SUPPLEMENTAL MATERIAL

Table S1. Post-hoc power calculation for the IVW analyses on modifiable risk factors and peripheral artery disease for analyses done in the Million Veteran Program cohort and the GoLEAD-SUMMIT cohort.

Risk factor	Sample size*	Ratio cases to controls*	R^2 of exposure by genetic variants†	Causal effect‡ (OR according to IVW)	Significance level	Power§
	MVP/GoLEAD-SUMMIT	MVP/GoLEAD-SUMMIT		MVP/GoLEAD-SUMMIT		MVP/GoLEAD-SUMMIT
Diabetes						
Type 2 diabetes	243,060 / 461,634	1:6.8 / 1:37.2	0.163	1.18 / 1.16	0.0025	**100% / 100%**
Fasting glucose	243,060 / 461,634	1:6.8 / 1:37.2	0.048	1.41[a] / 1.21[a]	0.0025	**100% / 93.4%**
Cholesterol						
LDL cholesterol	243,060 / 461,634	1:6.8 / 1:37.2	0.146	1.23 / 1.13	0.0025	**100% / 97.9%**
HDL cholesterol	243,060 / 461,634	1:6.8 / 1:37.2	0.137	0.84 / 0.81	0.0025	**100% / 100%**
Triglycerides	243,060 / 461,634	1:6.8 / 1:37.2	0.117	1.15 / 1.08	0.0025	**100% / 43.3%**
Smoking						
Smoking initiation	243,060 / 461,634	1:6.8 / 1:37.2	0.023	1.48 / 1.59	0.0025	**100% / 100%**
Smoking cessation	243,060 / 461,634	1:6.8 / 1:37.2	0.001	1.25 / 1.66	0.0025	**3.1% / 9.9%**
Cigarettes per day	243,060 / 461,634	1:6.8 / 1:37.2	0.01	1.90 / 1.87	0.0025	**100% / 100%**
Diet						
Alcohol consumption	243,060 / 461,634	1:6.8 / 1:37.2	0.002	0.95 / 1.87	0.0025	**0.4% / 50.5%**
Coffee consumption	243,060 / 461,634	1:6.8 / 1:37.2	0.0048	1.01[b] / 1.13[b]	0.0025	**0.2% / 1.8%**
Physical activity						
MVPA	243,060 / 461,634	1:6.8 / 1:37.2	0.00073	1.12 / 0.54	0.0025	**0.6% / 11.2%**
Sedentary behaviour	243,060 / 461,634	1:6.8 / 1:37.2	0.0008	1.19 / 0.78	0.0025	**1.3% / 1.2%**
Sleep						
Insomnia	243,060 / 461,634	1:6.8 / 1:37.2	0.026	1.10 / 1.20	0.0025	**31.2% / 56.6%**
Sleep duration	243,060 / 461,634	1:6.8 / 1:37.2	0.0069	0.69[c] / 0.63	0.0025	**98% / 87.3%**
Short sleep duration	243,060 / 461,634	1:6.8 / 1:37.2	NA	1.20 / 1.56	0.0025	**NA**
Long sleep duration	243,060 / 461,634	1:6.8 / 1:37.2	NA	0.82 / 0.75	0.0025	**NA**
Education						
Educational level	243,060 / 461,634	1:6.8 / 1:37.2	0.11	0.58 / 0.50	0.0025	**100% / 100%**

* Sample size and ratio cases to controls according to the outcome GWAS on PAD, in both the MVP and the GoLEAD-SUMMIT cohort

† Variance explained of exposure by genetic variants as reported in GWASs on the different modifiable risk factors

‡ OR per 1-SD change for continuous exposures

§ Calculated using an online power calculation tool (https://sb452.shinyapps.io/power/)

a OR per 1-SD increase in fasting glucose, using an SD of 0.5 mmol/L approximated from the study characteristics in the GWAS meta-analysis

b OR per 50% increase in coffee consumption. SD was not provided in GWAS meta-analysis

c OR per 1-SD increase in sleep duration, using an SD of 1.1 h as reported in the GWAS

Abbreviations: MVP: Genome wide association study on peripheral artery disease, executed by the Million veteran program; GoLEAD-SUMMIT: Genome wide association study, executed by the GoLEAD-SUMMIT consortium: IVW = inverse-variance weighted; LDL = low-density lipoprotein; HDL = high-density lipoprotein; MVP: MVPA = moderate-to-vigorous physical activity; NA: = not available; OR = odds ratio; PAD: peripheral artery disease.

Table S2A. Results of the main and sensitivity analyses of the Mendelian randomization study on cardiovascular risk factors and lifestyle behaviors with peripheral artery disease in the Million Veteran Program cohort.

	MR Method									
	IVW			Weighted median		MR-Egger				
Lifestyle factors	OR (95% CI)	P-value	Cochran's Q P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	Intercept value	Intercept P-value	Cochran's Q P-value
Diabetes										
Type 2 diabetes	1.18 (1.15;1.21)	**2.12E-34**	5.76E-20	1.19 (1.15;1.23)	**6.00E-21**	1.12 (1.06;1.17)	**2.16E-5**	0.004	0.012	8.41E-19
Fasting glucose	1.41 (1.11;1.79)	*5.23E-3*	1.55E-11	1.18 (0.98;1.43)	0.076	0.96 (0.63;1.46)	0.85	0.013	0.032	1.72E-9
Lipid metabolism										
LDL-C	1.23 (1.13;1.33)	**2.68E-6**	5.73E-15	1.26 (1.16;1.36)	**3.00E-8**	1.33 (1.15;1.54)	**1.20E-4**	-0.006	0.18	2.61E-14
HDL-C	0.84 (0.77;0.91)	**4.91E-5**	6.07E-16	0.90 (0.84;0.97)	*6.09E-3*	0.92 (0.81;1.04)	0.19	-0.007	0.06	1.46E-14
Triglycerides	1.15 (1.03;1.28)	*0.014*	1.05E-11	1.17 (1.07;1.27)	**5.37E-4**	1.08 (0.92;1.27)	0.35	0.005	0.35	1.69E-11
Smoking										
Smoking initiation	1.48 (1.38;1.59)	**1.28E-28**	6.83E-8	1.48 (1.35;1.62)	**1.45E-17**	1.98 (1.47;2.65)	**5.50E-6**	-0.006	0.05	1.39E-7
Smoking cessation	1.25 (0.92;1.70)	0.15	9.36E-11	1.29 (0.97:1.72)	0.085	0.59 (0.25;1.42)	0.24	0.028	0.07	7.26E-9
Number of cigarettes per day	1.90 (1.62;2.24)	**8.20E-15**	0.001	1.71 (1.42;2.06)	**1.04E-8**	1.66 (1.25;2.20)	**3.98E-4**	0.004	0.25	0.00129
Diet										
Alcohol consumption	1.12 (0.84;1.49)	0.42	2.37E-10	1.19 (0.85;1.67)	0.31	1.20 (0.62;2.31)	0.59	-0.001	0.83	1.59E-10
Coffee consumption	1.19 (0.92;1.54)	0.18	4.02E-6	1.10 (0.91;1.33)	0.34	1.08 (0.65;1.80)	0.75	0.005	0.67	2.57E-6
Physical activity										
MVPA	0.95 (0.37;2.44)	0.91	3.76E-04	0.97 (0.45;2.09)	0.95	0.16 (0.01;3.13)	0.23	0.32	0.22	0.00191
Sedentary behavior	1.01 (0.65;1.57)	0.98	0.142	1.02 (0.67;1.55)	0.94	NA	-	-0.003	0.99	0.0655
Sleep										
Insomnia	1.10 (1.05;1.14)	**1.53E-5**	2.3E-10	1.12 (1.06;1.18)	**2.06E-5**	0.99 (0.84;1.17)	0.92	0.005	0.23	2.98E-10
Sleep duration	0.69 (0.54;0.87)	**1.99E-3**	1.21E-11	0.76 (0.58;0.98)	*0.033*	1.00 (0.84;1.17)	1.00	-0.006	0.40	1.30E-11
Short sleep duration	1.20 (1.04;1.38)	*0.013*	0.0676	1.18 (0.99;1.40)	0.072	1.39 (0.84;2.29)	0.20	-0.005	0.54	0.0586
Long sleep duration	0.82 (0.59;1.12)	0.22	5.19E-5	0.92 (0.74;1.15)	0.47	2.09 (1.01;4.31)	*0.046*	-0.063	0.01	0.0334

Education										
Educational level	0.58 (0.54;0.62)	**1.50E-62**	2.01E-11	0.58 (0.53;0.64)	**3.79E-32**	0.59 (0.47;0.75)	**1.02E-5**	0.00	0.80	1.83E-11

Odds ratios display the association of listed cardiovascular risk factors and lifestyle behaviors with peripheral artery disease. The P-values of the OR are displayed in bold if below the Bonferroni-corrected threshold of 0.00294, and in bold-italic if between 0.00294 and 0.05.
Abbreviations: CI = confidence interval; HDL-C = High-density lipoprotein cholesterol; IVW = inverse-variance weighted; LDL-C = Low-density lipoprotein cholesterol; MR = Mendelian randomization; MR-PRESSO = Mendelian Randomization Pleiotropy RESidual Sum and Outlier; MVPA = Moderate-to-vigorous physical activity; NA = not applicable; OR = odds ratio; SD = standard deviation

Table S2B. Results of the main and sensitivity analyses of the Mendelian randomization study on cardiovascular risk factors and lifestyle behaviors with peripheral artery disease in the Million Veteran Program cohort.

	MR Method								
	IVW			Contamination Mixture		MR-PRESSO			
Risk factors	OR (95% CI)	P-value	Cochran's Q P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	Global test P-value	Distortion test P value
Diabetes									
Type 2 diabetes	1.18 (1.15;1.21)	**2.12E-34**	5.76E-20	1.19 (1.16;1.22)	**2.87E-19**	1.18 (1.15;1.21)	**1.38E-30**	<0.0001	0.93
Fasting glucose	1.41 (1.11;1.79)	*5.23E-3*	1.55E-11	1.18 (1.03;1.39)	*0.03*	1.26 (1.05;1.51)	*0.02*	<0.0001	**0.05**
Lipid metabolism									
LDL-C	1.23 (1.13;1.33)	**2.68E-6**	5.73E-15	1.27 (1.15;1.36)	**1.05E-5**	1.22 (1.14;1.31)	**8.14E-7**	<0.0001	0.963
HDL-C	0.84 (0.77;0.91)	**4.91E-5**	6.07E-16	0.85 (0.72;0.90)	**9.64E-6**	0.84 (0.78;0.89)	**2.12E-6**	<0.0001	0.92
Triglycerides	1.15 (1.03;1.28)	*0.014*	1.05E-11	1.16 (1.09;1.24)	**1.24E-3**	1.16 (1.06;1.27)	*0.003*	<0.0001	0.78
Smoking									
Smoking initiation	1.48 (1.38;1.59)	**1.28E-28**	6.83E-8	1.72 (1.59;1.89)	**2.73E-20**	1.47 (1.38;1.58)	**1.49E-24**	<0.0001	0.87
Smoking cessation	1.25 (0.92;1.70)	0.15	9.36E-11	NA	**-**	1.31 (0.99;1.73)	0.07	<0.0001	0.66
Number of cigarettes per day	1.90 (1.62;2.24)	**8.20E-15**	0.001	1.89 (1.68;2.41)	**3.81E-10**	1.85 (1.61;2.12)	**3.39E-11**	0.003	0.69
Diet									
Alcohol consumption	1.12 (0.84;1.49)	0.42	2.37E-10	1.60 (0.91;2.56)	0.09	1.27 (0.98;1.64)	0.07	<0.0001	0.57
Coffee consumption	1.19 (0.92;1.54)	0.18	4.02E-6	1.19 (1.02;1.65)	*0.03*	1.16 (1.00;1.34)	0.07	0.0001	0.69
Physical activity									
MVPA	0.95 (0.37;2.44)	0.91	3.76E-04	NA	-	1.22 (0.74;2.03)	0.48	0.002	0.18
Sedentary behavior	1.01 (0.65;1.57)	0.98	0.142	1.22 (0.30;3.56)	0.55	1.01 (0.65;1.57)	0.98	0.213	NA
Sleep									
Insomnia	1.10 (1.05;1.14)	**1.53E-5**	2.3E-10	1.23 (1.16;1.29)	**1.62E-7**	1.10 (1.05;1.14)	**1.40E-5**	<0.0001	0.98
Sleep duration	0.69 (0.54;0.87)	**1.99E-3**	1.21E-11	0.62 (0.44;0.77)	*4.02E-3*	0.75 (0.61;0.93)	*0.01*	<0.0001	0.26
Short sleep duration	1.20 (1.04;1.38)	*1.31E-2*	0.0676	1.28 (1.08;1.48)	*0.018*	1.20 (1.04;1.38)	*0.02*	0.071	NA

Long sleep duration	0.82 (0.59;1.12)	0.22	5.19E-5	0.96 (0.80;1.18)	0.65	0.85 (0.69;1.06)	0.22	0.0005	0.68
Education									
Educational level	0.58 (0.54;0.62)	**1.50E-62**	2.01E-11	0.44 (0.41;0.51)	**6.12E-38**	0.58 (0.53;0.61)	**3.86E-57**	<4E-5	0.93

Odds ratios display the association of listed cardiovascular risk factors and lifestyle behaviors with peripheral artery disease. The P-values of the OR are displayed in bold if below the Bonferroni-corrected threshold of 0.00294, and in bold-italic if between 0.00294 and 0.05.
Abbreviations: CI = confidence interval; HDL-C = High-density lipoprotein cholesterol; IVW = inverse-variance weighted; LDL-C = Low-density lipoprotein cholesterol; MR = Mendelian randomization; MR-PRESSO = Mendelian Randomization Pleiotropy RESidual Sum and Outlier; MVPA = Moderate-to-vigorous physical activity; NA = not applicable; OR = odds ratio; SD = standard deviation

Table S3A. Results of the main and sensitivity analyses the this Mendelian randomization study on cardiovascular risk factors and lifestyle behaviors with peripheral artery disease in the GoELAD-SUMMIT cohort.

	MR Method									
	IVW			Weighted median		MR-Egger				
Lifestyle factors	OR (95% CI)	P-value	Cochran's Q P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	Intercept value	Intercept P-value	Cochran's Q P-value
Diabetes										
Type 2 diabetes	1.16 (1.12;1.21)	**3.71E-14**	<0.0001	1.11 (1.04;1.18)	**0.0014**	1.02 (0.94;1.11)	0.57	0.01	3.37E-4	<0.0001
Fasting glucose	1.21 (0.91;1.61)	0.20	0.0126	1.15 (0.82;1.62)	0.40	1.06 (0.62;1.79)	0.84	0.004	0.55	0.01
Lipid metabolism										
LDL-C	1.13 (0.99;1.30)	0.07	<0.0001	1.13 (1.00;1.29)	0.052	1.34 (1.06;1.69)	*0.013*	-0.01	0.08	<0.0001
HDL-C	0.81 (0.73:0.91)	**2.14E-4**	<0.0001	0.78 (0.68;0.90)	**8.26E-4**	0.83 (0.69;0.99)	*0.038*	-0.001	0.76	<0.0001
Triglycerides	1.08 (0.93;1.25)	0.31	<0.0001	1.13 (0.98;1.31)	0.082	1.25 (1.02;1.54)	*0.033*	-0.01	0.05	0.0003
Smoking										
Smoking initiation	1.59 (1.42;1.76)	**2.87E-17**	<0.0001	1.70 (1.46;1.97)	**2.29E-12**	2.78 (1.76;4.38)	**1.08E-5**	-0.01	0.01	<0.0001
Smoking cessation	1.66 (1.12;2.45)	*0.012*	0.001	1.78 (1.17;2.70)	*0.0067*	0.78 (0.27;2.23)	0.65	0.03	0.13	2.80E-3
Number of cigarettes per day	1.87 (1.49;2.36)	**8.66E-8**	0.256	2.26 (1.61;3.16)	**2.26E-6**	2.09 (1.40;3.13)	**3.39E-4**	-0.004	0.52	0.24
Diet										
Alcohol consumption	1.87 (1.27;2.75)	**0.0015**	3.00E-4	2.41 (1.48;3.91)	**3.81E-4**	3.79 (1.85;7.75)	**2.66E-4**	-0.01	0.02	0.0001
Coffee consumption	1.13 (0.75;1.69)	0.56	<0.0001	1.00 (0.73;1.37)	1.00	1.08 (0.50;2.35)	0.84	0.002	0.90	0.0002
Physical activity										
MVPA	0.54 (0.10;2.99)	0.48	4.00E-4	1.27 (0.34;4.70)	0.72	-	-	-	-	-
Sedentary behavior	0.78 (0.4;1.35)	0.37	0.32	0.76 (0.40;1.42)	0.34	-	-	-	-	-
Sleep										
Insomnia	1.20 (1.13;1.28)	**1.06E-9**	0.002	1.21 (1.12;1.31)	**3.50E-6**	1.28 (1.02;1.63)	*0.037*	-0.003	0.57	<0.0001
Sleep duration	0.63 (0.48;0.83)	**8.28E-4**	0.093	0.51 (0.35;0.75)	**7.10E-4**	0.90 (0.31;2.56)	0.84	-0.01	0.49	0.087
Short sleep duration	1.56 (1.25;1.95)	***8.8E-5***	0.30	1.49 (1.10;2.02)	*0.01*	1.10 (0.51;2.37)	0.82	0.01	0.35	0.30
Long sleep duration	0.75 (0.56; 1.00)	0.053	0.092	0.72 (0.53;0.98)	*0.03*	1.14 (0.50;2.56)	0.76	-0.03	0.29	0.12
Education										

