Supplementary Material

Mendelian randomization shows diverticular disease and irritable bowel syndrome increase the risk of hemorrhoidal disease

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Supplementary Methods

Data

To study the causality effects between hemorrhoidal disease (HEM) and diverticular disease (DIV) or irritable bowel syndrome (IBS), we obtained genome-wide association study (GWAS) summary statistics from the GWAS Catalog.[1] We downloaded HEM data from Zheng *et al.* (GCST90014033),[2] DIV from Schafmayer *et al.* (GCST008105)[3] and IBS from Eijsbouts *et al.* (GCST90016564)[4] studies. For each disease, we selected the most comprehensive GWAS datasets available, which have the largest number of cases included. Specifically, the HEM study encompasses 218,920 cases, while the DIV and IBS datasets respectively comprise 35,857 and 53,400 cases.

Mendelian randomization

To assess whether causal effects exist between HEM and other gastrointestinal disorders such as DIV and IBS, and, if so, to evaluate the direction of causal effect, we performed bidirectional two-sample mendelian randomization (MR) analyses using the GWAS summary statistics of the above-described datasets. In the MR analysis, according to accepted rules,[5–7] we used genetic variants as instrumental variables (IVs) if these were: (i) significantly associated with the exposure; (ii) independent and not correlated with each other (not in linkage disequilibrium, LD); (iii) not directly associated with the outcome, that is not independently affecting both the outcome and the exposure (horizontal pleiotropy). To conduct these analyses, we used the R package TwoSampleMR v0.5.6.[8] More precisely, we selected IVs for HEM and DIV at a genome-wide significance (GWS) threshold ($P<5\times10^{-8}$), while for IBS a suggestive threshold ($P<5\times10^{-5}$) was adopted to achieve sufficient study power,[9] (since only 6 GWS loci have been identified for IBS so far)[4]. To remove variants in LD, we applied a clumping procedure selecting variants with a LD (r^2) <0.001 within 1 Mb distance. LD estimates were obtained from the 1000 Genomes Project EUR population (MAF>0.01).[10] To evaluate and remove directional (uncorrelated)[11] horizontal pleiotropy, we first used MR-PRESSO[12] to perform global and distortion tests to identify and remove IVs outliers ($P_{outlier}<0.05$), then used the MR Egger regression intercept test to confirm absence of any pleiotropic effects ($P_{Egger\ intercept}<0.05/4$)(**Supplementary Table 1**). After performing these steps, we obtained genetic variants for a given exposure trait, which were used as IVs in the MR analysis. Given the varied assumptions about the nature of the underlying pleiotropy in Mendelian randomization (MR) analysis,[13,14] we employed bidirectional two-sample MR analyses using multiple methods, including inverse variance weighted (IVW), MR Egger, weighted median, simple mode, and weighted mode. Estimated causal effects (beta estimates, bxy) were considered significant if the corresponding P value was less than 0.05 (**Supplementary Table 2** and **Supplementary Figure 1**). To confirm that a causal effect was not driven by a single variant, we performed a leave-one-out IVW regression analysis and used the least significant observed P value to assess whether the significance of a given causal effect was maintained (**Supplementary Table 3** and **Supplementary Figure 2**). Finally, to ensure that the identified causal associations are not biased by correlated horizontal pleiotropy, we employed the CAUSE[11] method (**Supplementary Table 4**), which accounts for both correlated and uncorrelated pleiotropy (with LD pruning parameters $r^2<0.001$ and $P<1\times10^{-3}$). CAUSE calculates Bayesian posterior probabilities of shared and causal effects, and then compares if the causal model fits the data better than the sharing model. In other words, CAUSE can distinguish causal effects from correlated pleiotropy (a situation when variants exert their influence on both traits due to a shared heritable factor). In addition, the method allows the use of overlapping GWAS samples, which is a relevant issue when UK Biobank[15] data is used in multiple GWAS studies of interest.

To enable replication and verification of all our analyses, we provide scripts as R Markdown Notebooks (.Rmd) at https://github.com/jsimonas/mr-hem-div-ibs.

Supplementary Results

Methodological considerations compared to the study by Zhu *et al*.

Because of the discrepant results we obtained compared to Zhu et al,[16] additional analyses were conducted in order to try and understand the reasons behind this. First, we performed MR analyses with the same GWAS datasets and adopting Zhu et al's pipeline for IV variant selection (as much as possible based on their methods description, as they did not provide source code or details of the specific software and packages they used). Thus, according to Zhu et al, IVs were selected by clumping HEM-associated genetic variants ($P<5\times10^{-10}$) based on LD at $r^2<0.001$ within 10 Kb distance (1000 Genomes Project EUR population), and then removing clumped variants showing association ($P<0.05$) with DIV and IBS. The remaining variants were utilized as IVs in MR analyses with IVW, MR Egger, Weighted median and Simple mode methods. By these means, we obtained results overall similar (although not identical) to Zhu et al, let aside minor variations in the number of IVs identified, the effect estimates and the significance of P values (a side by side comparison is reported in **Supplementary Table 5**; for reproducibility, a report of these analyses including results, source code and software versions is provided at https://github.com/jsimonas/mr-hem-div-ibs. However, in this repetition of Zhu et al's MR analysis, we made the observation that the number of IVs exceeded the number of independent loci originally identified in the source HEM GWAS,[2] which is of concern as it may reflect multiple LD-proxies being present from the same locus among the selected IVs (thus breaching the core assumption of the IWV method requiring the use of independent [uncorrelated] IVs.[17,18] This is likely due to the narrow window (only 10 Kb) Zhu et al used in their LD pruning step for independent IV selection (one IV per region/locus), while LD window sizes of 250 Kb - 10 Mb are usually adopted as default parameters.[8,19] Zhu et al did not provide a list of IVs used in their MR, hence we could not explore this phenomenon further in relation to their original results. However, in our repetition of their MR analysis, we detected 306 IV pairs (out of 301 total IVs) showing complete LD with r^2=1 (based on pre-calculated r^2 values from 1000 Genomes EUR population using LDlinkR v1.2.3[20] (**Supplementary Figure 3 and Supplementary Table 6**). Instead, as a comparison, no LD was observed across the whole set of IV markers identified in our MR analyses, performed using a 1 Mb window with $P<5\times10^{-8}$ for LD pruning prior to IV selection (maximum LD value r^2=0.056; for more details and reproducibility, source code is provided at https://github.com/jsimonas/mr-hem-div-ibs).

In addition, Zhu et al adopted a P value-driven strategy to control for horizontal pleiotropy, by removing from the IV set all SNPs showing association with P<0.05 also with the outcome. While extremely conservative, this is based on an arbitrary cutoff for statistical significance (generally less-stringent P values are used, see [21] as an example) and may also lead to the exclusion of an excess of markers (including some with relevant vertical pleiotropic effects), given that at a nominal level (P<0.05) a large number of false positives (as high as 30%)[22] will result from testing millions of GWAS

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markers (8,494,288 variants in the HEM GWAS). To avoid the use of arbitrary P value thresholds, multiple methods such as MR-PRESSO[12] and HEIDI-outlier[23] have been developed to detect horizontal pleiotropy (we have used MR-PRESSO in our analyses).

Also different are the IBS GWAS datasets used as outcome in the MR analyses by Zhu et al (Dönertaş et al[24] and Jiang et al[25]), in that they did not take advantage of results derived from the latest and largest IBS GWAS meta-analysis (Eijsbouts et al[4]). However, this is unlikely crucial to the discrepant findings, since different results were also obtained when applying different pipelines (Zhu et al's versus ours) to the same data set as in the HEM (exposure) and DIV (outcome) MR analyses (**Supplementary Figure 4 and Supplementary Table 7**).

Finally, Zhu et al only conducted MR analyses unidirectionally, testing potential causal effects of HEM (exposure) on DIV and IBS (outcomes), thus missing the (instead) significant reverse effects that both DIV and IBS (exposures) have on HEM risk (outcome), as we showed in our bi-directional MR tests (including when using the same GWAS datasets used by Zhu et al, **Supplementary Figure 4 and Supplementary Table 7)**.

