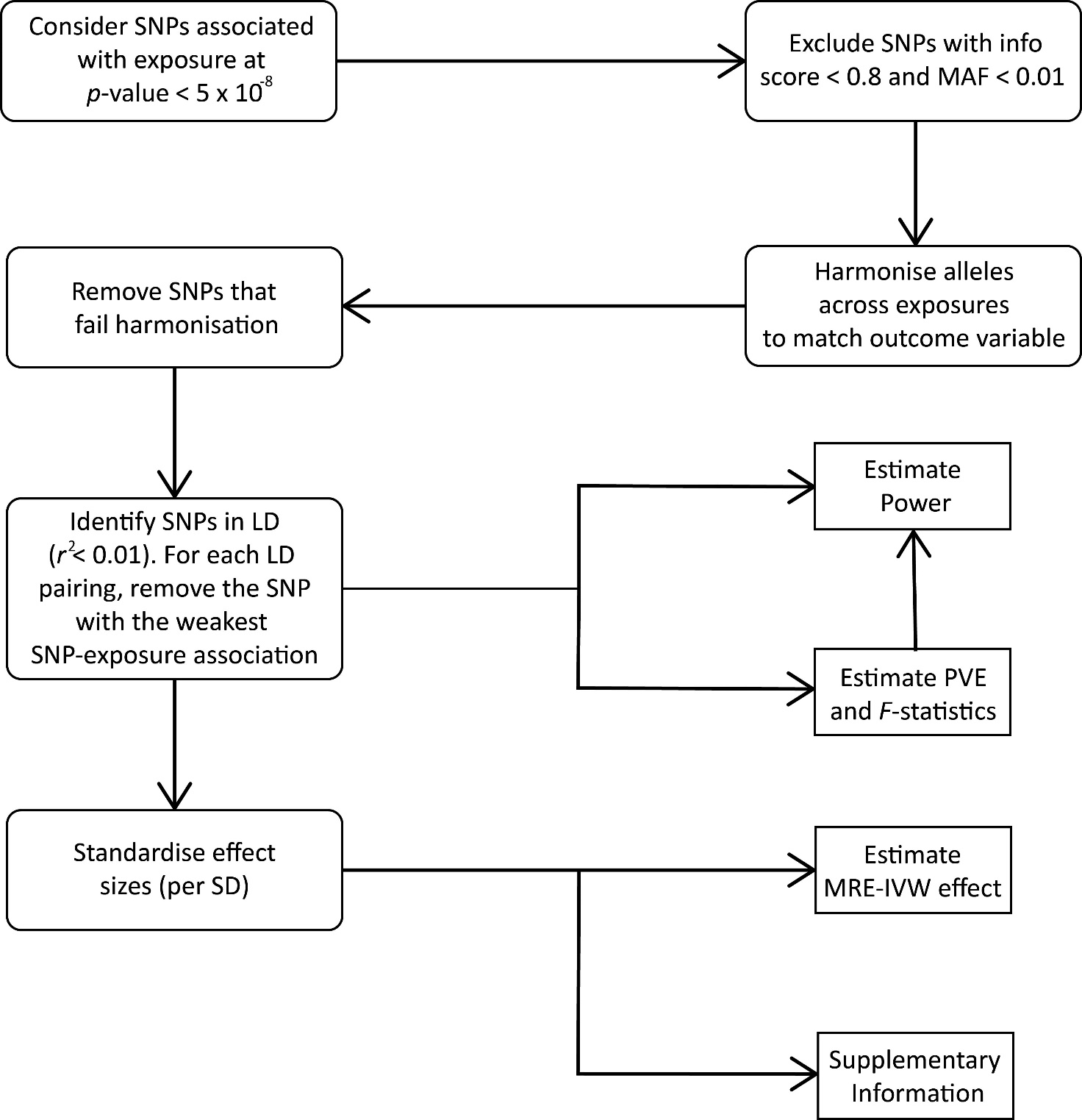
**Tables**

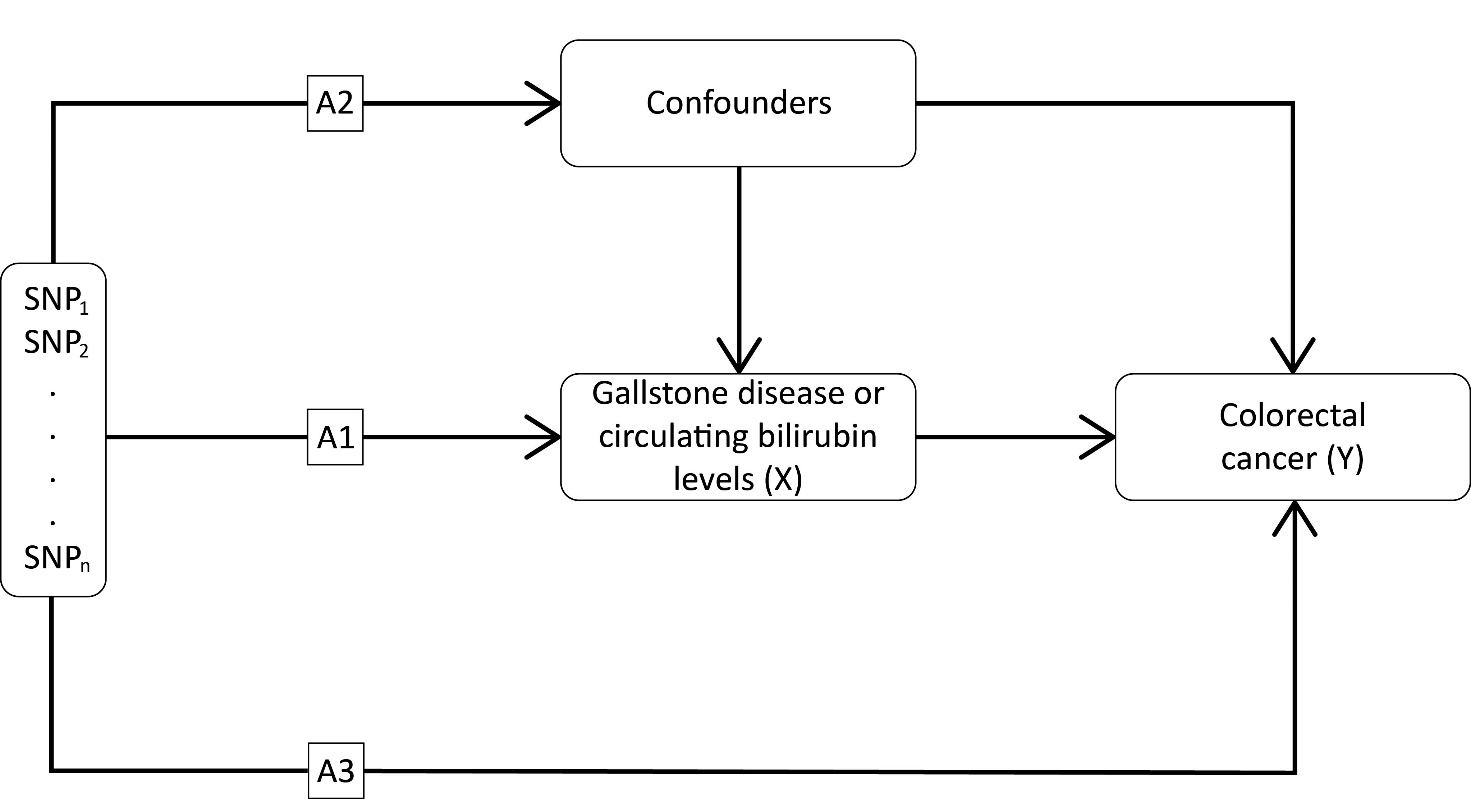
|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **CI ()** | **-value** |
| **Bilirubin** |  |  |  |
| MRE-IVW |  |  |  |
|  |  |  |  |
| **Gallstone Disease** |  |  |  |
| MRE-IVW |  |  |  |
| WME |  |  |  |
| WMO |  |  |  |
| MR-Egger | 0.52 |  |  |

