Supplementary Note for Mendelian randomization accounting for correlated and uncorrelated pleiotropic effects using genome-wide summary statistics.

Jean Morrison [*1], Nicholas Knoblauch[1], Joseph Marcus[1], Matthew Stephens[1,2], and Xin He [†1]

[1]Department of Human Genetics, University of Chicago
[2]Department of Statistics, University of Chicago

April 20, 2020

Contents

[*]jeanm@uchicago.edu
[†]xinhe@uchicago.edu

Supplementary Tables 1,2,6 and 7

Method	HH	HL	LH	LL	HH	HL	LH	LL
	$q = 0$				$q = 0.3$			
CAUSE	1.00	1.00	1.00	0.99	1.00	1.00	1.00	0.99
Egger Regression	0.97	0.88	0.61	0.48	0.96	0.82	0.59	0.45
GSMR	1.00	1.00	0.90	0.89	1.00	1.00	0.88	0.85
IVW Regression	1.00	1.00	0.99	0.92	1.00	1.00	0.95	0.87
LCV GCP	1.00	1.00	1.00	0.95	0.96	0.97	0.97	0.94
MR-PRESSO	1.00	1.00	0.91	0.87	1.00	1.00	0.89	0.83
Weighted Median	1.00	1.00	0.95	0.88	1.00	1.00	0.91	0.83
Weighted Mode	1.00	0.94	0.91	0.77	1.00	0.91	0.89	0.74
	$q = 0.1$				$q = 0.4$			
CAUSE	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.97
Egger Regression	0.97	0.83	0.60	0.44	0.94	0.81	0.58	0.41
GSMR	1.00	1.00	0.90	0.89	1.00	1.00	0.86	0.83
IVW Regression	1.00	1.00	0.98	0.92	1.00	1.00	0.92	0.84
LCV GCP	1.00	1.00	1.00	0.96	0.91	0.95	0.94	0.94
MR-PRESSO	1.00	1.00	0.91	0.87	1.00	1.00	0.85	0.80
Weighted Median	1.00	1.00	0.94	0.87	1.00	0.99	0.87	0.79
Weighted Mode	1.00	0.94	0.90	0.77	0.99	0.85	0.85	0.67
	$q = 0.2$				$q = 0.5$			
CAUSE	1.00	1.00	1.00	1.00	1.00	1.00	0.99	0.95
Egger Regression	0.96	0.84	0.54	0.45	0.92	0.75	0.52	0.44
GSMR	1.00	1.00	0.89	0.87	1.00	1.00	0.85	0.79
IVW Regression	1.00	1.00	0.97	0.90	1.00	1.00	0.90	0.80
LCV GCP	0.98	0.99	0.99	0.96	0.88	0.92	0.90	0.86
MR-PRESSO	1.00	1.00	0.90	0.85	1.00	1.00	0.84	0.77
Weighted Median	1.00	1.00	0.93	0.84	1.00	0.98	0.84	0.74
Weighted Mode	1.00	0.93	0.90	0.72	0.98	0.84	0.82	0.66

Supplementary Table 1: Area under curve values for CAUSE and other methods for ROC curves shown in Figure 2c and Extended Data Figure 1. Column labels (HH, HL, LH, and LL) indicate the power of trait M and Y GWAS (H = high power, L = low power) with the first letter referring to trait M and the second letter referring to trait Y.

Abbreviation	Trait	Sample Size	Cases	Controls	PMID	First Author (Year)
tg	triglycerides	188577			24097068	Willer (2013)
ldl	ldl	188577			24097068	Willer (2013)
hdl	hdl	188577			24097068	Willer (2013)
height	height	253288			25282103	Wood (2014)
bmi	body mass index	322154			25673413	Locke (2015)
bf	body fat percentage	100716			26833246	Lu (2016)
bw	birth weight	153781			27680694	Horikoshi (2016)
dbp	diastolic blood pressure	757601			30224653	Evangelou (2018)
sbp	systolic blood pressure	757601			30224653	Evangelou (2018)
fg	fasting glucose	46186			20081858	Dupuis (2010)
smoke	ever regular smoker	1232091			30643251	Liu (2019)
alcohol	drinks per week	941280			30643251	Liu (2019)
cad	coronary artery disease	547261	122733	424528	29212778	van der Harst (2017)
stroke	any stroke	446696	40585	406111	29531354	Malik (2018)
t2d	type 2 diabetes	69033	12171	56862	22885922	Morris (2012)
asthma	asthma	142486	23948	118538	29273806	Demenais (2018)

Supplementary Table 2: Genome wide association studies for common diseases and risk factors

Abbreviation	Trait	Sample Size	Cases	Controls	PMID	First Author (Year)
baso	basophil count	173480			27863252	Astle (2016)
eo	eosinophil count	173480			27863252	Astle (2016)
hct	hematocrit	173480			27863252	Astle (2016)
irf	immature fraction of reticulocytes	173480			27863252	Astle (2016)
lymph	lymphocyte count	173480			27863252	Astle (2016)
mch	mean corpuscular hemoglobin	173480			27863252	Astle (2016)
mono	monocyte count	173480			27863252	Astle (2016)
mpv	mean platelet volume	173480			27863252	Astle (2016)
neut	neutrophil count	173480			27863252	Astle (2016)
pdw	platelet distribution width	173480			27863252	Astle (2016)
plt	platelet count	173480			27863252	Astle (2016)
rdw	red cell distribution width	173480			27863252	Astle (2016)
ret	reticulocyte count	173480			27863252	Astle (2016)
sle	lupus	23210	7219	15991	26502338	Bentham (2015)
ra	rheumatoid arthritis	103638	29880	73758	24390342	Okada (2014)
ibd	irritable bowel disease	96486	42950	53536	26192919	Liu (2015)
asthma	asthma	142486	23948	118538	29273806	Demenais (2018)
allg	allergic disease	360838	180129	180709	29083406	Ferreira (2017)

Supplementary Table 6: Genome wide association studies for blood cell traits and immune-mediated disesase.

Traits	CAUSE	IVW	Egger	Wtd Med	Wtd Mode	MR-PRESSO	LCV GCP	LCV pval	CAUSE q	GC	GC pval
White Blood Cell Traits											
eo → allg	$\mathbf{4 \cdot 10^{-11}} \uparrow$	$\mathbf{4 \cdot 10^{-38}} \uparrow$	**0.00021** ↑	$\mathbf{3.2 \cdot 10^{-46}} \uparrow$	**0.014** ↑	$\mathbf{1.1 \cdot 10^{-43}} \uparrow$	0.13	0.27	0.81	0.39	$1.9 \cdot 10^{-18}$
eo → Asthma	$\mathbf{1.9 \cdot 10^{-5}} \uparrow$	$\mathbf{1.5 \cdot 10^{-19}} \uparrow$	**0.015** ↑	$\mathbf{3.1 \cdot 10^{-12}} \uparrow$	0.9 ↑	$\mathbf{2.6 \cdot 10^{-21}} \uparrow$	0.06	0.76	0.62	0.37	$9.9 \cdot 10^{-8}$
baso → allg	0.14 ↑	**0.018** ↑	0.84 ↓	**0.021** ↑	0.28 ↑	**0.02** ↑	0.01	0.91	0.06	0.13	0.0046
eo → ra	**0.042** ↑	$\mathbf{8.1 \cdot 10^{-9}} \uparrow$	0.069 ↑	$\mathbf{1.6 \cdot 10^{-6}} \uparrow$	**0.00091** ↑	$\mathbf{4.5 \cdot 10^{-9}} \uparrow$	0.2	0.36	0.31	0.09	0.015
baso → Asthma	0.91 ↑	0.11 ↑	0.68 ↑	0.11 ↑	0.51 ↑	0.54 ↑	−0.18	0.025	0.03	0.14	0.1
mono → sle	0.74 ↓	**0.03** ↓	0.077 ↓	0.065 ↓	0.36 ↓	0.12 ↓	0.05	0.62	0.03	−0.08	0.11
lymph → ibd	0.9 ↑	0.12 ↑	0.094 ↑	**0.025** ↑	**0.022** ↑	**0.0059** ↑	−0.26	0.7	0.03	−0.1	0.12
neut → Asthma	0.26 ↓	0.11 ↑	$\mathbf{2.1 \cdot 10^{-5}} \uparrow$	0.6 ↑	0.21 ↓	0.099 ↓	−0.34	0.47	0.05	0.11	0.23
eo → sle	0.55 ↑	0.12 ↑	0.46 ↑	**0.007** ↑	0.39 ↑	0.098 ↑	−0.41	0.43	0.05	0.06	0.28
lymph → allg	0.4 ↓	**0.0032** ↓	**0.014** ↓	0.052 ↓	0.46 ↓	**0.00029** ↓	0	0.54	0.04	−0.04	0.28
baso → sle	0.91 ↓	0.97 ↑	0.4 ↑	0.2 ↑	0.81 ↑	0.51 ↑	−0.05	0.65	0.03	−0.09	0.34
mono → ibd	0.49 ↓	0.16 ↓	0.59 ↑	0.68 ↓	0.091 ↑	0.35 ↓	−0.04	0.93	0.05	−0.06	0.43
baso → ra	0.99 ↑	0.38 ↑	0.95 ↑	**0.05** ↑	0.063 ↑	0.15 ↑	0.09	0.61	0.03	−0.03	0.47
mono → allg	1 ↑	0.058 ↓	0.24 ↓	**0.02** ↓	0.078 ↓	0.14 ↓	0.45	0.37	0.03	0.02	0.5
neut → sle	0.16 ↓	**0.0036** ↓	0.068 ↓	**0.042** ↓	**0.039** ↓	**0.0042** ↓	0.14	0.48	0.06	−0.05	0.52
neut → allg	0.7 ↑	**0.0034** ↑	$\mathbf{7.5 \cdot 10^{-10}} \uparrow$	**0.0043** ↑	0.51 ↑	0.14 ↑	−0.07	0.72	0.03	0.03	0.53
eo → ibd	0.4 ↑	0.73 ↑	0.43 ↓	**0.00057** ↑	$\mathbf{4.8 \cdot 10^{-6}} \uparrow$	**0.017** ↑	−0.01	0.91	0.05	0.04	0.54
neut → ibd	0.21 ↑	0.18 ↓	**0.003** ↓	$\mathbf{3.2 \cdot 10^{-5}} \downarrow$	$\mathbf{4.6 \cdot 10^{-9}} \downarrow$	0.11 ↓	−0.39	0.3	0.06	0.05	0.71
lymph → ra	1 ↑	1 ↑	0.42 ↓	0.24 ↓	0.063 ↓	0.18 ↓	−0.15	0.3	0.03	−0.01	0.78
lymph → sle	0.9 ↓	0.68 ↓	0.77 ↓	**0.035** ↑	0.14 ↑	0.42 ↑	−0.52	0.23	0.03	−0.01	0.83
mono → ra	1 ↑	0.64 ↓	0.55 ↓	**0.0098** ↓	$\mathbf{6.6 \cdot 10^{-5}} \downarrow$	0.26 ↓	0.02	0.88	0.03	0.01	0.87
baso → ibd	1 ↓	0.051 ↓	0.87 ↓	**0.0082** ↓	0.41 ↓	**0.0051** ↓	0.36	0.18	0.03	−0.01	0.88
mono → Asthma	0.61 ↓	0.68 ↓	0.96 ↑	0.59 ↑	0.7 ↑	0.51 ↓	−0.26	0.69	0.03	0.01	0.88
neut → ra	0.97 ↑	0.46 ↓	0.21 ↓	**0.019** ↑	**0.017** ↑	0.73 ↓	−0.02	0.6	0.03	−0.01	0.89
lymph → Asthma	0.85 ↓	0.13 ↓	0.17 ↓	0.076 ↓	0.42 ↓	0.18 ↓	−0.3	0.69	0.03	0	1
Red Blood Cell Traits											
hct → Asthma	0.95 ↓	**0.0024** ↓	**0.0055** ↓	0.13 ↓	0.21 ↓	**0.0065** ↓	0.52	0.11	0.03	−0.1	0.025
hct → ibd	0.99 ↑	0.25 ↑	0.6 ↓	0.9 ↑	0.15 ↓	0.26 ↑	−0.04	0.9	0.03	0.12	0.033
rdw → ra	**0.03** ↑	$\mathbf{1.5 \cdot 10^{-9}} \uparrow$	**0.00052** ↑	$\mathbf{1.1 \cdot 10^{-6}} \uparrow$	$\mathbf{1.5 \cdot 10^{-5}} \uparrow$	$\mathbf{5.7 \cdot 10^{-9}} \uparrow$	0.24	0.47	0.27	0.06	0.039
rdw → Asthma	0.064 ↑	$\mathbf{5.1 \cdot 10^{-6}} \uparrow$	0.55 ↑	**0.0042** ↑	0.15 ↑	$\mathbf{1.2 \cdot 10^{-6}} \uparrow$	0.51	0.023	0.13	0.1	0.046
ret → sle	0.53 ↓	**0.049** ↓	0.67 ↓	**0.024** ↓	**0.023** ↓	0.06 ↓	−0.31	0.7	0.04	−0.1	0.063
irf → sle	0.5 ↓	0.12 ↓	0.11 ↓	0.38 ↓	0.72 ↓	0.073 ↓	−0.37	0.85	0.07	−0.1	0.076
mch → ibd	0.87 ↓	0.096 ↓	0.42 ↓	0.47 ↓	0.1 ↓	0.052 ↓	0.07	0.61	0.04	−0.07	0.16
rdw → sle	0.056 ↑	$\mathbf{2.4 \cdot 10^{-10}} \uparrow$	**0.039** ↑	**0.00015** ↑	**0.0012** ↑	$\mathbf{1.7 \cdot 10^{-8}} \uparrow$	0.48	0.28	0.35	0.11	0.18
mch → sle	0.11 ↓	$\mathbf{4.5 \cdot 10^{-9}} \downarrow$	$\mathbf{4.4 \cdot 10^{-6}} \downarrow$	$\mathbf{6.4 \cdot 10^{-6}} \downarrow$	$\mathbf{4 \cdot 10^{-4}} \downarrow$	$\mathbf{1.5 \cdot 10^{-7}} \downarrow$	**0.6**	$5.2 \cdot 10^{-11}$	0.16	−0.06	0.19
ret → Asthma	0.4 ↓	0.11 ↓	0.45 ↓	0.36 ↓	0.72 ↑	0.2 ↓	−0.01	0.67	0.06	−0.04	0.29
ret → ra	0.12 ↓	**0.0034** ↓	0.082 ↑	**0.018** ↓	0.084 ↑	**0.00023** ↓	0.29	0.49	0.08	−0.03	0.29
hct → ra	0.98 ↓	0.88 ↓	0.94 ↑	**0.022** ↑	**0.025** ↑	0.61 ↓	0.17	0.64	0.03	−0.04	0.31
mch → Asthma	0.1 ↓	**0.01** ↓	0.24 ↓	0.067 ↓	0.14 ↓	**0.011** ↓	0.29	0.37	0.07	−0.03	0.35
ret → allg	1 ↓	0.15 ↓	0.8 ↓	0.68 ↓	0.38 ↑	0.38 ↓	−0.01	0.82	0.03	−0.02	0.42
mch → ra	0.12 ↓	$\mathbf{1.1 \cdot 10^{-6}} \downarrow$	$\mathbf{6.9 \cdot 10^{-6}} \downarrow$	$\mathbf{2 \cdot 10^{-4}} \downarrow$	$\mathbf{3.1 \cdot 10^{-8}} \downarrow$	$\mathbf{2.8 \cdot 10^{-6}} \downarrow$	0.43	0.54	0.12	0.02	0.48
hct → allg	0.8 ↑	0.93 ↑	0.45 ↑	0.17 ↑	0.13 ↑	0.64 ↑	−0.01	0.95	0.03	−0.02	0.5
irf → ibd	0.32 ↓	0.16 ↓	0.53 ↓	$\mathbf{1.2 \cdot 10^{-5}} \downarrow$	$\mathbf{2.6 \cdot 10^{-5}} \downarrow$	**0.0015** ↓	0.03	0.78	0.03	−0.03	0.52
hct → sle	0.71 ↓	0.86 ↓	0.67 ↑	**0.036** ↑	0.082 ↑	0.84 ↑	0.34	0.52	0.04	0.03	0.52
rdw → ibd	1 ↑	0.5 ↑	0.73 ↑	0.58 ↑	0.83 ↓	0.38 ↑	−0.19	0.67	0.03	0.03	0.55
irf → Asthma	0.49 ↓	0.16 ↓	0.7 ↓	0.12 ↓	0.34 ↓	0.2 ↓	0.17	0.69	0.05	0.02	0.64
ret → ibd	1 ↑	0.86 ↑	0.37 ↓	0.05 ↑	0.14 ↓	0.41 ↑	−0.04	0.96	0.03	0.02	0.68
irf → allg	0.36 ↓	**0.023** ↓	0.17 ↓	**0.0095** ↓	**0.016** ↓	**0.038** ↓	0.17	0.93	0.06	0.01	0.68
rdw → allg	1 ↑	0.86 ↓	0.19 ↓	0.62 ↓	0.77 ↓	0.85 ↓	0.12	0.7	0.03	0.01	0.81
mch → allg	0.84 ↓	0.58 ↓	0.88 ↑	0.3 ↓	0.85 ↓	0.38 ↓	0.24	0.7	0.03	0	0.84
irf → ra	1 ↓	0.79 ↓	0.91 ↑	0.42 ↓	0.24 ↓	0.67 ↓	0.01	0.88	0.03	0	0.95
Platelet Traits											
pdw → ibd	1 ↓	0.42 ↑	0.97 ↑	**0.008** ↑	**0.015** ↑	0.055 ↑	−0.33	0.76	0.03	0.09	0.06
pdw → sle	0.4 ↑	0.45 ↑	0.18 ↓	0.54 ↑	0.53 ↓	0.42 ↑	0.03	0.99	0.05	0.12	0.065
pdw → allg	0.19 ↓	**0.00011** ↓	0.28 ↓	**0.00095** ↓	**0.027** ↓	**0.00016** ↓	0.11	0.66	0.21	−0.05	0.072
mpv → sle	0.54 ↑	0.77 ↑	0.8 ↑	0.76 ↑	0.63 ↑	0.58 ↑	0.02	0.49	0.04	0.06	0.14
plt → ra	1 ↑	0.91 ↑	0.37 ↓	**0.00031** ↓	$\mathbf{6.1 \cdot 10^{-5}} \downarrow$	0.7 ↓	−0.18	0.44	0.03	0.03	0.23
plt → Asthma	1 ↓	0.61 ↑	0.82 ↓	0.59 ↑	0.6 ↑	0.55 ↑	0	0.77	0.03	0.05	0.24
mpv → Asthma	1 ↓	0.63 ↓	0.53 ↓	0.99 ↓	0.79 ↓	0.68 ↓	−0.04	0.67	0.03	−0.05	0.25
plt → sle	1 ↓	0.35 ↑	0.31 ↑	**0.023** ↑	0.12 ↑	0.85 ↑	0.05	0.69	0.03	−0.04	0.33
mpv → allg	0.18 ↓	0.071 ↓	0.34 ↓	**0.029** ↓	**0.0079** ↓	0.088 ↓	−0.04	0.88	0.07	−0.02	0.42
pdw → ra	1 ↓	0.6 ↓	0.17 ↓	**0.0048** ↓	**0.0018** ↓	0.5 ↓	0.08	0.81	0.03	−0.02	0.55
pdw → Asthma	0.29 ↓	**0.015** ↓	0.057 ↓	0.07 ↓	0.12 ↓	**0.0085** ↓	0.09	0.97	0.05	−0.03	0.59
plt → ibd	0.8 ↑	0.75 ↑	0.77 ↑	0.93 ↓	0.67 ↑	0.49 ↑	−0.15	0.8	0.03	0.03	0.62
mpv → ibd	0.63 ↑	0.39 ↑	0.66 ↓	0.4 ↑	0.49 ↑	0.16 ↑	−0.08	0.79	0.03	0.03	0.63
mpv → ra	0.99 ↑	0.46 ↓	0.86 ↓	**0.05** ↓	**0.0039** ↓	0.82 ↓	0.1	0.81	0.03	0.01	0.76
plt → allg	1 ↓	0.22 ↓	0.075 ↓	0.56 ↓	0.61 ↓	0.38 ↓	−0.06	0.92	0.03	0	0.89