Supplementary Table 8 reports a summary of key methodological differences and their expected effects on the outcome of MR analyses. A report of analysis including source code is also provided at https://github.com/jsimonas/mr-hem-div-ibs.

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Supplementary Tables

Supplementary Table 1. Results of MR-PRESSO and MR-Egger.
The table shows the results of MR-PRESSO obtained on IVs selected by association with exposure and independence by LD, and of MR-Egger after removing IVs with suspected pleiotropy identified by MR-PRESSO. For MR- PRESSO we report the P-value of the Global test, which indicates presence of pleiotropy when significant, and the P-value of the Distortion test, which indicates the significance of the pleiotropy effect on the causal estimate. The MR-Egger intercept test performed after removing outliers identified by MR-PRESSO estimates presence of residual pleiotropy.

Exposure	Outcome	Method	Estimate	Estimate Type	P
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	MR-PRESSO global test	194.95	RSSobs	<5e-04
HEM (Zheng et al.)	DIV (Schafmayer et al.)	MR-PRESSO global test	431.78	RSSobs	<5e-04
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	MR-PRESSO global test	242.20	RSSobs	<5e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	MR-PRESSO global test	348.41	RSSobs	<5e-04
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	MR-PRESSO distortion test	11.37	distortion coefficient	0.78
HEM (Zheng et al.)	DIV (Schafmayer et al.)	MR-PRESSO distortion test	64.75	distortion coefficient	0.12
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	MR-PRESSO distortion test	-9.85	distortion coefficient	0.62
DIV (Schafmayer et al.)	HEM (Zheng et al.)	MR-PRESSO distortion test	22.57	distortion coefficient	0.13
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	MR Egger intercept test (after outlier removal)	0.0093	MR Egger intercept	0.014
HEM (Zheng et al.)	DIV (Schafmayer et al.)	MR Egger intercept test (after outier removal)	-0.00050	MR Egger intercept	0.23
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	MR Egger intercept test (after outlier removal)	0.0021	MR Egger intercept	0.49
DIV (Schafmayer et al.)	HEM (Zheng et al.)	MR Egger intercept test (after outlier removal)	-0.0062	MR Egger intercept	0.29

Supplementary Table 2. Mendelian Randomization results.
The table shows the causal estimates from different MR methods. For each pair of exposure-outcome, we indicate the MR method, the number of IVs used in the statistical test (nIVs), the causal effect in standard deviation units (Beta) and its standard error (SE), the significance of the estimate (P), as well as odds-ratio (OR) and the lower and upper 95% confidence interval (C.I.) estimates.

Exposure	Outcome	MR method	nIVs	Beta	SE	P	OR	OR lower C.I. 95%	OR upper C.I. 95%
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	MR Egger	93	-0.2101	0.115	7.15e-02	0.811	0.647	1.016
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	Weighted median	93	-0.0106	0.040	7.91e-01	0.989	0.915	1.070
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	Inverse variance weighted	93	0.0645	0.036	7.20e-02	1.067	0.994	1.144
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	Simple mode	93	-0.0638	0.101	5.29e-01	0.938	0.770	1.144
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	Weighted mode	93	-0.0638	0.092	4.89e-01	0.938	0.784	1.123
HEM (Zheng et al.)	DIV (Schafmayer et al.)	MR Egger	86	0.0217	0.013	9.34e-02	1.022	0.997	1.048
HEM (Zheng et al.)	DIV (Schafmayer et al.)	Weighted median	86	0.0014	0.003	6.82e-01	1.001	0.995	1.008
HEM (Zheng et al.)	DIV (Schafmayer et al.)	Inverse variance weighted	86	0.0069	0.004	7.70e-02	1.007	0.999	1.015
HEM (Zheng et al.)	DIV (Schafmayer et al.)	Simple mode	86	0.0013	0.008	8.62e-01	1.001	0.987	1.016
HEM (Zheng et al.)	DIV (Schafmayer et al.)	Weighted mode	86	-0.0007	0.007	9.22e-01	0.999	0.986	1.013
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	MR Egger	84	0.0512	0.070	4.66e-01	1.053	0.918	1.207
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	Weighted median	84	0.0811	0.023	3.88e-04	1.084	1.037	1.134
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	Inverse variance weighted	84	0.0981	0.022	1.21e-05	1.103	1.056	1.153
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	Simple mode	84	0.0671	0.063	2.89e-01	1.069	0.945	1.210
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	Weighted mode	84	0.0892	0.050	7.98e-02	1.093	0.991	1.206
DIV (Schafmayer et al.)	HEM (Zheng et al.)	MR Egger	43	2.9043	1.328	3.45e-02	18.252	1.353	246.265
DIV (Schafmayer et al.)	HEM (Zheng et al.)	Weighted median	43	0.7513	0.268	5.06e-03	2.120	1.253	3.585
DIV (Schafmayer et al.)	HEM (Zheng et al.)	Inverse variance weighted	43	1.5708	0.425	2.17e-04	4.810	2.092	11.058
DIV (Schafmayer et al.)	HEM (Zheng et al.)	Simple mode	43	0.6704	0.510	1.96e-01	1.955	0.720	5.312
DIV (Schafmayer et al.)	HEM (Zheng et al.)	Weighted mode	43	0.7934	0.361	3.37e-02	2.211	1.089	4.489

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Supplementary Table 3. Leave-one-out IVW analysis results.
The table shows the causal estimates obtained in the leave-one-out IVW analysis. The column "SNP" indicates which SNP was removed as IV from the analysis. "All" show the causal estimates obtained with all IVs and the IVW test, as reported in **Supplementary Table 2**. In addition, the table represents all SNPs that were used as IVs for MR analyses.

Exposure	Outcome	SNP	Beta	SE	P
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs10460504	0.070	0.036	5.14e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs10807610	0.065	0.036	7.43e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs10838738	0.062	0.036	8.62e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs10956488	0.064	0.036	7.54e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs11045079	0.064	0.036	7.45e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs11176001	0.069	0.037	5.81e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs1156533	0.065	0.036	7.23e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs11578225	0.064	0.036	7.61e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs11585073	0.070	0.036	5.50e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs11635984	0.064	0.036	7.52e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs11770437	0.061	0.036	9.04e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs11942410	0.065	0.036	7.30e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs12153515	0.062	0.036	8.70e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs12594232	0.067	0.036	6.33e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs13017210	0.066	0.036	6.87e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs13271626	0.063	0.036	7.97e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs13632	0.067	0.036	6.11e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs145163454	0.070	0.036	5.31e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs1542726	0.063	0.036	8.31e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs16831319	0.063	0.036	7.88e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs1689549	0.067	0.036	6.32e-02

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HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs17293632	0.062	0.037	8.82e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs174767	0.060	0.036	9.44e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs17824374	0.066	0.036	6.73e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs1838392	0.079	0.036	2.75e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs1858015	0.066	0.036	6.75e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs2060285	0.062	0.036	8.69e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs2186797	0.066	0.036	6.66e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs2327426	0.069	0.036	5.47e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs2421206	0.064	0.036	7.78e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs2525570	0.062	0.036	8.45e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs2555004	0.066	0.036	6.86e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs2581260	0.068	0.036	5.60e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs2597301	0.061	0.036	9.20e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs2687965	0.062	0.036	8.35e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs2832279	0.062	0.036	8.67e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs2861709	0.060	0.036	9.26e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs28663472	0.056	0.035	1.08e-01
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs2912053	0.073	0.036	4.12e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs3012065	0.063	0.036	7.95e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs3253	0.065	0.036	7.08e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs34161672	0.067	0.036	6.42e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs34417560	0.062	0.036	8.54e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs34532102	0.067	0.036	6.33e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs35384758	0.061	0.036	8.91e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs3757582	0.062	0.036	8.48e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs3851366	0.065	0.036	7.25e-02

