1 **Table A. Blood pressure and anthropometric outcomes**

Outcome	Beta [95% CI]	# SNPs in IV
Systolic blood pressure (mmHg)		
UKB, 2SLS	3.34 [2.34, 4.34]	1
UKB, IVW	2.65 [1.40, 3.89]	25
UKB, MVMR	2.59 [1.39, 3.79]	25
FinnMetSeq, 2SLS	-0.08 [-0.56, 0.40]	1
ICBP, IVW	1.24 [-2.81, 5.29]	9*
Diastolic blood pressure (mmHg)		
UKB, 2SLS	0.51 [-0.06, 1.08]	1
UKB, IVW	1.12 [0.34, 1.91]	25
UKB, MVMR	1.11 [0.32, 1.91]	25
FinnMetSeq, 2SLS	-0.34 [-0.82, 0.14]	1
ICBP, IVW	1.58 [-0.90, 4.07]	9*
Body mass index (kg/m^2)		
UKB, 2SLS	0.90 [0.65, 1.15]	1
UKB, IVW	0.15 [-1.00, 1.29]	25
GIANT 2018 exome, 2SLS	0.03 [-0.11, 0.18]	1
GIANT 2012, IVW	0.01 [-0.11, 0.13]	9*
Body fat percentage		
UKB, 2SLS	1.31 [0.97, 1.64]	1
UKB, IVW	0.60 [-0.57, 1.76]	25
BFP GWAS, 2SLS	-0.07 [-0.26, 0.13]	1
BFP GWAS, IVW	0.00 [-0.19, 0.19]	9*
Waist circumference (cm)		
UKB, 2SLS	1.87 [1.24, 2.50]	1
UKB, IVW	0.58 [-1.85, 3.01]	25
EXTEND, 2SLS	0.46 [0.13, 0.79]	1
GIANT 2015, IVW	0.04 [-0.12, 0.19]	9*

2 Beta and 95% confidence interval (CI) for one additional drink per day of alcohol, and number
3 of SNPs in instrumental variable (IV). * indicates the main SNP, rs1229984, was not available in
4 this dataset.
5

6 **Table B. Serum biomarkers**

Outcome	Beta [95% CI]	# SNPs in IV
Cholesterol (mmol/L)		
UKB, 2SLS	0.21 [0.15, 0.27]	1
UKB, IVW	0.12 [-0.06, 0.31]	25
UKB, MVMR	0.13 [-0.06, 0.32]	25
GLGC 2017, 2SLS	-0.04 [-0.33, 0.25]	1
GLGC 2013, IVW	-0.36 [-0.73, 0.01]	10*
LDL (mmol/L)		
UKB, 2SLS	0.20 [0.15, 0.24]	1
UKB, IVW	0.12 [0.00, 0.25]	25

UKB, MVMR	0.12 [-0.01, 0.25]	25
GLGC 2017, 2SLS	0.00 [-0.29, 0.30]	1
GLGC 2013, IVW	-0.14 [-0.32, 0.04]	10*
HDL (mmol/L)		
UKB, 2SLS	0.00 [-0.02, 0.02]	1
UKB, IVW	0.02 [-0.03, 0.07]	25
UKB, MVMR	0.03 [-0.02, 0.07]	25
GLGC 2017, 2SLS	0.20 [-0.09, 0.49]	1
GLGC 2013, IVW	0.24 [0.00, 0.49]	10*
Triglycerides (mmol/L)		
UKB, 2SLS	-0.05 [-0.10, 0.01]	1
UKB, IVW	-0.17 [-0.41, 0.07]	25
UKB, MVMR	-0.17 [-0.41, 0.08]	25
GLGC 2017, 2SLS	-0.26 [-0.55, 0.03]	1
GLGC 2013, IVW	-0.96 [-1.61, -0.31]	10*
HbA1C (mmol/mol)		
UKB, 2SLS	-0.41 [-0.70, -0.13]	1
UKB, IVW	-0.28 [-0.74, 0.19]	25
EXTEND, 2SLS	-0.27 [-0.80, 0.25]	1
MAGIC, IVW	0.00 [-0.07, 0.06]	9*

Beta and 95% confidence interval (CI) for one additional drink per day of alcohol, and number of SNPs in instrumental variable (IV). * indicates the main SNP, rs1229984, was not available in this dataset.