Educational level	0.50 (0.45;0.56)	**2.63E-38**	<0.0001	0.44 (0.38;0.52)	**5.24E-25**	0.51 (0.35;0.75)	**4.61E-4**	0.00	0.91	<0.0001

Odds ratios display the association of listed cardiovascular risk factors and lifestyle behaviors with peripheral artery disease. The P-values of the OR are displayed in bold if below the Bonferroni-corrected threshold of 0.00294, and in bold-italic if between 0.00294 and 0.05.
Abbreviations: CI = confidence interval; HDL-C = High-density lipoprotein cholesterol; IVW = inverse-variance weighted; LDL-C = Low-density lipoprotein cholesterol; MR = Mendelian randomization; MR-PRESSO = Mendelian Randomization Pleiotropy RESidual Sum and Outlier; MVPA = Moderate-to-vigorous physical activity; NA = not applicable; OR = odds ratio; SD = standard deviation

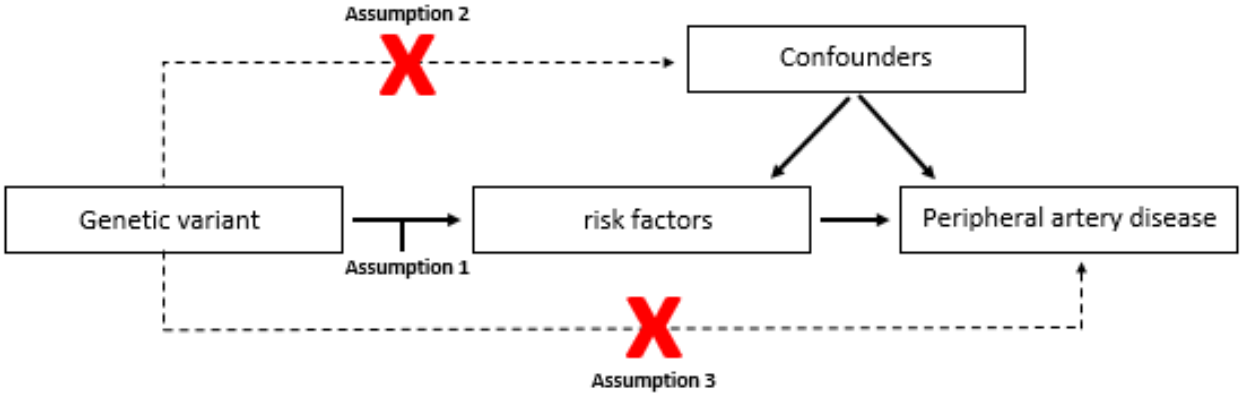
Table S3B. Results of the main and sensitivity analyses the this Mendelian randomization study on cardiovascular risk factors and lifestyle behaviors with peripheral artery disease in the GoELAD-SUMMIT cohort.

	MR Method								
	IVW			Contamination Mixture		MR-PRESSO			
Risk factors	OR (95% CI)	P-value	Cochran's Q P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	Global test P-value	Distortion test P value
Diabetes									
Type 2 diabetes	1.16 (1.12;1.21)	**3.71E-14**	<0.0001	1.14 (1.05;1.20)	**1.56E-3**	1.15 (1.11;1.19)	**1.17E-12**	<0.0001	0.61
Fasting glucose	1.21 (0.91;1.61)	0.20	0.0126	1.11 (0.81;1.42)	0.52	1.21 (0.91;1.61)	0.21	0.017	NA
Lipid metabolism									
LDL-C	1.13 (0.99;1.30)	0.07	<0.0001	1.18 (1.08;1.29)	**0.0025**	1.15 (1.05;1.26)	*0.0045*	<0.0001	0.77
HDL-C	0.81 (0.73:0.91)	**2.14E-4**	<0.0001	0.72 (0.62;0.83)	**6.95E-4**	0.81 (0.73;0.90)	**0.0001**	<0.0001	0.99
Triglycerides	1.08 (0.93;1.25)	0.31	<0.0001	1.14 (1.01;1.29)	*0.034*	1.14 (1.02;1.28)	*0.027*	<0.0001	0.47
Smoking									
Smoking initiation	1.59 (1.42;1.76)	**2.87E-17**	<0.0001	1.75 (1.54;2.10)	**3.53E-9**	1.57 (1.41;1.75)	**1.19E-15**	<0.0001	0.87
Smoking cessation	1.66 (1.12;2.45)	*0.012*	0.001	3.11 (1.64;4.73)	**6.48E-4**	1.90 (1.33;2.69)	**0.0021**	0.001	0.051
Number of cigarettes per day	1.87 (1.49;2.36)	**8.66E-8**	0.256	2.47 (1.90;3.11)	**7.15E-5**	1.87 (1.49;2.36)	**2.67E-06**	0.22	NA
Diet									
Alcohol consumption	1.87 (1.27;2.75)	**0.0015**	3.00E-4	2.47 (1.04;3.61)	*0.044*	1.87 (1.27;2.75)	**0.0021**	<0.0001	NA
Coffee consumption	1.13 (0.75;1.69)	0.56	<0.0001	0.96 (0.74;1.24)	0.76	1.03 (0.73;1.47)	0.86	0.0019	0.15
Physical activity									
MVPA	0.54 (0.10;2.99)	0.48	4.00E-4	1.94 (0.57;6.19)	0.23	1.94 (0.95;3.93)	0.18	0.00396	**0.0075**
Sedentary behavior	0.78 (0.44;1.35)	0.37	0.32	0.67 (0.16;4.03)	0.29	0.78 (0.44;1.35)	0.44	0.46	NA
Sleep									
Insomnia	1.20 (1.13;1.28)	**1.06E-9**	0.002	1.25 (1.18;1.34)	**4.02E-7**	1.21 (1.14;1.27)	**1.28E-10**	0.0021	0.90
Sleep duration	0.63 (0.48;0.83)	**8.28E-4**	0.093	0.56 (0.37;1.00)	0.053	0.63 (0.48;0.83)	**0.0013**	0.089	NA

Short sleep duration	1.56 (1.25;1.95)	***8.8E-5***	0.30	1.57 (1.14;2.12)	*0.0044*	1.56 (1.25;1.95)	**0.0006**	0.32	NA
Long sleep duration	0.75 (0.56; 1.00)	0.053	0.092	0.63 (0.39;1.04)	0.052	0.75 (0.56;1.00)	0.10	0.12	NA
Education									
Educational level	0.50 (0.45;0.56)	**2.63E-38**	<0.0001	0.38 (0.33;0.44)	**8.14E-24**	0.51 (0.46;0.56)	**2.67E-36**	<4E-5	0.90

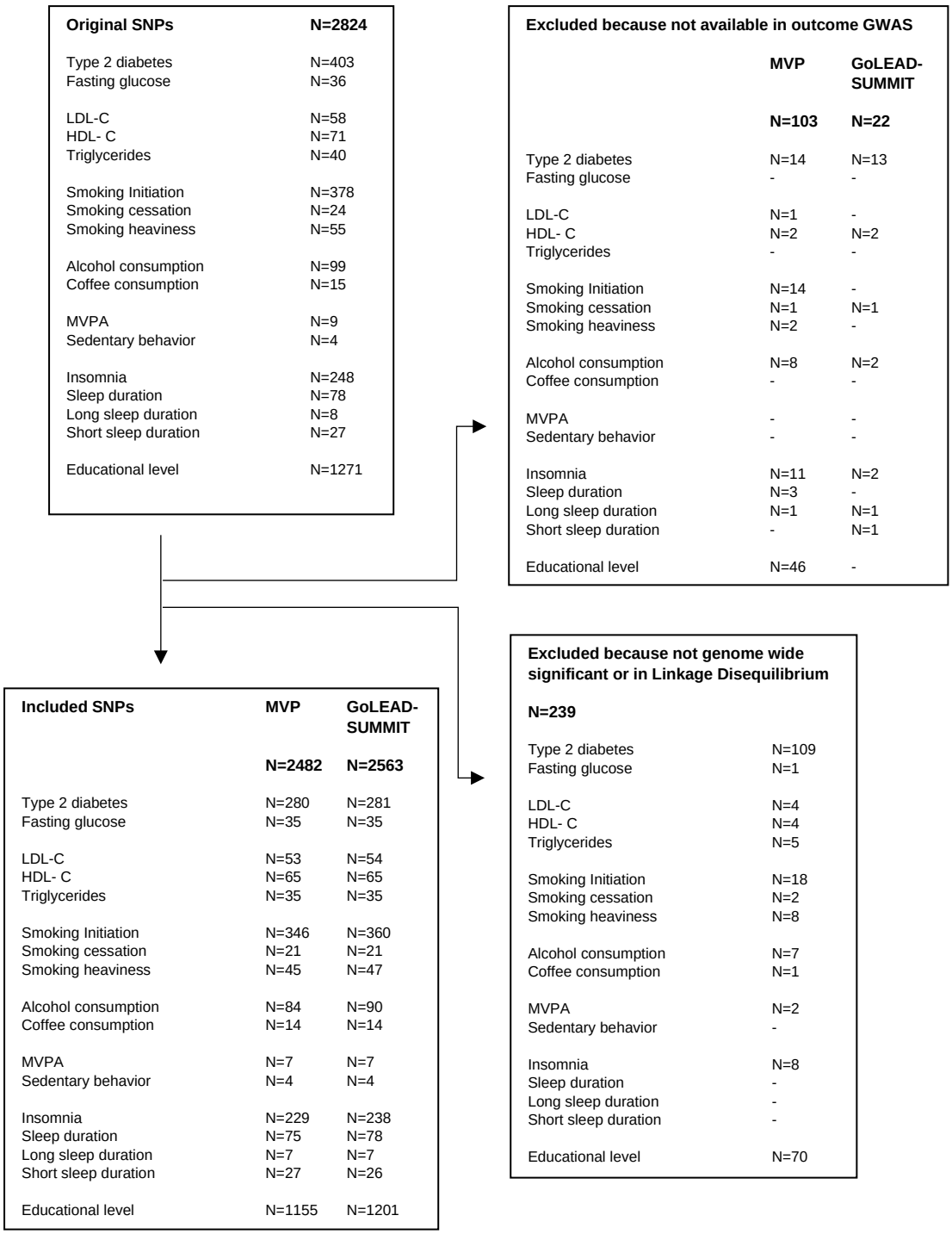
Odds ratios display the association of listed cardiovascular risk factors and lifestyle behaviors with peripheral artery disease. The P-values of the OR are displayed in bold if below the Bonferroni-corrected threshold of 0.00294, and in bold-italic if between 0.00294 and 0.05.
Abbreviations: CI = confidence interval; HDL-C = High-density lipoprotein cholesterol; IVW = inverse-variance weighted; LDL-C = Low-density lipoprotein cholesterol; MR = Mendelian randomization; MR-PRESSO = Mendelian Randomization Pleiotropy RESidual Sum and Outlier; MVPA = Moderate-to-vigorous physical activity; NA = not applicable; OR = odds ratio; SD = standard deviation

Figure S1. Overview of the instrumental variable assumptions of the MR design.



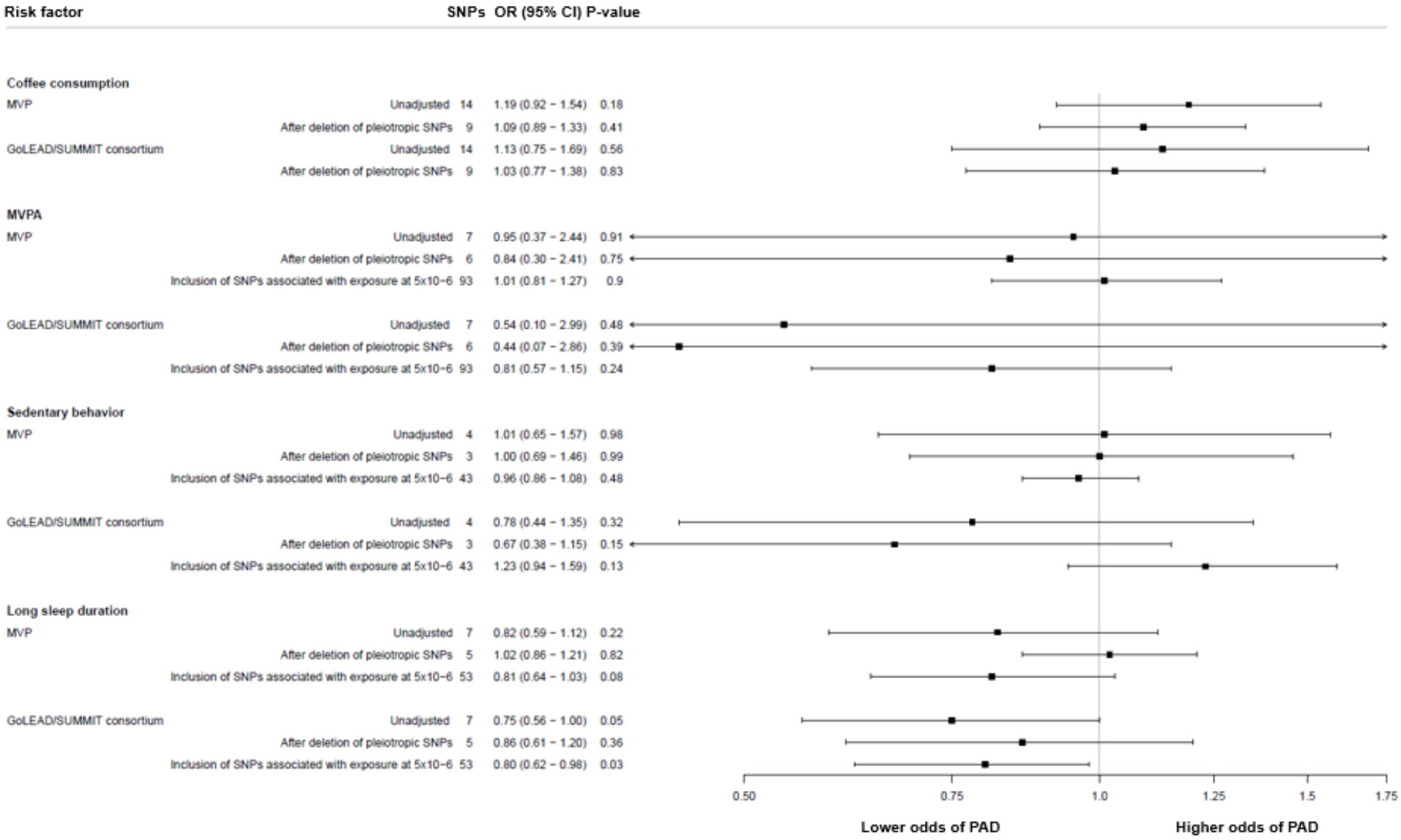
Mendelian randomization assumptions: (i) the SNPs are associated with the exposure; (ii) the SNPs are independent of confounders of the risk factor– outcome association; and (iii) the SNPs influence the outcome only via the exposure

Figure S2. Flowchart of all included single nucleotide polymorphisms in this mendelian randomization study on on cardiovascular risk factors and lifestyle behaviors with peripheral artery disease.



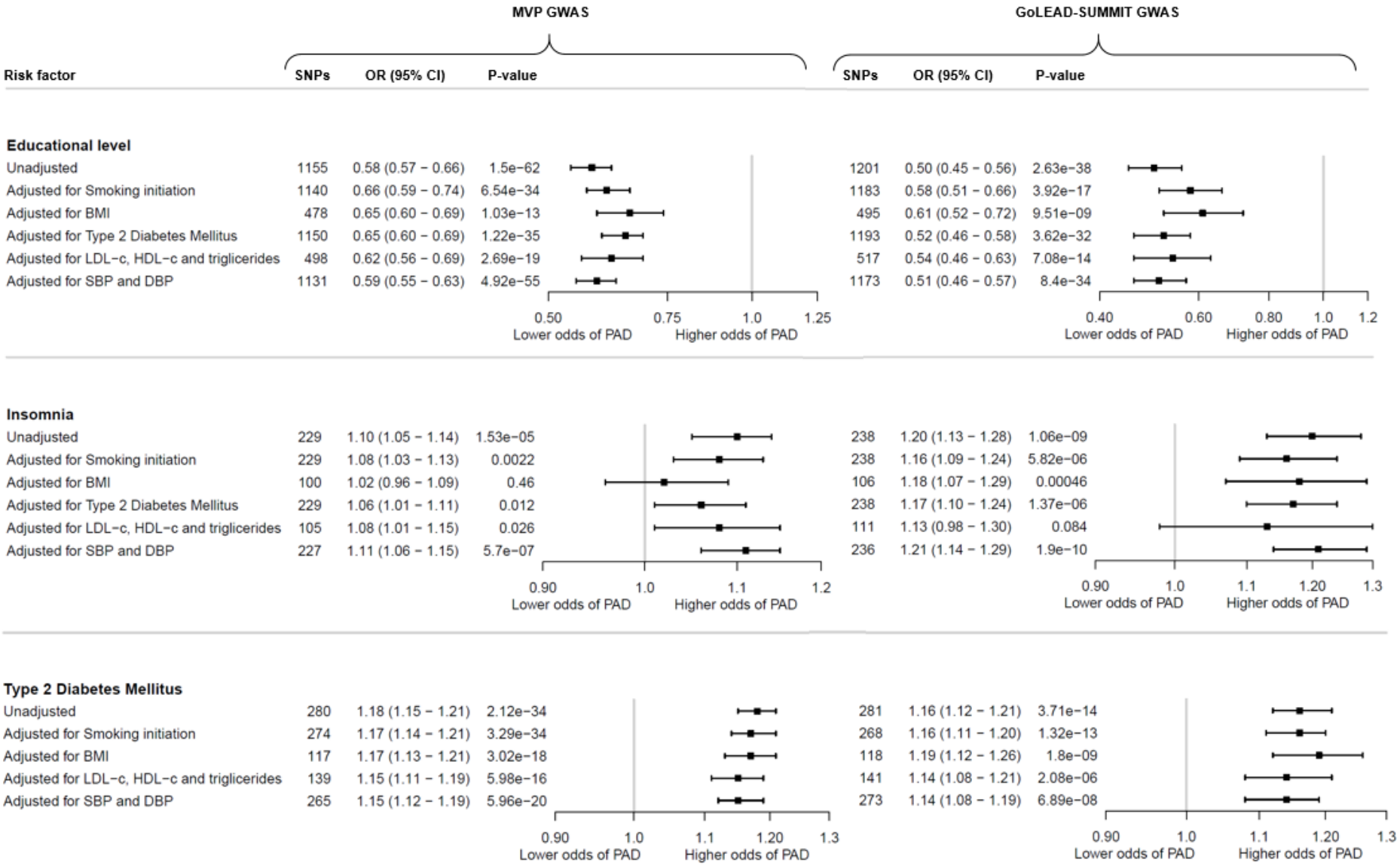
Abbreviations: SNPs = single nucleotide polymorphisms; LDL-C = Low density lipoprotein cholesterol; HDL-C = High density lipoprotein cholesterol; MVPA = Moderate to vigorous physical activity; MVP: Genome wide association study on peripheral artery disease, executed by the Million veteran program; GoLEAD-SUMMIT: Genome wide association study, executed by the GoLEAD-SUMMIT consortium

Figure S3. Sensitivity analyses for weak IVs: Results of IVW analysis after manual exclusion of possible pleiotropic SNPs in in exposures with <20 SNPs, and results of IVW analysis for MVPA, sedentary behaviour and long sleep duration using a more liberal threshold ($P<5x10^{-6}$) for selecting SNPs.