Supplementary Table 7: Summary of results for blood cell traits and immune-mediated diseases grouped by blood cell category. Columns 2-7 give the p-value for each MR method. Values are bold if $p < 0.05$. Arrows indicate the sign of the corresponding effect estimate. LCV GCP and LCV pval give estimated GCP from LCV and p-value testing that GCP=0. Values are bold if estimated GCP> 0.6. The "CAUSE q" column gives the posterior median of q in the CAUSE sharing model. GC and GC pval give the genetic correlation and p-value testing that genetic correlation is zero estimated by LD score regression. In each section, pairs are ordered by increasing genetic correlation p-value.

SN1 Empirical Parameter Estimation

Analysis with CAUSE is comprised of two main steps (see Extended Data Figure 4). The first step is to estimate nuisance parameters ρ, which accounts for overlap in the two GWAS samples and the parameters defining the empirical joint prior distribution for $\beta_{M,j}$ and θ_j. We do this in two sub-steps. First, we select a panel of candidate covariance matrices $\Sigma_0, \ldots, \Sigma_K$. Second, we fix $\gamma = \eta = 0$ and compute the maximum a posteriori (MAP) values of ρ and $\pi_0, \ldots, \pi_K$.

The set of candidate covariance matrices should be large enough that a flexible joint distribution can be fit for $\beta_{M,j}$ and θ_j, but not so large that evaluating the likelihood becomes burdensome. To choose this set, we first apply the Adaptive Shrinkage (ASH) method proposed by Stephens [1] to estimate the distributions of $\boldsymbol{\beta}_M$ and $\boldsymbol{\beta}_Y$ separately. Briefly, given a set of summary statistics for a single study, ASH estimates a sparse unimodal distribution for the marginal effects. This distribution is flexible and parameterized as a mixture of univariate normal distributions centered at 0. ASH uses the model

$$\beta_{\cdot,j} | \varpi_0, \ldots, \varpi_L, \varsigma_0, \ldots, \varsigma_L \sim \sum_{l=0}^{L} \varpi_l N(0, \varsigma_l^2),$$

where $\varsigma_0, \ldots, \varsigma_L$ are a fixed grid of variances with $\varsigma_0 = 0$. ASH estimates the mixing proportions $\varpi_0, \ldots, \varpi_L$ using a prior on $\boldsymbol{\varpi}$ that encourages more weight to be given to ϖ_0, the proportion of effects equal to 0. Despite starting with a large number of candidate variances, ASH solutions tend to place most of the weight on only a few values. The resulting solution is sparse (most of the estimated effects are 0) and parsimonious (there are few components in the model with non-zero mixing proportion).

Let $\varsigma_{M,0}, \ldots, \varsigma_{M,l_M}$ and $\varsigma_{Y,0}, \ldots, \varsigma_{Y,l_Y}$ be the set of variances with non-zero weight in the ASH estimates for traits M and Y respectively. Because ASH encourages sparsity, in all cases $\varsigma_{M,0} = \varsigma_{L,0} = 0$. We construct the panel of candidate 2×2 covariance matrices by taking all pairs of these variances as diagonal elements and setting the off diagonal elements to be 0. Thus if $l_M = 4$ and $l_Y = 3$, our method produces a set of $(4+1)(3+1) = 20$ candidate covariance matrices.

In the second step, we fix $\gamma = \eta = 0$ and calculate the MAP values of ρ and $\pi_0, \ldots, \pi_K$. We use a Dirichlet$(10, 1, \ldots, 1)$ prior on $\pi_0, \ldots, \pi_K$ with π_0 corresponding to the covariance matrix of all zeros. This prior is the same prior used by default in ASH and encourages a sparse solution, however the weights may be adjusted by the user in the CAUSE software. We use a prior on $z = \tanh^{-1}(\rho)$ of $z \sim N(0, 0.25)$, which is a weak prior encouraging ρ to be close to zero. To calculate the MAP estimate, we use coordinate descent, alternating between optimization of ρ with $\boldsymbol{\pi}$ fixed and optimization of $\boldsymbol{\pi}$ with ρ fixed. As observed by Stephens [1] and others, maximization in $\boldsymbol{\pi}$ is a convex optimization problem that can be completed quickly. In practice, we find that convergence is usually reached within five iterations.

SN2 Prior Distributions for γ and η

In most cases, little prior information is available about the size of the causal or confounding effect. Differences in variable scaling and covariate adjustment across GWAS may make it difficult to predict the magnitude of these effects. Fortunately, we find that CAUSE results are robust to a wide range in prior distributions for these parameters. We require that the same prior be used for γ and η. If this is not the case false positives can arise when the true shared factor effect is better represented by the prior on γ than the prior on η. We use normal prior distributions with mean 0 and variance $\sigma^2_{\gamma\eta}$ for γ and η.

To assess the robustness of CAUSE to changes in $\sigma^2_{\gamma\eta}$, we analyze data simulated from three scenarios using a range of values for $\sigma^2_{\gamma\eta}$. The three scenarios are 1) a setting with a causal effect ($\gamma = \sqrt{0.05}$, $\eta = 0$, $q = 0$), 2) a setting with no causal effect but some correlated pleiotropy ($\gamma = 0$, $\eta = \sqrt{0.05}$, $q = 0.3$), and 3) a setting with neither a casual effect or correlated pleiotropy ($\gamma = 0$, $\eta = 0$, $q = 0$). We analyze simulated data using three values of $\sigma^2_{\gamma\eta}$. These are chosen so that $\sqrt{0.05}$, is at the 80th, 65th, and 51st quantile of the $N(0, \sigma^2_{\gamma\eta})$ distribution, giving small, medium, and large values of $\sigma_{\gamma\eta}$ respectively. All simulations are conducted with sample sizes $N_M = N_Y = 40,000$, the high power setting used in other simulations.

We compare p-values and posterior median estimates for γ, η, and q under the causal and sharing models across different values of $\sigma^2_{\gamma\eta}$. The Pearson correlation in p-values was greater than 0.95 for all settings and

between all pairs of values of $\sigma^2_{\gamma\eta}$. The correlation in posterior medians was higher than 0.8 for all parameters and all settings except for estimates of q in setting 1 under the causal model. These had a somewhat lower correlation (minimum correlation 0.51). However, in all cases the posterior median of q in the causal model was very low – less than 0.05. These results demonstrate that very similar inference can be obtained using a wide range of prior distributions for γ and η.

By default, $\sigma^2_{\gamma\eta}$ is chosen using the data. We use a set of variants with trait M p-value $< 10^{-3}$ and compute $\hat{\gamma}_{max} = \max|\frac{\hat{\beta}_2}{\hat{\beta}_1}|$. This is the largest magnitude of causal estimate that could be achieved using only one variant. We then choose $\sigma^2_{\gamma\eta}$ so that the prior probability that γ or η has magnitude larger than $\hat{\gamma}_{max}$ is 0.05.

SN3 Approximating posteriors of γ, η, and q

We use an adaptive variation of a simple grid posterior approximation[2] to approximate the joint posterior distribution of γ, η, and q. To compute this approximation, we begin with initial bounds on γ and η of $(-1, 1)$. These will be adaptively expanded as needed. The bounds on q are fixed at $(0, 1)$.

