SUPPLEMENTAL MATERIALS

THE IMPACT OF RISK FACTORS FOR MAJOR CARDIOVASCULAR DISEASES - A COMPARISON OF LIFE-TIME OBSERVATIONAL AND MENDELIAN RANDOMIZATION FINDINGS

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Supplementary Table 1. Sensitivity Mendelian randomization analyses of associations of risk factors with coronary heart disease. MR Egger estimates are given both for a univariate (risk factors analyzed one by one) and a multivariate model (including all risk factors in the same model). Number of independent SNPs used as instruments is given in parenthesis for each risk factor.

	Test	Estimate	95%CI lower	95%CI higher	*P*-value
	Smoking (n=97)				
Univariate	MR Egger	2.98	0.93	9.51	0.064
Univariate	Weighted median	2.32	1.62	3.34	<0.0001
Univariate	Heterogeneity	Q=107			0.15
Multivariate	MR Egger	1.55	1.15	2.09	0.0043
	Diabetes (n=40)				
Univariate	MR Egger	1.39	1.07	1.80	0.013
Univariate	Weighted median	1.13	1.06	1.21	0.00031
Univariate	Heterogeneity	Q=89			0.0001
Multivariate	MR Egger	1.07	1.02	1.13	0.010
	BMI (N=79)				
Univariate	MR Egger	1.56	1.22	1.99	0.00034
Univariate	Weighted median	1.49	1.29	1.72	<0.0001
Univariate	Heterogeneity	Q=103			0.018
Multivariate	MR Egger	1.18	1.06	1.32	0.0021
	HDL (n=84)				
Univariate	MR Egger	1.01	.085	1.20	0.91
Univariate	Weighted median	0.92	0.83	1.03	0.16
Univariate	Heterogeneity	Q=279			<0.0001
Multivariate	MR Egger	0.93	0.84	1.04	0.21
	Triglycerides (n=51)				
Univariate	MR Egger	1.10	0.94	1.29	0.24
Univariate	Weighted median	1.21	1.08	1.35	0.00069
Univariate	Heterogeneity	Q=144			<0.0001
Multivariate	MR Egger	1.03	0.90	1.18	0.64

	LDL (n=76)				
Univariate	MR Egger	1.54	1.36	1.75	<0.0001
Univariate	Weighted median	1.52	1.40	1.66	<0.0001
Univariate	Heterogeneity	Q=245			<0.0001
Multivariate	MR Egger	1.36	1.25	1.48	<0.0001
	Systolic blood pressure (n=228)				
Univariate	MR Egger	1.03	1.01	1.06	0.0049
Univariate	Weighted median	1.03	1.03	1.04	<0.0001
Univariate	Heterogeneity	Q=488			<0.0001
Multivariate	MR Egger	1.03	1.02	1.04	<0.0001

Supplementary Table 2. Sensitivity Mendelian randomization analyses of associations of risk factors with ischemic stroke. MR Egger estimates are given both for a univariate (risk factors analyzed one by one) and a multivariate model (including all risk factors in the same model). Number of independent SNPs used as instruments is given in parenthesis for each risk factor.

	Test	Estimate	95%CI lower	95%CI higher	*P*-value
	Smoking (n=97)				
Univariate	MR Egger	1.33	0.48	3.69	0.57
Univariate	Weighted median	1.52	1.11	2.07	0.0084
Univariate	Heterogeneity	Q=150			0.0635
Multivariate	MR Egger	1.50	1.12	2.01	0.0059
	Diabetes (n=42)				
Univariate	MR Egger	1.17	0.94	1.47	0.16
Univariate	Weighted median	1.17	1.10	1.25	<0.0001
Univariate	Heterogeneity	Q=70			0.0022
Multivariate	MR Egger	1.07	1.02	1.13	0.011
	BMI (n=78)				
Univariate	MR Egger	0.96	0.72	1.28	0.79
Univariate	Weighted median	1.07	0.92	1.25	0.35
Univariate	Heterogeneity	Q=130			0.0001
Multivariate	MR Egger	0.99	0.89	1.10	0.80
	HDL (n=87)				
Univariate	MR Egger	1.13	1.01	1.27	0.047
Univariate	Weighted median	1.01	0.93	1.10	0.81
Univariate	Heterogeneity	Q=122			0.0057
Multivariate	MR Egger	0.97	0.87	1.07	0.51
	Triglycerides (n=53)				
Univariate	MR Egger	0.95	0.84	1.07	0.37
Univariate	Weighted median	1.01	0.91	1.10	0.91
Univariate	Heterogeneity	Q=61			0.14
Multivariate	MR Egger	1.02	0.90	1.16	0.73

	LDL (n=77)				
Univariate	MR Egger	1.17	1.06	1.29	0.0017
Univariate	Weighted median	1.12	1.03	1.21	0.0047
Univariate	Heterogeneity	Q=145			<0.0001
Multivariate	MR Egger	1.02	0.94	1.11	0.60
	Systolic blood pressure (n=229)				
Univariate	MR Egger	1.03	1.01	1.05	0.019
Univariate	Weighted median	1.03	1.02	1.03	<0.0001
Univariate	Heterogeneity	Q=342			<0.0001
Multivariate	MR Egger	1.02	1.02	1.03	<0.0001

Supplementary Table 3. Sensitivity Mendelian randomization analyses of associations of risk factors with heart failure. MR Egger estimates are given both for a univariate (risk factors analyzed one by one) and a multivariate model (including all risk factors in the same model). Number of independent SNPs used as instruments is given in parenthesis for each risk factor.

