## Separating the effects of risk factors from type 2 diabetes on coronary and peripheral artery disease Electronic Supplementary Material (ESM)

ESM Methods 1: Mendelian randomisation analysis assumptions

Mendelian randomisation requires three assumptions: (1) the instrument must affect the exposure (relevance), (2) the instrument must not share any common causes with the outcome (independence), and (3) the instrument must only affect the outcome through the exposure (exclusion restriction). To obtain a point estimate, we must make a further assumption, such as monotonicity. This assumption states that the exposure is a monotonic (i.e. an always increasing or always decreasing) function of the instrument (monotonicity). Mendelian randomisation performed using MR-Egger requires two alternative assumptions: the instrument strength independent of direct effect (INSIDE) assumption and the no measurement error (NOME) assumption. Finally, two-step Mendelian randomisation for mediation assumes no interaction between the exposure and the mediator.

## ESM Methods 2: Non-collapsibility of odds ratio

The non-collapsibility of odds ratios can pose a problem when using summary statistics from logistic regression for binary mediators and outcomes in multivariable Mendelian randomisation. To assess whether this is likely to have impacted our results, we performed a novel GWAS of liability to type 2 diabetes using a linear mixed model. Specifically, we performed a GWAS of type 2 diabetes using 24884 cases and 437996 controls from UK Biobank. The GWAS was conducted using the Medical Research Council Integrative Epidemiology Unit GWAS pipeline. Further details regarding the pipeline can be found here: https://doi.org/10.5523/bris.pnoat8cxo0u52p6ynfaekeigi. Type 2 diabetes was defined as a binary variable based on the presence of the ICD-10 code 'E11' as a main or secondary diagnosis in the hospital inpatient admissions data (UK Biobank data-field 41270). We used a BOLT-LMM model for the GWAS and adjusted for age, sex and chip. Individuals whose genetic sex did not match their reported gender; individuals with sex chromosome karvotypes putatively different from XX or XY; individuals who were outliers in heterozygosity and missing rates; and individuals with high levels of relatedness (3rd degree) to more than 200 other individuals in the biobank were excluded prior to the analysis. The GWAS is publicly available from the IEU OpenGWAS project. The code related to the GWAS can be found here: https://github.com/venexia/T2DLinearGWAS-UKB. We were then able to repeat our Mendelian randomisation analyses, where there was no sample overlap with UK Biobank, using this GWAS and compare the results with our main analysis to assess the impact on our results.





ESM Figure 2: Univariate Mendelian randomisation estimates for the effect of the risk factors on liability to type 2 diabetes that meet the 5% FDR threshold (ESM Table 2)





ESM Figure 3: Univariate Mendelian randomisation estimates for the effect of liability to type 2 diabetes on the risk factors that meet the 5% FDR threshold (ESM Table 2)





ESM Figure 4: Univariate Mendelian randomisation estimates for the effect of the risk factors on liability to coronary artery disease that meet the 5% FDR threshold (ESM Table 2)