**Table 1:** **Two-sample** **Mendelian randomisation analysis of the relationship between circulating levels of bilirubin and gallstone disease with risk of colorectal cancer**. MRE-IVW, multiplicative random effects inverse variance weighted; WME, weighted median; WMO, weighted mode; CI (), confidence interval; , odds ratio per genetically predicted standard deviation unit increase in bilirubin; odds ratio per genetically predicted standard deviation (of the log odds of gallstone disease) log unit increase of the risk of gallstone disease, caveated by issues discussed in the main text.

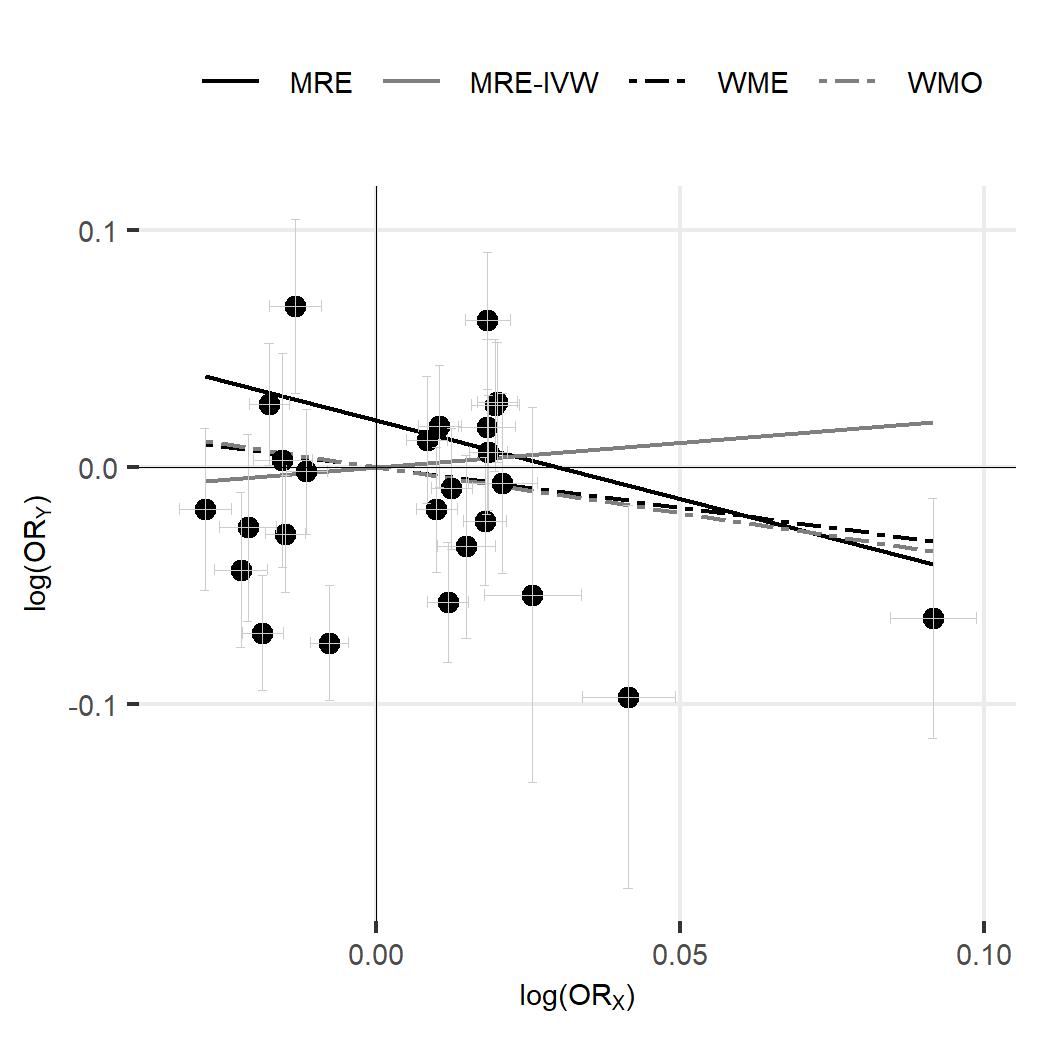
**FIGURES**

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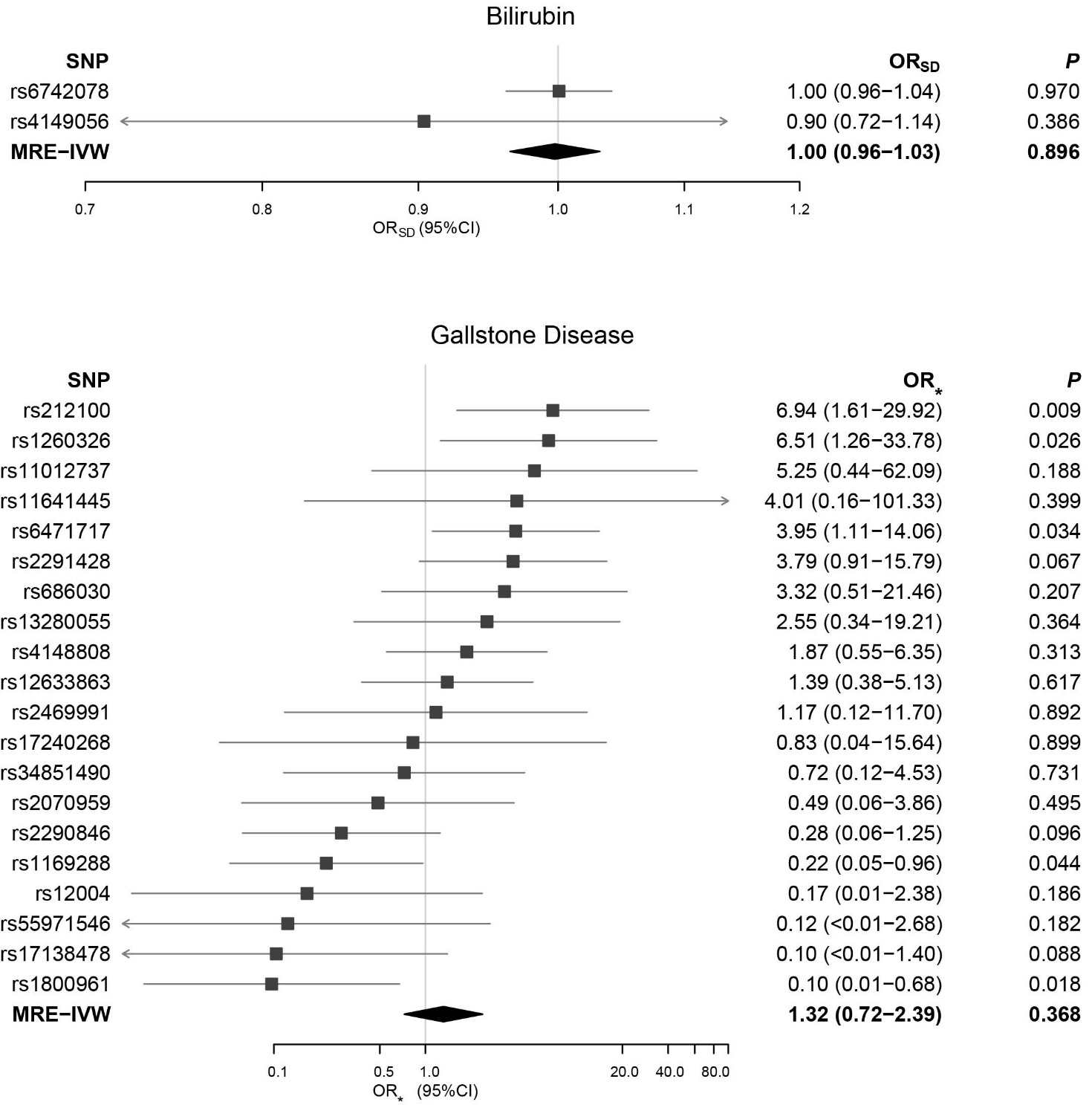
**Figure 1: Flow chart of single nucleotide polymorphism filtering.** EA, effect allele; MAF, minor allele frequency; LD, linkage disequilibrium; PVE, proportion of variation explained; SD, standard deviation; MRE-IVW, multiplicative random effects inverse variance weighted.