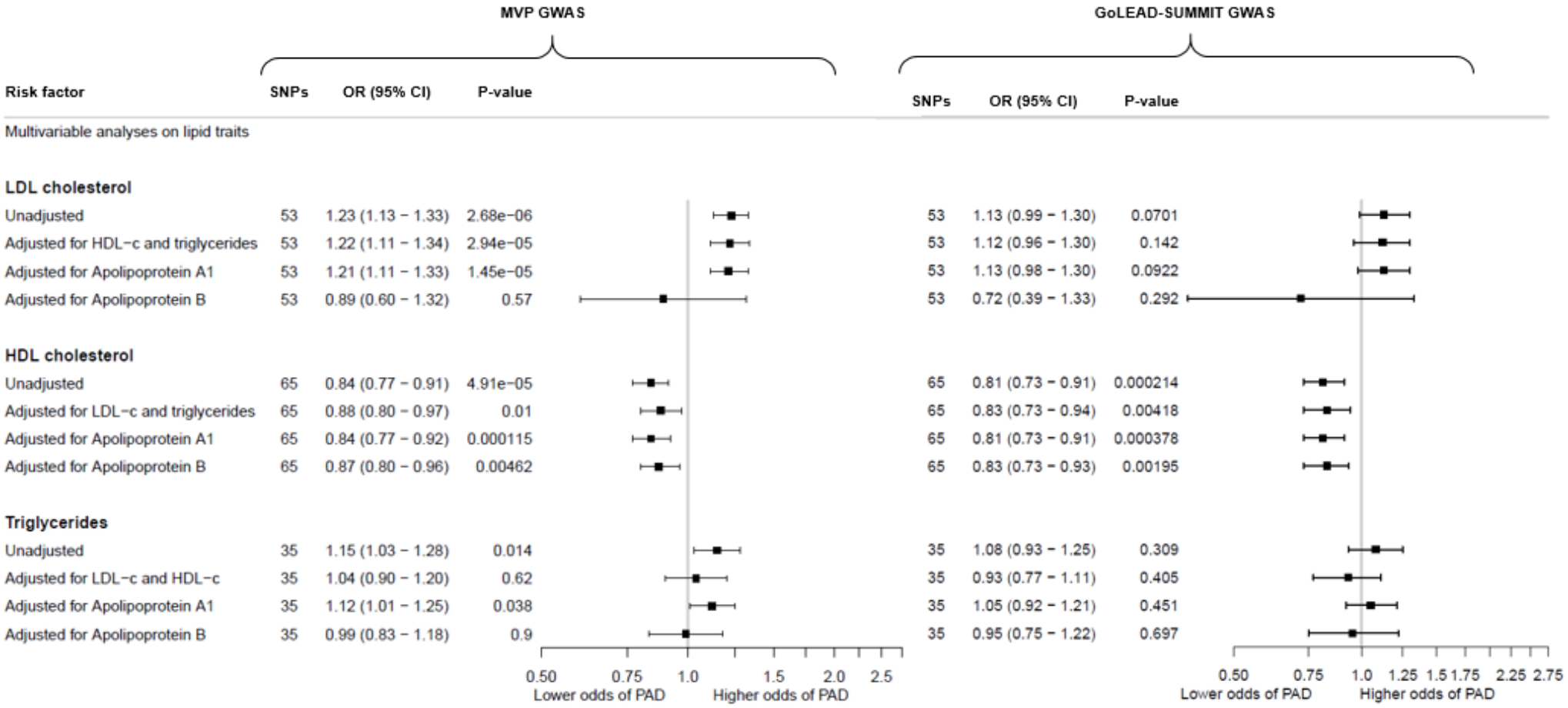
Odds ratios represent the associations of peripheral artery disease with listed risk factors.
Abbreviations: CI, confidence interval; OR, odds ratio; SNPs, single nucleotide polymorphisms MVP: Genome wide association study on peripheral artery disease, executed by the Million veteran program; MVPA; MVPA = moderate-to-vigorous physical activity, GoLEAD-SUMMIT: Genome wide association study, executed by the GoLEAD-SUMMIT consortium, IV; Instrumental variable, IVW; Inverse Variant Weighted

Figure S4. Sensitivity analyses to adjust for the genetic correlation between potential mediators of the relationship between educational level, insomnia, type 2 diabetes and peripheral artery disease.



Odds ratios represent the associations of peripheral artery disease with listed risk factors.
Abbreviations: CI, confidence interval; BMI: body mass index; DBP; diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; SNPs, single nucleotide polymorphisms, SBP; systolic blood pressure, MVP: Genome wide association study on peripheral artery disease, executed by the Million veteran program; GoLEAD-SUMMIT: Genome wide association study, executed by the GoLEAD-SUMMIT consortium

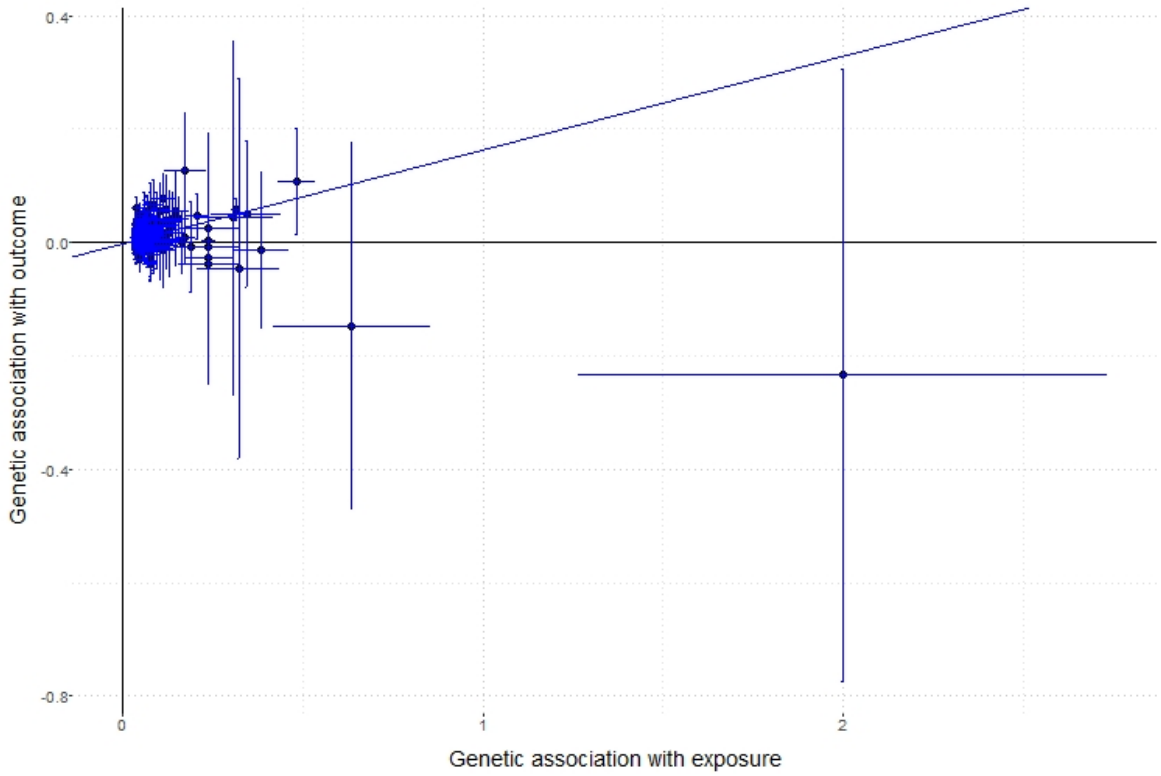
Figure S5. Sensitivity analyses to adjust for the genetic correlation between lipid traits and the lipid subfractions apolipoprotein A1 and B.



Odds ratios represent the associations of peripheral artery disease with listed risk factors.
Abbreviations: CI, confidence interval; GWAS, genome wide association study, HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; SNPs, single nucleotide polymorphisms; PAD, peripheral artery disease, MVP: Genome wide association study on peripheral artery disease, executed by the Million veteran program; GoLEAD-SUMMIT: Genome wide association study, executed by the GoLEAD-SUMMIT consortium.

Figure S6A. The association between the SNPs and type 2 diabetes versus the association between the SNPs and peripheral artery disease.
The regression line was calculated using the inverse-variance weighted method.
Abbreviations: SNP = single nucleotide polymorphism**. A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.

A.



B.

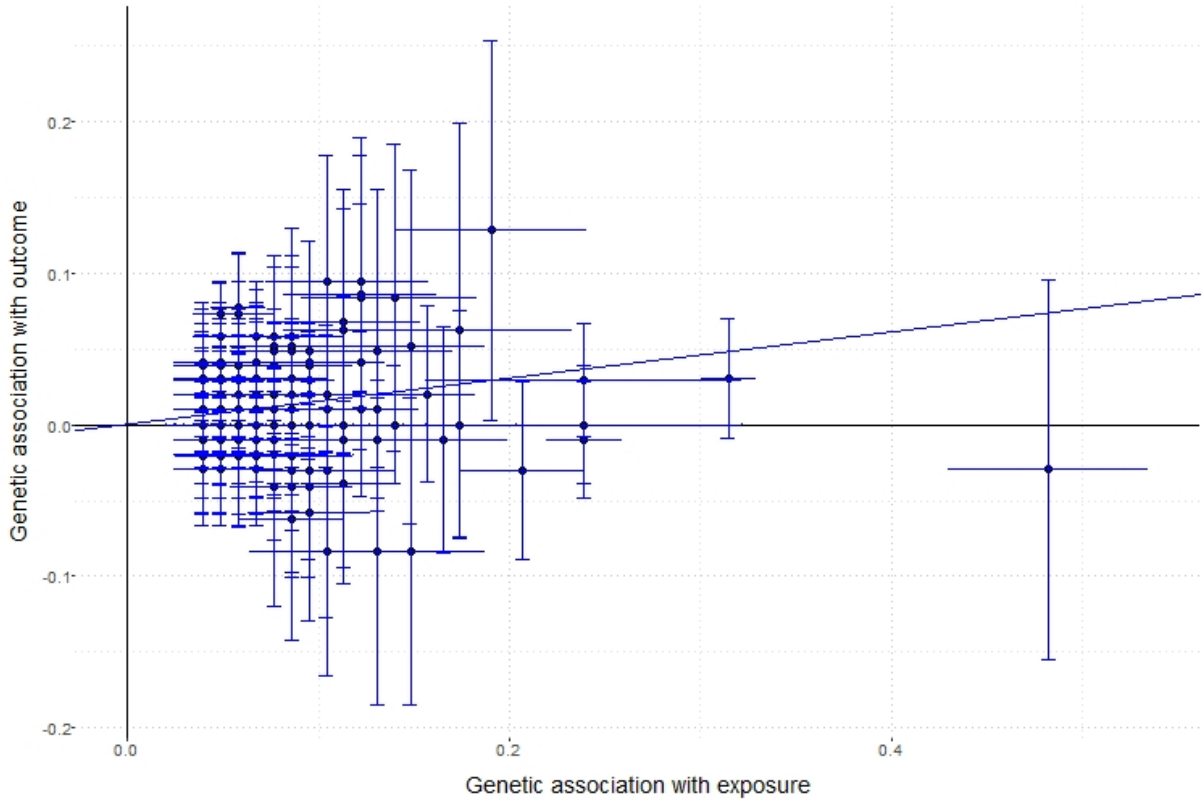
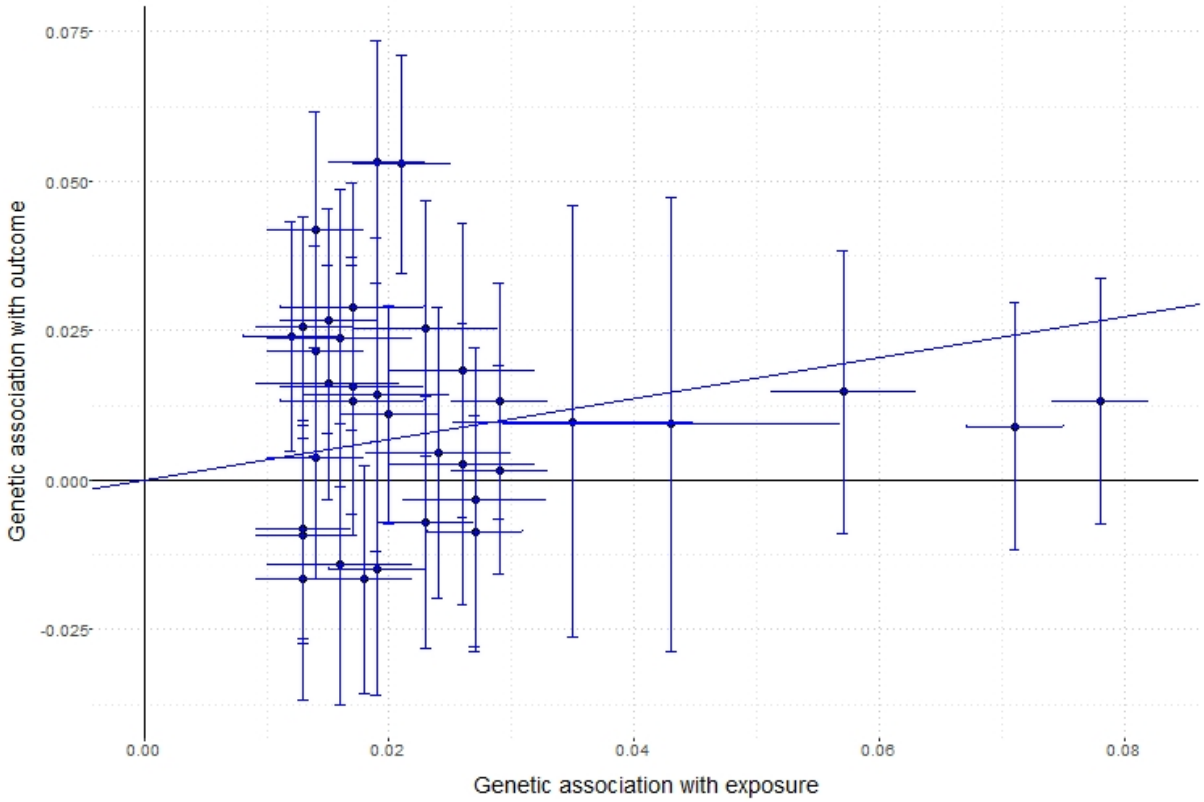


Figure S6B. The association between the SNPs and 1 mmol/L change in glucose versus the association between the SNPs and peripheral artery disease.

The regression line was calculated using the inverse-variance weighted method.

Abbreviations: SD = standard deviation; SNP = single nucleotide polymorphism **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.

A.



B.