The approximation proceeds as follows:

1. The domain of (γ, η, q) is divided into a coarse set of cubes. The approximate posterior probability of each cube is computed by approximating the likelihood within the cube as constant and equal to the likelihood at the midpoint of the cube.

2. After the first rough approximation, the bounds of γ and η are expanded so that less than 0.001 of the posterior mass falls in the cubes closest to the boundary. These bounds are then fixed.

3. The grid is then iteratively refined until no cube contains more than 1% of the posterior density. At each iteration, all cubes containing more than this are subdivided into nine smaller cubes and the posterior is re-estimated.

SN4 Effects of LD

In this section we explore the question of whether the CAUSE model and likelihood are valid for variants in LD. For simplicity, in this section only, we assume that the GWAS for traits M and Y have no overlapping samples and have the same LD structure. CAUSE relies on two assumptions. The first is that the joint likelihood of all pairs of summary statistics can be factorized into the product of the likelihood for each variant. Variants in LD are not independent, however, by pruning variants so that the set is nearly independent, we can approximate this condition. The second assumption is that

$$\mathrm{Cov}(\hat{\beta}_{Y,j}, \hat{\beta}_{M,j} | Z_j, \gamma, \eta, \beta_{M,j}) = (\gamma + Z_j\eta)\mathrm{Var}(\beta_{M,j}) = (\gamma + Z_j\eta)\left(\mathrm{Var}(\hat{\beta}_{M,j}) - s^2_{M,j}\right). \quad (1)$$

Without LD, this is a consequence of Methods Equation 4 and the assumption that $\hat{\beta}_{M,j}$ and $\hat{\beta}_{Y,j}$ are unbiased estimates of $\beta_{M,j}$ and $\beta_{Y,j}$. In the presence of LD, the expectation of $\hat{\beta}_{\cdot,j}$ ($\cdot$ may be M or Y) is not $\beta_{\cdot,j}$, but a combination of $\beta_{\cdot,j}$ and a contribution from each variant in LD with variant j. Using results from [3],

$$E[\hat{\beta}_{\cdot,j}] = \sum_k \frac{r_{jk}s_{\cdot,j}}{s_{\cdot,k}}\beta_{\cdot,k} \equiv \beta^*_{\cdot,j}, \quad (2)$$

where r_{jk} is the correlation between variant j and variant k. We refer to $\beta^*_{\cdot,j}$ as the *LD-transformed effects*. Note that if allele frequencies are the same in the two GWAS populations then $s_{M,j} = cs_{Y,j}$ where c is a constant depending on sample size. Thus

$$\frac{r_{jk}s_{M,j}}{s_{M,k}} = \frac{r_{jk}s_{Y,j}}{s_{Y,k}} \equiv h_{j,k}. \quad (3)$$

We now derive $\text{Cov}(\hat{\beta}_{Y,j}, \hat{\beta}_{M,j}|\mathbf{Z}, \gamma, \eta, \boldsymbol{\beta}_M)$ in the presence of LD, where $\mathbf{Z}$ is a vector with jth element equal to Z_j and $\boldsymbol{\beta}_M$ is a vector with jth element equal to $\beta_{M,j}$. We assume that direct effects are independent so $\text{Cov}(\beta_{M,j}, \beta_{M,k}) = 0$ if $j \neq k$ and $\text{Cov}(\beta_{M,j}, \theta_k) = 0$ for all j and k. We also assume that $\hat{\beta}_{M,j}$ and $\hat{\beta}_{Y,j}$ are independent conditional on $\beta^*_{M,j}$ and $\beta^*_{Y,j}$. With these assumptions,

$$\begin{aligned}\text{Cov}\left(\hat{\beta}_{Y,j}, \hat{\beta}_{M,j}|\mathbf{Z}, \gamma, \eta, \boldsymbol{\beta}_M\right) =& \text{Cov}\left(\sum_k h_{j,k}\beta_{Y,k}, \sum_k h_{j,k}\beta_{M,k}\middle|\mathbf{Z}, \gamma, \eta\right) \\ =& \sum_k h^2_{j,k}\text{Cov}\left(\beta_{Y,k}, \beta_{M,k}|Z_k, \gamma, \eta\right) \\ =& \sum_k h^2_{j,k}\left(\gamma + Z_k\eta\right)\text{Var}\left(\beta_{M,k}\right), \end{aligned} \tag{4}$$

and

$$\text{Var}(\hat{\beta}_{M,j}|\mathbf{Z}) = \text{Var}(\beta^*_{M,j}) + s^2_{M,j} = \sum_k h^2_{j,k}\text{Var}(\beta_{M,k}) + s^2_{M,j}. \tag{5}$$

Suppose that the variant correlation structure can be decomposed into independent LD blocks and that there is at most one M effect variant per block. If this variant has index k' then, for any variant in the block

$$\begin{aligned}\text{Cov}\left(\hat{\beta}_{Y,j}, \hat{\beta}_{M,j}\middle|\mathbf{Z}, \gamma, \eta, \boldsymbol{\beta}_M\right) =& h^2_{j,k'}\left(\gamma + Z_{k'}\eta\right)\text{Var}(\beta_{M,k'}) \\ =& \left(\gamma + Z_{k'}\eta\right)\left(\text{Var}(\hat{\beta}_{M,j}) - s^2_{M,j}\right). \end{aligned} \tag{6}$$

This means that, if $Z_{k'} = 1$, then variant k' induces correlation between effect estimates for other variants in the block, even when $\gamma = 0$. However, if we use only one variant per LD block to estimate parameters then there is no distortion in the proportion of correlated variants. If $\gamma = 0$, then the proportion of variants with correlated effect estimates will be equal q, the proportion of true effect variants acting through U. In this case, CAUSE will not have an increased false positive rate but may have lower power if the variants selected to use in estimation are far from the true causal variants. To maximize power, we prune for LD prioritizing variants with low trait M p-values.

More generally, a block may contain multiple causal variants for M, with some acting on U (correlated pleiotropic variants) and others not. Equation 4 implies that a correlated pleiotropic variant in LD with variant j will induce non-zero correlation between $\hat{\beta}_{Y,j}$ and $\hat{\beta}_{M,j}$ even if $\gamma = 0$ and $Z_j = 0$. The presence of non-shared variants in a block reduces the correlation, but will not eliminate it. If M is highly polygenic and q is large, the proportion of blocks containing at least one shared variant may be much larger than the true value of q. In this case, LD can create an impression that a larger proportion of variants have correlated effects, which can lead to inflated estimates of q and higher false positive rates using CAUSE. We assume that these settings are rare. However, our simulations are conducted under moderately dense conditions using 1000 effect variants and only 1,170 LD blocks, demonstrating that CAUSE still performs well even under somewhat unfavorable conditions.

SN5 Connections with LCV

O'Connor and Price [4] propose an approach to identifying pairs of traits with causal relationships that uses a latent causal variable (LCV) model. This model is similar to the CAUSE model with $\gamma = 0$. Rather than modeling both correlated pleiotropy and a causal effect, the LCV model includes only a shared factor (U in the CAUSE model) and estimates the "genetic causality proportion" (GCP). The GCP reflects the relative proportions of heritability of each trait that are explained by a shared factor. A causal effect (with no additional correlated pleiotropy from other sources) is equivalent to a model in which all variants act through a shared factor. In this case, the GCP is equal to 1 or -1 depending on the direction of the effect. LCV estimates the GCP and computes a test statistic testing whether GCP$= 0$. Models with non-zero GCP are not necessarily causal and this p-value is not intended as a test of causality. O'Connor and Price [4] use an estimated GCP larger than 0.6 to suggest a possible causal relationship.

Because the LCV model is similar to the CAUSE model with $\gamma = 0$, we can derive an expression for GCP in terms of CAUSE parameters under this condition. The LCV model uses two parameters q_M^{lcv} and q_Y^{lcv}, the square root of the proportions of trait M and Y heritability explained by the shared factor. Here we use the same trait M and Y notation used in our discussion of CAUSE. In terms of CAUSE parameters these are

$$q_M^{lcv} = \sqrt{q} \tag{7}$$

$$q_Y^{lcv} = \frac{\sqrt{q}\eta h_M}{h_Y} \tag{8}$$

The GCP is then defined as

$$GCP = \frac{\log|q_Y^{lcv}| - \log|q_M^{lcv}|}{\log|q_M^{lcv}| + \log|q_Y^{lcv}|} = \frac{\log(\eta h_M/h_Y)}{\log(q\eta h_M/h_Y)}. \tag{9}$$

From this formula, we see that GCP is non-zero if η and q are both non-zero. For example, if the heritability of the two traits is equal, $q = 0.3$ and $\eta = \sqrt{0.05}$ then GCP$= 0.55$.

SN6 Additional Simulation Results

SN6.1 Effects of the prior on q

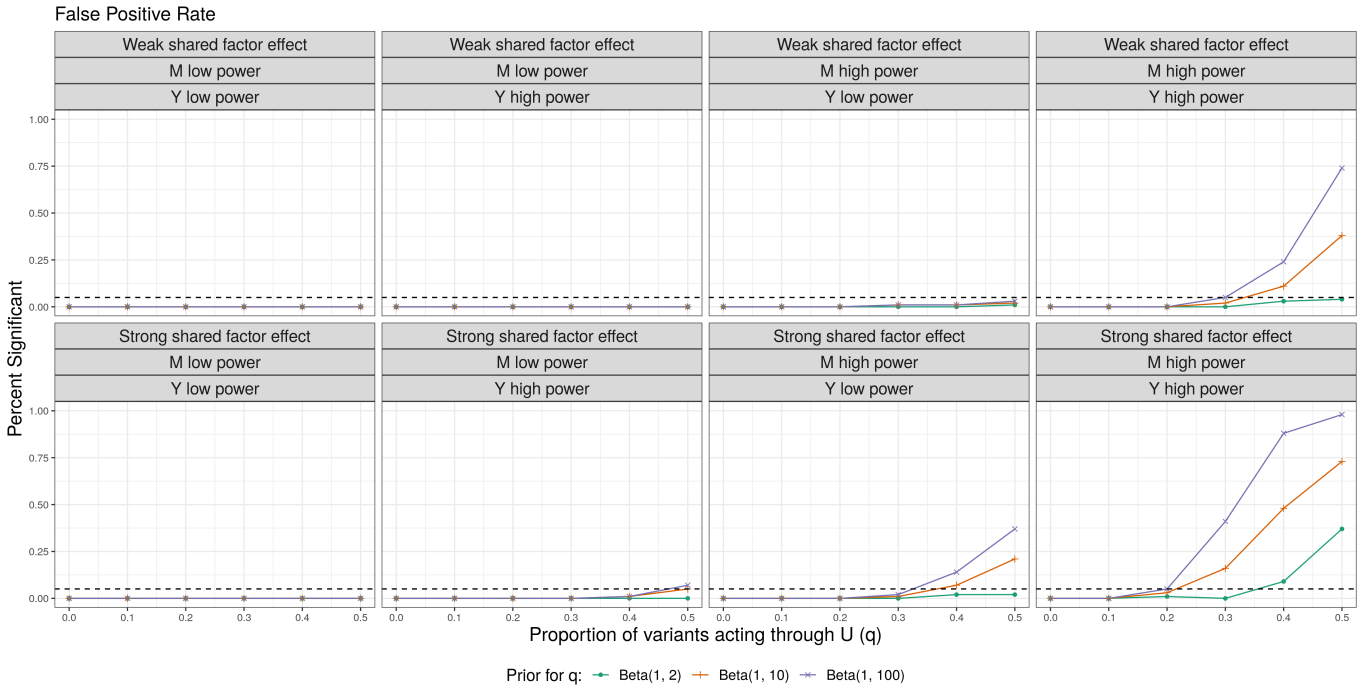
The choice of prior on q can affect the power and robustness of CAUSE. The default choice of a Beta$(1, 10)$ prior is used in the main Results. Here we compare simulation performance using Beta$(1, 2)$, Beta$(1, 10)$, and Beta$(1, 100)$ distributions. The Beta$(1, 2)$ distribution is quite lenient, placing 25% of the prior mass on values above 0.5. The Beta$(1, 100)$ distribution is sharply peaked close to zero, placing 95% of the prior mass below 0.03. In order for the CAUSE model to be identifiable, the prior on q must be asymmetric, placing more weight on values less than 0.5. Figure SN1 shows results for simulations described in the main Results (analogous to main text Figure 2). As we would expect, CAUSE with the Beta$(1, 100)$ prior has high false positive rate when the true proportion of correlated pleiotropy is large. CAUSE with the Beta$(1, 2)$ prior has fewer false positives for large values of q but also reduced power. We found the Beta$(1, 10)$ prior to be an attractive compromise because its power is only slightly worse than power obtained using the Beta$(1, 100)$ prior but the false positive rate is substantially improved. CAUSE shows the same performance in ROC curves for the three prior choices (Figure SN1c). One consequence of these results is that using a more permissive prior for q may be a better choice for higher powered studies. Results of CAUSE for pairs of GWAS traits using different priors can be seen online at the CAUSE website (see URLs).