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HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs4233681	0.067	0.036	6.13e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs4345978	0.066	0.036	6.96e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs4423457	0.067	0.036	6.51e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs4556017	0.057	0.036	1.12e-01
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs4670149	0.068	0.036	5.88e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs4671051	0.060	0.036	9.19e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs4843407	0.066	0.036	6.66e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs4910165	0.068	0.036	6.04e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs4937872	0.052	0.033	1.22e-01
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs4951080	0.065	0.036	7.18e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs4959352	0.067	0.036	6.40e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs545754	0.065	0.036	7.01e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs57116599	0.062	0.036	8.43e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs58579887	0.066	0.036	6.60e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs61026653	0.062	0.036	8.70e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs62061554	0.066	0.036	6.82e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs62368263	0.066	0.036	6.88e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs6462976	0.070	0.036	5.16e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs6482359	0.062	0.036	8.76e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs6498573	0.061	0.036	8.93e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs6723226	0.059	0.035	9.65e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs6792493	0.064	0.036	7.69e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs6839705	0.059	0.036	9.84e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs6867042	0.060	0.036	9.28e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs7183672	0.066	0.036	6.72e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs722587	0.078	0.036	2.78e-02

HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs72707023	0.063	0.036	8.10e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs7423637	0.059	0.035	9.67e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs755209	0.067	0.036	6.43e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs7559714	0.064	0.036	7.57e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs7594056	0.061	0.036	8.96e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs7749659	0.065	0.036	7.32e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs7778418	0.060	0.036	9.77e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs7795564	0.062	0.036	8.72e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs78378222	0.067	0.036	6.25e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs7994724	0.066	0.036	6.91e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs806169	0.066	0.036	6.91e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs8106090	0.064	0.036	7.82e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs847148	0.067	0.036	6.47e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs854786	0.061	0.036	8.78e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs900400	0.062	0.036	8.84e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs920778	0.067	0.036	6.12e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs9306894	0.065	0.036	7.24e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs9322356	0.066	0.036	6.79e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs9847710	0.066	0.036	7.14e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	rs9853475	0.061	0.036	9.10e-02
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	All	0.064	0.036	7.20e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs10460504	0.007	0.004	8.04e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs10807610	0.007	0.004	7.86e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs10838738	0.007	0.004	7.48e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs10956488	0.007	0.004	8.67e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs11045079	0.007	0.004	7.45e-02

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HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs11176001	0.007	0.004	7.27e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs1156533	0.007	0.004	8.89e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs11578225	0.007	0.004	7.97e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs11585073	0.007	0.004	6.74e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs11635984	0.007	0.004	7.22e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs11770437	0.006	0.004	1.04e-01
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs12153515	0.007	0.004	8.82e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs12594232	0.007	0.004	5.53e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs13271626	0.006	0.004	9.81e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs145163454	0.006	0.004	1.49e-01
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs1542726	0.008	0.004	5.25e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs16831319	0.007	0.004	8.73e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs1689549	0.007	0.004	8.00e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs174767	0.007	0.004	9.20e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs17824374	0.007	0.004	7.67e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs1838392	0.008	0.004	3.38e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs1858015	0.007	0.004	7.36e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs2060285	0.007	0.004	8.27e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs2186797	0.007	0.004	5.79e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs2327426	0.007	0.004	7.55e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs2421206	0.007	0.004	7.77e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs2525570	0.006	0.004	1.14e-01
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs2555004	0.007	0.004	6.66e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs2581260	0.007	0.004	7.87e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs2597301	0.007	0.004	8.73e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs2605097	0.007	0.004	8.12e-02

HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs2687965	0.007	0.004	7.53e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs2832279	0.007	0.004	7.59e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs2861709	0.006	0.004	9.82e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs28663472	0.007	0.004	7.77e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs2912053	0.007	0.004	8.78e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs3012065	0.007	0.004	8.63e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs34161672	0.007	0.004	8.11e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs34417560	0.007	0.004	8.79e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs34532102	0.007	0.004	6.84e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs35384758	0.006	0.004	9.62e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs3851366	0.007	0.004	5.94e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs4233681	0.007	0.004	5.54e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs4345978	0.007	0.004	8.14e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs4423457	0.007	0.004	7.68e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs4579999	0.006	0.004	1.07e-01
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs4670149	0.007	0.004	7.41e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs4671051	0.007	0.004	8.84e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs4843407	0.007	0.004	7.90e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs4910165	0.008	0.004	4.13e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs4937872	0.007	0.004	8.11e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs4951080	0.007	0.004	7.96e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs4959352	0.007	0.004	8.02e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs545754	0.007	0.004	6.74e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs57116599	0.007	0.004	7.12e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs58579887	0.007	0.004	8.03e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs61026653	0.007	0.004	7.90e-02

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HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs62061554	0.007	0.004	8.29e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs6462976	0.007	0.004	7.35e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs6482359	0.007	0.004	8.43e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs6498573	0.007	0.004	6.00e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs6723226	0.007	0.004	8.19e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs677355	0.004	0.004	2.92e-01
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs6792493	0.007	0.004	8.37e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs6839705	0.007	0.004	6.68e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs6867042	0.007	0.004	8.20e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs7183672	0.007	0.004	9.38e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs722587	0.007	0.004	5.99e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs72707023	0.007	0.004	7.12e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs755209	0.007	0.004	7.59e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs7559714	0.007	0.004	7.45e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs7594056	0.007	0.004	9.36e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs7749659	0.007	0.004	7.62e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs7778418	0.005	0.004	1.67e-01
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs7795564	0.007	0.004	9.15e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs78378222	0.007	0.004	6.91e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs7994724	0.008	0.004	5.44e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs806169	0.007	0.004	8.67e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs847148	0.007	0.004	5.74e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs854786	0.007	0.004	7.19e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs900400	0.007	0.004	8.83e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs920778	0.007	0.004	7.81e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs9306894	0.008	0.004	4.30e-02

HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs9322356	0.007	0.004	7.64e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs9847710	0.007	0.004	6.30e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	rs9853475	0.007	0.004	8.81e-02
HEM (Zheng et al.)	DIV (Schafmayer et al.)	All	0.007	0.004	7.70e-02
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs10010358	0.097	0.023	1.89e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs10044618	0.099	0.023	1.20e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs10156602	0.096	0.023	2.50e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs10231223	0.101	0.022	6.36e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs10268606	0.099	0.023	1.33e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs10917847	0.097	0.023	1.92e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs111491723	0.099	0.022	1.04e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs112215352	0.098	0.023	1.56e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs113742420	0.099	0.023	1.29e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs11608	0.098	0.023	1.54e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs11656412	0.098	0.023	1.43e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs11738752	0.098	0.023	1.45e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs117391602	0.100	0.023	1.00e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs117654599	0.098	0.023	1.34e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs12358694	0.101	0.022	6.89e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs12464541	0.096	0.023	2.31e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs1248825	0.096	0.023	2.51e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs12530635	0.100	0.023	1.04e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs12549729	0.099	0.023	1.28e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs12727764	0.103	0.022	2.85e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs12771611	0.101	0.023	8.10e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs1280622	0.099	0.023	1.37e-05

IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs12974306	0.102	0.022	5.00e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs13013095	0.095	0.022	2.28e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs13031167	0.093	0.023	5.35e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs13250534	0.098	0.023	1.50e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs13251888	0.101	0.023	8.30e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs13321176	0.094	0.022	2.81e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs142888522	0.101	0.022	6.93e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs150079703	0.098	0.023	1.67e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs1631779	0.100	0.023	1.07e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs17210284	0.099	0.023	1.37e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs17331469	0.095	0.022	2.38e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs188488	0.105	0.022	1.42e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs189713900	0.097	0.023	1.85e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs189827057	0.096	0.023	2.26e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs2041946	0.095	0.022	2.32e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs2055084	0.099	0.022	1.02e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs20551	0.098	0.023	1.56e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs2123209	0.098	0.023	1.46e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs213368	0.096	0.023	2.01e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs2197542	0.099	0.023	1.17e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs2213287	0.095	0.023	2.55e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs2409729	0.094	0.022	2.80e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs2546969	0.096	0.023	2.03e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs2669290	0.098	0.023	1.49e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs2728934	0.098	0.023	1.72e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs2731562	0.098	0.023	1.69e-05

IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs2828078	0.100	0.023	9.89e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs3096652	0.097	0.023	1.73e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs3134615	0.097	0.023	1.80e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs35094163	0.096	0.023	2.09e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs35356207	0.102	0.022	4.50e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs35418299	0.097	0.023	1.87e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs4697055	0.096	0.023	2.02e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs4943187	0.099	0.023	1.40e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs5017929	0.101	0.023	7.25e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs56152539	0.099	0.022	9.52e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs56336528	0.095	0.022	2.31e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs56884006	0.102	0.022	4.36e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs6471719	0.099	0.023	1.27e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs6696068	0.096	0.023	2.19e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs6799861	0.095	0.022	2.24e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs6887323	0.096	0.023	2.26e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs6914949	0.096	0.023	2.00e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs7106434	0.089	0.021	3.06e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs71615648	0.098	0.023	1.41e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs72676302	0.098	0.023	1.37e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs7326447	0.100	0.023	9.91e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs74174359	0.100	0.023	1.03e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs75963624	0.097	0.023	1.56e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs77327887	0.098	0.023	1.42e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs7751504	0.100	0.023	8.95e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs78142456	0.099	0.023	1.26e-05

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IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs7857379	0.099	0.023	1.34e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs79600573	0.099	0.023	1.26e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs80094675	0.100	0.023	9.16e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs8106322	0.098	0.023	1.53e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs9358949	0.095	0.023	2.63e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs940468	0.105	0.021	9.55e-07
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs9513519	0.097	0.023	2.07e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs9597797	0.095	0.022	2.24e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs9874850	0.101	0.022	6.50e-06
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	rs996762	0.099	0.023	1.43e-05
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	All	0.098	0.022	1.21e-05
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs112609918	1.509	0.428	4.27e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs117811194	1.613	0.428	1.67e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs12041565	1.584	0.433	2.49e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs12293535	1.580	0.434	2.72e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs12764415	1.599	0.432	2.19e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs12942267	1.626	0.429	1.53e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs1473813	1.569	0.433	2.91e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs17309930	1.550	0.436	3.82e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs1802575	1.548	0.437	4.01e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs1888693	1.566	0.434	3.06e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs1973232	1.581	0.433	2.63e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs2009593	1.601	0.432	2.13e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs2049865	1.629	0.425	1.28e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs2056544	1.554	0.434	3.41e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs208814	1.613	0.430	1.73e-04

DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs2131755	1.604	0.433	2.11e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs2280028	1.591	0.434	2.46e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs2784255	1.612	0.430	1.76e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs3113037	1.595	0.433	2.34e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs34126945	1.596	0.432	2.16e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs3732760	1.593	0.434	2.40e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs3775010	1.579	0.434	2.71e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs387505	1.619	0.428	1.57e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs4333882	1.467	0.435	7.51e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs4515160	1.584	0.433	2.53e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs505922	1.243	0.316	8.43e-05
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs528521778	1.541	0.432	3.64e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs6001870	1.580	0.433	2.64e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs61814883	1.550	0.434	3.54e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs61823192	1.583	0.431	2.37e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs62125298	1.626	0.428	1.43e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs6714546	1.562	0.433	3.08e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs6734367	1.672	0.453	2.24e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs7086249	1.570	0.439	3.51e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs7098322	1.608	0.434	2.10e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs71472433	1.529	0.432	3.94e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs7281388	1.534	0.433	3.99e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs7609897	1.583	0.439	3.12e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs7800548	1.386	0.401	5.45e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs875107	1.672	0.416	5.72e-05
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs9482094	1.536	0.433	3.87e-04

DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs9520339	1.595	0.436	2.51e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	rs9555371	1.606	0.435	2.21e-04
DIV (Schafmayer et al.)	HEM (Zheng et al.)	All	1.571	0.425	2.17e-04

Supplementary Table 4. MR estimates using CAUSE.
The table shows the causal estimates from the CAUSE MR method. For each pair of exposure-outcome, we indicate the number of IVs used in the statistical test, the causal effect in standard deviation units (Gamma), the significance of the estimate (P), as well as the odds-ratio (OR) and the lower and upper 95% confidence interval.

Exposure	**Outcome**	**nIVs**	**Gamma**	**P**	**OR**	**OR lower C.I. 95%**	**OR upper C.I. 95%**
HEM (Zheng et al.)	IBS (Eijsbouts et al.)	744	0.07	1.74e-01	1.07	1.00	1.15
HEM (Zheng et al.)	DIV (Schafmayer et al.)	740	0.01	9.81e-02	1.01	1.00	1.01
IBS (Eijsbouts et al.)	HEM (Zheng et al.)	608	0.11	4.62e-02	1.12	1.04	1.20
DIV (Schafmayer et al.)	HEM (Zheng et al.)	652	0.94	9.60e-03	2.56	1.55	4.14

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Supplementary Table 5. Comparison of MR results using the pipeline described by Zhu et al.
The table shows the MR results obtained by Zhu et al[16] and by our estimates obtained using the pipeline and thresholds described in Zhu et al. For each outcome (exposure is always HEM, using the GWAS by Zheng et al[2]), we report the number of IVs and the causal estimate (Beta) and the P-value from the IVW test obtained by Zhu et al, and those obtained by us when following the pipeline and thresholds described in Zhu et al.

	Zhu et al. study		Repetition of Zhu et al. study	
Outcome	**nIVs**	**Beta (P)**	**nIVs**	**Beta (P)**
DIV (Schafmayer et al.)	213	-0.0046 (0.00036)	184	-0.0032 (0.027)
IBS (Dönertaş et al)	258	-0.0020 (0.0012)	278	-0.0019 (0.0011)
DIV (Dönertaş et al)	236	-0.0018 (0.000026)	255	-0.0011 (0.00008)
IBS (Jiang et al)	263	-0.0514 (0.47)	290	-0.083 (0.22)

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Supplementary Table 6. List of IVs in complete LD found using the window threshold described in Zhu et al.
The table lists SNP pairs in complete LD (r^2=1) that were found when using a window of 10Kb in the LD clumping process, along with their chromosomal location.

Chromosome	SNP1	SNP2
1	rs11578225	rs11581918
1	rs145163454	rs144737447
1	rs145163454	rs2227246
1	rs144737447	rs2227246
1	rs77979353	rs10800428
1	rs145163454	rs1209731
1	rs144737447	rs1209731
1	rs2227246	rs1209731
1	rs1894692	rs6025
12	rs74097857	rs11176001
13	rs1262776	rs1626445
15	rs17293632	rs56062135
2	rs113645544	rs7575552
2	rs57640566	rs79433506
2	rs57640566	rs1113419
2	rs79433506	rs1113419
2	rs57640566	rs113494688
2	rs79433506	rs113494688
2	rs1113419	rs113494688
2	rs57640566	rs113629868
2	rs79433506	rs113629868
2	rs1113419	rs113629868
2	rs113494688	rs113629868
2	rs57640566	rs79464516
2	rs79433506	rs79464516
2	rs1113419	rs79464516
2	rs113494688	rs79464516
2	rs113629868	rs79464516
2	rs4292050	rs6731260
2	rs2124969	rs7567781
2	rs59019419	rs59541669
3	rs2336162	rs2581797
3	rs2336162	rs4519686
3	rs2581797	rs4519686
3	rs2336162	rs9846976
3	rs2581797	rs9846976
3	rs4519686	rs9846976
3	rs2564938	rs1529544

3	rs9847710	rs4687697
3	rs6438003	rs6792493
3	rs56394279	rs3851366
4	rs6533183	rs6839705
4	rs17824374	rs7674065
4	rs7661046	rs4340757
4	rs7661046	rs7378179
4	rs4340757	rs7378179
4	rs7661046	rs10029738
4	rs4340757	rs10029738
4	rs7378179	rs10029738
4	rs7661046	rs12645910
4	rs4340757	rs12645910
4	rs7378179	rs12645910
4	rs10029738	rs12645910
4	rs7661046	rs4376087
4	rs4340757	rs4376087
4	rs7378179	rs4376087
4	rs10029738	rs4376087
4	rs12645910	rs4376087
4	rs7661046	rs17019341
4	rs4340757	rs17019341
4	rs7378179	rs17019341
4	rs10029738	rs17019341
4	rs12645910	rs17019341
4	rs4376087	rs17019341
4	rs7661046	rs72731556
4	rs4340757	rs72731556
4	rs7378179	rs72731556
4	rs10029738	rs72731556
4	rs12645910	rs72731556
4	rs4376087	rs72731556
4	rs17019341	rs72731556
4	rs7661046	rs144044336
4	rs4340757	rs144044336
4	rs7378179	rs144044336
4	rs10029738	rs144044336
4	rs12645910	rs144044336
4	rs4376087	rs144044336
4	rs17019341	rs144044336
4	rs72731556	rs144044336
4	rs62343635	rs2200943