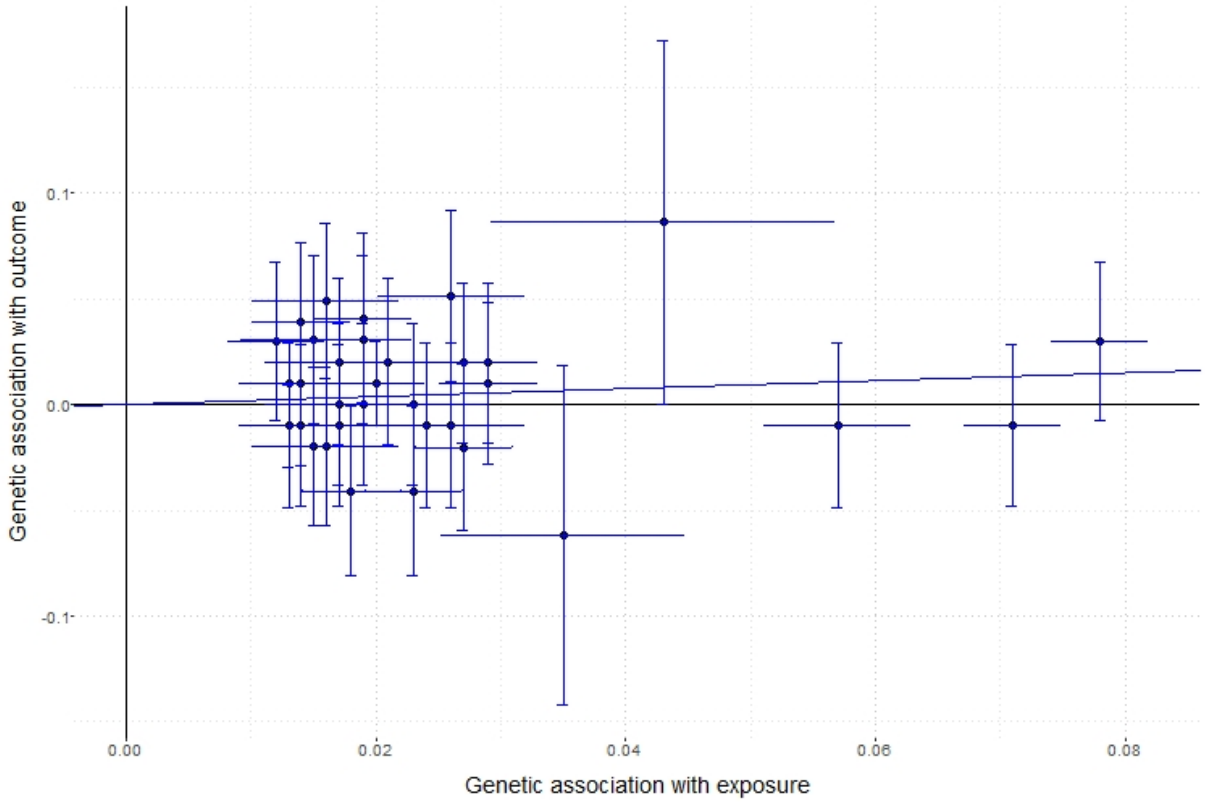
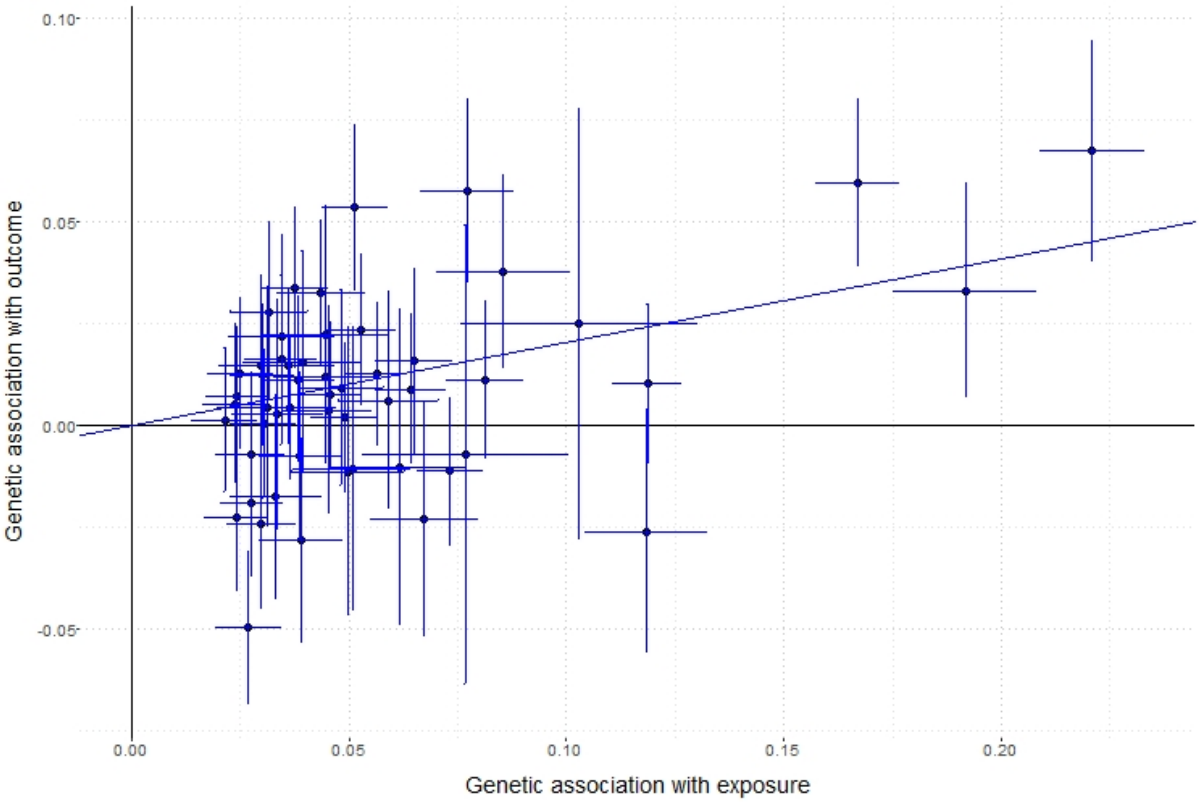


Figure S6C. The association between the SNPs and 1 SD change in LDL-C versus the association between the SNPs and peripheral artery disease.
The regression line was calculated using the inverse-variance weighted method.
Abbreviations: SNP = single nucleotide polymorphism **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.

A.



B.

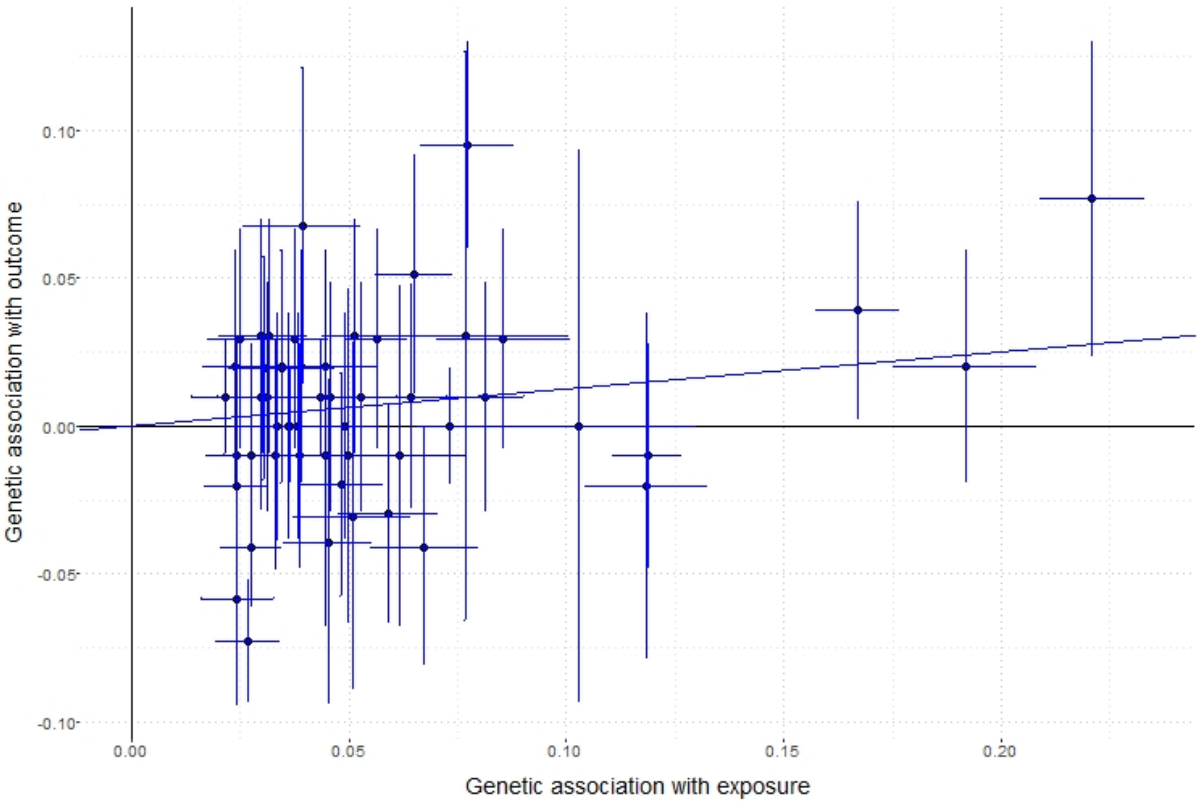
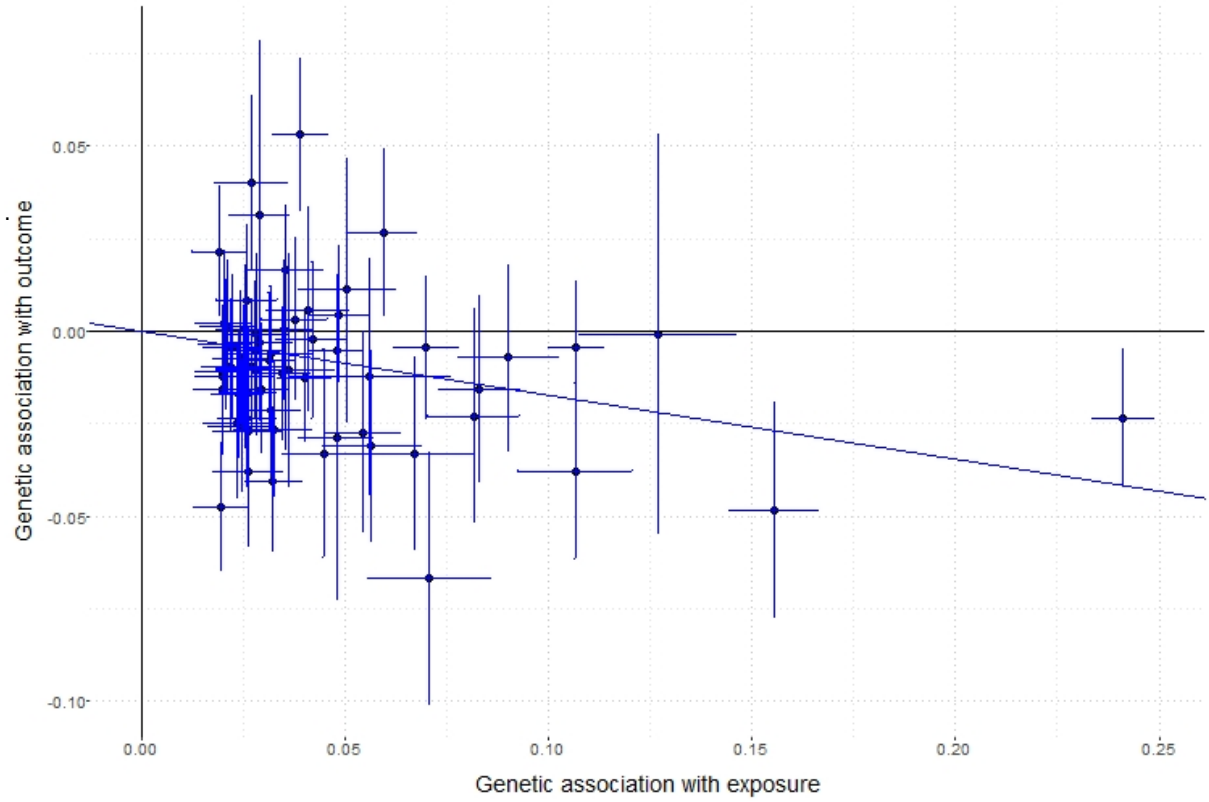


Figure S6D. The association between the SNPs and 1 SD change in HDL cholesterol versus the association between the SNPs and peripheral artery disease.
The regression line was calculated using the inverse-variance weighted method.
Abbreviations: SD = standard deviation; SNP = single nucleotide polymorphism. **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.

A.



B.

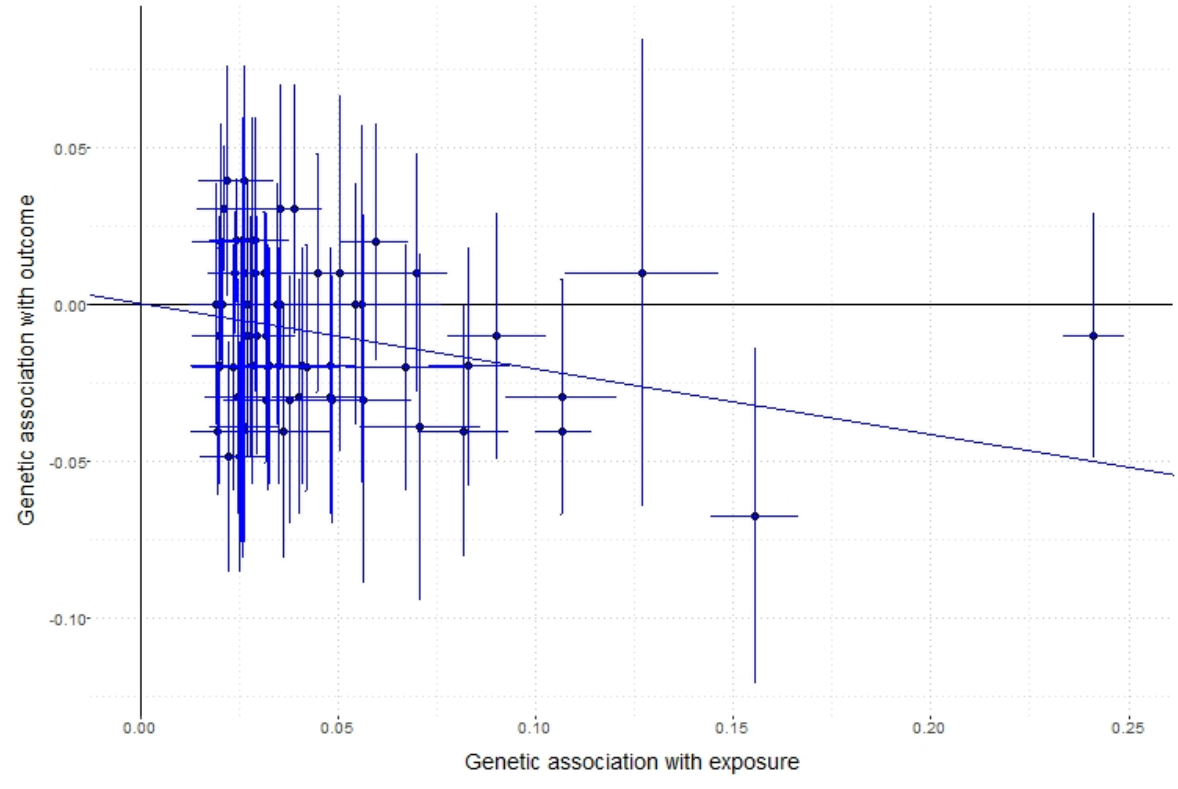
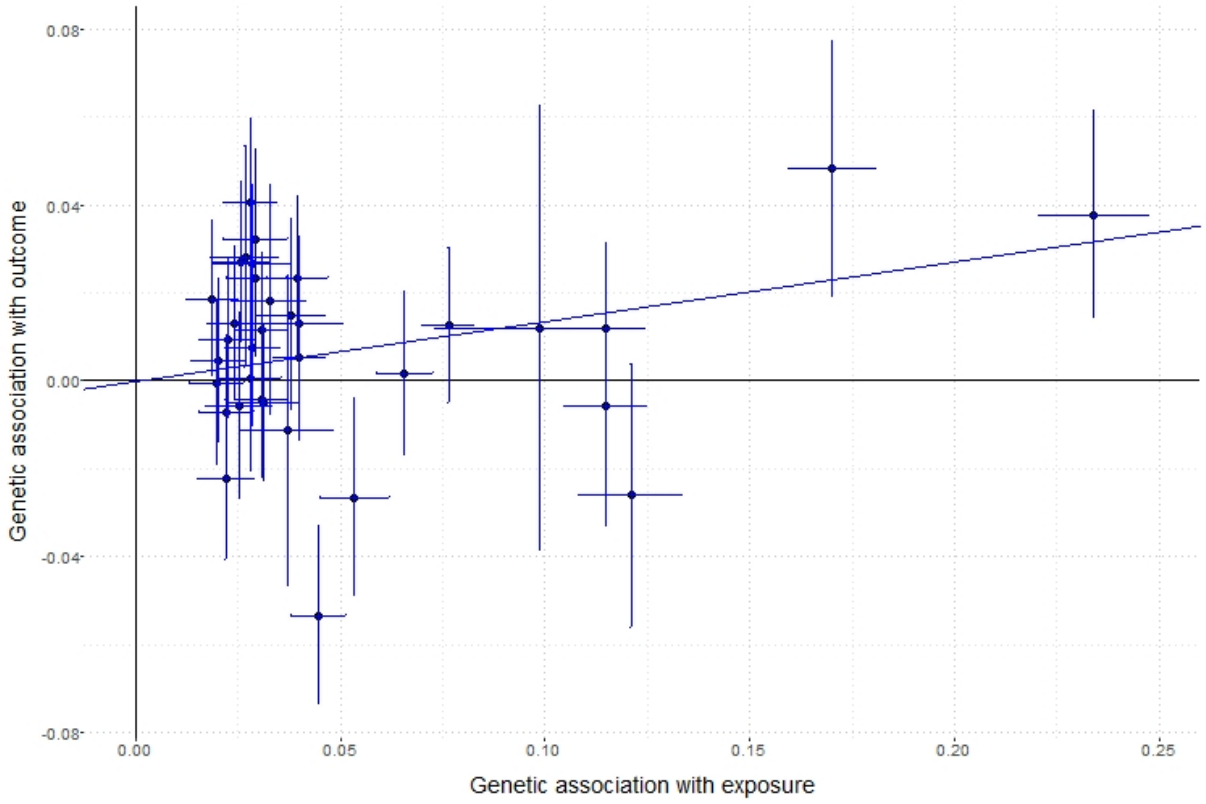


Figure S6E. The association between the SNPs and 1 SD change in Triglyceride level versus the association between the SNPs and peripheral artery disease.
The regression line was calculated using the inverse-variance weighted method.
Abbreviations: SNP = single nucleotide polymorphism . **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.