SN6.2 Parameter estimation

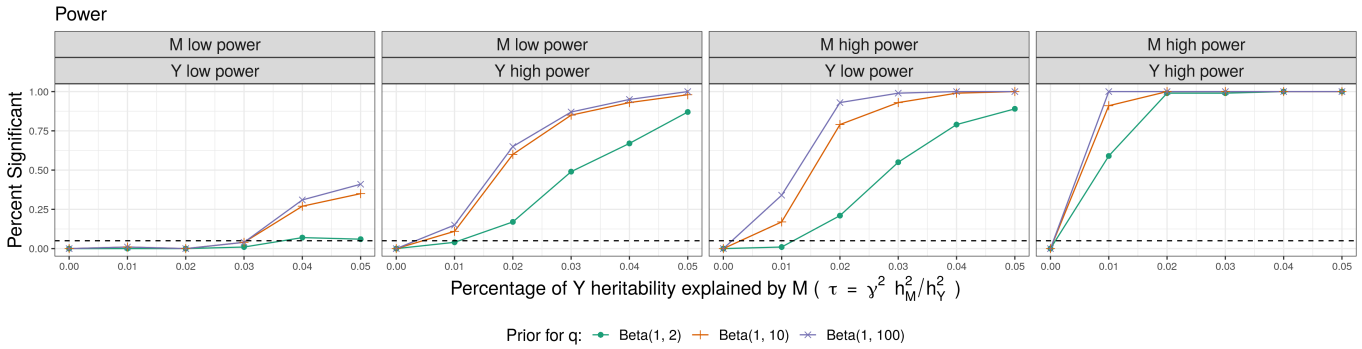
In the main Results, we focus on CAUSE's performance in terms of power to detect causal effects and false discovery rate. CAUSE also produces point estimates for parameters γ, η, and q as medians of marginal posterior distributions from either the sharing or causal model. Figure SN2 compares point estimation of the causal effect, γ, in simulations with a causal effect and no correlated pleiotropy using CAUSE and other methods. All methods display some shrinkage. For methods besides CAUSE, shrinkage is attributed to imperfect ascertainment of instruments. In every simulated data set, there is some chance of including variants that are genome-wide significant by chance and are not tagging a causal trait M variant. These variants are uncorrelated with Y and lead to underestimation of the causal effect. As the power of the trait M GWAS increases, shrinkage diminishes because there are more strong M effect variants meeting the inclusion criteria.

Some of the shrinkage in the CAUSE estimator is also due to uncertainty about which variants are M effect variants. CAUSE uses all variants, and the strength of each variant's affect on the estimate is proportionate to the strength of its association with M. Variants that do not tag an M effect variant but have strong associations with M by chance push the causal estimate downward. The CAUSE estimate is also shrunk by the prior on γ which is a wide normal distribution centered at zero. The prior on q does not affect the point estimate of γ in these experiments but does influence the width of the posterior distribution for γ, with narrower posteriors corresponding to stronger priors on q (Figure SN2(b)).

(a) False Positive Rate



(b) Power



(c) False Positive Rate vs Power

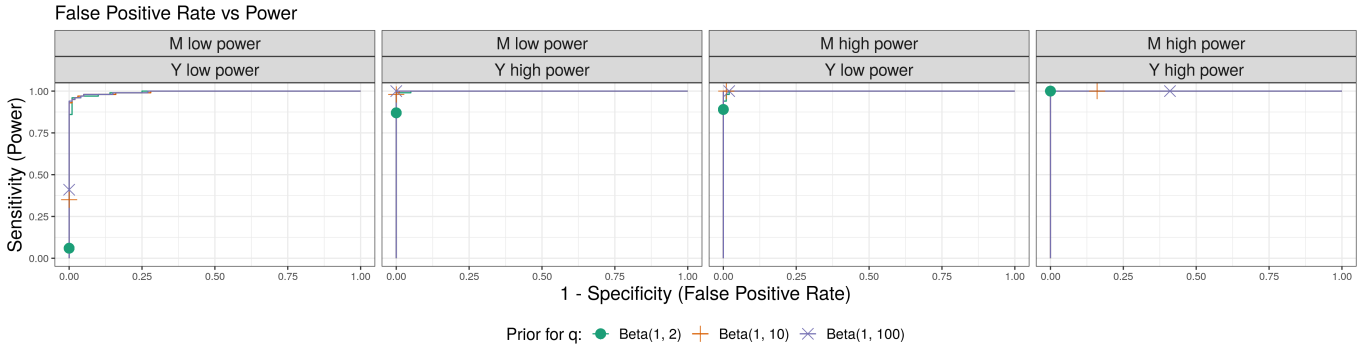


Figure SN1: Performance of CAUSE using different priors for q simulated data. (a) False positive rate averaged over 100 simulated data sets in settings with no causal effect and a proportion of correlated pleiotropic variants (q) ranging from 0 to 50%. (b) Power averaged over 100 simulated data sets in settings with a causal effect and no shared factor. (c) Comparison of false positive-power trade-off. We compare the power when $\gamma = \sqrt{0.05}$ and there is no shared factor to the false positive rate when there is no causal effect, but a proportion $q = 0.3$ of variants act through a shared factor with effect $\eta = \sqrt{0.05}$ on Y. There are 100 simulations each in the causal and non-causal scenarios. Curves are created by varying the significance threshold. Points indicate the power and false positive rate achieved at a threshold of $p \leq 0.05$.

CAUSE obtains a smaller mean squared error (MSE) than Egger regression and the modal estimator for nearly every parameter value. MSE for Egger regression is not shown in Figure SN2c because it is much larger than the MSE for any other method and including it in the plot masks differences between other methods. CAUSE's MSE is smaller or comparable to other methods for small causal effects and grows for larger effects, reflecting its shrinkage.

We find that accurately estimating q and η is more challenging than estimating of γ. Posterior distributions for q and η are strongly dependent and are affected by the prior distribution of q. In some cases, posterior distributions may be multimodal, making the posterior median a poor summary. Figure SN3 shows average posterior medians for q and η in simulations with correlated pleiotropy and no causal effect. As expected, posterior medians of q are shrunk more closely to zero when the prior places more weight on small values. This leads to wide credible intervals for η because there is little information about this parameter if q is small. Using the Beta$(1, 2)$ prior for q we find that credible intervals for η are slightly narrower and that the posterior median is less shrunk relative to the true value but that credible intervals for q are quite wide. We are only able to obtain accurate estimates of q and η in the highest power scenarios.

SN6.3 Causal effects with shared factors

We explore simulation scenarios with both a causal effect and correlated pleiotropy. We focus primarily on settings with antagonistic correlated pleiotropy (correlation in the opposite direction from the causal effect), since we expect these scenarios to be the most difficult.

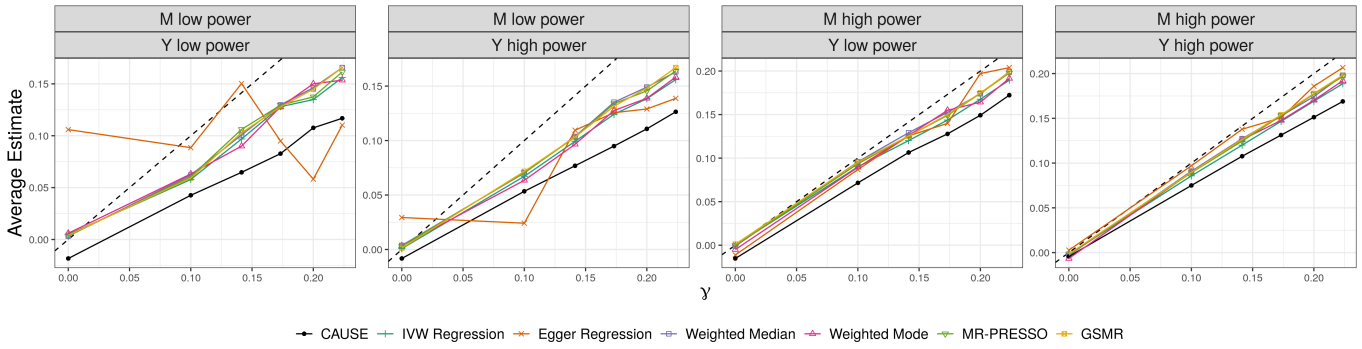
We first examine how a shared factor affects the power of each method. We simulate data with a causal of 0.2 and a proportion of variants, $q = 0.1$ or 0.3 acting through a shared factor with effect η ranging from -0.4 to 0.1. The power of CAUSE and other methods is shown in Figure SN4. A detection is only counted if the sign of the point estimate is positive. We did not find that erroneously detecting negative causal effects was a problem for any method (Egger regression detected one across all simulations and no other methods detected any). We find that CAUSE is able to maintain power when the shared factor effect has a smaller magnitude than the causal effect, but that when the shared factor effect is equal to the causal effect or larger and in the opposite direction, the power of CAUSE decreases. For larger antagonistic effects, correlation from the shared factor cancels out the correlation from the causal effect and the pattern of effect estimates becomes similar to the pattern created by a shared factor only.

Next we compare the ability of CAUSE and other methods to discriminate a scenario with a causal effect and a shared factor from one with only a shared factor. The LCV GCP estimate is included in these comparisons. In each comparison, the non-null scenario is identical to the null scenario but with the addition of a causal effect. We consider shared factors accounting for 10% and 30% of trait M variants and causal effects of $\gamma = -1 * \eta$ or $\gamma = -2 * \eta$. The shared factor effect η is the same in all comparisons. Curves showing the trade-off between false and true positives are shown in Figure SN5. We find that, although CAUSE has lower power when there is an antagonistic shared factor, it is able to discriminate causal and non-causal scenarios at least as well as other methods.

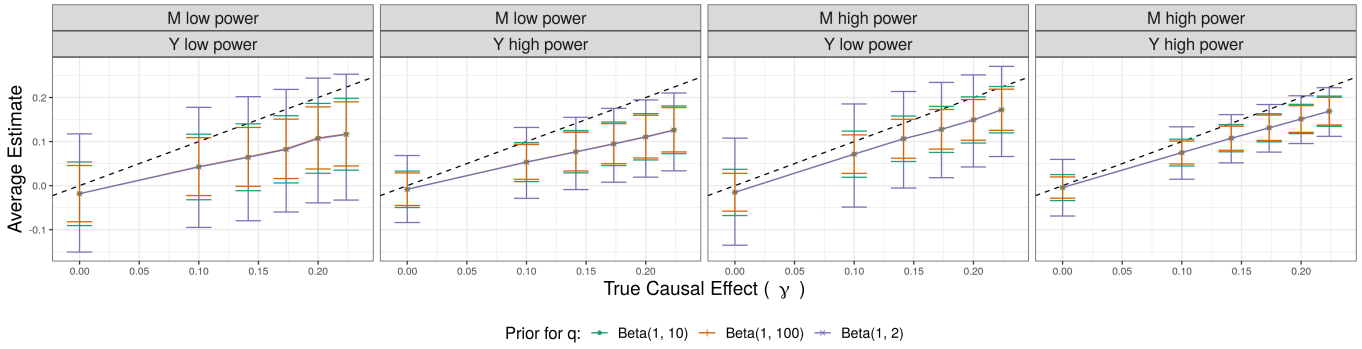
SN6.4 Asymptotic behavior

In the main simulation results, we find that CAUSE has higher false positive rate for large q when the trait M GWAS has high power than when the trait M GWAS has low power. We expect that with a large enough sample size, CAUSE's false positive rate should drop to zero. To verify this expectation, we conducted a small set of simulations with very high powered GWAS for both trait M and trait Y. Figure SN6 shows results using for three different levels of correlated pleiotropy ($q = 0.1$, 0.3, and 0.5). We find that, consistent with our expectations, with very high powered GWAS, CAUSE is always able to identify the correct model. Figure SN6 includes results for data simulated using the LD structure used in other simulations (left) and data simulated with no LD, showing that some false positives obtained by CAUSE are due to the functional inflation of q that results from variants in LD. Although the power of these simulated studies is beyond what would be expected from current GWAS sample sizes, these explorations verify that CAUSE is behaving as expected and suggest that, as GWAS sample sizes continue to grow, it will be possible to obtain more accurate MR results.

(a)



(b)



(c)

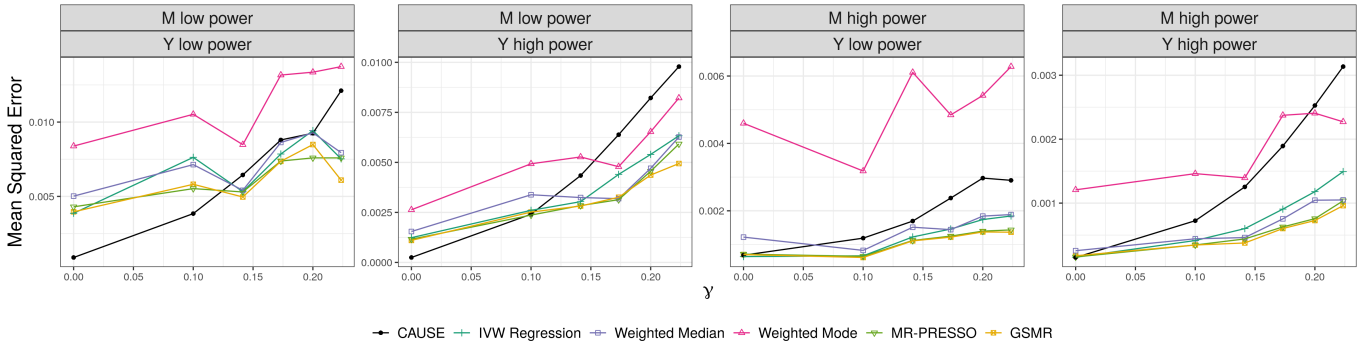
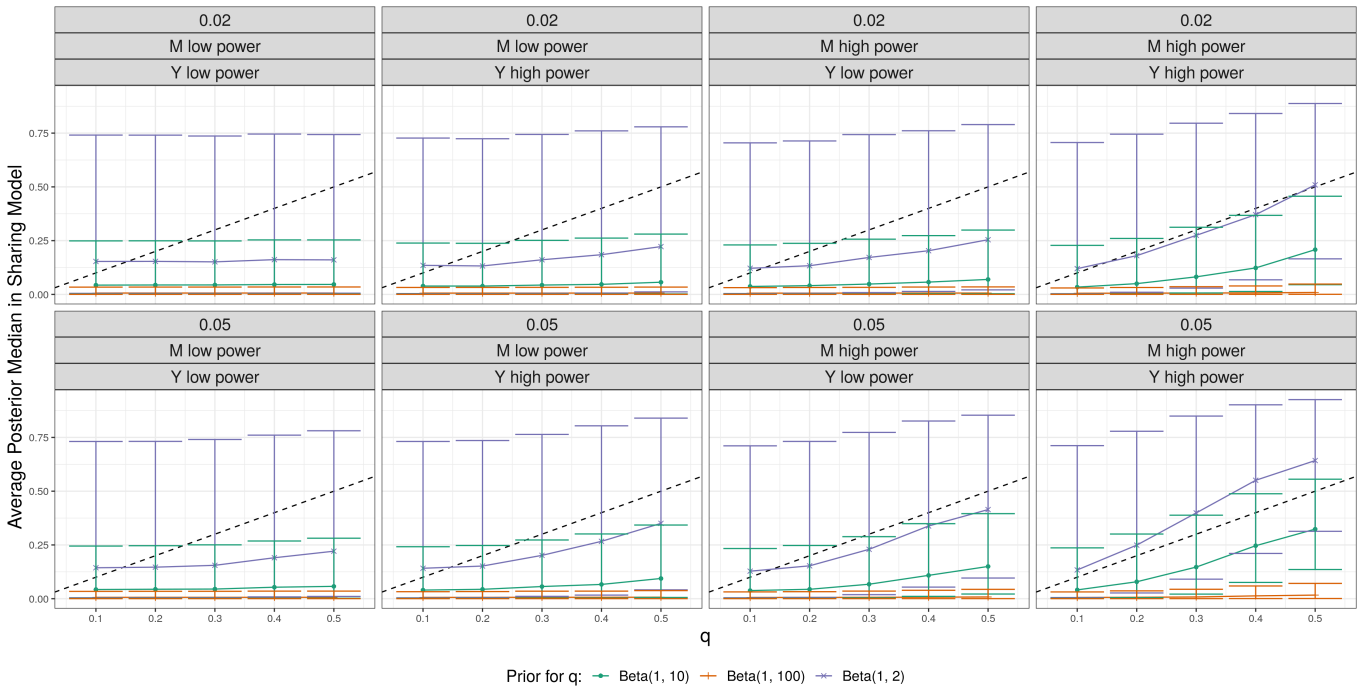