4	rs6845536	rs7663578
5	rs4527146	rs4245972
5	rs4527146	rs72703070
5	rs4245972	rs72703070
5	rs3749618	rs4957080
5	rs3749618	rs113896354
5	rs4957080	rs113896354
5	rs7701852	rs3811910
5	rs6449607	rs62366958
5	rs7701852	rs62368263
5	rs3811910	rs62368263
5	rs6449607	rs62368271
5	rs62366958	rs62368271
5	rs7701852	rs17824230
5	rs3811910	rs17824230
5	rs62368263	rs17824230
6	rs1853148	rs9372480
7	rs4143205	rs10281352
7	rs4143205	rs6462976
7	rs10281352	rs6462976
7	rs4143205	rs6965764
7	rs10281352	rs6965764
7	rs6462976	rs6965764
7	rs17171704	rs3890819
7	rs3757582	rs3801458
7	rs2411046	rs7778418
7	rs10257317	rs10279449
7	rs10257317	rs10271184
7	rs10279449	rs10271184
7	rs7794668	rs10241865
7	rs28856331	rs847648
7	rs28856331	rs9718453
7	rs847648	rs9718453
7	rs28856331	rs11514917
7	rs847648	rs11514917
7	rs9718453	rs11514917
7	rs869332	rs4729866
7	rs10808120	rs12666317
7	rs4729873	rs13221979
7	rs712707	rs712715
7	rs712707	rs712718
7	rs712715	rs712718

7	rs712707	rs712719
7	rs712715	rs712719
7	rs712718	rs712719
7	rs712707	rs12540484
7	rs712715	rs12540484
7	rs712718	rs12540484
7	rs712719	rs12540484
7	rs4731377	rs11772303
7	rs4731377	rs62481385
7	rs11772303	rs62481385
7	rs4731377	rs67338333
7	rs11772303	rs67338333
7	rs62481385	rs67338333
7	rs3757780	rs12668077
8	rs268561	rs268624
8	rs268561	rs268572
8	rs268624	rs268572
8	rs268561	rs187907
8	rs268624	rs187907
8	rs268572	rs187907
8	rs7001162	rs11985375
8	rs13280922	rs13281864
8	rs13280922	rs7016334
8	rs13281864	rs7016334
8	rs13280922	rs6991708
8	rs13281864	rs6991708
8	rs7016334	rs6991708
8	rs13280922	rs1838392
8	rs13281864	rs1838392
8	rs7016334	rs1838392
8	rs6991708	rs1838392
8	rs13280922	rs10429277
8	rs13281864	rs10429277
8	rs7016334	rs10429277
8	rs6991708	rs10429277
8	rs1838392	rs10429277
8	rs13280922	rs11994908
8	rs13281864	rs11994908
8	rs7016334	rs11994908
8	rs6991708	rs11994908
8	rs1838392	rs11994908
8	rs10429277	rs11994908

8	rs13280922	rs13273979
8	rs13281864	rs13273979
8	rs7016334	rs13273979
8	rs6991708	rs13273979
8	rs1838392	rs13273979
8	rs10429277	rs13273979
8	rs11994908	rs13273979
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8	rs13281864	rs4446768
8	rs7016334	rs4446768
8	rs6991708	rs4446768
8	rs1838392	rs4446768
8	rs10429277	rs4446768
8	rs11994908	rs4446768
8	rs13273979	rs4446768
8	rs13255849	rs4446768
8	rs13280922	rs7003794
8	rs13281864	rs7003794
8	rs7016334	rs7003794
8	rs6991708	rs7003794
8	rs1838392	rs7003794
8	rs10429277	rs7003794
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8	rs13281864	rs13255749
8	rs7016334	rs13255749
8	rs6991708	rs13255749
8	rs1838392	rs13255749
8	rs10429277	rs13255749

8	rs11994908	rs13255749
8	rs13273979	rs13255749
8	rs13255849	rs13255749
8	rs4446768	rs13255749
8	rs7003794	rs13255749
8	rs13280922	rs4581086
8	rs13281864	rs4581086
8	rs7016334	rs4581086
8	rs6991708	rs4581086
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8	rs11994908	rs4581086
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8	rs4446768	rs4581086
8	rs7003794	rs4581086
8	rs13255749	rs4581086
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8	rs13281864	rs6984663
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8	rs6991708	rs6984663
8	rs1838392	rs6984663
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8	rs7003794	rs6984663
8	rs13255749	rs6984663
8	rs4581086	rs6984663
8	rs7001162	rs56289931
8	rs11985375	rs56289931
8	rs13274381	rs56289931
8	rs13280922	rs2008517
8	rs13281864	rs2008517
8	rs7016334	rs2008517
8	rs6991708	rs2008517
8	rs1838392	rs2008517
8	rs10429277	rs2008517
8	rs11994908	rs2008517
8	rs13273979	rs2008517
8	rs13255849	rs2008517

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8	rs4446768	rs2008517
8	rs7003794	rs2008517
8	rs13255749	rs2008517
8	rs4581086	rs2008517
8	rs6984663	rs2008517
8	rs13280922	rs2732143
8	rs13281864	rs2732143
8	rs7016334	rs2732143
8	rs6991708	rs2732143
8	rs1838392	rs2732143
8	rs10429277	rs2732143
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8	rs13273979	rs2732143
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8	rs13255749	rs2732143
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8	rs7016334	rs2732127
8	rs6991708	rs2732127
8	rs1838392	rs2732127
8	rs10429277	rs2732127
8	rs11994908	rs2732127
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8	rs13255849	rs2732127
8	rs4446768	rs2732127
8	rs7003794	rs2732127
8	rs13255749	rs2732127
8	rs4581086	rs2732127
8	rs6984663	rs2732127
8	rs2008517	rs2732127
8	rs2732143	rs2732127
8	rs13280922	rs2639942
8	rs13281864	rs2639942
8	rs7016334	rs2639942
8	rs6991708	rs2639942
8	rs1838392	rs2639942
8	rs10429277	rs2639942

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8	rs11994908	rs2639942
8	rs13273979	rs2639942
8	rs13255849	rs2639942
8	rs4446768	rs2639942
8	rs7003794	rs2639942
8	rs13255749	rs2639942
8	rs4581086	rs2639942
8	rs6984663	rs2639942
8	rs2008517	rs2639942
8	rs2732143	rs2639942
8	rs2732127	rs2639942
8	rs3098869	rs3110262
8	rs3098869	rs4074908
8	rs3110262	rs4074908
9	rs10793962	rs75444660
9	rs78590974	rs28632066

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Supplementary Table 7. Mendelian Randomization results using datasets from Zhu et al.
The table shows the Mendelian Randomization results when using the same datasets that were used by Zhu et al.[16] Columns are the same as in **Supplementary Table 2**.