A.



B. .

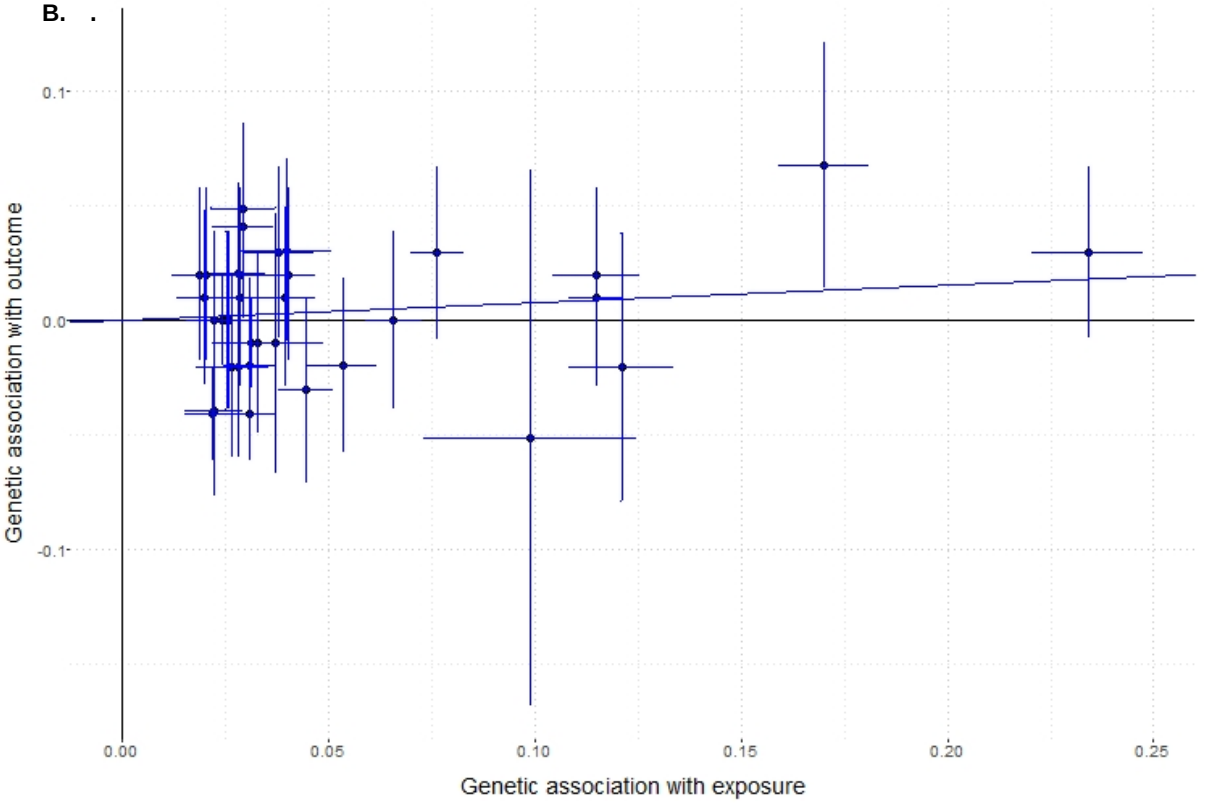
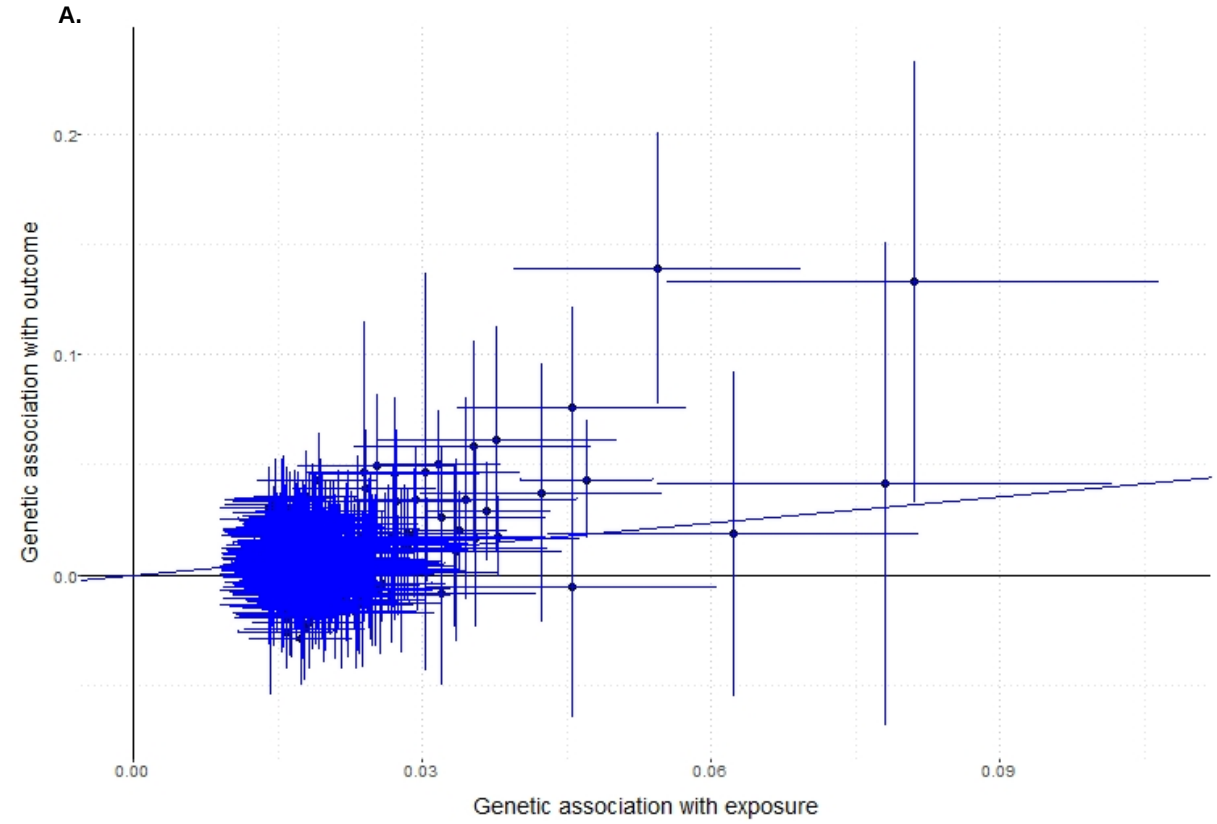


Figure S6F. The association between the SNPs and smoking initiation versus the association between the SNPs and peripheral artery disease.

The regression line was calculated using the inverse-variance weighted method.

Abbreviations: SNP = single nucleotide polymorphism. **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.



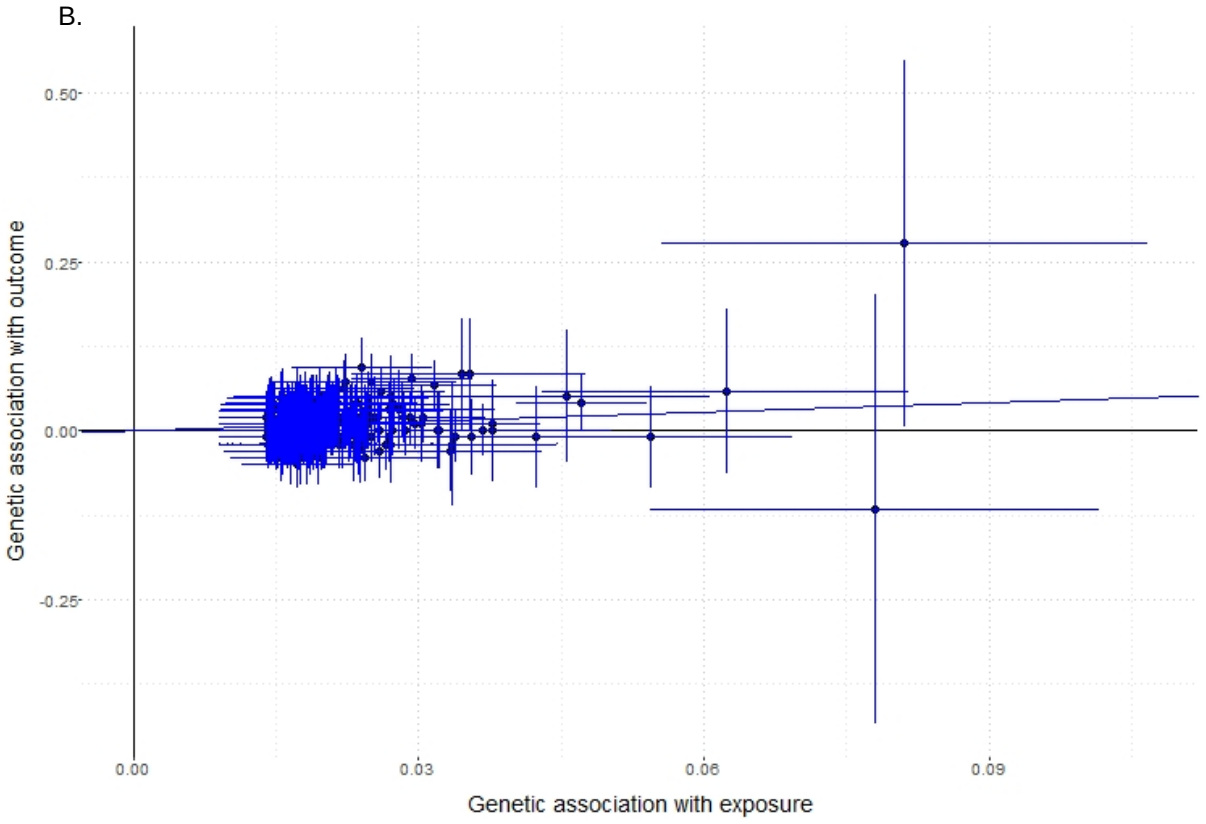
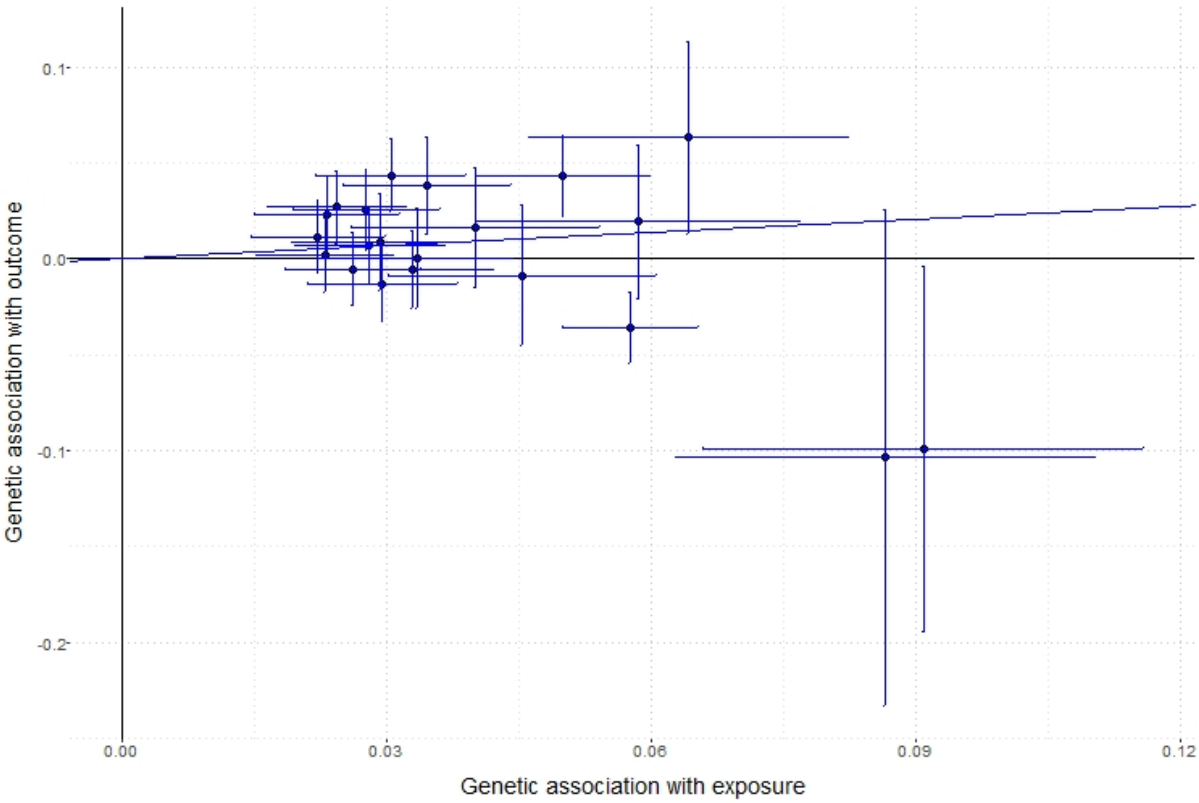


Figure S6G. The association between the SNPs and smoking cessation versus the association between the SNPs and peripheral artery disease.

The regression line was calculated using the inverse-variance weighted method.

Abbreviations: SNP = single nucleotide polymorphism. **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.

A.



B.

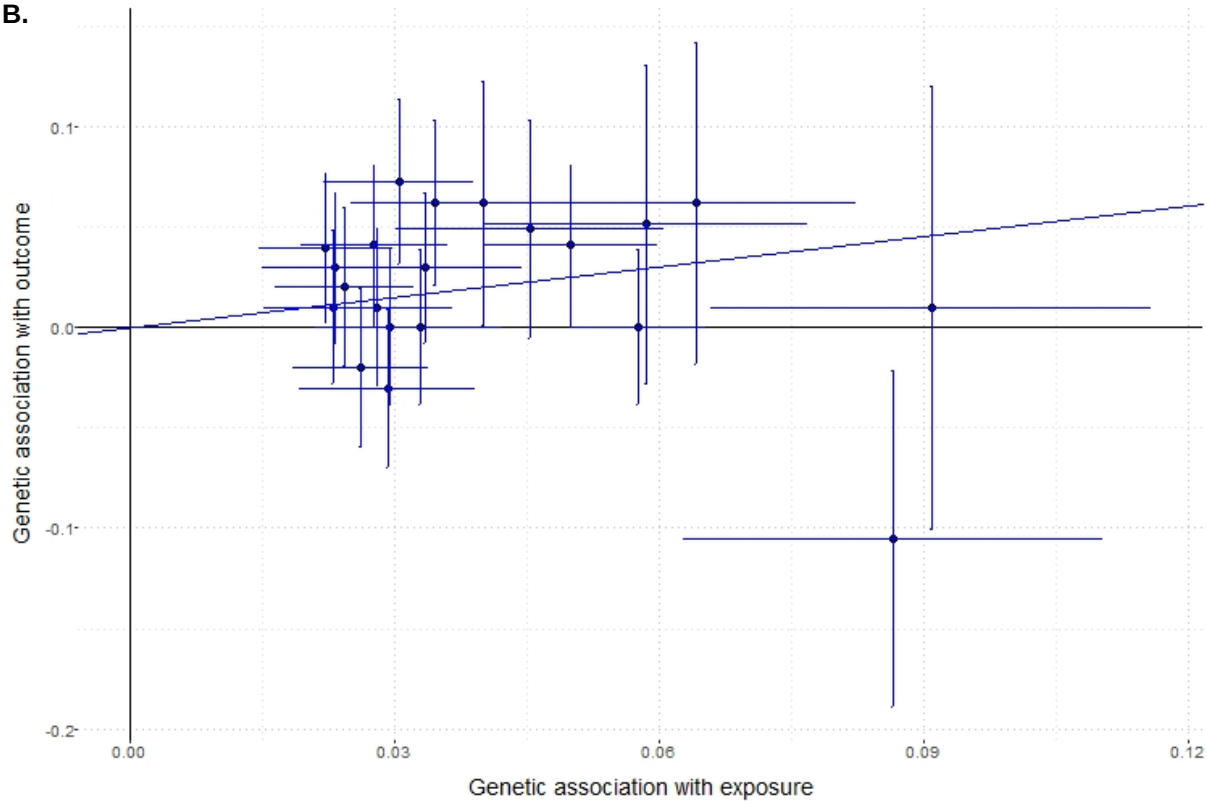
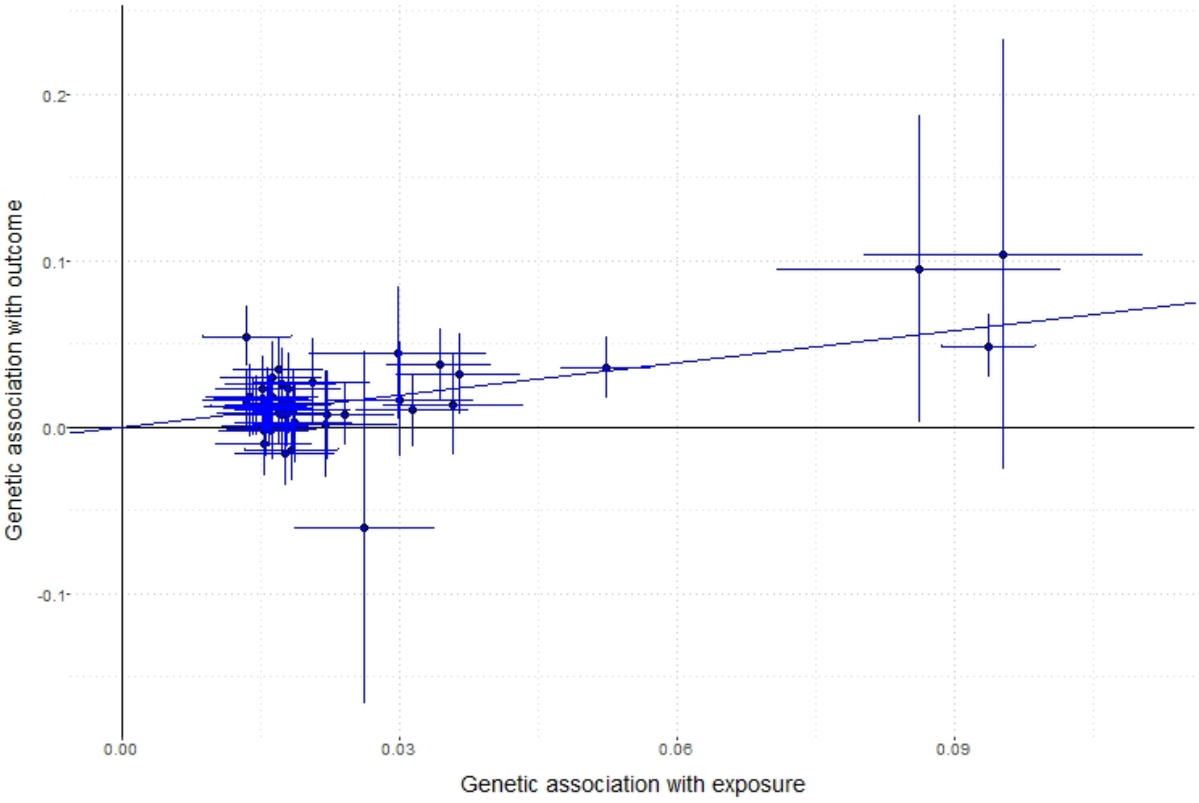


Figure S6H. The association between the SNPs and smoking heaviness versus the association between the SNPs and peripheral artery disease.
The regression line was calculated using the inverse-variance weighted method.
Abbreviations: SNP = single nucleotide polymorphism. **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.