Figure SN2: Point estimation of γ for simulated data with a causal effect and no correlated pleiotropy. (a) Comparing CAUSE to other MR methods, points indicate the average point estimate over 100 simulations. CAUSE is run with the default Beta$(1, 10)$ prior for q. The dotted black line shows the true parameter value. (b) Comparing different priors for q. Error bars show average upper and lower extents of 95% credible intervals. CAUSE obtains the same point estimate using different priors but the posterior distribution is more peaked using a stronger prior on q. (c) Comparing mean squared error across methods. Egger regression is omitted because it obtains an MSE much larger than the other methods. CAUSE results using the default prior are shown. Note that the vertical axes in (c) are not the same across panels.

(a) Estimation of q



(b) Estimation of η

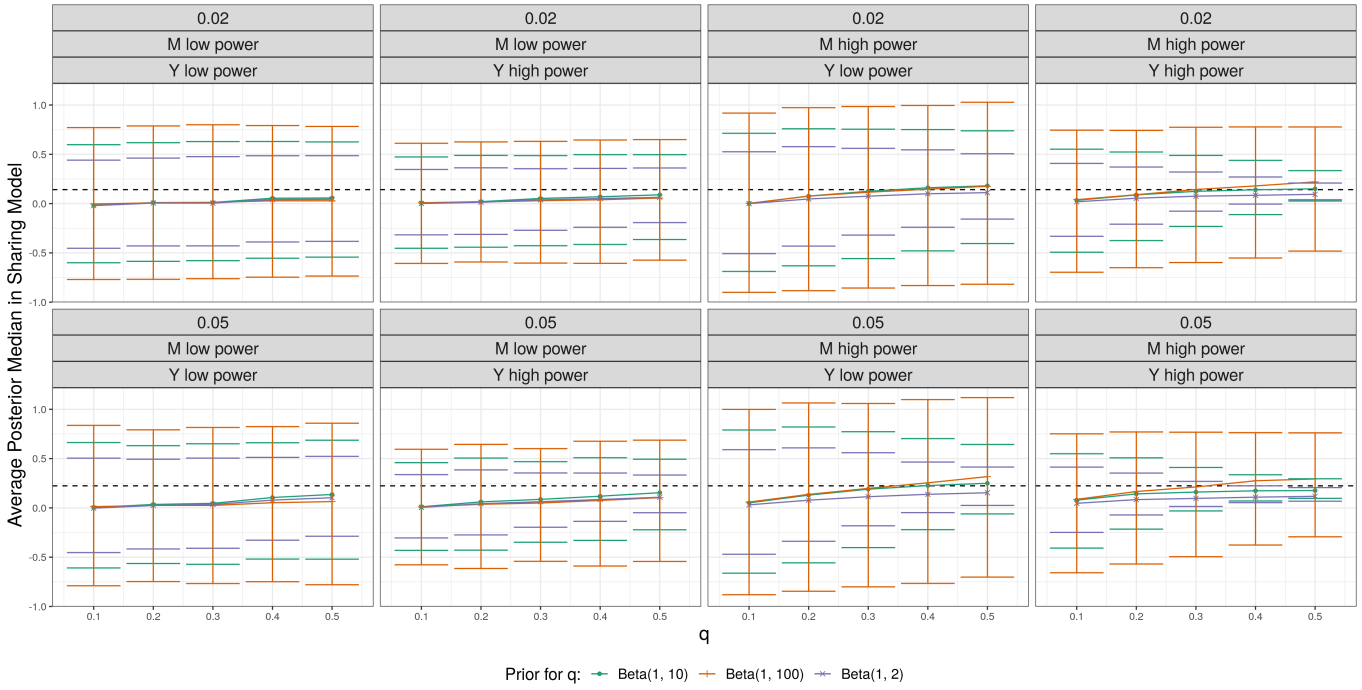


Figure SN3: Estimation of q and η from the sharing model in simulations with no causal effect. Points show the average posterior median over 100 simulations. Upper and lower ends of vertical bars indicate the average upper and lower boundary of 95% credible intervals. Dotted lines show the true value of the parameter with estimates shown, either q (a) or η (b).

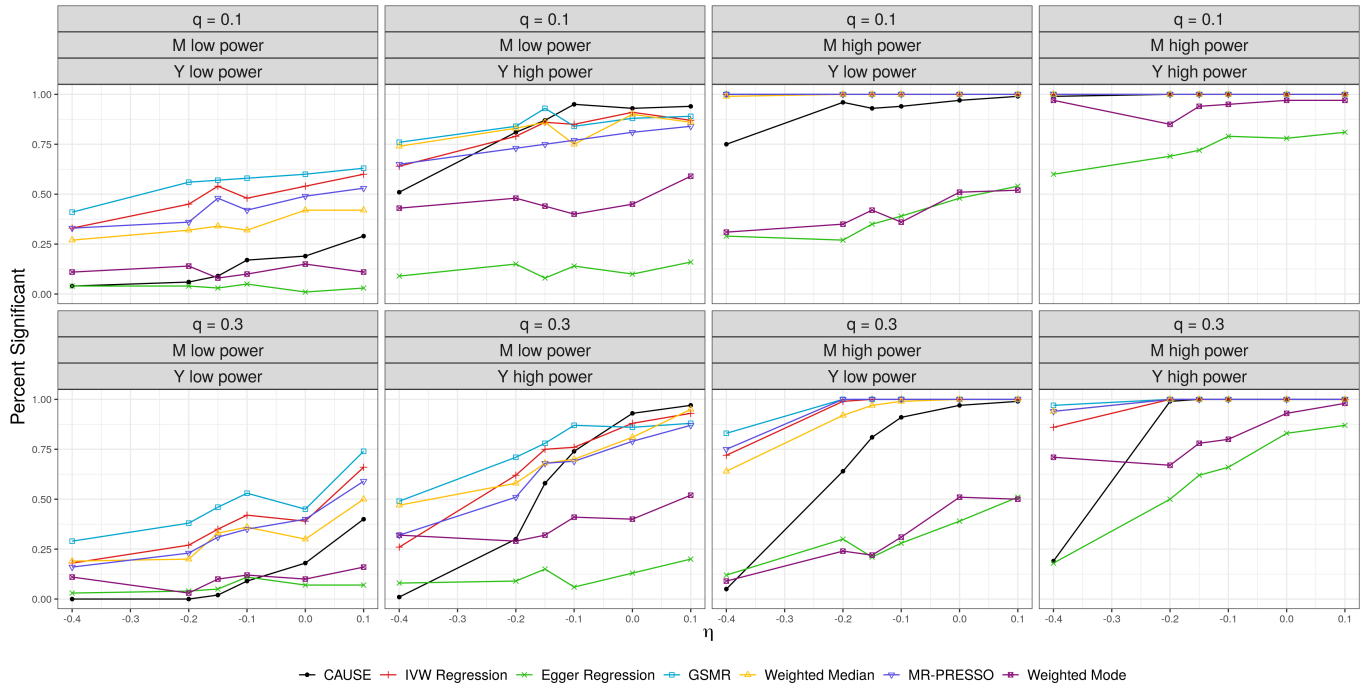


Figure SN4: Power comparison in simulations with both a causal effect and correlated pleiotropy. In all simulations, the causal effect is 0.2. Either 10% (top row) or 30% (bottom row) of variants display correlated pleiotropy with effect size given on the horizontal axis. Points indicate the proportion on simulations detected to have a positive causal effect by each method.

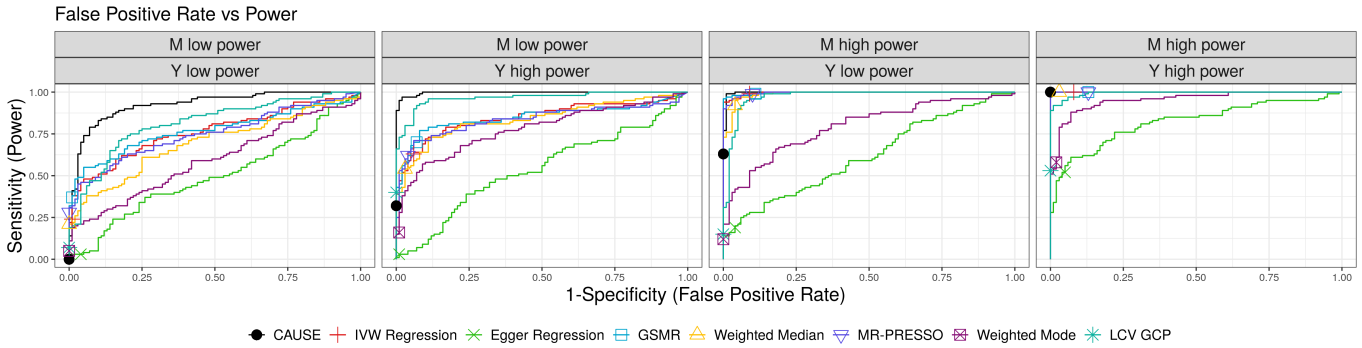
SN7 Existing Information About Pairs of GWAS Traits

We provide brief summaries of literature about the relationships of the 12 risk factors and four diseases examined in the main Results. We have classified the relationship of each pair as considered causal (C), supported by literature (S), unknown (U), implausible and unsupported by literature (I), or considered non-causal (N). We classify a trait pair as considered causal if there are clinical trial or similar results supporting a causal effect and the effect is generally accepted in the literature. We classify pairs as supported by literature if there are strong molecular or physiological hypotheses supporting the effect and observational correlations. We classify pairs as implausible if there is no suggestion of a causal effect in the literature there is no genetic correlation. Effects of HDL on CAD and stroke are classified as considered to be non-causal, discussed below. All remaining trait pairs are classified as unknown or ambiguous. These include pairs that are correlated observationally but clinical trial or molecular evidence does not support a causal effect and pairs that are subject to ongoing debate. Below we summarize the literature used to make each classification, grouped by risk factor. At the end of the summary for each risk factor we list in parenthesis our classification of its relationship with CAD, stroke, T2D, and asthma in that order.

