IBS (outcome) as in Zhu *et al*. In contrast to Zhu *et al*, no significant findings were obtained in our analysis in this direction (see HEM exposure in figure 1). However, when either DIV or IBS were tested as exposure on HEM as outcome, significant observations were made using multiple MR models (see HEM outcome in figure 1). In particular, MR based on the IVW method resulted in strongest and most significant findings, both for IBS and for DIV showing predisposing effects on HEM. Remarkably, DIV was associated with nearly five times increased HEM risk (OR=4.8; $p=2\times10^{-4}$). While their results were limited to testing HEM as exposure, discrepancies with Zhu *et al* are most likely due to the fact that they used IVs variants that are in LD and therefore not independent (as required for MR analyses; a detailed analysis of methodological issues is reported in the online supplemental material).

In summary, we show that DIV and IBS significantly predispose to HEM. This is in

line with real-world data, as a most recent colonoscopy study also demonstrated: not only were patients with DIV more likely to have internal HEM (OR=2.21) but also those with more than 10 diverticula had the highest risk of HEM (OR=3.33).[10] Indeed, DIV was deemed by the authors even more important than diet or constipation for internal HEM development.

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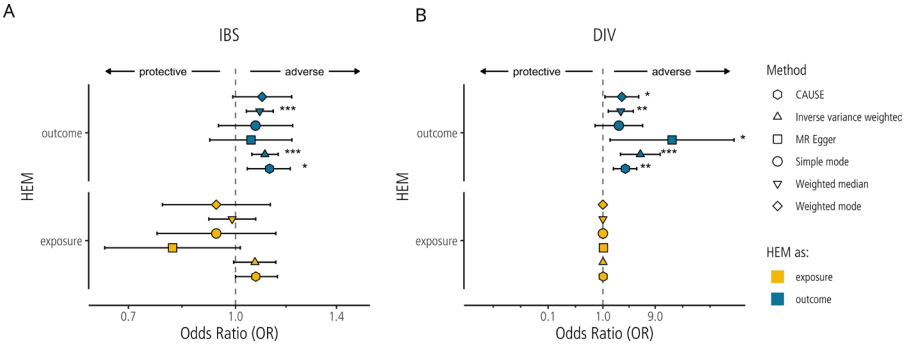

Figure 1 Bi-directional Mendelian randomisation (MR) analyses indicate a causal relationship between the effects of SNPs associated with DIV and IBS, respectively, on the development of HEM. The graph illustrates the associations between (A) IBS and HEM as well as (B) DIV and HEM, with ORs and their corresponding 95% CIs shown on the x-axis. The y-axis represents HEM as either an exposure or an outcome variable. MR analyses were conducted by using inverse variance weighted (IVW), MR Egger, weighted median, simple mode, weighted mode and CAUSE methods. Significance levels: *p<0.05; **p<0.01; ***p<0.001; else not significant. DIV, diverticular disease; HEM, haemorrhoidal disease.

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2023-330364).

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