Overall health rating			OR 2 22 (95% CI 1 71 2 89): 53 SNPs
		-	OR 1.80 (05% CI 1.60, 2.02); 136 SNDo
Diastalia blaad prossure -			OR 1.30 (05% CI 1.60, 2.02), 130 SNP3
Diastolic blood pressure -			OR 1.79 (95% CI 1.54, 2.06); 172 SNPS
LDL direct -			OR 1.77 (95% CI 1.54, 2.04); 133 SNPS
Systolic blood pressure -			OR 1.76 (95% CI 1.48, 2.11); 156 SNPs
Waist-to-hip ratio -			OR 1.62 (95% CI 1.21, 2.16); 30 SNPs
Waist circumference -		-	OR 1.57 (95% CI 1.41, 1.75); 214 SNPs
Cholesterol -		-	OR 1.57 (95% CI 1.37, 1.80); 146 SNPs
Body mass index -			OR 1.52 (95% CI 1.42, 1.64); 489 SNPs
Total cholesterol -		-	OR 1.52 (95% CI 1.37, 1.69); 85 SNPs
Body fat percentage -		-	OR 1.52 (95% CI 1.33, 1.73); 245 SNPs
Fasting insulin -			OR 1.48 (95% CI 1.20, 1.82); 14 SNPs
Whole body fat mass -		-	OR 1.39 (95% CI 1.27, 1.51); 269 SNPs
Trunk fat mass -		-	OR 1.29 (95% CI 1.18, 1.42); 274 SNPs
Alanine aminotransferase -		-	OR 1.29 (95% CI 1.13, 1.46); 172 SNPs
Trunk fat percentage -		-	OR 1.27 (95% CI 1.13, 1.43); 226 SNPs
Triglycerides -		-	OR 1 27 (95% CI 1 17, 1 37): 205 SNPs
Lipoprotein A			OR 1 26 (95% CI 1 21, 1 31); 14 SNPs
Glucose -		-	OR 1.25 (95% CI 1.11, 1.41); 95 SNPs
Weight -		-	OP 1 24 (05% CI 1 13, 1 36): 320 SNPc
Chreated becomediable		2	OR 1.22 (05% CI 1.13, 1.30); 323 SNPS
		-	OR 1.22 (95% CI 1.15, 1.30); 262 SNPS
Aspartate aminotransferase			OR 1.20 (95% CI 1.07, 1.34); 199 SNPs
Fasting glucose -			OR 1.15 (95% CI 1.03, 1.29); 30 SNPs
Hip circumference -			OR 1.14 (95% CI 1.03, 1.26); 274 SNPs
Urate -		-	OR 1.13 (95% CI 1.05, 1.21); 222 SNPs
High light scatter reticulocyte count -		-	OR 1.13 (95% CI 1.05, 1.21); 266 SNPs
Reticulocyte count -		-	OR 1.12 (95% CI 1.04, 1.21); 248 SNPs
Red blood cell (erythrocyte) count -		-	OR 1.11 (95% CI 1.03, 1.19); 297 SNPs
Immature reticulocyte fraction -		-	OR 1.10 (95% CI 1.01, 1.20); 182 SNPs
Reticulocyte percentage -		-	OR 1.10 (95% CI 1.02, 1.18); 239 SNPs
High light scatter reticulocyte percentage -		-	OR 1.10 (95% CI 1.03, 1.17); 270 SNPs
Gamma glutamyltransferase -		-	OR 1.09 (95% CI 1.02, 1.17); 249 SNPs
Cystatin C -		-	OR 1.09 (95% CI 1.02, 1.16); 270 SNPs
Mean corpuscular haemoglobin -			OR 0.94 (95% CI 0.90, 0.99); 311 SNPs
Mean sphered cell volume -			OR 0.91 (95% CI 0.86, 0.97): 283 SNPs
Fluid intelligence score -			OR 0.91 (95% CI 0.85, 0.97); 41 SNPs
Creatinine -			OR 0.88 (95% CI 0.80, 0.98): 283 SNPs
Trunk predicted mass	-		OR 0.88 (95% CI 0.80, 0.97); 405 SNPs
Trunk fat-free mass			OR 0.88 (95% CI 0.79, 0.97); 405 SNPs
SHBG -			OR 0.88 (95% CI 0.82, 0.94); 232 SNPs
			OP 0.84 (05% CI 0.77, 0.91); 213 SNPc
Apolipoprotein A -			OR 0.04 (95% CI 0.77, 0.91); 215 SNPS
Sitting beight			OR 0.03 (95% CI 0.75, 0.91), 345 SNP5
Sitting height -			OR 0.82 (95% CI 0.76, 0.87); 426 SNPs
Standing height -			OR 0.81 (95% CI 0.77, 0.86); 574 SNPs
HDL cholesterol -			OR 0.81 (95% CI 0.75, 0.87); 239 SNPs
Testosterone -			OR 0.77 (95% CI 0.62, 0.96); 83 SNPs
Forced expiratory volume in 1-second (FEV1) -	-		OR 0.77 (95% CI 0.66, 0.89); 153 SNPs
Past tobacco smoking -			OR 0.75 (95% CI 0.59, 0.96); 40 SNPs
Birth weight of first child			OR 0.73 (95% CI 0.61, 0.88); 40 SNPs
Forced vital capacity (FVC) -	-		OR 0.73 (95% CI 0.64, 0.82); 212 SNPs
Birth weight -	-		OR 0.69 (95% CI 0.61, 0.79); 83 SNPs
Drive faster than motorway speed limit -			OR 0.56 (95% CI 0.36, 0.85); 12 SNPs
Usual walking pace -			OR 0.55 (95% CI 0.35, 0.86); 29 SNPs
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	0.06 0.12 0.2 0.5	<del>~</del>	

OR and 95% CI for the effect of the traits on coronary artery disease

ESM Figure 5: Univariate Mendelian randomisation estimates for the effect of the risk factors on liability to peripheral artery disease that meet the 5% FDR threshold (ESM Table 2)