	Test	Estimate	95%CI lower	95%CI higher	*P*-value
	Smoking (n=123)				
Univariate	MR Egger	1.48	0.63	3.50	0.36
Univariate	Weighted median	1.86	1.43	2.41	<0.0001
Univariate	Heterogeneity	Q=164			0.0051
Multivariate	MR Egger	1.28	1.05	1.57	0.016
	Diabetes (n=42)				
Univariate	MR Egger	1.07	0.91	1.26	0.40
Univariate	Weighted median	1.07	1.02	1.12	0.0051
Univariate	Heterogeneity	Q=73			0.0010
Multivariate	MR Egger	1.05	1.02	1.08	0.0011
	BMI (n=78)				
Univariate	MR Egger	1.57	1.21	2.03	0.00057
Univariate	Weighted median	1.67	1.46	1.92	<0.0001
Univariate	Heterogeneity	Q=167			<0.0001
Multivariate	MR Egger	1.57	1.46	1.68	<0.0001
	HDL (n=86)				
Univariate	MR Egger	0.94	0.84	1.06	0.33
Univariate	Weighted median	0.94	0.87	1.02	0.14
Univariate	Heterogeneity	Q=189			<0.0001
Multivariate	MR Egger	0.98	0.92	1.06	0.67
	Triglycerides (n=53)				
Univariate	MR Egger	1.17	1.05	1.31	0.0055
Univariate	Weighted median	1.16	1.07	1.25	0.00038
Univariate	Heterogeneity	Q=91			0.0004
Multivariate	MR Egger	1.02	0.93	1.12	0.65

	LDL (n=77)				
Univariate	MR Egger	1.11	1.02	1.21	0.012
Univariate	Weighted median	1.10	1.01	1.2	0.023
Univariate	Heterogeneity	Q=198			<0.0001
Multivariate	MR Egger	1.02	0.96	1.08	0.54
	Systolic blood pressure (n=231)				
Univariate	MR Egger	1.02	0.99	1.03	0.068
Univariate	Weighted median	1.02	1.01	1.03	<0.0001
Univariate	Heterogeneity	Q=361			<0.0001
Multivariate	MR Egger	1.02	1.01	1.02	<0.0001

Supplementary Table 4. Sensitivity Mendelian randomization analyses of associations of risk factors with atrial fibrillation. MR Egger estimates are given both for a univariate (risk factors analyzed one by one) and a multivariate model (including all risk factors in the same model). Number of independent SNPs used as instruments is given in parenthesis for each risk factor.

	Test	Estimate	95%CI lower	95%CI higher	*P*-value
	Smoking (n=125)				
Univariate	MR Egger	1.61	0.70	3.69	0.26
Univariate	Weighted median	1.01	0.79	1.29	0.91
Univariate	Heterogeneity	Q=190			0.0001
Multivariate	MR Egger	1.14	0.88	1.47	0.33
	Diabetes (n=42)				
Univariate	MR Egger	0.99	0.86	1.13	0.85
Univariate	Weighted median	0.98	0.94	1.03	0.43
Univariate	Heterogeneity	Q=59			0.024
Multivariate	MR Egger	0.96	0.92	1.01	0.12
	BMI (n=77)				
Univariate	MR Egger	1.16	0.96	1.39	0.11
Univariate	Weighted median	1.35	1.21	1.52	<0.0001
Univariate	Heterogeneity	Q=100			0.029
Multivariate	MR Egger	1.23	1.12	1.35	<0.0001
	HDL (n=86)				
Univariate	MR Egger	1.01	0.92	1.12	0.79
Univariate	Weighted median	0.99	0.93	1.06	0.83
Univariate	Heterogeneity	Q=168			0.0001
Multivariate	MR Egger	0.92	0.84	1.01	0.077
	Triglycerides (n=51)				
Univariate	MR Egger	1.04	0.91	1.18	0.55
Univariate	Weighted median	0.98	0.91	1.06	0.61
Univariate	Heterogeneity	Q=157			<0.0001
Multivariate	MR Egger	0.93	0.83	1.04	0.20

	LDL (n=79)				
Univariate	MR Egger	1.03	0.96	1.10	0.38
Univariate	Weighted median	0.97	0.92	1.03	0.33
Univariate	Heterogeneity	Q=141			<0.0001
Multivariate	MR Egger	1.01	0.94	1.08	0.83
	Systolic blood pressure (n=231)				
Univariate	MR Egger	1.01	0.98	1.02	0.93
Univariate	Weighted median	1.01	1.01	1.02	<0.0001
Univariate	Heterogeneity	Q=442			<0.0001
Multivariate	MR Egger	1.01	1.00	1.01	0.0055