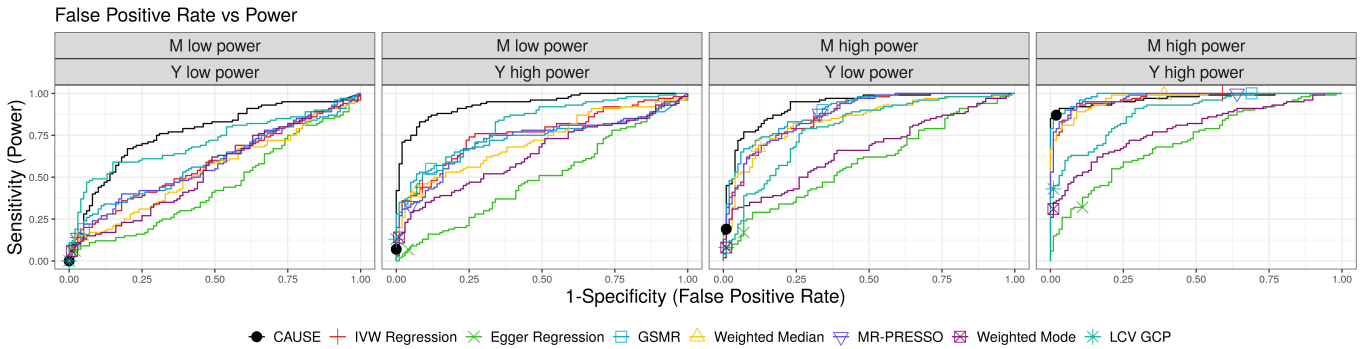
- Alcohol: Alcohol consumption is difficult to study due to its correlation with other dietary and lifestyle factors. Observational studies have suggested a protective effect of moderate alcohol consumption on cardiovascular disease including CAD and stroke [5]. This is the opposite direction of effect suggested by modal MR of alcohol on CAD, the only method to find a causal effect of alcohol on any trait at $p < 0.05$. In a clinical trial, Davies et al. [6] find moderate alcohol consumption associated with increased insulin sensitivity, and decreased triglycerides, but no effect on fasting glucose. To our knowledge, there is no evidence linking alcohol consumption and asthma. (U, U, U, I)

- Smoking: Smoking is a well-known risk factor for cardiovascular disease (CVD), including CAD and stroke, and has been studied extensively through observational and molecular studies over the last several decades [7]. This report also concludes that smoking is a cause of T2D, and that there may be a causal relationship between smoking and asthma, but this remains inconclusive. No MR methods are able to detect effects of smoking on either diabetes risk or asthma. Associations between smoking

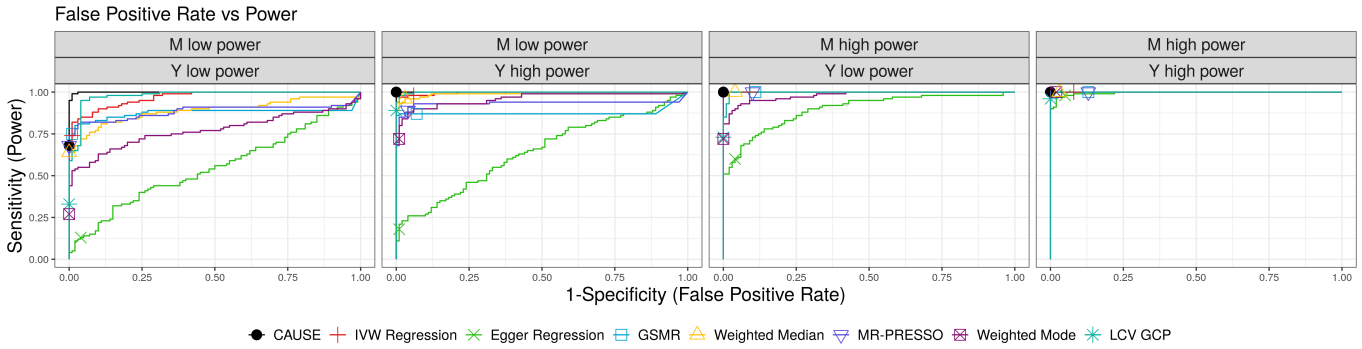
(a) (Null) $q = 0.1, \eta = -\sqrt{0.02}, \gamma = 0$ vs (Non-Null). $q = 0.1, \eta = -\sqrt{0.02}, \gamma = \sqrt{0.02}$



(b) (Null) $q = 0.3, \eta = -\sqrt{0.02}, \gamma = 0$ vs (Non-Null). $q = 0.3, \eta = -\sqrt{0.02}, \gamma = \sqrt{0.02}$



(c) (Null) $q = 0.1, \eta = -\sqrt{0.02}, \gamma = 0$ vs (Non-Null). $q = 0.1, \eta = -\sqrt{0.02}, \gamma = 2 * \sqrt{0.02}$



(d) (Null) $q = 0.3, \eta = -\sqrt{0.02}, \gamma = 0$ vs (Non-Null). $q = 0.3, \eta = -\sqrt{0.02}, \gamma = 2 * \sqrt{0.02}$

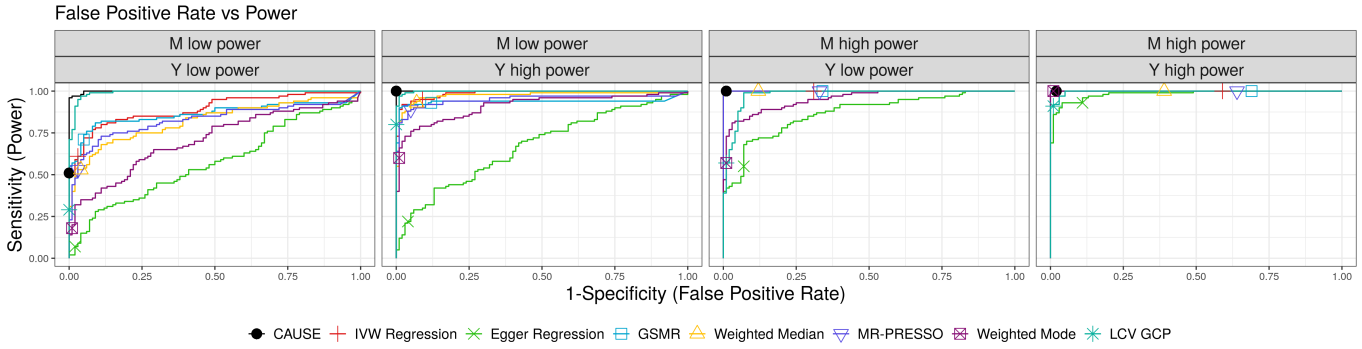


Figure SN5: Comparison of false positive-power trade-off. There are 100 simulations each in the causal and non-causal scenarios. Curves are created by varying the significance threshold. Points indicate the power and false positive rate achieved at a threshold of $p \leq 0.05$ or $\hat{GCP}0.06$ for LCV.

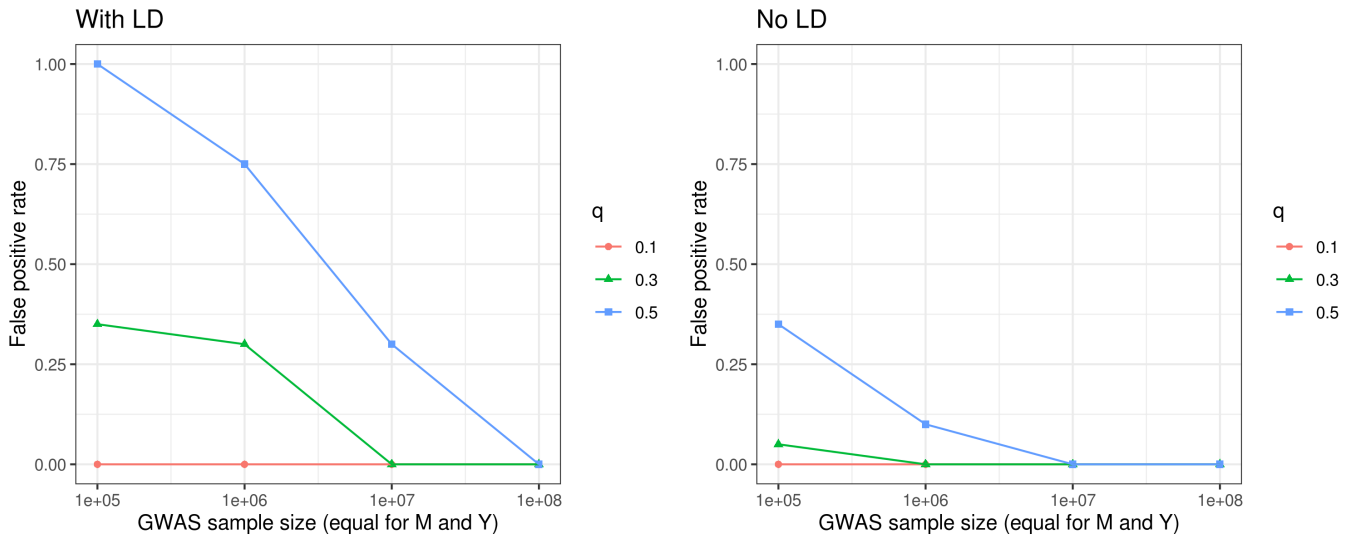


Figure SN6: False positive rate for CAUSE with increasing sample size. The confounder effect is $\eta = \sqrt{0.05}$. Each point shows the average over 20 simulations. In the left panel we show results using the same LD structure used in the paper. The right panel shows results using data with no LD.

behavior and asthma risk may be confounded by effects of parental smoking behavior. (C, C, C, S)

- Blood pressure (SBP, DBP): Two recent clinical trials have studied effects of intensive blood pressure lowering in groups with high risk of CVD. The ACCORD study [8] included individuals with T2D which is associated with elevated risk of CVD. The SPRINT trial [9] included individuals with baseline systolic blood pressure above 130 mm Hg and excluding those with prior stroke. Both studies had primary composite outcomes including both myocardial infarction and stroke. ACCORD did not find a significant effect of intensive blood pressure lowering on the composite outcome but did find evidence of an effect on stroke, a secondary outcome. The SPRINT trial was stopped early due to a significantly lower rate of cardiovascular events in the intensive treatment group suggesting a causal effect. The difference between treatment groups in SPRINT was driven primarily by a decrease in heart failure and a post-hoc analysis of stroke is not significant [10]. This may be attributable to the lower stroke risk of the SPRINT population, which may reduce power to detect an effect. Although the two studies have somewhat different outcomes, we classify the relationships of blood pressure with CAD and stroke both as considered causal due to strong observational evidence and support in clinical trials. To our knowledge, no randomized trials have examined relationships between blood pressure and T2D risk or asthma risk. Because blood pressure and asthma are also not genetically correlated, we classify that relationship as implausibly causal. Blood pressure and T2D are genetically correlated so this relationship is classified as unknown. (C, C, U, I)

- Fasting Glucose: Blood glucose control and insulin sensitivity are disrupted in T2D. Impaired fasting glucose is one of the diagnostic criteria for diabetes so it would be reasonable to expect these traits to share most of their genetic variants. CAUSE finds a significant result in both directions which is consistent with this expectation. It has been suggested that elevated levels of blood glucose can contribute to T2D risk by encouraging more insulin production which eventually overtaxes the pancreas. The causal ordering between elevated is unclear plausibly reciprocal (i.e. there may be causal relationships in both directions). In a meta analysis of cohort studies, Sarwar et al. [11] find a strong correlation between T2D and CVD. However, they find that the relationship between CVD and fasting glucose is non-linear and not significant in lower ranges. It is possible that this association is mediated by diabetic disruption of lipid profiles rather than elevated blood glucose. Fasting glucose is genetically correlated with stroke and CAD but existing literature does not provide clear evidence of a causal effect so these effects are classified as unknown. Fasting glucose and asthma are not genetically correlated and have not been linked in epidemiological literature. (U, U, S, I)

- Birth Weight: Horikoshi et al. [12] study genetic effects on birth weight and genetic correlation with

other traits including CAD, T2D, and asthma. They find a strong negative genetic correlation between birth weight and both CAD and T2D and no significant genetic correlation with asthma. In our study we additionally find no significant genetic correlation with stroke. Explanations for the observed genetic correlations are unknown and may result from a combination of both maternal and fetal genetics. Tyrrell et al. [13] observe a negative correlation between paternal diabetes and birth weight and a positive correlation between maternal diabetes and birth weight. This is consistent with a model in which fetal inheritance of diabetes risk alleles lowers birth weight by impeding glucose metabolism but exposure to maternal high glucose during gestation increases birth weight. Horikoshi et al. [12] suggest that the relationship between birth weight and CAD may be mediated by effects on blood pressure. If this were the case, we might also expect an effect on stroke risk, though no methods except Egger regression find evidence of this relationship in our data. (U, U, U, I)

- Height: Inverse correlations between adult height and both heart disease and stroke have been found in observational studies, with stronger and more consistent results for heart disease [14, 15]. In a Mendelian randomization study, Nüesch et al. [16] find evidence of a causal effect of height on CAD but not stroke. The authors suggest that the effect of height on CAD may be mediated by effects on lung function and lipid profiles. This study uses overlapping data and similar approaches to those used here so cannot be viewed as independent evidence. However, based on strong observational correlation and presence of a physiological explanation for a possible effect, we classify the effect of height of CAD as supported. We classify the effect of height on stroke as unknown. Height is not expected to be causally related to T2D or asthma and is not genetically correlated with either of these traits. (S, U, I, I)

- BMI and Body Fat Percentage: We use the same classifications for body fat percentage and BMI because they are closely related and, there is not always research examining the two traits separately, and we have not found qualitatively different evidence for the two traits. Overweight and obesity is often considered a risk factor for CVD. Recently, Khan et al. [17] combined data from 10 prospective longitudinal cohort studies in the Cardiovascular Disease Lifetime Risk Pooling Project to estimate lifetime risk of CVD in BMI categories. They find increased risk of CVD in the highest categories with risk increasing for groups with higher BMI. This trend was strongest for cardiac outcomes and was weaker for stroke. Observational associations are suggestive but don't establish causality or the mechanism of association. However, because the correlations are found across studies and remain after controlling for lifestyle factors such as smoking, we categorize the relationships between BMI/body fat and CAD/stroke as supported. Obesity is typically considered a risk factor for T2D, primarily supported by consistent observational associations with higher risk in higher BMI categories [18]. Additional research has supported body fat as a stronger predictor of T2D than BMI [19]. Associations have been found between BMI and asthma in children, including in a Mendelian randomization study [20, 21]. However, the mechanism of this association is unknown and complicated by other environmental factors such as maternal BMI during gestation. It is also possible for asthma to increase risk of high BMI through decreased physical activity [22]. In a longitudinal study of a Swedish birth cohort Ekström et al. [22] observe higher BMI throughout childhood for females with persistent asthma but not for males or for children with transient asthma or asthma which onset after 4 years. Based on these findings, we categorize the relationship between BMI and body fat and asthma as unknown. (S, S, S, U)