A.



B. .

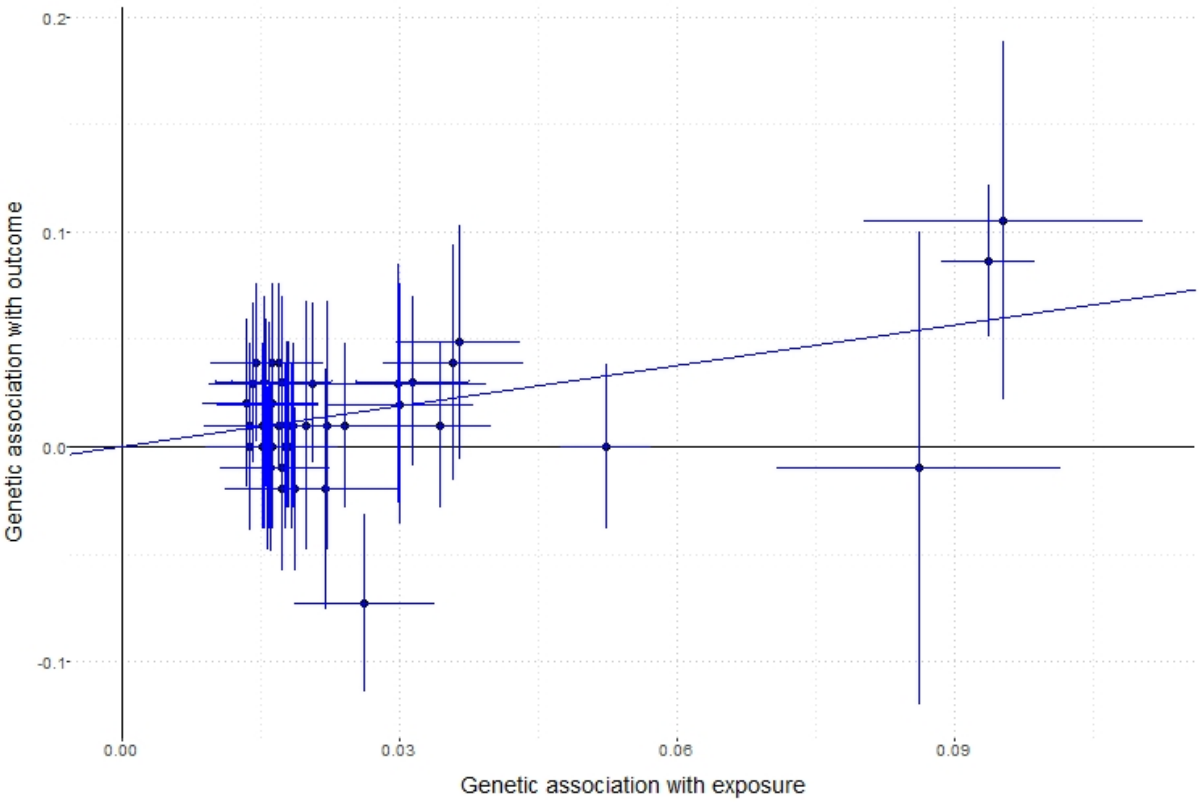
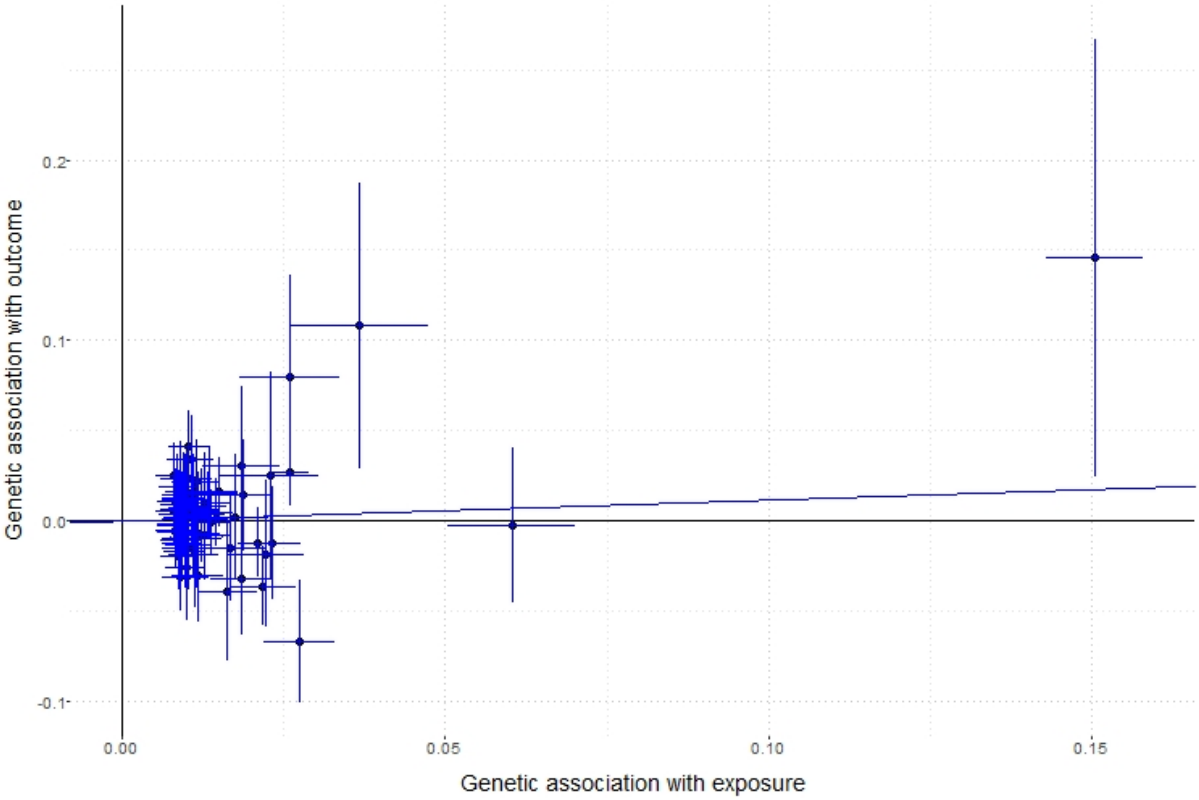


Figure S6I. The association between the SNPs and alcohol consumption versus the association between the SNPs and peripheral artery disease.
The regression line was calculated using the inverse-variance weighted method.
Abbreviations: SNP = single nucleotide polymorphism. **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.

A.



B. .

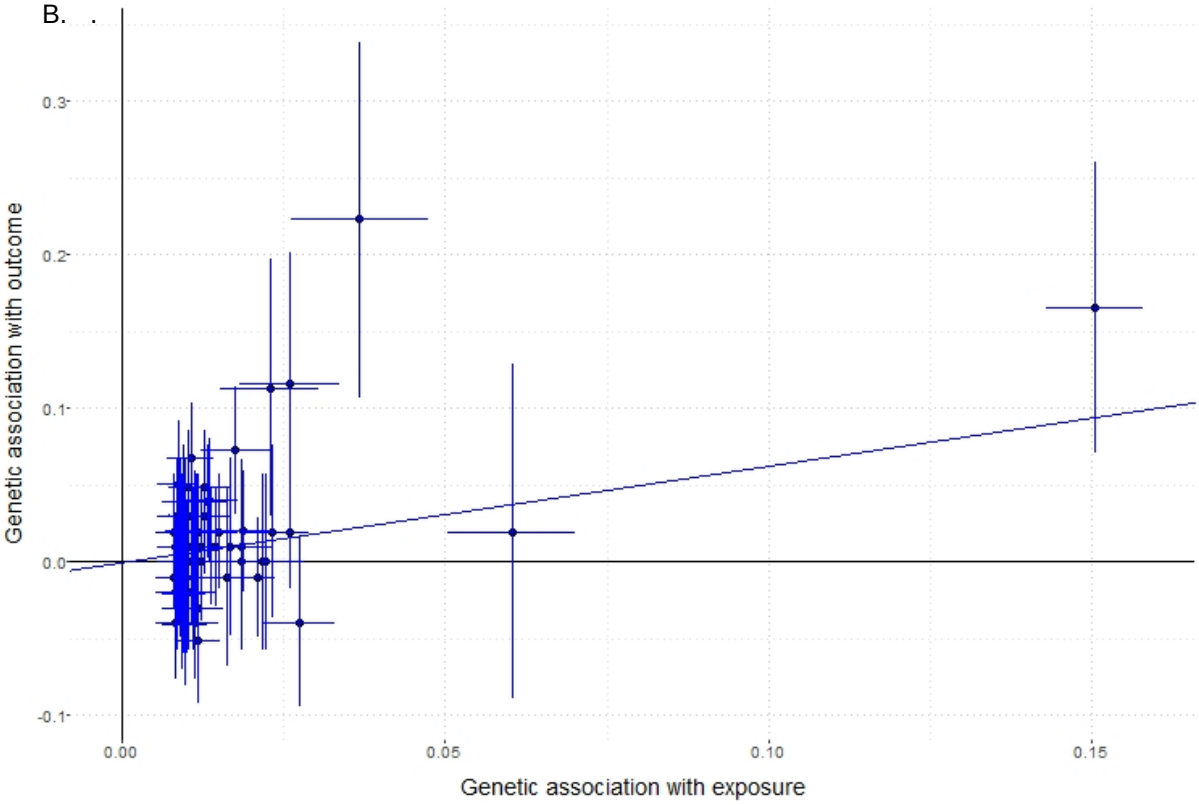
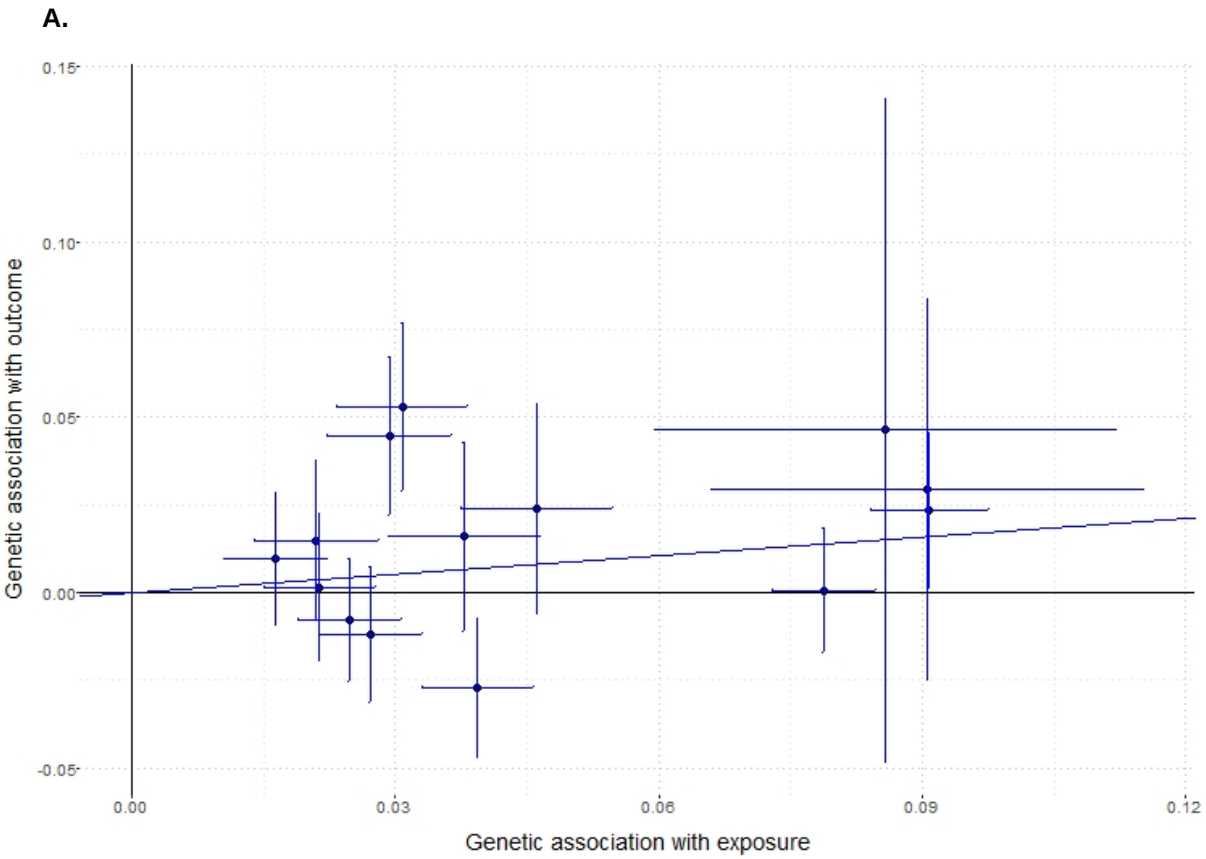


Figure S6J. The association between the SNPs and coffee consumption versus the association between the SNPs and peripheral artery disease.
The regression line was calculated using the inverse-variance weighted method.
Abbreviations: SNP = single nucleotide polymorphism. **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.



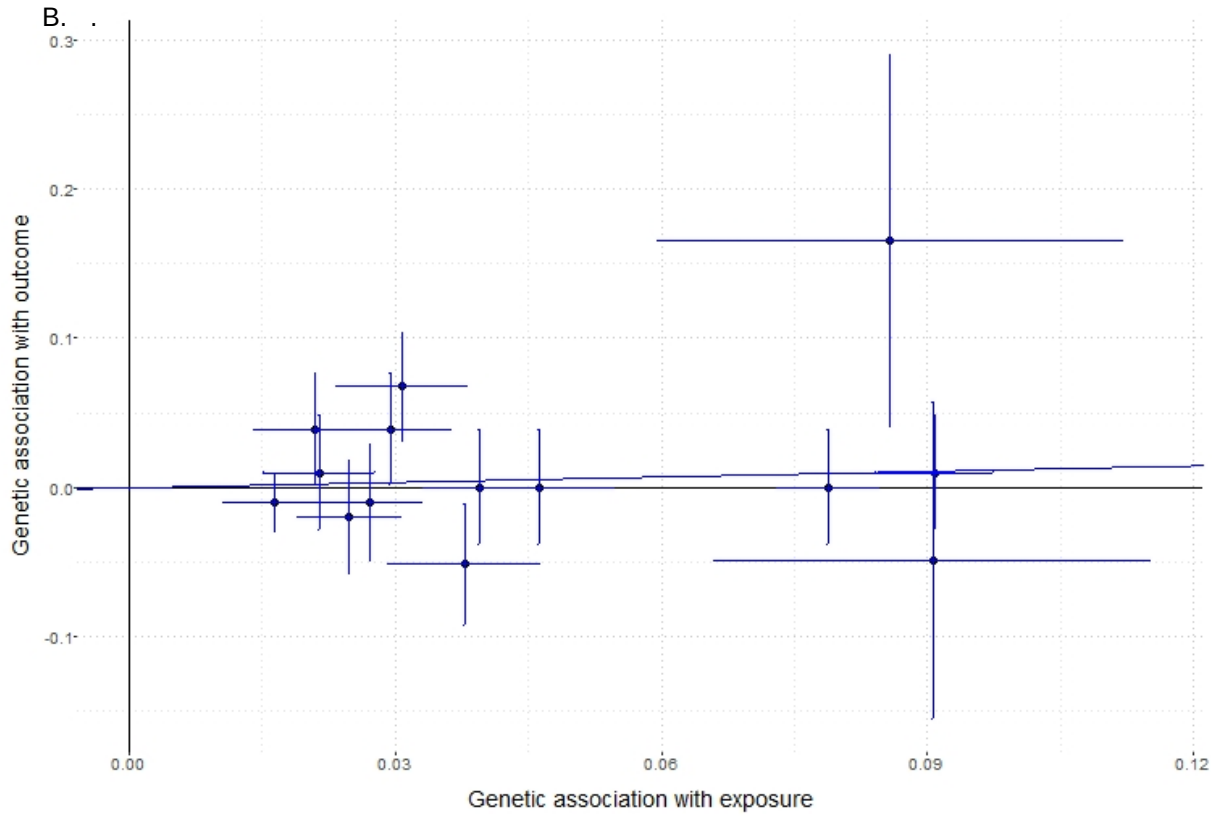


Figure S6K. The association between the SNPs and Moderate to vigorous physical activity versus the association between the SNPs and peripheral artery disease.