Exposure	Outcome	MR method	nIVs	Beta	SE	P	OR	OR lower C.I. 95%	OR upper C.I. 95%
HEM (Zheng et al.)	IBS (Dönertaş et al.)	MR Egger	96	-0.0024	0.004	5.49e-01	0.998	0.990	1.005
HEM (Zheng et al.)	IBS (Dönertaş et al.)	Weighted median	96	0.0007	0.002	6.54e-01	1.001	0.998	1.004
HEM (Zheng et al.)	IBS (Dönertaş et al.)	Inverse variance weighted	96	0.0019	0.001	1.20e-01	1.002	1.000	1.004
HEM (Zheng et al.)	IBS (Dönertaş et al.)	Simple mode	96	-0.0019	0.004	6.53e-01	0.998	0.990	1.007
HEM (Zheng et al.)	IBS (Dönertaş et al.)	Weighted mode	96	-0.0021	0.004	5.66e-01	0.998	0.991	1.005
HEM (Zheng et al.)	IBS (Jiang et al.)	MR Egger	96	-0.7158	0.511	1.64e-01	0.489	0.180	1.330
HEM (Zheng et al.)	IBS (Jiang et al.)	Weighted median	96	-0.0404	0.209	8.47e-01	0.960	0.637	1.448
HEM (Zheng et al.)	IBS (Jiang et al.)	Inverse variance weighted	96	-0.0818	0.158	6.04e-01	0.921	0.676	1.256
HEM (Zheng et al.)	IBS (Jiang et al.)	Simple mode	96	-0.1186	0.528	8.23e-01	0.888	0.315	2.502
HEM (Zheng et al.)	IBS (Jiang et al.)	Weighted mode	96	-0.1752	0.437	6.90e-01	0.839	0.356	1.977
HEM (Zheng et al.)	DIV (Schafmayer et al.)	MR Egger	86	0.0217	0.013	9.34e-02	1.022	0.997	1.048
HEM (Zheng et al.)	DIV (Schafmayer et al.)	Weighted median	86	0.0014	0.003	6.74e-01	1.001	0.995	1.008
HEM (Zheng et al.)	DIV (Schafmayer et al.)	Inverse variance weighted	86	0.0069	0.004	7.70e-02	1.007	0.999	1.015
HEM (Zheng et al.)	DIV (Schafmayer et al.)	Simple mode	86	0.0013	0.008	8.66e-01	1.001	0.986	1.017
HEM (Zheng et al.)	DIV (Schafmayer et al.)	Weighted mode	86	-0.0007	0.007	9.22e-01	0.999	0.986	1.013
HEM (Zheng et al.)	DIV (Dönertaş et al.)	MR Egger	93	0.0052	0.003	1.20e-01	1.005	0.999	1.012
HEM (Zheng et al.)	DIV (Dönertaş et al.)	Weighted median	93	-0.0001	0.001	9.05e-01	1.000	0.997	1.002
HEM (Zheng et al.)	DIV (Dönertaş et al.)	Inverse variance weighted	93	0.0008	0.001	4.25e-01	1.001	0.999	1.003
HEM (Zheng et al.)	DIV (Dönertaş et al.)	Simple mode	93	0.0041	0.003	2.14e-01	1.004	0.998	1.011
HEM (Zheng et al.)	DIV (Dönertaş et al.)	Weighted mode	93	-0.0037	0.003	2.53e-01	0.996	0.990	1.003
IBS (Dönertaş et al.)	HEM (Zheng et al.)	MR Egger	31	0.5137	1.425	7.21e-01	1.672	0.102	27.286

IBS (Dönertaş et al.)	HEM (Zheng et al.)	Weighted median	31	0.4994	0.810	5.37e-01	1.648	0.337	8.056
IBS (Dönertaş et al.)	HEM (Zheng et al.)	Inverse variance weighted	31	0.7398	0.566	1.91e-01	2.096	0.691	6.354
IBS (Dönertaş et al.)	HEM (Zheng et al.)	Simple mode	31	0.3527	1.458	8.10e-01	1.423	0.082	24.767
IBS (Dönertaş et al.)	HEM (Zheng et al.)	Weighted mode	31	-0.0678	1.340	9.60e-01	0.934	0.068	12.914
IBS (Jiang et al.)	HEM (Zheng et al.)	MR Egger	32	0.0087	0.009	3.56e-01	1.009	0.991	1.027
IBS (Jiang et al.)	HEM (Zheng et al.)	Weighted median	32	0.0081	0.006	1.70e-01	1.008	0.997	1.020
IBS (Jiang et al.)	HEM (Zheng et al.)	Inverse variance weighted	32	0.0055	0.004	1.94e-01	1.006	0.997	1.014
IBS (Jiang et al.)	HEM (Zheng et al.)	Simple mode	32	0.0113	0.011	3.26e-01	1.011	0.989	1.034
IBS (Jiang et al.)	HEM (Zheng et al.)	Weighted mode	32	0.0113	0.010	2.48e-01	1.011	0.993	1.031
DIV (Schafmayer et al.)	HEM (Zheng et al.)	MR Egger	43	2.9043	1.328	3.45e-02	18.252	1.353	246.265
DIV (Schafmayer et al.)	HEM (Zheng et al.)	Weighted median	43	0.7513	0.276	6.56e-03	2.120	1.233	3.644
DIV (Schafmayer et al.)	HEM (Zheng et al.)	Inverse variance weighted	43	1.5708	0.425	2.17e-04	4.810	2.092	11.058
DIV (Schafmayer et al.)	HEM (Zheng et al.)	Simple mode	43	0.6704	0.493	1.81e-01	1.955	0.745	5.133
DIV (Schafmayer et al.)	HEM (Zheng et al.)	Weighted mode	43	0.7934	0.393	5.00e-02	2.211	1.023	4.778
DIV (Dönertaş et al.)	HEM (Zheng et al.)	MR Egger	43	-0.3639	2.046	8.60e-01	0.695	0.013	38.327
DIV (Dönertaş et al.)	HEM (Zheng et al.)	Weighted median	43	2.2848	1.033	2.70e-02	9.824	1.297	74.429
DIV (Dönertaş et al.)	HEM (Zheng et al.)	Inverse variance weighted	43	2.7346	0.683	6.31e-05	15.404	4.035	58.806
DIV (Dönertaş et al.)	HEM (Zheng et al.)	Simple mode	43	0.8351	2.107	6.94e-01	2.305	0.037	143.217
DIV (Dönertaş et al.)	HEM (Zheng et al.)	Weighted mode	43	2.2690	1.645	1.75e-01	9.670	0.384	243.228

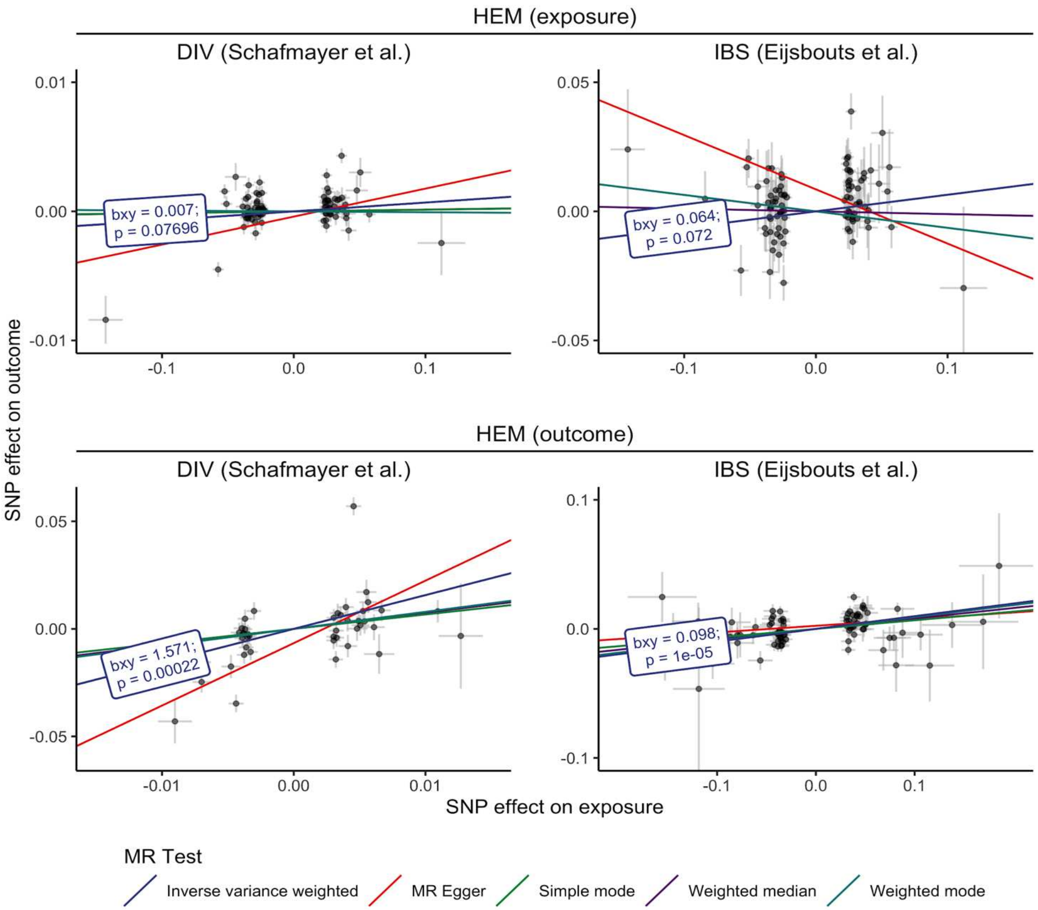
Supplementary Table 8. Impact of differences in the MR pipeline used by Zhu et al.
The table lists the different steps necessary to select IVs and control for confounding in a Mendelian Randomization analysis, the corresponding action taken by Zhu et al and by us, and the potential impact on the MR estimates when different choices are made.