- HDL: Low levels of HDL cholesterol are correlated with increased risk of heart disease and stroke in observational studies. However, HDL is also correlated with other known CAD risk factors including LDL cholesterol. Voight et al. [23] identify a large effect monogenic variant affecting HDL independent of LDL and triglyceride levels and demonstrate no association between this variant and CAD. Additionally, Burgess and Bowden [24] use multivariable MR to adjust for LDL cholesterol and triglyceride levels and find no effect of HDL on CAD conditional on these variables. In addition to this evidence, there are several Mendelian variants with large effects on HDL cholesterol levels that do not have clear effects on cardiovascular disease, and clinical trials of HDL raising drugs have failed to consistently show an effect. In combination, this evidence has created significant doubts that HDL cholesterol is protective for atherosclerosis as had been previously hypothesized [25]. Dyslipidemia (high LDL

cholesterol, high trigylycerides, low HDL cholesterol) is often associated with T2D. This observation has been attributed to secondary effects of insulin resistance [26] but there have also been suggestions that imbalanced lipids could play a role in disease development and that particularly, HDL may be protective for pancreatic β-cells [27]. A Mendelian randomization study [28] using overlapping data to the data used here finds nominal associations for some tests including association between genetically higher LDL and lower risk of diabetes and weaker associations for higher HDL and lower disease risk. We note that the association between genetically predicted LDL and T2D has opposite sign from the observational association. Fall et al. [28] conclude that they have not identified consistent evidence for a causal role of circulating lipids and cite several possible confounding factors that may affect MR results. Based on this we classify the relationship of HDL with T2D as unknown. HDL cholesterol and asthma have not been linked and are not genetically correlated. (N, N, U, I)

- LDL: LDL cholesterol has been studied extensively through randomized trials of LDL lowering drugs and through MR studies of strong Mendelian LDL effect variants. Cholesterol Treatment Trialsists Collaborators [29] meta-analyze 14 statin trials and find a significant reduction in incidence of coronary heart disease and events related to vascular disease including myocardial infarction and stroke. In addition to this evidence, studies of individuals with monogenic forms of high LDL cholesterol find that these individuals are at high risk for atherosclerosis, or a buildup of plaque in the arteries that can lead to heart disease and stroke and find higher incidence of CAD for individuals with monogenic high LDL cholesterol than for those without those mutations [30, 31]. Based on this evidence, we classify relationships of LDL with CAD and stroke as considered causal. Based on research summarized in the HDL section, we classify the relationship of LDL and T2D as unknown. We further note that genetic and observational studies suggest different directions of association between LDL and T2D with high LDL often observed in individuals with T2D but genetically lower LDL associated with higher risk using some methods. Meta analysis of trials of statin therapy, which lowers LDL, indicates that statin use raises risk of T2D [32, 33]. However, it is unknown if this risk is mediated by statin effects on LDL cholesterol or other mechanisms. Neither [32] nor [33] find an association between changes in LDL cholesterol and differences in T2D risk across studies. Statins reduce LDL cholesterol through inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR). Swerdlow et al. [34] show that at least some of the effect of statins on T2D risk is likely mediated by statin effects on HMGCR using two genetic variants in the HMGCR gene. One of these variants has an allele that is associated with lower HMGCR expression and higher T2D risk. The other was not able to be assessed for expression association and has suggestive but non-significant association with T2D risk. However, both variants have pleiotropic effects, decreasing LDL cholesterol and increasing BMI, body weight, waist to hip ratio, and plasma insulin. Therefore, although the action of HMGCR may be mediating statin effects on T2D, it is not known if these are also mediated by lowered LDL cholesterol. LDL cholesterol and asthma have not been linked and are not genetically correlated. (C, C, U, I)

- Triglycerides: Like LDL cholesterol, high triglyceride levels are positively correlated with risk of heart disease and stroke. Whether this relationship is causal and if triglycerides should be a therapeutic target has been debated and there is conflicting evidence. In a summary from the American Heart Association, Miller et al. [35] note that associations with cardiovascular disease disappear after controlling for other factors including HDL and non-HDL cholesterol levels. They conclude from a range of epidemiological and molecular evidence that triglyceride levels are not directly atherogenic but are useful biomarkers for cardiovascular disease due to high correlation with levels of risk increasing particles. However, a recent meta analysis of clinical trials of lipid lowering therapies that reduce triglycerides more than they reduce LDL cholesterol does find a significant effect of triglycerides on risk of cardiovascular events [36]. This association was strongly influenced by a single outlying study and becomes non-significant when that study is removed. Two Mendelian randomization studies adjusting for LDL and HDL found a significant effect of triglycerides on CAD [37, 24]. Based on this research we classify the relationship of triglycerides and CAD as supported though we note that this issue is still debated and classify triglycerides and stroke as unknown. Based on research summarized under HDL we classify the effect of triglycerides on T2D as unknown. Triglycerides and asthma have not been linked and are not genetically correlated, so we classify that relationship as implausible. (S,

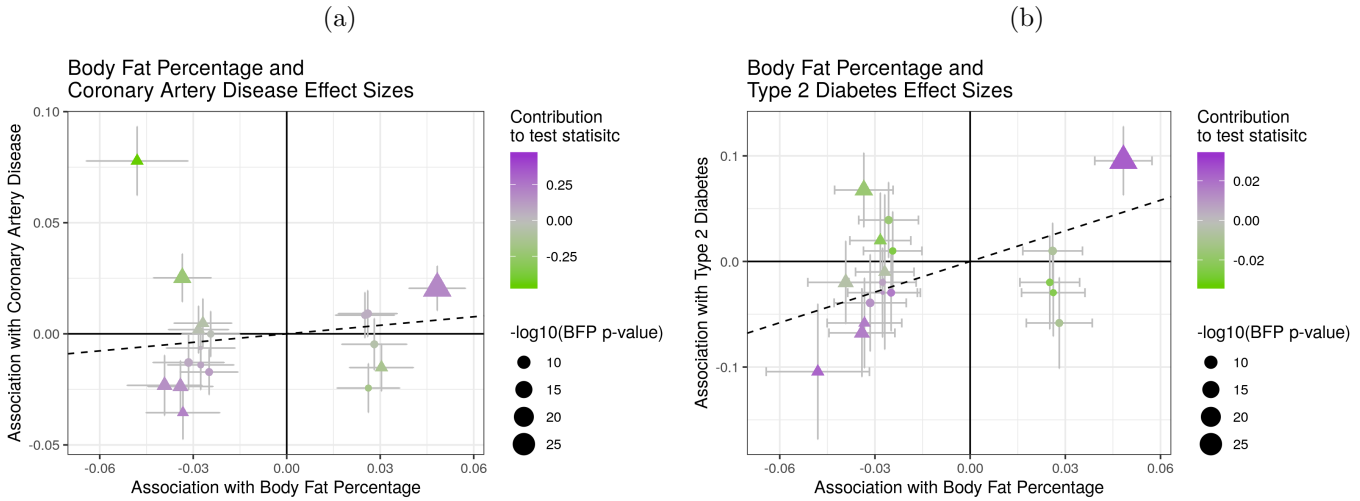


Figure SN7: Effect size estimates and variant level contribution to CAUSE test statistics for four trait pairs. Effect estimates for trait M (horizontal axis) are plotted against estimates for trait Y (vertical axis). Error bars have length 1.96 times the standard error of the estimate. Triangles indicate variants reaching genome-wide significance for trait M ($p < 5 \cdot 10^{-8}$). Variants with trait M p-value $< 5 \cdot 10^{-6}$ are shown. Dotted lines show the IVW estimate obtained using only genome-wide significant variants. (a) Body fat percentage (M) and CAD (Y). (b) Body fat percentage (M) and T2D (Y).

U, U, I)

SN8 Discussion of selected negative results of CAUSE

In main Table 1, there are several pairs of traits that are often considered to be causal and have some literature support, but CAUSE does not find a significant result. In order to understand these results more thoroughly, we examine the data and point-wise contribution to the CAUSE test statistic for these trait pairs.

SN8.1 Body fat percentage and CAD and T2D

Effect size plots for BF $\rightarrow$ CAD and BF $\rightarrow$ T2D are shown in Figure SN7, illustrating why CAUSE obtains a negative result. For both CAD and T2D there is significant heterogeneity in effect size correlation and slightly sub-threshold variants are not consistent with a causal effect. Causal effects of body fat percentage are found more strongly by the weighted median, weighted mode, and in the case of T2D, MR-PRESSO, methods that down weight variants with heterogeneous or "outlying" effect size correlations.

SN8.2 Triglycerides and CAD

The effect of triglycerides on heart disease risk has been debated with conflicting evidence and opinions in the literature (see SN Section SN7). It is complicated by the fact that triglycerides are both genetically and observationally correlated with several CAD risk factors including LDL cholesterol. Two Mendelian randomization studies, Do et al. [37] and Burgess and Bowden [24], have tested for a causal effect of triglycerides on heart disease controlling for LDL and HDL cholesterol. Both studies find in favor of a causal effect. In the data, we see that some variants are strongly associated with triglyceride levels but not with CAD or in the opposite direction from the main trend (Figure SN8a). Some of these variants are also strongly associated with LDL cholesterol or systolic blood pressure (Figures SN8b,c), and there appears to be less heterogeneity even when variants associated with these factors are removed, though this also eliminates all variants most strongly associated with triglycerides (Figure SN8d). In order to assess whether complex pleiotropy between triglycerides, LDL, and SBP could explain CAUSE's negative result, we ran CAUSE twice using two different subsets of variants. First using only variants with LDL p-value > 0.05 we

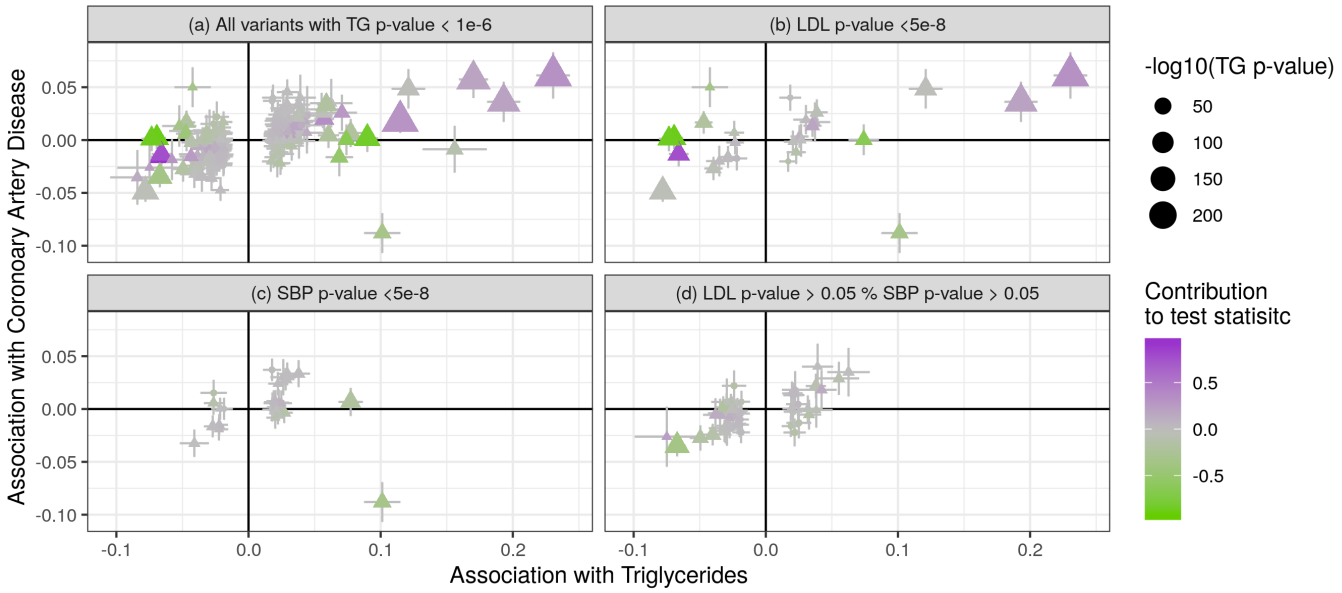


Figure SN8: Effect size estimates and variant level contribution to CAUSE test statistics for triglycerides and coronary artery disease. Symbols and error bars as in previous plots. Dotted lines show the IVW estimate obtained using only genome-wide significant variants. (a) All variants with triglycerides p-value $< 1 \cdot 10^{-}6$. Dotted line shows MR estimate using genome-wide significant variants. (b) Only variants with LDL p-value $< 5 \cdot 10^{-8}$. (c) Only variants with SBP p-value $< 5 \cdot 10^{-8}$. (d) Only variants with LDL p-value > 0.05 and SBP p-value > 0.05.

obtained a p-value from CAUSE of 0.3 suggesting that LDL does not fully explain the heterogeneity of effect correlation. Second, using only variants with LDL p-value > 0.05 and SBP p-value > 0.05, we obtained a p-value from CAUSE of 0.044. These analyses are exploratory and more work needs to be done to fully understand this relationship.

SN9 Results using a low powered blood pressure GWAS

We use a lower-powered GWAS for systolic and diastolic blood pressure [38] to shed light on the performance of each method. This study includes only 69,395 individuals, about 10% of the sample size of the GWAS performed by Evangelou et al. used in the main Results. We note that the Ehret et al. study is a subset of the sample used by Evangelou et al. Results using the lower powered GWAS are shown in Table SN1. Interestingly, IVW regression and Egger regression are unable to detect the effect of blood pressure on CAD using the smaller study. An explanation for this can be seen in the effect estimates for SBP and CAD plotted in Figure SN9. Only seven variants reach genome wide significance. Six have correlated effects on both traits but one highly significant variant contradicts this pattern with a negative association with SBP and a strong positive association with CAD. The weighted median, weighted mode, and MR-PRESSO all down weight outliers through different mechanisms and are therefore able to detect the effect. CAUSE uses variants that do not reach genome-wide significance which contribute to evidence of a causal effect and models multiple sources of pleiotropy allowing it to accommodate the outlying variant and detect the effect.