Table C. Binary variable outcomes

Outcome	OR [95% CI]	# SNPs in IV
Myocardial infarction		
UKB, 2SLS	1.67 [1.28, 2.18]	1
UKB, IVW	1.29 [1.09, 1.51]	25
UKB, MVMR	1.10 [0.88, 1.36]	25
CARDIoGRAMplusC4D, 2SLS	1.10 [0.97, 1.26]	1
CARDIoGRAMplusC4D, IVW	1.07 [0.92, 1.26]	18
Stroke		
UKB, 2SLS	1.61 [1.12, 2.33]	1
UKB, IVW	1.54 [1.22, 1.95]	25
UKB, MVMR	1.42 [1.04, 1.94]	25
MEGASTROKE, 2SLS	1.03 [0.86, 1.23]	1
MEGASTROKE, IVW	1.01 [0.91, 1.12]	25
Ischemic stroke		
UKB, 2SLS	1.43 [0.83, 2.47]	1
UKB, IVW	1.15 [0.80, 1.65]	25

MEGASTROKE, 2SLS	1.03 [0.85, 1.25]	1
MEGASTROKE, IVW	1.01 [0.90, 1.13]	25
Hemorrhagic stroke		
UKB, 2SLS	1.86 [0.86, 4.02]	1
UKB, IVW	2.25 [1.41, 3.60]	25
UKB, MVMR	2.37 [1.30, 4.30]	25
Heart failure		
UKB, 2SLS	1.63 [1.06, 2.50]	1
UKB, IVW	1.25 [0.90, 1.73]	25
UKB, MVMR	1.03 [0.75, 1.41]	25
HERMES, 2SLS	1.13 [0.95, 1.35]	1
HERMES, IVW	0.93 [0.73, 1.20]	23
Atrial fibrillation		
UKB, 2SLS	1.40 [1.08, 1.83]	1
UKB, IVW	1.26 [1.07, 1.48]	25
UKB, MVMR	1.24 [1.00, 1.54]	25
AF HRC 2018, 2SLS	1.08 [0.96, 1.21]	1
AF HRC 2018, IVW	1.07 [0.95, 1.19]	24
Type 2 diabetes		
UKB, 2SLS	1.35 [1.04, 1.76]	1
UKB, IVW	1.24 [0.75, 2.04]	25
UKB, MVMR	1.18 [0.93, 1.50]	25
DIAMANTE exome T2D, 2SLS	1.29 [0.79, 2.10]	1
DIAMANTE exome T2D adj BMI, 2SLS	1.02 [0.62, 1.69]	1
DIAGRAM GWAS, 2SLS	0.93 [0.74, 1.16]	1
DIAGRAM GWAS, IVW	0.83 [0.54, 1.27]	25
Any cardiovascular disease		
UKB, 2SLS	1.60 [1.33, 1.92]	1
UKB, IVW	1.38 [1.21, 1.57]	25
All-cause death		
UKB, 2SLS	1.44 [1.09, 1.90]	1
UKB, IVW	1.31 [1.08, 1.59]	25

Odds ratio (OR) and 95% confidence interval (CI) for one additional drink per day of alcohol, and number of SNPs in instrumental variable (IV). * indicates the main SNP, rs1229984, was not available in this dataset.