Step/Parameter	Zhu et al	Juzenas et al	Possible effect on MR outcome
Choice of significance cutoff in the GWAS of the exposure	5×10-10	5×10-8	An excessively stringent GWAS P-value threshold could result in the exclusion of SNPs with significant effects, while an excessively lenient P-value threshold might introduce bias to the analyses by including false positive signals. Typically, in GWAS studies, the P value of 5×10-8 is used as a threshold to define significant loci.
LD clumping r^2 cutoff	0.001	0.001	The squared correlation coefficient (r^2) is employed to quantify LD within a specific population. Choosing an inappropriate r^2 threshold will result in the selection of correlated genetic variants and presence of LD between genetic variants that will serve as instrumental variables (IVs). The LD between IVs can lead to confounding, by introducing collinearity in the linear regression model and enhancing the possibility to introduce pleiotropy, thus ultimately violating a crucial assumption of the MR method. Notably, during the clumping procedure, the ability to r^2 remove LD between IV is not only influenced by the cutoff itself but also by the distance over which the r^2 threshold is applied.
LD clumping window cutoff	10 Kb	1 Mb	Similar to the r^2 threshold, employing a narrow LD clumping window might lead to the overlook of extended LD patterns. This oversight will result in the selection of non-independent (correlated) variants as IVs, thereby contradicting the key assumptions of the MR model.
Control for uncorrelated horizontal pleiotropy	Remove IVs if outcome GWAS $P < 0.05$	Remove IVs if MR-PRESSO outlier test ($P<0.05$)	Uncorrelated horizontal pleiotropy arises when a genetic variant (or variants) impacts an outcome through pathways unrelated to the exposure, leading it to independently influence different traits. Employing the genome-wide association-based threshold of $P < 0.05$ is rarely practiced and a conservative approach might lead to excluding a significant number of SNPs that could potentially possess vertical pleiotropic effects, thus masking the causal effect we aim to find. There are multiple methods developed to account for this phenomenon by identifying outlier IVs - i.e., IVs with potential pleiotropic effect - such as MR-PRESSO or HEIDI-outlier

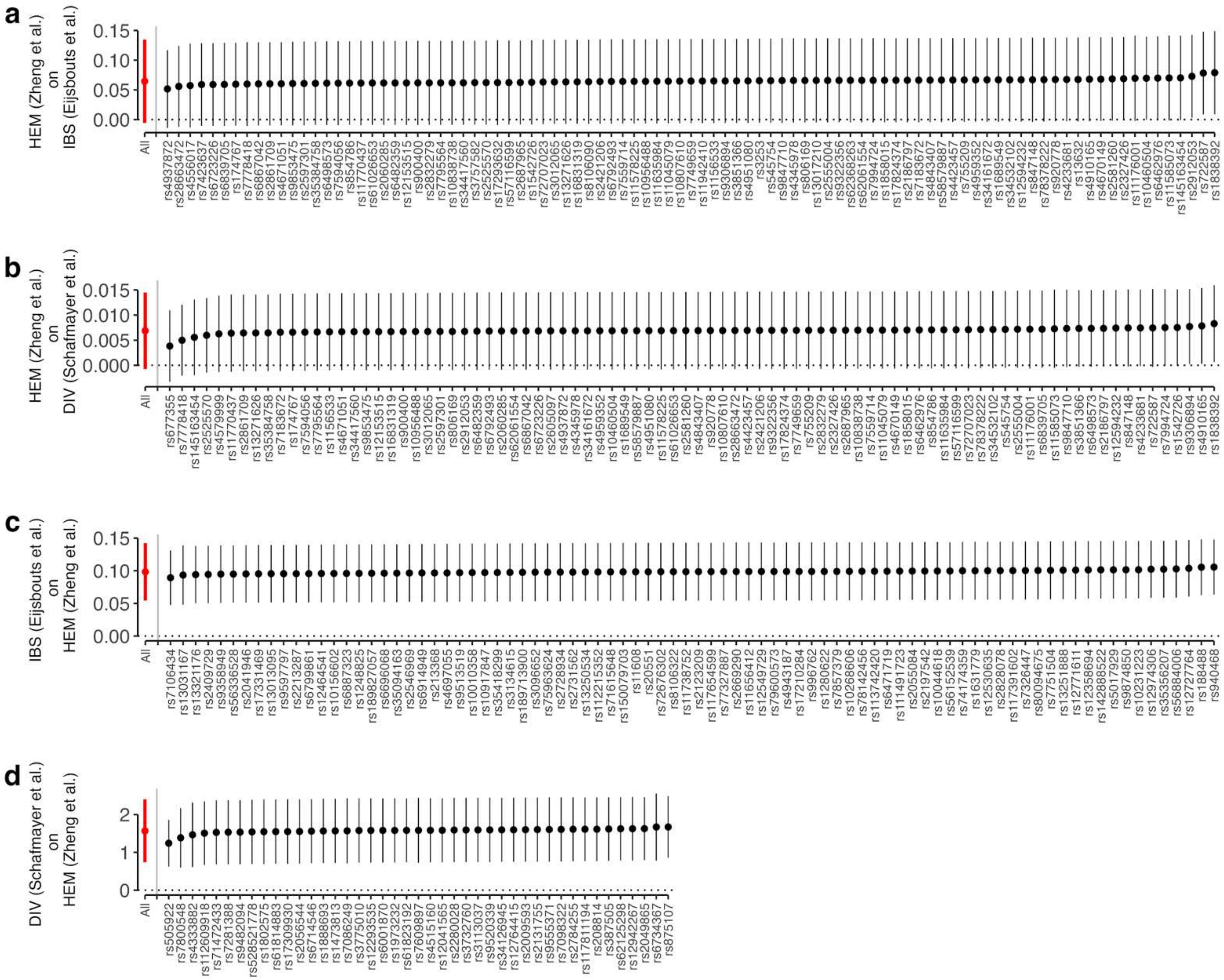
Juzenas S, *et al. Gut* 2024; 73:1–2. doi: 10.1136/gutjnl-2023-330364

Control for correlated horizontal pleiotropy	-	Check estimates from CAUSE	Correlated horizontal pleiotropy occurs when a subset of genetic variants (utilized as IVs) influence both traits due to a common heritable factor. This situation can mimic causal associations, hence leading to false positives. When there are samples being included in both the GWAS of the exposure and in the GWAS of the outcome, such as UKBiobank samples, the presence of correlated pleiotropy cannot be detected with standard pleiotropic outlier detection, such as MR-PRESSO. CAUSE can instead account for this phenomenon.