The regression line was calculated using the inverse-variance weighted method.

Abbreviations: SNP = single nucleotide polymorphism. **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.

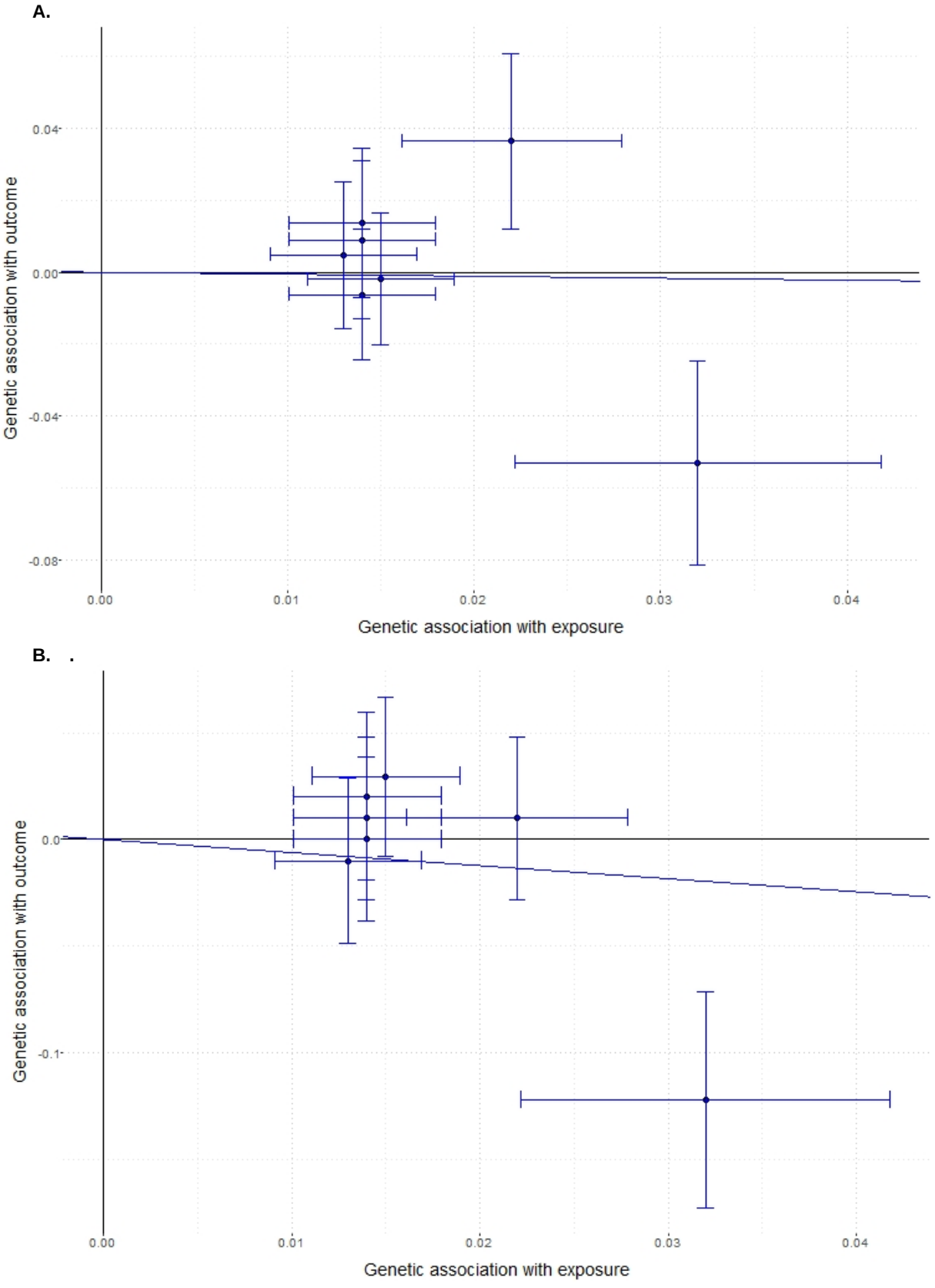
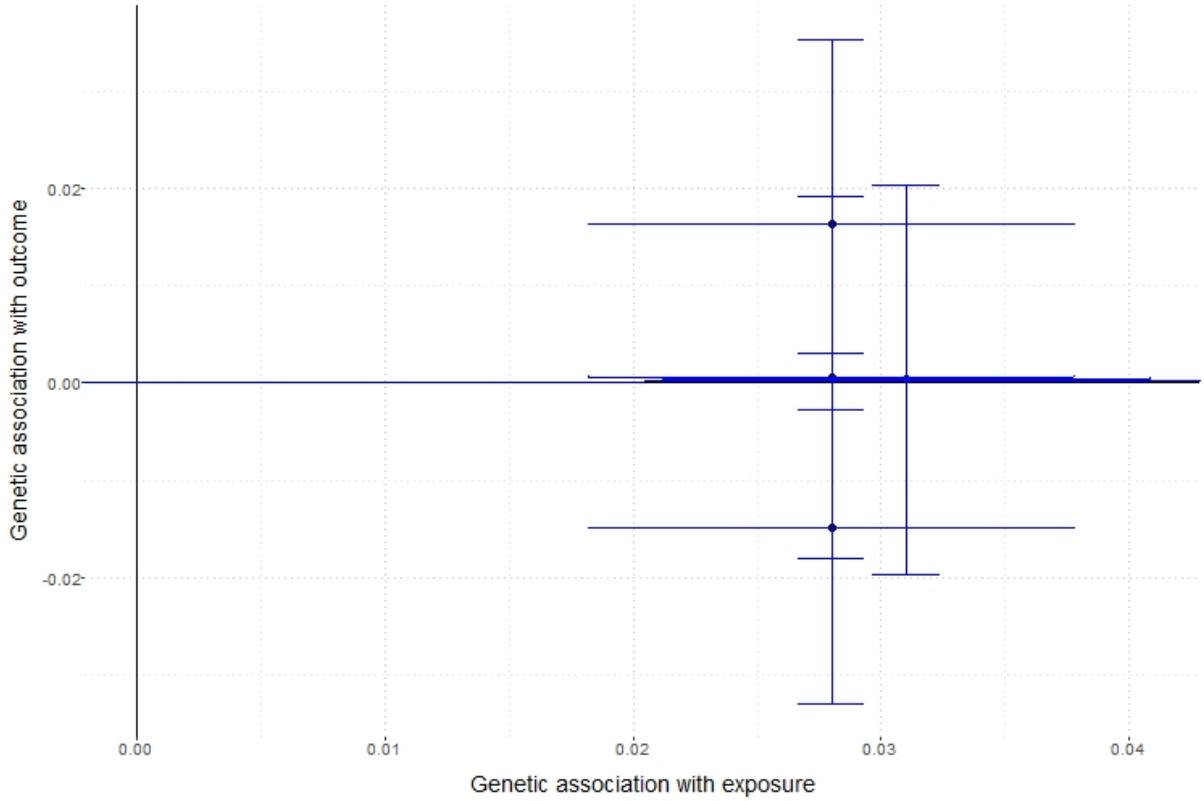


Figure S6L. The association between the SNPs and sedentary behavior versus the association between the SNPs and peripheral artery disease.
The regression line was calculated using the inverse-variance weighted method.
Abbreviations: SNP = single nucleotide polymorphism. **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.

A.



B. .

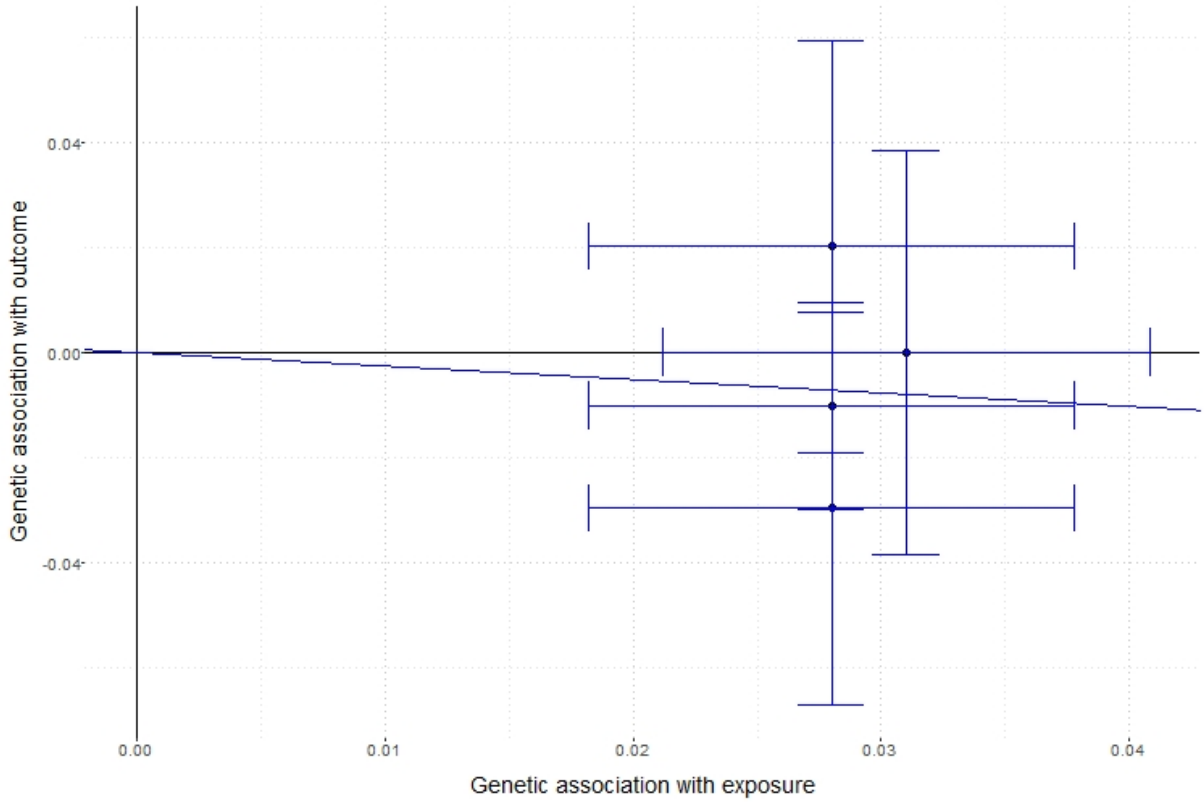
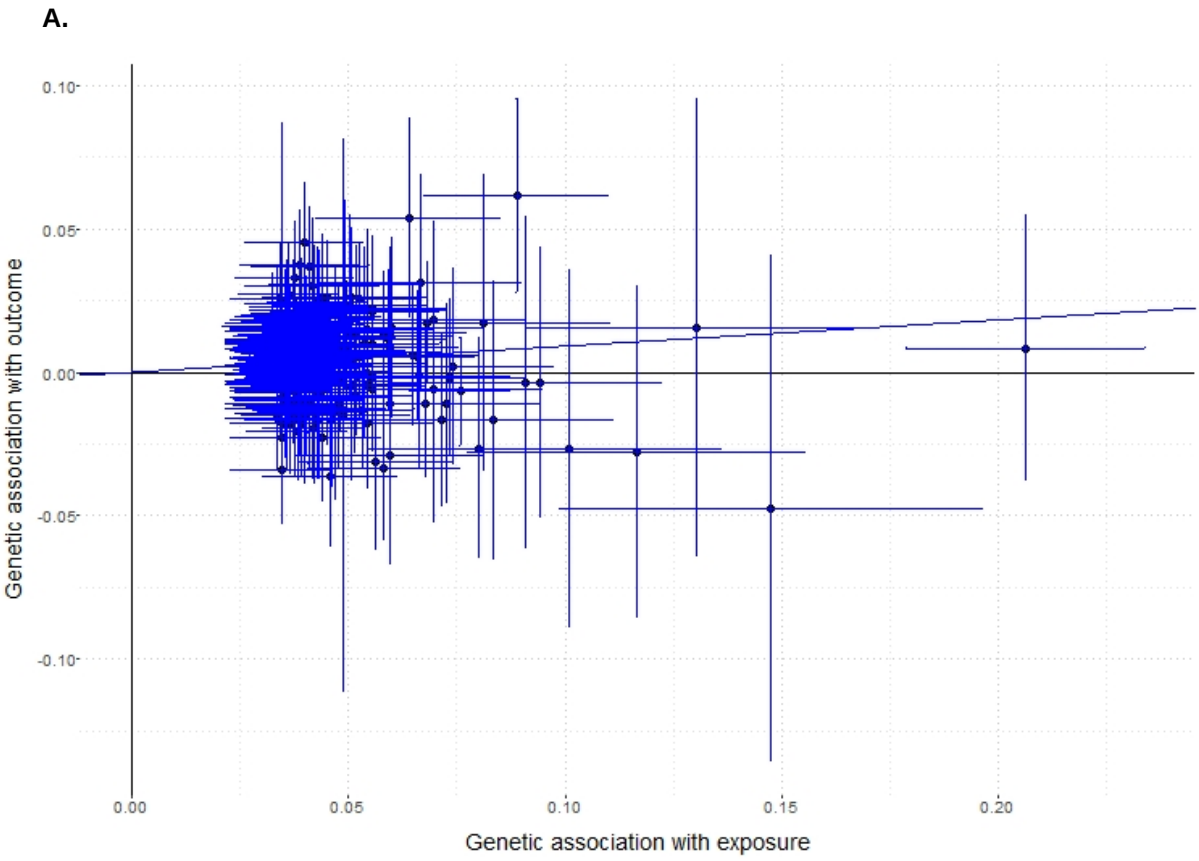


Figure S6M. The association between the SNPs and insomnia versus the association between the SNPs and peripheral artery disease.
The regression line was calculated using the inverse-variance weighted method.
Abbreviations: SNP = single nucleotide polymorphism. **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.



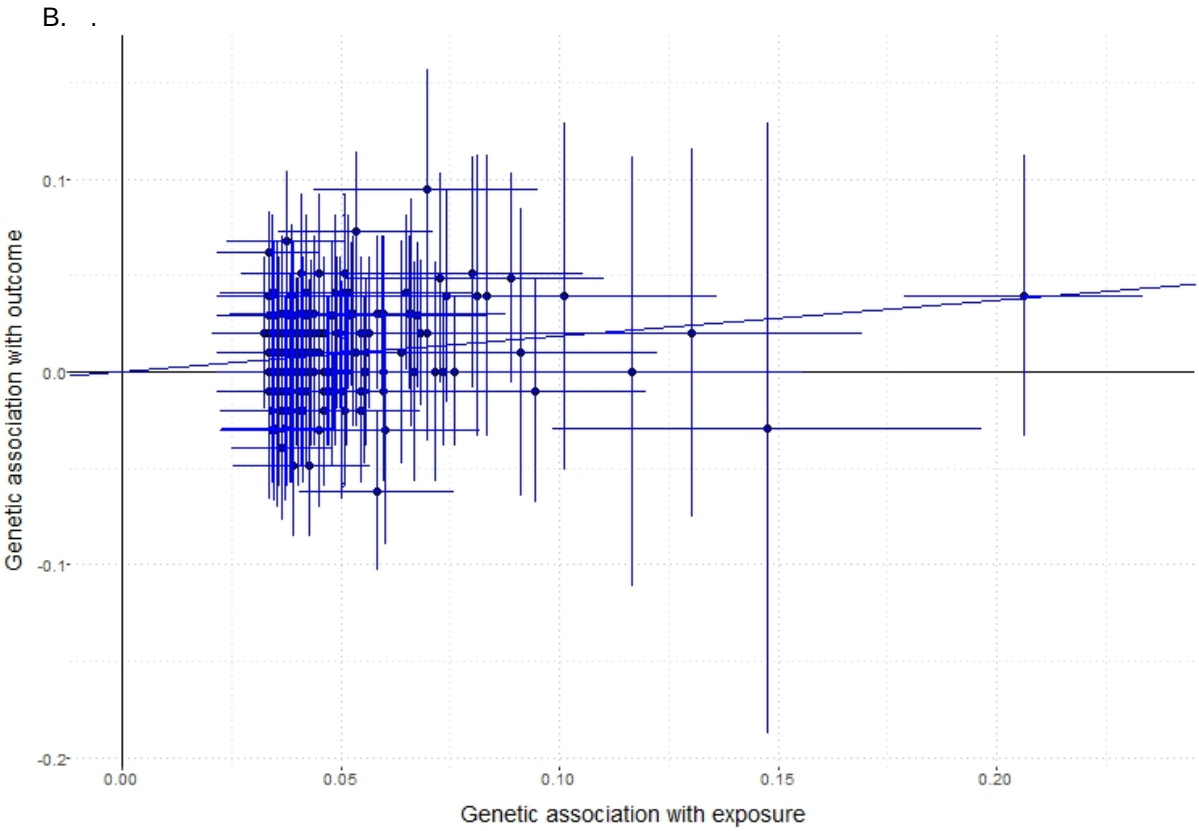


Figure S6N. The association between the SNPs and sleep duration versus the association between the SNPs and peripheral artery disease.

The regression line was calculated using the inverse-variance weighted method.

Abbreviations: SNP = single nucleotide polymorphism. **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.