18   **Table D. Risk factor outcome MVMR results**

Outcome	Beta	LCL	UCL
Cholesterol (mmol/L)			
Alcohol (per +1 drink/day)	0.128	-0.063	0.320
BMI (kg/m^2)	-0.025	-0.091	0.042
LDL (mmol/L)			
Alcohol (per +1 drink/day)	0.123	-0.005	0.251
BMI (kg/m^2)	-0.005	-0.050	0.040
HDL (mmol/L)			
Alcohol (per +1 drink/day)	0.026	-0.019	0.071
BMI (kg/m^2)	-0.023	-0.039	-0.007
Triglycerides (mmol/L)			
Alcohol (per +1 drink/day)	-0.170	-0.415	0.075
BMI (kg/m^2)	0.006	-0.079	0.092
Systolic blood pressure (mmHg)			
Alcohol (per +1 drink/day)	2.590	1.391	3.788
BMI (kg/m^2)	0.373	-0.047	0.792
Diastolic blood pressure (mmHg)			
Alcohol (per +1 drink/day)	1.115	0.315	1.915
BMI (kg/m^2)	0.062	-0.218	0.342

19   Beta, 95% lower confidence limit (LCL), and 95% upper confidence limit (UCL) for outcomes
20   with positive findings in the 2SLS or inverse variance weighted Mendelian randomization
21   analyses.
22
23

24 **Table E. Disease outcome MVMR results**

Outcome	OR	LCL	UCL
Myocardial infarction			
Alcohol (per +1 drink/day)	1.10	0.88	1.36
Systolic blood pressure (mmHg)	1.04	0.98	1.11
Smoking (ever/never)	1.35	0.77	2.37
LDL (mmol/L)	1.28	0.69	2.36
All Stroke			
Alcohol (per +1 drink/day)	1.42	1.04	1.94
Systolic blood pressure (mmHg)	1.04	0.95	1.13
Smoking (ever/never)	0.64	0.28	1.45
LDL (mmol/L)	1.10	0.45	2.68
Hemorrhagic Stroke			
Alcohol (per +1 drink/day)	2.37	1.30	4.30
Systolic blood pressure (mmHg)	0.98	0.85	1.13
Atrial fibrillation			
Alcohol (per +1 drink/day)	1.24	1.00	1.54
Systolic blood pressure (mmHg)	1.00	0.95	1.06
BMI (kg/m^2)	1.05	0.99	1.11
Type 2 diabetes			
Alcohol (per +1 drink/day)	1.18	0.93	1.50
BMI (kg/m^2)	1.46	1.35	1.59

25 Odds ratio (OR), 95% lower confidence limit (LCL), and 95% upper confidence limit (UCL) for
26 outcomes with positive findings in the 2SLS or inverse variance weighted Mendelian
27 randomization analyses.

28 **Table F. IVW MR stratified analysis for continuous variables**

Outcome	Male	Female	p value sex difference	Never smokers	Current smokers	p value smoking difference
Systolic blood pressure (mmHg)	2.62 [1.66, 3.58]	2.84 [0.61, 5.06]	0.86	2.23 [0.93, 3.52]	2.71 [1.20, 4.23]	0.63
Diastolic blood pressure (mmHg)	1.23 [0.63, 1.83]	0.91 [-0.44, 2.26]	0.67	1.37 [0.45, 2.30]	1.59 [0.69, 2.49]	0.74
Body mass index (kg/m^2)	0.18 [-0.69, 1.05]	0.26 [-1.44, 1.97]	0.93	0.28 [-0.88, 1.44]	0.15 [-0.86, 1.16]	0.87
Body fat percentage	0.56 [-0.35, 1.48]	0.79 [-0.93, 2.51]	0.82	0.67 [-0.55, 1.89]	0.68 [-0.30, 1.65]	0.99
Waist circumference	0.60 [-1.37, 2.58]	0.82 [-2.62, 4.26]	0.92	0.64 [-1.82, 3.11]	0.69 [-1.39, 2.76]	0.98
Cholesterol (mmol/L)	0.17 [0.01, 0.32]	0.04 [-0.24, 0.31]	0.42	0.08 [-0.14, 0.29]	0.07 [-0.05, 0.20]	0.99
LDL (mmol/L)	0.14 [0.04, 0.24]	0.07 [-0.12, 0.26]	0.51	0.09 [-0.05, 0.23]	0.06 [-0.02, 0.13]	0.70
HDL (mmol/L)	0.03 [-0.01, 0.06]	0.01 [-0.07, 0.10]	0.74	0.01 [-0.05, 0.06]	0.07 [0.04, 0.10]	0.06
Triglycerides (mmol/L)	-0.13 [-0.33, 0.08]	-0.23 [-0.55, 0.08]	0.59	-0.14 [-0.40, 0.12]	-0.24 [-0.41, -0.07]	0.54
HbA1C (mmol/mol)	-0.11 [-0.60, 0.37]	-0.52 [-1.00, -0.05]	0.24	-0.40 [-0.98, 0.18]	-0.45 [-0.86, -0.05]	0.89