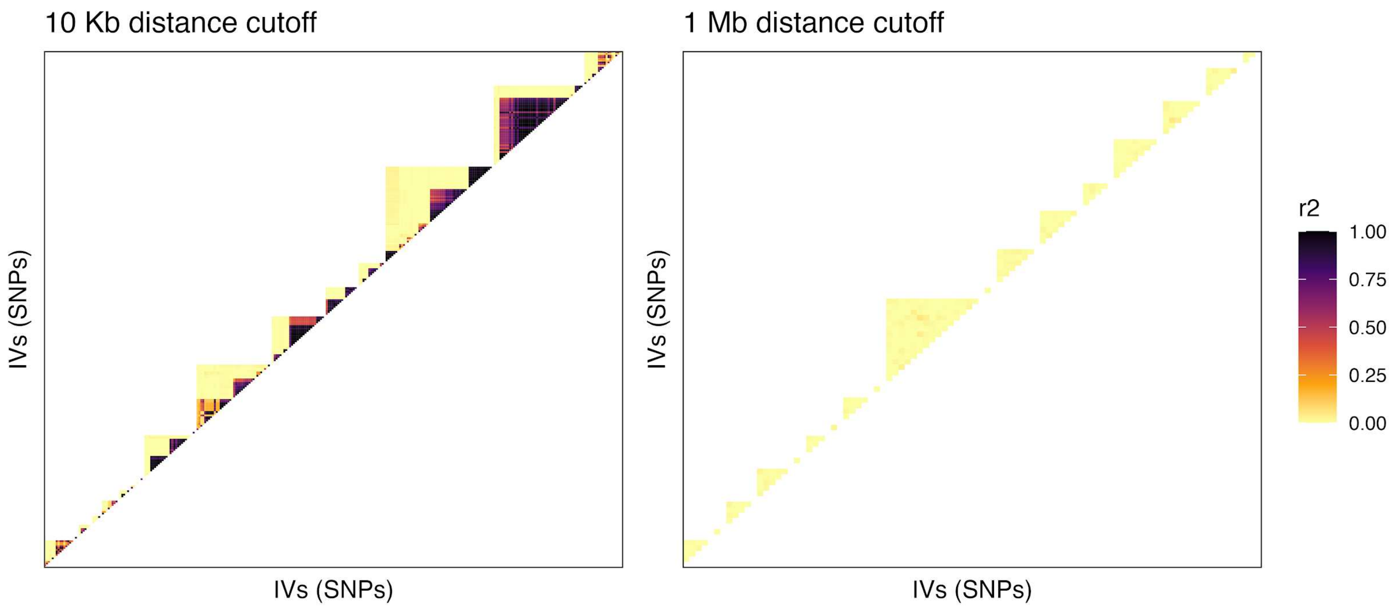
Supplementary Figures



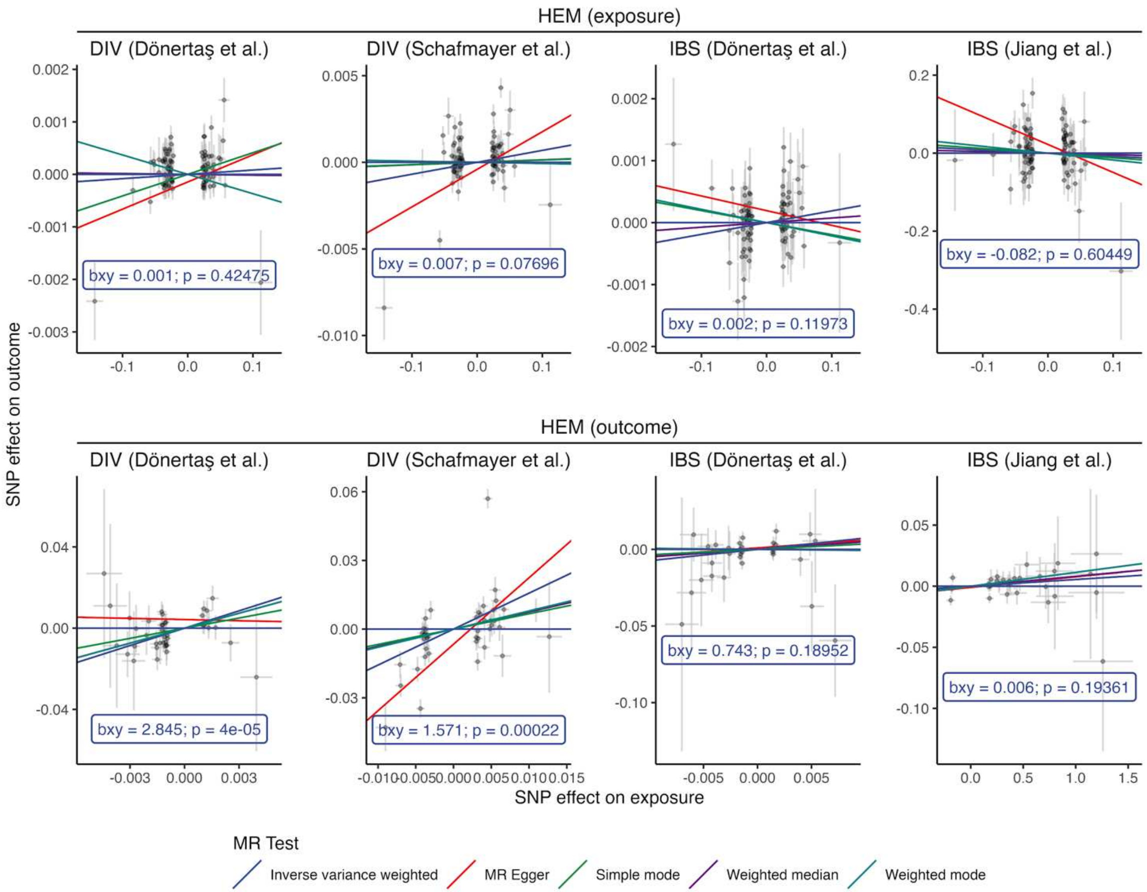
Supplementary Figure 1. Scatter plots of the SNP associations with the exposure (x-axis) against the SNP associations of the outcome (y-axis) with fitted lines of MR analyses with inverse variance weighted (IVW), MR Egger, Simple mode, Weighted median, and Weighted mode. The error bars of individual SNPs show the standard error of the estimated association between the SNP and the exposure and the SNP and the outcome. The slopes (bxy), which indicates the causal effect, and the statistical significance (P values) of IVW method (method with greatest statistical power if all IVs are valid) are annotated in blue color. Left upper panel shows HEM (exposure) SNPs (N=86) effects on DIV (outcome); Right upper - HEM (exposure) SNPs (N=93) effects on IBS (outcome); Left lower - DIV (exposure) SNPs (N=43) effects on HEM (outcome); Right lower - IBS (exposure) SNP (N=84) effects on HEM (outcome). More comprehensive results of the analyses are provided in the **Supplementary Table 2**.



Supplementary Figure 2. Results of the leave-one-out IVW regression analyses. The figure shows results of the leave-one-out IVW regression analyses, in which the IVW method was conducted excluding one SNP at a time (indicated in the x-axis) from the analysis. Circles represent causal estimates and bars the error rates. The causal estimate obtained with all SNPs is shown in red (**a**) HEM as exposure and IBS as outcome; (**b**) HEM as exposure and DIV as outcome; (**c**) IBS as exposure and HEM as outcome; (**d**) DIV as exposure and HEM as outcome. Detailed results of these analyses are provided in the **Supplementary Table 3**.



Supplementary Figure 3. Linkage disequilibrium among SNPs in the HEM GWAS summary statistics dataset using different distance thresholds for clumping. The figure represents squared correlation (r^2) values between SNP pairs (x and y axes) after performing a clumping procedure using $P<5\times10^{-10}$ with $r^2<0.001$ and 10 Kb or $P<5\times10^{-8}$ with $r^2<0.001$ and 1 Mb windows as distance thresholds. The 10 Kb threshold was used in Zhu *et al.* study[16], while in our analyses 1 Mb threshold was used for clumping. For more details, the rsIDs of SNP (IV) pairs, which are in complete linkage disequilibrium (r^2=1) are provided in the **Supplementary Table 6**.



Supplementary Figure 4. Results of methodological refinement of the Zhu et al study.[16] Scatter plots of the SNP associations with the exposure (x-axis) against the SNP associations of the outcome (y-axis) with fitted lines of MR analyses with different methods. The error bars of individual SNPs show the standard error of the estimated association between the SNP and the exposure and the SNP and the outcome. The slopes (bxy), representing the causal estimate and statistical significance (P values) of the inverse variance weighted (IVW) method are annotated in blue color. Accompanying and more detailed results are provided in the **Supplementary Table 7**.