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**Figure 2: Mendelian randomization (MR) and the key assumptions required to obtain an unbiased estimate of the causal effect.** (A1) genetic variants used as instrumental variables are only associated with the modifiable risk factor (X; gallstone disease or circulating bilirubin levels); (A2) there exists no instrument-outcome confounding including, but not limited to, conventional confounders of the exposure-outcome relationship; (A3) genetic variants only influence the risk of CRC (Y) through the risk factor (X).

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**Figure 3: Single nucleotide polymorphism (SNP) exposure association estimates for gallstone disease risk against the SNP-outcome association estimates for colorectal cancer risk.** Causal effect given by each Mendelian randomisation (MR) estimators, caveated by issues discussed in the main text. MRE-IVW, multiplicative random effects inverse variance weighted; WME, weighted median; WMO, weighted mode; , log odds ratio (OR) per genetically predicted standard deviation increase in the exposure for each allele; , log odds ratio in the outcome for each additional allele.

**Figure 4: Forest plots of instrumental variable Wald ratios and causal effect estimates of the relationship between circulating bilirubin levels and gallstone disease with colorectal cancer**. Causal effects estimated using the multiplicative random effects inverse variance weighted (MRE-IVW) method. , odds ratio per genetically predicted standard deviation unit increase in bilirubin; odds ratio per genetically predicted standard deviation (of the log odds of gallstone disease) log unit increase of the risk of gallstone disease, caveated by issues discussed within the main text; SNP, single nucleotide polymorphism; CI, confidence interval.

**Table Legends:**

**Table 1:** **Two-sample** **Mendelian randomisation analysis of the relationship between circulating levels of bilirubin and gallstone disease with risk of colorectal cancer**. MRE-IVW, multiplicative random effects inverse variance weighted; WME, weighted median; WMO, weighted mode; CI (), confidence interval; , odds ratio per genetically predicted standard deviation unit increase in bilirubin; odds ratio per genetically predicted standard deviation (of the log odds of gallstone disease) log unit increase of the risk of gallstone disease, caveated by issues discussed in the main text.