29 Betas and 95% confidence intervals for strata and p-values for Cochran's Q test for heterogeneity between strata pairs (male/female
30 and never smokers/current smokers)
31

32 **Table G. 2SLS MR stratified analysis for continuous variables**

Outcome	Male	Female	p value sex difference	Never smokers	Current smokers	p value smoking difference
Systolic blood pressure (mmHg)	2.95 [1.86, 4.05]	4.10 [2.22, 5.97]	0.30	2.73 [1.19, 4.28]	3.01 [1.03, 4.98]	0.83
Diastolic blood pressure (mmHg)	0.68 [0.03, 1.33]	0.29 [-0.75, 1.34]	0.54	0.45 [-0.44, 1.33]	1.54 [0.38, 2.70]	0.14
Body mass index (kg/m^2)	0.80 [0.54, 1.05]	1.05 [0.54, 1.55]	0.38	0.87 [0.48, 1.26]	0.73 [0.22, 1.23]	0.66
Body fat percentage	1.26 [0.92, 1.61]	1.37 [0.70, 2.04]	0.78	1.27 [0.74, 1.80]	1.22 [0.53, 1.90]	0.91
Waist circumference	1.75 [1.08, 2.43]	2.04 [0.83, 3.26]	0.68	1.68 [0.71, 2.64]	1.60 [0.32, 2.88]	0.92
Cholesterol (mmol/L)	0.24 [0.18, 0.30]	0.15 [0.05, 0.26]	0.16	0.15 [0.06, 0.23]	0.18 [0.06, 0.29]	0.67
LDL (mmol/L)	0.22 [0.17, 0.26]	0.16 [0.08, 0.24]	0.22	0.15 [0.08, 0.22]	0.13 [0.04, 0.22]	0.72
HDL (mmol/L)	0.00 [-0.02, 0.02]	-0.01 [-0.05, 0.03]	0.64	-0.02 [-0.05, 0.01]	0.06 [0.02, 0.10]	0.0036
Triglycerides (mmol/L)	-0.03 [-0.10, 0.04]	-0.07 [-0.16, 0.01]	0.47	0.00 [-0.08, 0.08]	-0.11 [-0.24, 0.01]	0.15
HbA1C (mmol/mol)	-0.23 [-0.59, 0.13]	-0.70 [-1.16, -0.23]	0.12	-0.61 [-1.02, -0.21]	-0.60 [-1.25, 0.05]	0.98

33 Betas and 95% confidence intervals for strata and p-values for Cochran's Q test for heterogeneity between strata pairs (male/female
34 and never smokers/current smokers)