Current tobacco smoking -			OR 3.61 (95% CI 1.39, 9.39); 16 SNPs
Overall health rating -			OR 2.67 (95% CI 1.81, 3.93); 52 SNPs
Body fat percentage -		-	OR 1.92 (95% CI 1.68, 2.19); 236 SNPs
Waist circumference -		-	OR 1.81 (95% CI 1.62, 2.03); 215 SNPs
Cigarettes per day -			OR 1.79 (95% CI 1.51, 2.11); 20 SNPs
Body mass index -		-	OR 1.70 (95% CI 1.56, 1.85); 478 SNPs
Trunk fat percentage -		-	OR 1.68 (95% CI 1.49, 1.89); 218 SNPs
Whole body fat mass -		-	OR 1.65 (95% CI 1.50, 1.81); 260 SNPs
Waist-to-hip ratio -			OR 1.63 (95% CI 1.19, 2.24); 30 SNPs
Fasting insulin -			OR 1.56 (95% CI 1.18, 2.05); 14 SNPs
Systolic blood pressure -		-	OR 1.55 (95% CI 1.36, 1.78); 154 SNPs
Trunk fat mass -		-	OR 1.55 (95% CI 1.41, 1.70); 267 SNPs
Sodium in urine -			OR 1.50 (95% CI 1.10, 2.04); 32 SNPs
Alcohol intake frequency -			OR 1.47 (95% CI 1.15, 1.88); 38 SNPs
Weight -		-	OR 1.39 (95% CI 1.27, 1.53); 323 SNPs
Hip circumference -		-	OR 1.31 (95% CI 1.19, 1.45); 267 SNPs
Diastolic blood pressure -		-	OR 1.27 (95% CI 1.11, 1.44); 171 SNPs
Glucose -		-	OR 1.26 (95% CI 1.10, 1.44); 97 SNPs
Alanine aminotransferase -		-	OR 1.26 (95% CI 1.12, 1.41); 188 SNPs
Triglycerides -		-	OR 1.25 (95% CI 1.16, 1.35); 216 SNPs
Glycated haemoglobin -		-	OR 1.20 (95% CI 1.12, 1.28); 286 SNPs
LDL direct -		-	OR 1.18 (95% CI 1.07, 1.30); 148 SNPs
Basal metabolic rate -		-	OR 1.18 (95% CI 1.06, 1.31); 363 SNPs
Apolipoprotein B -		-	OR 1.17 (95% CI 1.08, 1.26); 150 SNPs
Lipoprotein A -			OR 1.15 (95% CI 1.11, 1.19); 20 SNPs
Total cholesterol		-	OR 1.15 (95% CI 1.05, 1.26); 82 SNPs
Reticulocyte count -		-	OR 1.14 (95% CI 1.06, 1.22); 255 SNPs
High light scatter reticulocyte count -		-	OR 1.14 (95% CI 1.06, 1.21); 273 SNPs
High light scatter reticulocyte percentage -		-	OR 1.13 (95% CI 1.06, 1.20); 279 SNPs
Reticulocyte percentage -		-	OR 1.13 (95% CI 1.05, 1.20); 255 SNPs
Neuroticism score -		-	OR 1.12 (95% CI 1.05, 1.18); 63 SNPs
Phosphate -		-	OR 1.11 (95% CI 1.03, 1.21); 136 SNPs
Urate -		-	OR 1.10 (95% CI 1.02, 1.18); 227 SNPs
Monocyte percentage -			OR 0.93 (95% CI 0.88, 0.99); 290 SNPs
Monocyte count -			OR 0.93 (95% CI 0.88, 0.98); 305 SNPs
SHBG -			OR 0.86 (95% CI 0.80, 0.93); 240 SNPs
Apolipoprotein A -			OR 0.86 (95% CI 0.80, 0.92); 221 SNPs
Impedance of whole body -	-		OR 0.81 (95% CI 0.72, 0.91); 342 SNPs
HDL cholesterol -			OR 0.80 (95% CI 0.74, 0.85); 246 SNPs
Birth weight -			OR 0.79 (95% CI 0.69, 0.92); 80 SNPs
Forced vital capacity (FVC)	-		OR 0.77 (95% CI 0.68, 0.87); 211 SNPs
Past tobacco smoking -			OR 0.68 (95% CI 0.53, 0.86); 41 SNPs
Usual walking pace			OR 0.34 (95% CI 0.17, 0.66); 28 SNPs
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	0.03 0.12 0.2 0.5	<del>,</del>	



ESM Figure 6: Comparison plot illustrating the difference in all Mendelian randomisation estimates when using a linear GWAS model for liability to type 2 diabetes versus a logistic GWAS model for liability to type  $2~{\rm diabetes}$ 



Univariate MR • Two-step MR for mediation, direct effect • Two-step MR for mediation, indirect effect