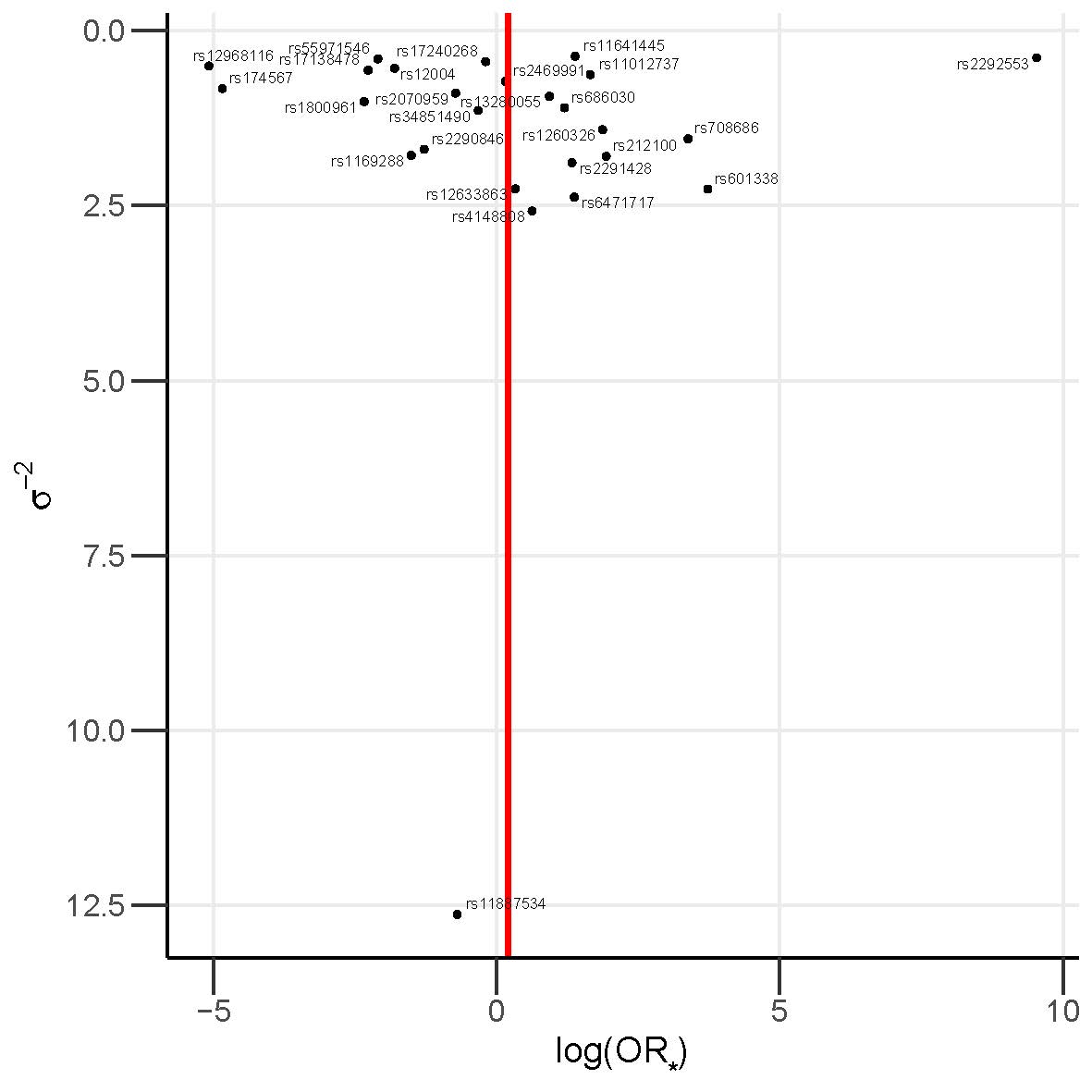
**Figure Legends:**

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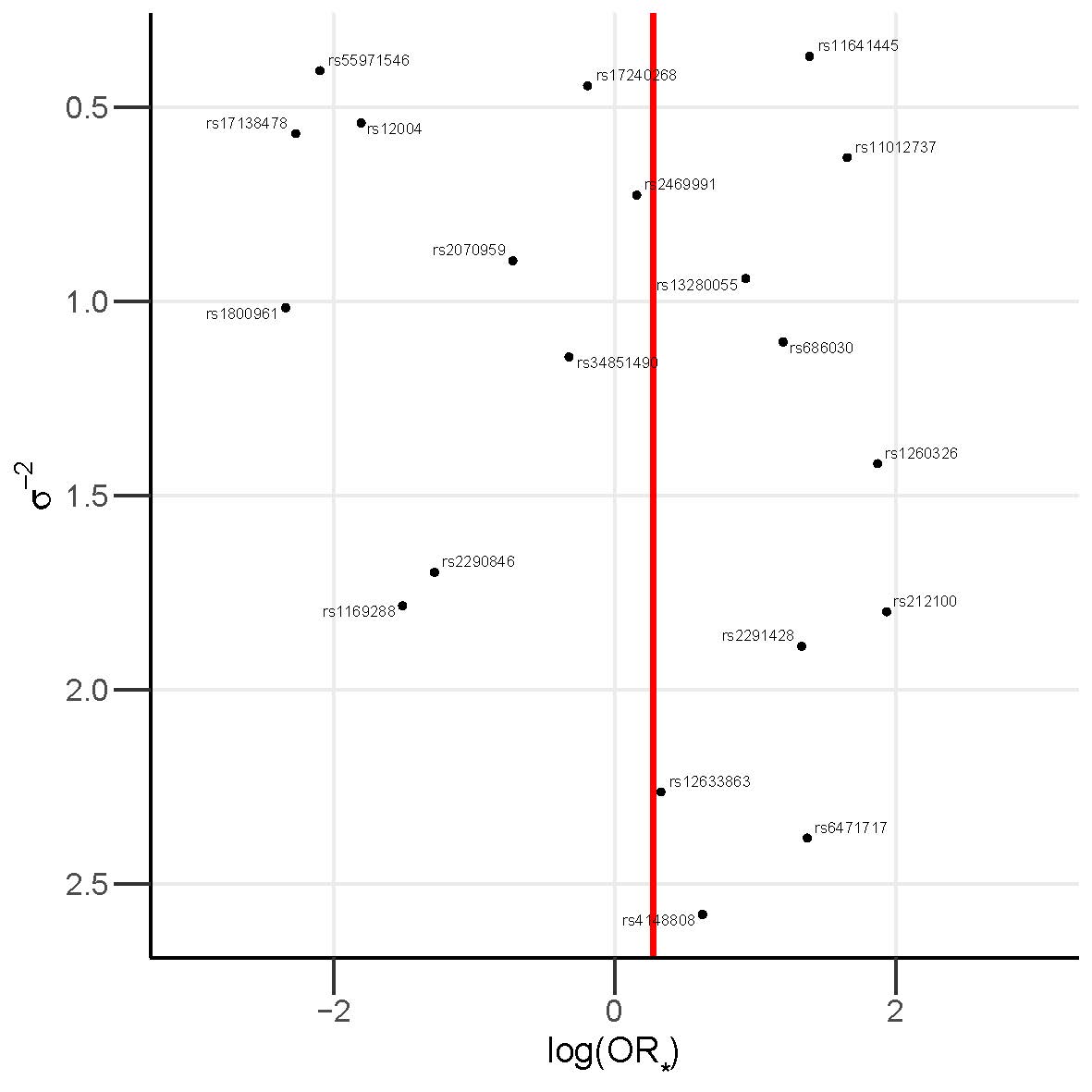
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**Supplementary Figure 1: Funnel plot of causal effect estimates for gallstone disease on colorectal cancer risk, with all 26 valid instrumental variables.** Red line shows multiplicative random effects inverse variance weighted causal effect estimate. , log odds ratio per genetically predicted standard deviation (of the log odds of gallstone disease) log unit increase of the risk of gallstone disease; , Wald ratio estimate precision.

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**Supplementary Figure 2: Funnel plot of causal effect estimates for gallstone disease on colorectal cancer risk excluding six single nucleotide polymorphisms showing heterogeneity excluded.** Red line shows multiplicative random effects inverse variance weighted causal effect estimate. , log odds ratio per genetically predicted standard deviation (of the log odds of gallstone disease) log unit increase of the risk of gallstone disease; , Wald ratio estimate precision.

**Supplementary Tables Legends:**

**Supplementary Table 1:** Single nucleotide polymorphisms (SNPs) used as instrumental variables in the Mendelian randomisation analysis.

**Supplementary Table 2:** Assessing the suitability of IVs for each exposure for use in Mendelian randomisation analysis.

**Supplementary Table 3:** Causal estimates from each Mendelian randomisation method for each exposure and CRC risk.

**Supplementary Table 4:** Summary of the 14 CRC GWAS in the meta-analysis.

**Supplementary Table 5:** Gallstone disease GWAS demographic summary.

**Supplementary Table 6:** Circulating bilirubin levels GWAS demographic summary.

**Supplementary Figure Legends:**

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