35

36

Table H. IVW MR stratified analysis for binary variables

Outcome	Male	Female	p value sex difference	Never smokers	Current smokers	p value smoking difference
Myocardial infarction	1.22 [1.02, 1.47]	1.17 [0.75, 1.84]	0.86	1.48 [1.10, 2.01]	1.22 [0.94, 1.59]	0.35
Stroke	1.44 [1.16, 1.79]	1.63 [0.98, 2.69]	0.67	1.92 [1.30, 2.83]	1.25 [0.87, 1.78]	0.11
Ischemic stroke	1.18 [0.86, 1.63]	0.96 [0.44, 2.08]	0.62	1.30 [0.72, 2.36]	0.82 [0.51, 1.33]	0.24
Hemorrhagic stroke	1.96 [1.21, 3.18]	2.66 [0.98, 7.22]	0.59	5.35 [2.24, 12.78]	1.04 [0.49, 2.18]	0.01
Heart failure	1.28 [0.94, 1.73]	0.89 [0.47, 1.71]	0.33	1.85 [1.09, 3.15]	1.36 [0.88, 2.09]	0.38
Atrial fibrillation	1.23 [1.06, 1.43]	1.20 [0.81, 1.78]	0.90	1.55 [1.16, 2.06]	1.17 [0.84, 1.62]	0.21
Type 2 diabetes	1.23 [0.80, 1.88]	1.15 [0.60, 2.21]	0.88	1.38 [0.79, 2.39]	1.27 [0.88, 1.82]	0.80
Any cardiovascular disease	1.34 [1.18, 1.53]	1.23 [0.93, 1.63]	0.58	1.61 [1.32, 1.96]	1.29 [1.06, 1.58]	0.13
All-cause death	1.38 [1.15, 1.67]	0.99 [0.68, 1.46]	0.13	0.95 [0.67, 1.35]	1.30 [1.02, 1.67]	0.15

Odds ratios and 95% confidence intervals for strata and p-values for Cochran's Q test for heterogeneity between strata pairs (male/female and never smokers/current smokers)

41 **Table I. 2SLS MR stratified analysis for binary variables**

Outcome	Male	Female	p value sex difference	Never smokers	Current smokers	p value smoking difference
Myocardial infarction	1.67 [1.31, 2.12]	1.13 [0.57, 2.24]	0.29	1.88 [1.15, 3.08]	1.15 [0.75, 1.78]	0.15
Stroke	1.55 [1.07, 2.25]	1.59 [0.73, 3.44]	0.96	1.59 [0.84, 2.98]	1.20 [0.67, 2.17]	0.53
Ischemic stroke	1.54 [0.89, 2.65]	1.02 [0.31, 3.35]	0.54	1.46 [0.56, 3.86]	0.77 [0.35, 1.66]	0.31
Hemorrhagic stroke	1.64 [0.73, 3.70]	2.25 [0.48, 10.42]	0.72	2.42 [0.61, 9.57]	1.47 [0.41, 5.23]	0.60
Heart failure	1.86 [1.23, 2.80]	0.82 [0.31, 2.15]	0.13	1.58 [0.71, 3.52]	1.39 [0.70, 2.77]	0.81
Atrial fibrillation	1.44 [1.12, 1.85]	1.12 [0.61, 2.04]	0.45	1.35 [0.86, 2.12]	1.33 [0.78, 2.27]	0.96
Type 2 diabetes	1.36 [1.05, 1.76]	1.20 [0.68, 2.14]	0.70	1.58 [0.99, 2.52]	1.07 [0.66, 1.74]	0.26
Any cardiovascular disease	1.68 [1.40, 2.00]	1.14 [0.76, 1.72]	0.09	1.56 [1.14, 2.15]	1.37 [0.99, 1.91]	0.57
All-cause death	1.66 [1.24, 2.21]	0.92 [0.52, 1.64]	0.07	0.85 [0.52, 1.39]	1.11 [0.75, 1.65]	0.40

42 Odds ratios and 95% confidence intervals for strata and p-values for Cochran's Q test for heterogeneity between strata pairs

43 (male/female and never smokers/current smokers)

44

45   **Table J. Additional analysis of blood count data by instrument variable group.**

Variable	Heterozygous + homozygous group	Wildtype	p-value	F statistic
Hemoglobin (g/dL)	14.23	14.21	0.0179	5.6
Hematocrit (%)	41.24	41.15	0.00237	9.2
Mean corpuscular volume (fL)	91.08	91.35	2.37e-13	53.7

46   Mean for each value by instrument variable status; p-value and F statistic from ANOVA.