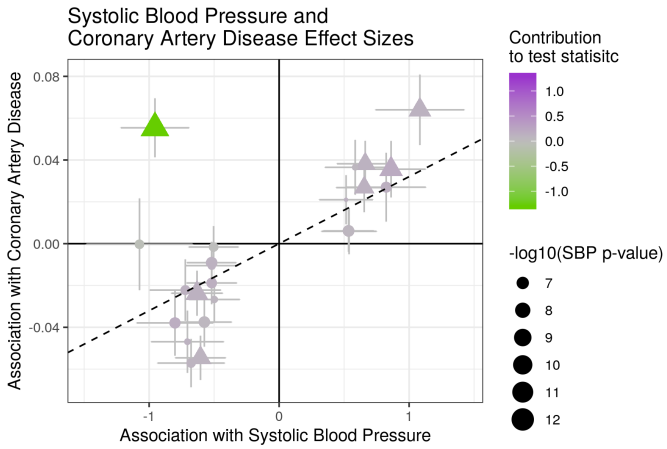


Figure SN9: Effect size estimates and variant level contribution to CAUSE test statistics for systolic blood pressure (SBP) and coronary artery disease (CAD). Effect estimates for SBP are taken from the GWAS of Ehret et al. which has lower power than the study used in the main Results. Symbols and error bars as in previous plots. The dotted line shows the IVW estimate obtained using only genome-wide significant ($p < 5 \cdot 10^{-8}$) variants.

Traits	CAUSE	IVW	Egger	Wtd Med	Wtd Mode	MR-PRESSO	LCV GCP	LCV pval	CAUSE q	GC	GC pval
SBP → CAD	**0.0017** ↑	0.061 ↑	0.43 ↓	**$1.1 \cdot 10^{-9}$** ↑	**$1.5 \cdot 10^{-11}$** ↑	**0.00091** ↑	0.49	0.043	0.54	0.34	$7.3 \cdot 10^{-15}$
DBP → CAD	**0.0012** ↑	0.064 ↑	0.87 ↑	**$4.7 \cdot 10^{-8}$** ↑	**$1.8 \cdot 10^{-7}$** ↑	**0.013** ↑	0.58	0.053	0.38	0.29	$1.4 \cdot 10^{-10}$
SBP → Stroke	**0.0024** ↑	**0.0053** ↑	0.26 ↓	**0.00044** ↑	**0.0037** ↑	**0.0075** ↑	0.13	0.34	0.54	0.37	$1.8 \cdot 10^{-7}$
DBP → Stroke	**0.0021** ↑	**$2.3 \cdot 10^{-6}$** ↑	0.74 ↑	**$8.7 \cdot 10^{-5}$** ↑	**0.0048** ↑	**$6.9 \cdot 10^{-5}$** ↑	0.12	0.43	0.38	0.34	$2.2 \cdot 10^{-5}$
SBP → T2D	0.25 ↑	**0.017** ↑	0.29 ↑	0.19 ↑	0.32 ↑	**0.022** ↑	−0.28	0.35	0.1	0.18	0.0033
DBP → T2D	0.11 ↑	0.081 ↑	**0.039** ↑	0.16 ↑	0.26 ↑	0.13 ↑	−0.19	0.42	0.12	0.12	0.079
DBP → Asthma	1 ↓	0.52 ↓	0.33 ↑	0.44 ↓	0.59 ↓	0.53 ↓	−0.06	0.77	0.04	0.06	0.37
SBP → Asthma	1 ↓	0.84 ↓	0.64 ↑	0.72 ↓	0.66 ↓	0.55 ↓	−0.14	0.79	0.04	0.01	0.82

Table SN1: Summary of results using the lower powered blood pressure GWAS of Ehret et al. Columns 2-7 give the p-value for each MR method. Values are bold if $p < 0.05$. Arrows indicate the sign of the corresponding effect estimate. LCV GCP and LCV pval give estimated GCP from LCV and p-value testing that GCP=0. Values are bold if estimated GCP> 0.6. The "CAUSE q" column gives the posterior median of q in the CAUSE sharing model. GC and GC pval give the genetic correlation and p-value testing that genetic correlation is zero estimated by LD score regression. In each section, pairs are ordered by increasing genetic correlation p-value.

References

[1] Matthew Stephens. "False discovery rates: a new deal". In: *Biostatistics* 18.2 (2017), pp. 275–295.

[2] Richard McElreath. *Statistical Rethinking: A Bayesian Course with Examples in R and Stan.* Boca Raton, FL: CRC Press, Taylor and Francis Group, 2016.

[3] Xiang Zhu and Matthew Stephens. "Bayesian large-scale multiple regression with summary statistics from genome-wide association studies". In: *Annals of Applied Statistics* 11.3 (2017), pp. 1561–1592.

[4] Luke J O'Connor and Alkes L. Price. "Distinguishing genetic correlation from causation across 52 diseases and complex traits". In: *Nature Genetics* 50 (2018), pp. 1728–1734.

[5] Paul E. Ronksley, Susan E. Brien, Barbara J. Turner, Kenneth J. Mukamal, and William A. Ghali. "Association of alcohol consumption with selected cardiovascular disease outcomes: A systematic review and meta-analysis". In: *Bmj* 342.7795 (2011), p. 479.

[6] Michael J. Davies, David J. Baer, Joseph T. Judd, Ellen D. Brown, William S. Campbell, et al. "Effects of moderate alcohol intake on fasting insulin and glucose concentrations and insulin sensitivity in postmenopausal women: A randomized controlled trial". In: *Journal of the American Medical Association* 287.19 (2002), pp. 2559–2562.

[7] U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General.* Tech. rep. Atlanta: U.S. Department of Health et al., 2014.

[8] William C. Cushman, Gregory W. Evans, Robert P. Byington, David C. Goff, Richard H. Grimm, et al. "Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus". In: *New England Journal of Medicine* 362.17 (2010), pp. 1575–1585.

[9] Jackson T. Wright, Jeff D. Williamson, Paul K. Whelton, Joni K. Snyder, Kaycee M. Sink, et al. "A Randomized Trial of Intensive Versus Standard Blood-Pressure Control". In: *New England Journal of Medicine* 373.22 (2015), pp. 2103–2116.

[10] Daniel T. Lackland, Robert M. Carey, Adriana B. Conforto, Clive Rosendorff, Paul K. Whelton, et al. "Implications of recent clinical trials and hypertension guidelines on stroke and future cerebrovascular research". In: *Stroke* 49.3 (2018), pp. 772–779.

[11] N. Sarwar, P. Gao, S. R. Kondapally Seshasai, R. Gobin, S. Kaptoge, et al. "Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies". In: *The Lancet* 375.9733 (2010), pp. 2215–2222.

[12] Momoko Horikoshi, Robin N. Beaumont, Felix R. Day, Nicole M. Warrington, Marjolein N. Kooijman, et al. "Genome-wide associations for birth weight and correlations with adult disease". In: *Nature* 538.7624 (2016), pp. 248–252.

[13] Jessica S. Tyrrell, Hanieh Yaghootkar, Rachel M. Freathy, Andrew T. Hattersley, and Timothy M. Frayling. "Parental diabetes and birthweight in 236 030 individuals in the UK Biobank study". In: *International Journal of Epidemiology* 42.6 (2013), pp. 1714–1723.

[14] D. A. Leon, G. D. Smith, M. Shipley, and D. Strachan. "Adult height and mortality in London: Early life, socioeconomic confounding, or shrinkage?" In: *Journal of Epidemiology and Community Health* 49.1 (1995), pp. 5–9.

[15] S. Goya Wannamethee, A. Gerald Shaper, P. H. Whincup, and M. Walker. "Adult height, stroke, and coronary heart disease". In: *American Journal of Epidemiology* 148.11 (1998), pp. 1069–1076.

[16] Eveline Nüesch, Caroline Dale, Tom M. Palmer, Jon White, Brendan J. Keating, et al. "Adult height, coronary heart disease and stroke: A multi-locus Mendelian randomization meta-analysis". In: *International Journal of Epidemiology* 45.6 (2016), pp. 1927–1937.

[17] Sadiya S. Khan, Hongyan Ning, John T. Wilkins, Norrina Allen, Mercedes Carnethon, et al. "Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity". In: *JAMA Cardiology* 3.4 (2018), pp. 280–287.

[18] Micael L Ganz, Neil WIntfeld, Qian Li, Veronica Alas, Jakob Langer, et al. "The association of body mass index with the risk of type 2 diabetes: A case-control study nested in an electronic health records system in the United States". In: *Diabetology and Metabolic Syndrome* 6.1 (2014), pp. 1–8.

[19] Ara Jo and Arch G. Mainous. "Informational value of percent body fat with body mass index for the risk of abnormal blood glucose: A nationally representative cross-sectional study". In: *BMJ Open* 8.4 (2018), pp. 1–7.

[20] K. G. Tantisira, A. A. Litonjua, S. T. Weiss, and A. L. Fuhlbrigge. "Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP)". In: *Thorax* 58.12 (2003), pp. 1036–1041.

[21] Raquel Granell, A. John Henderson, David M. Evans, George Davey Smith, Andrew R. Ness, et al. "Effects of BMI, Fat Mass, and Lean Mass on Asthma in Childhood: A Mendelian Randomization Study". In: *PLoS Medicine* 11.7 (2014), pp. 1–14.

[22] Sandra Ekström, Jessica Magnusson, Inger Kull, Niklas Andersson, Matteo Bottai, et al. "Body Mass Index Development and Asthma Throughout Childhood". In: *American Journal of Epidemiology* 186.2 (2017), pp. 255–263.

[23] Benjamin F. Voight, Gina M. Peloso, Marju Orho-Melander, Ruth Frikke-Schmidt, Maja Barbalic, et al. "Plasma HDL cholesterol and risk of myocardial infarction: A mendelian randomisation study". In: *The Lancet* 380.9841 (2012), pp. 572–580.

[24] Stephen Burgess and Jack Bowden. "Integrating summarized data from multiple genetic variants in Mendelian randomization: bias and coverage properties of inverse-variance weighted methods". In: *arXiv* (2015). arXiv: `1512.04486`.

[25] Daniel J Rader and G Kees Hovingh. "HDL and cardiovascular disease". In: *The Lancet* 384.9943 (2014), pp. 618–625.

[26] Arshag D Moordian. "Dyslipidemia in type 2 diabetes mellitus". In: *Nature Clinical Practice* 5.3 (2009), pp. 150–159.

[27] Jannick Pétremand, Julien Puyal, Jean Yves Chatton, Jessica Duprez, Florent Allagnat, et al. "HDLs protect pancreatic β-cells against ER stress by restoring protein folding and trafficking". In: *Diabetes* 61.5 (2012), pp. 1100–1111.

[28] Tove Fall, Weijia Xie, Wenny Poon, Hanieh Yaghootkar, Reedik Magi, et al. "Using genetic variants to assess the relationship between circulating lipids and type 2 diabetes". In: *Diabetes* 64.7 (2015), pp. 2676–2684.

[29] Cholesterol Treatment Trialsists Collaborators. "Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins". In: *The Lancet* (2005).

[30] Jonathan C. Cohen, Eric Boerwinkle, Thomas H. Mosley Jr, and Helen H. Hobbs. "Sequence Variations in PCSK0, Low LDL and Protection against Coronary Heart Disease". In: *Heart Disease* (2011), pp. 1264–1272.

[31] Daniel J. Rader, Jonathan Cohen, and Helen H. Hobbs. "Monogenic hypercholesterolemia: New insights in pathogenesis and treatment". In: *Journal of Clinical Investigation* 111.12 (2003), pp. 1795–1803.

[32] Naveed Sattar, David Preiss, Heather M. Murray, Paul Welsh, Brendan M. Buckley, et al. "Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials". In: *The Lancet* 375.9716 (2010), pp. 735–742.

[33] Jill P. Crandall, Kieren Mather, Swapnil N. Rajpathak, Ronald B. Goldberg, Karol Watson, et al. "Statin use and risk of developing diabetes: Results from the diabetes prevention program". In: *BMJ Open Diabetes Research and Care* 5.1 (2017).

[34] Daniel I. Swerdlow, David Preiss, Karoline B. Kuchenbaecker, Michael V. Holmes, Jorgen E.L. Engmann, et al. "HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: Evidence from genetic analysis and randomised trials". In: *The Lancet* 385.9965 (2015), pp. 351–361.

[35] Michael Miller, Neil J. Stone, Christie Ballantyne, Vera Bittner, Michael H. Criqui, et al. "Triglycerides and cardiovascular disease: A scientific statement from the American Heart Association". In: *Circulation* 123.20 (2011), pp. 2292–2333.

[36] Nicholas A. Marston, Robert P. Giugliano, Kyung Ah Im, Michael G. Silverman, Michelle L. O'Donoghue, et al. "Association Between Triglyceride Lowering and Reduction of Cardiovascular Risk Across Multiple Lipid-Lowering Therapeutic Classes: A Systematic Review and Meta-Regression Analysis of Randomized Controlled Trials". In: *Circulation* 140.16 (2019), pp. 1308–1317.

[37] Ron Do, Cristen J. Willer, Ellen M. Schmidt, Sebanti Sengupta, Chi Gao, et al. "Common variants associated with plasma triglycerides and risk for coronary artery disease". In: *Nature Genetics* 45.11 (2013), pp. 1345–1353.

[38] Georg B. Ehret, Patricia B. Munroe, Kenneth M. Rice, Murielle Bochud, Andrew D. Johnson, et al. "Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk". In: *Nature* 478.7367 (2011), pp. 103–109. arXiv: `NIHMS150003`.

[39] Evangelos Evangelou, Helen R. Warren, David Mosen-Ansorena, Borbala Mifsud, Raha Pazoki, et al. "Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits". In: *Nature Genetics* 50.12 (2018), pp. 1755–1755.