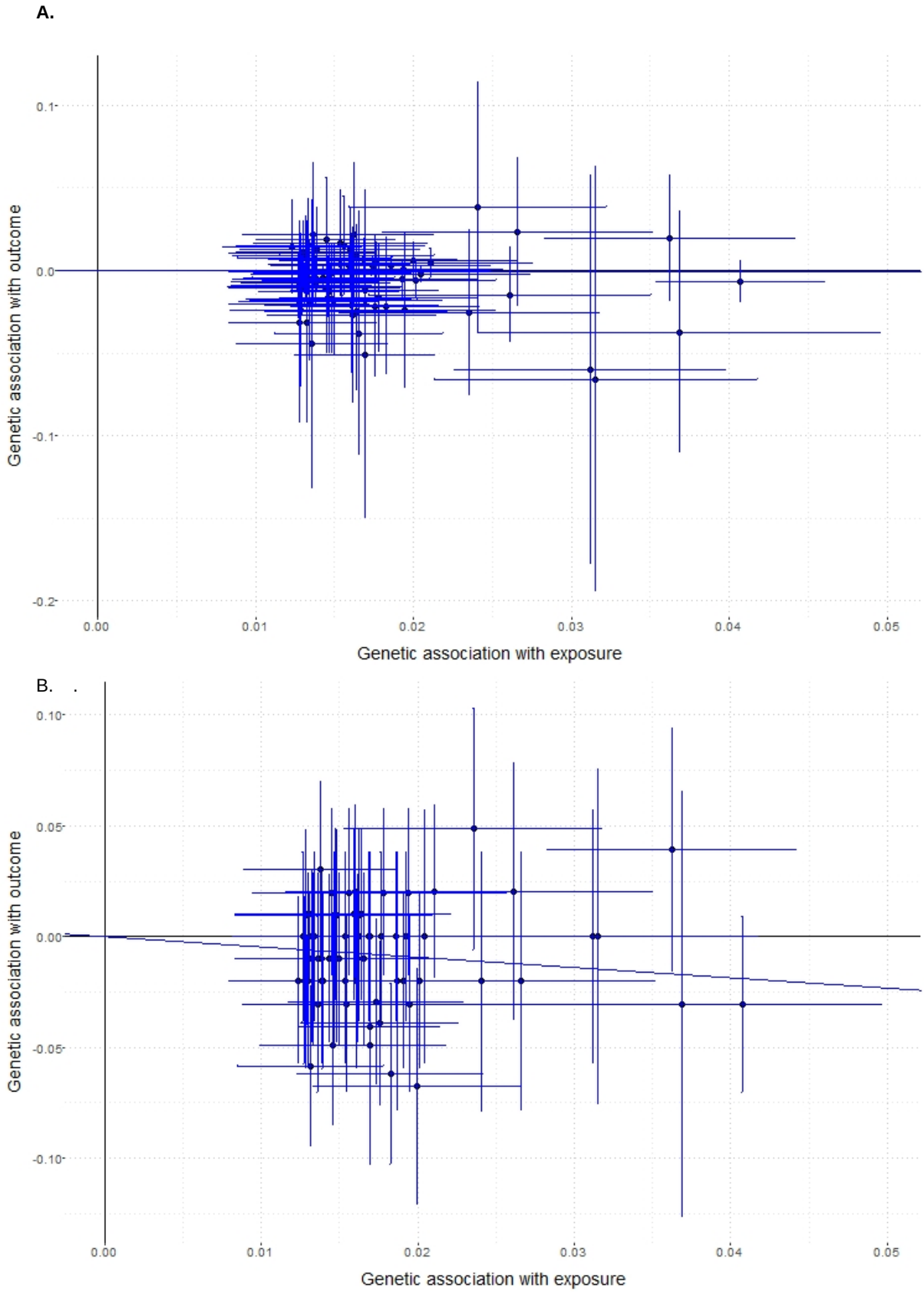
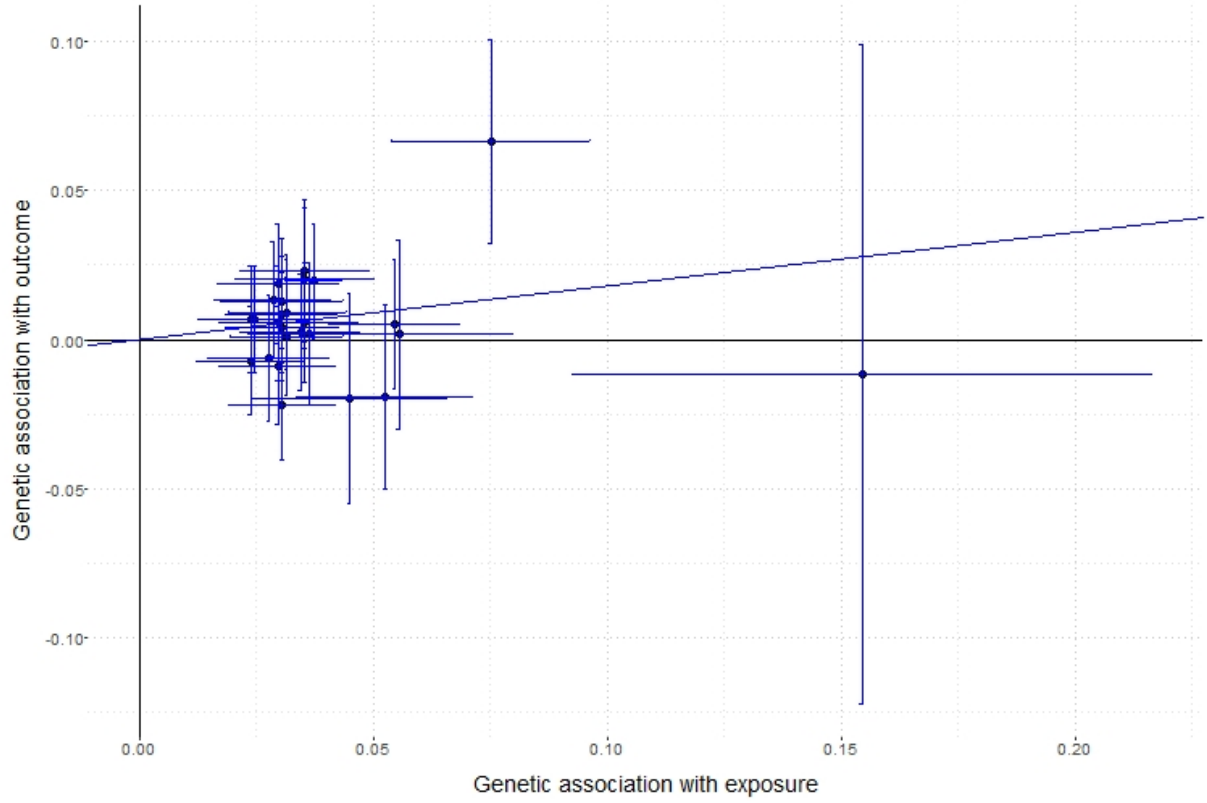


Figure S6O. The association between the SNPs and short sleep duration versus the association between the SNPs and peripheral artery disease.
The regression line was calculated using the inverse-variance weighted method.
Abbreviations: SNP = single nucleotide polymorphism. **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.

A.



B. .

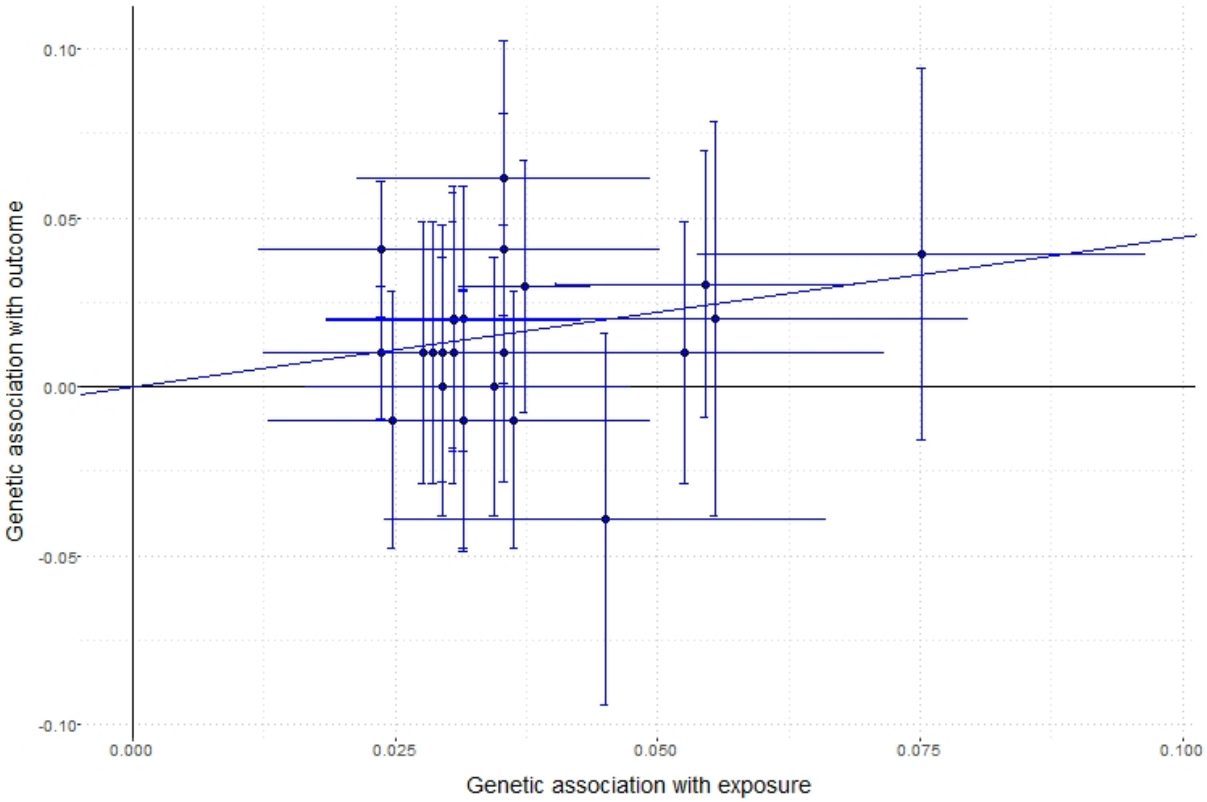


Figure S6P. The association between the SNPs and long sleep duration versus the association between the SNPs and peripheral artery disease.
The regression line was calculated using the inverse-variance weighted method.
Abbreviations: SNP = single nucleotide polymorphism. **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.

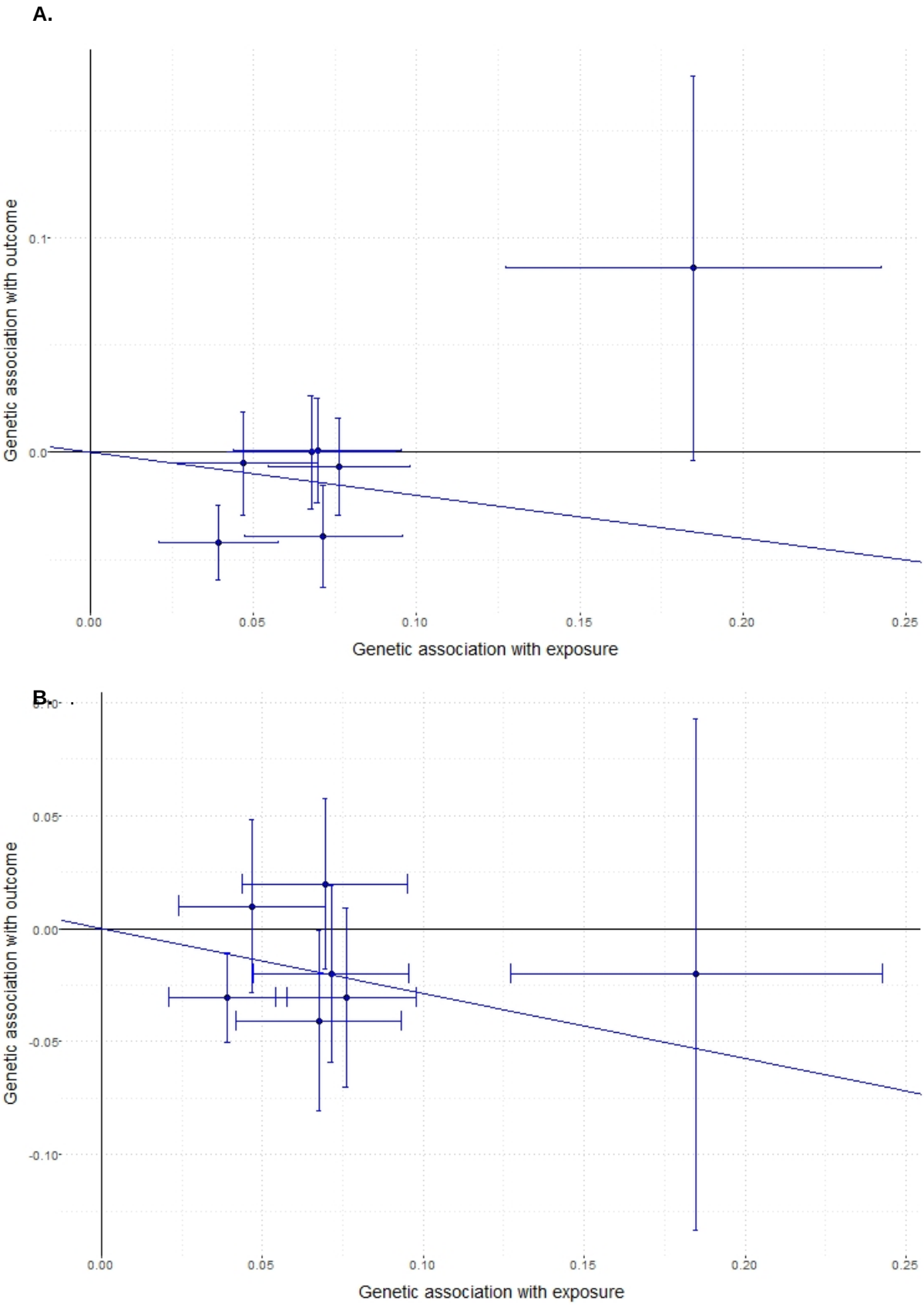
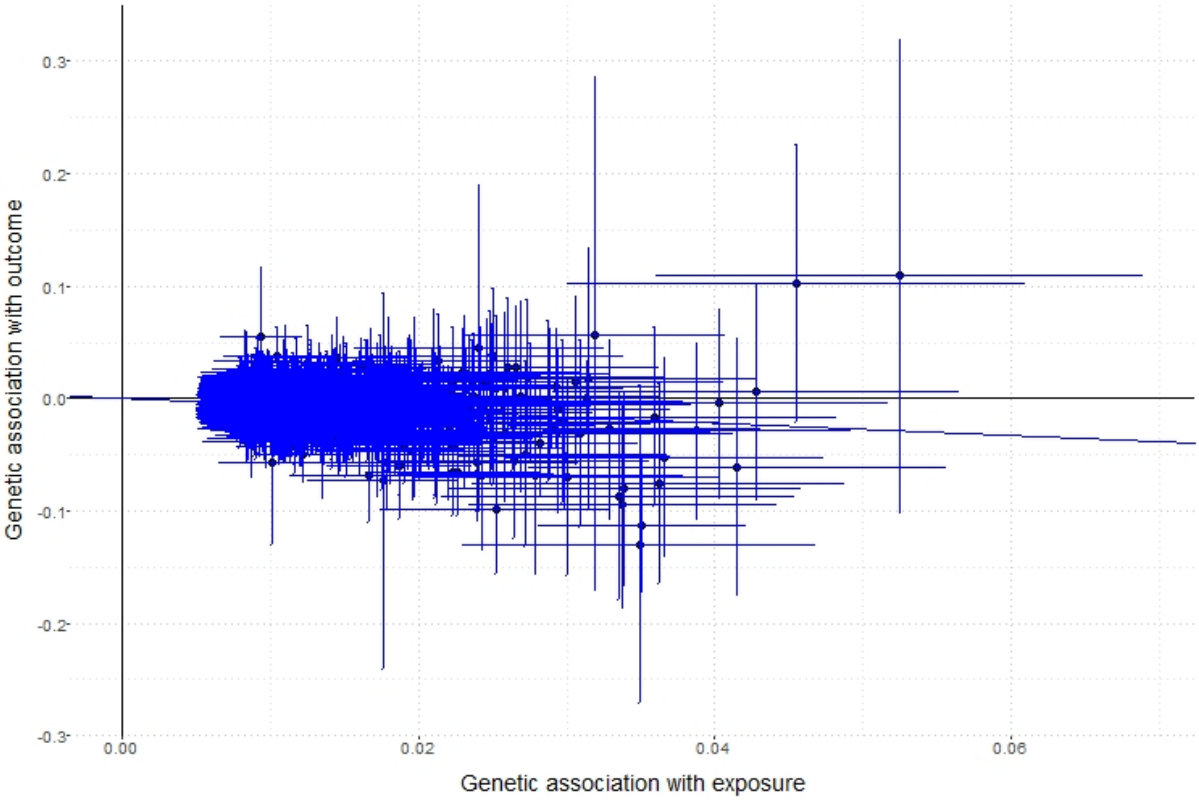


Figure S6Q. The association between the SNPs and educational status versus the association between the SNPs and peripheral artery disease.

The regression line was calculated using the inverse-variance weighted method.
Abbreviations: SNP = single nucleotide polymorphism. **A.** Associations between exposure and peripheral artery disease found using genome wide association study executed by the Million veteran program; **B.** Associations between exposure and peripheral artery disease found using the GoLEAD-SUMMIT Genome wide association study.

A.



B.