In-depth Mendelian randomization analysis of causal factors for coronary artery disease

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Supplementary Notes:

Note S1: P_{cj}, P_{dj}, P_{vj} definitions

To correctly select SNPs from GWAS data or meta-GWAS data, we here defined P_c and P_d as proportion cutoffs in sample sizes of causal variables and of a disease of study, respectively, and defined P_v as p-value cutoff in the causal data. We also defined

$$P_{cj} = \sum_{i=1}^{n} s_{ij} / max_{j=1}^{m}\left(\sum_{i=1}^{n} s_{ij}\right) \quad ,$$
$$P_{dj} = s_{dj} / max_{j=1}^{m}(s_{dj}) \quad ,$$
$$P_{vj} = \min_{j=1}^{m} (p_{ij})$$

where *n* is number of casual variables, *m*, number of SNPs in GWAS data, s_{ij} , sample size for SNP_j in causal variable *i*, s_{dj}, sample size for SNP_j in the disease data and p_{ij}, p-value for t-testing for association of SNP_j with casual variable *i* in regression analysis.

Note S2: An algorithm for selecting SNPs with reducing linkage disequilibrium

Since most of GWAS data do not give linkage disequilibrium (LD) values between SNPs, we use the following algorithm to remove SNPs with strong LD. Suppose we have a GWAS dataset with G SNPs each having chromosome position (bp), major allele frequency, beta values, p-values, sample sizes(N) of LDL, HDL, TG, and CAD in GWAS analysis. To choose a SNP as a valid instrument variable, we first calculate P_{vj}, P_{cj} and P_{dj}. The algorithm for choosing SNPs without strong LD is given as

Step 1: All SNPs meeting $P_{vj} < P_v$ are chosen from the GWAS data and sub-dataset A is generated with these SNPs from the GWAS data.

Step 2: All SNPs meeting $P_{cj} > P_c$ are chosen from the sub-dataset A and sub-dataset B is generated with these chosen SNPs from sub-dataset A.

Step 3: All SNPs meeting $P_{dj} > P_d$ are chosen from sub-dataset B and sub-dataset C is generated with these chosen SNPs from sub-dataset B.

Step 4: Order SNPs by chromosomes.

Step 5: Choose chromosome 1 and order SNPs by positions in hg19 from the smallest position to the largest one.

Step 6: Set DI =(largest position-smallest position)/AIL where DI is distance index and AIL is adjacent interval length.

Step 7: If DI ≤ 1, then only one SNP at the smallest or largest position in this chromosome is chosen, otherwise, if distance between positions j+1 and j >AIL and distance between positions j+2 and j+1 >AIL, SNPs at positions j and j+1 are chosen where j =1, …, N_i where N is the largest position on chromosome *i*.

Step 8: Repeat step 7 from j= position1 to the third largest position.

Step 9: Repeat step 5 through step 8 until chromosome 22.

Step 10: Use these SNP chosen to create sub-dataset D from sub-dataset C.

Note S3: Mathematic models for balance between LDL-c and HDL-c to determine causal effect of TG on CAD

From the results which TG was not associated with the risk for CAD by using the 83 shared SNPs in the SNP338 dataset as instrumental variables (**Fig. 6a**), we can infer

that the 64 SNPs shared with HDL-c and TG (**Fig. 3d**) were associated with HDL-c but their genes mostly had strong negative pleiotropic effects on TG and although 35 shared SNPs with LDL-c and TG were associated with LDL-c, their genes mostly had strong positive pleiotropic effect on TG. In MVMR analysis, after adjusting for HDL-c and LDL-c, if pleiotropic effects of SNPs associated with HDL-c and with LDL-c were balanced, TG is not associated with CAD. These results can be explained by the following multivariate regression model:

$$\sum_{j=1}^{m}\beta_{CADj} = a + \beta_{TG}\sum_{j=1}^{m}\beta_{TGj} + \beta_{LDL}\sum_{j=1}^{m}\beta_{LDLj} + \beta_{HDL}\sum_{j=1}^{m}\beta_{HDLj} + \beta_{e}\sum_{j=1}^{m}e_{j}$$

where a is intersection; j, SNP_j ; β_{xj}, a regression coefficient of SNP_j on a factor x (x = TG, HDL-c, LDL-c, or CAD); β_x, regression coefficient of risk factor x on CAD; and e_j, random effect. When m (number of SNPs selected) is larger, $\sum_j^m e_j \approx 0$. In testing for association of TG with risk for CAD using the shared SNPs as instrumental variables, if TG and HDL-c share SNP_j, both $|\beta_{TGj}|$ and $|\beta_{HDLj}|$ are larger, or if TG and LDL-c share SNP_j, both $|\beta_{TGj}|$ and $|\beta_{LDLj}|$ are larger. For the convenience, we replace β_{TGj} with β_{TGj_h}if SNP_j is shared with HDL-c and TG or with β_{TGj_l}if SNP_j is shared with LDL-c and TG, the regression above can be changed as

$$\sum_{j}^{m}\beta_{CADj} = a + \beta_{TG}(\sum_{j_h}^{m_h}\beta_{TGj_h} + \sum_{j_l}^{m_l}\beta_{TGj_l}) + \beta_{LDL}\sum_{j}^{m}\beta_{LDLj} + \beta_{HDL}\sum_{j}^{m}\beta_{HDLj} + \beta_{e}\sum_{j}^{m}e_{j}$$

where $m_h + m_l = m$. In balance of pleiotropic effects between HDL-c and LDL-c, $\sum_{j_h}^{m_h}\beta_{TGj_h} + \sum_{j_l}^{m_l}\beta_{TGj_l} = 0$ and then $\beta_{TG} = 0$. This is case in the 83 shared SNPs in the SNP338 dataset (**Fig. 6a**). In the case of unbalance, if $\sum_{j_h}^{m_h}\beta_{TGj_h} + \sum_{j_l}^{m_l}\beta_{TGj_l} > 0$ and $\sum_{j}^{m}\beta_{CADj} > 0$, or $\sum_{j_h}^{m_h}\beta_{TGj_h} + \sum_{j_l}^{m_l}\beta_{TGj_l} < 0$ and $\sum_{j}^{m}\beta_{CADj} < 0$, then $\beta_{TG} > 0$ in statistics due to positive pleiotropic effect of SNPs associated with LDL-c, examples can

be found in the 99 (**Fig. 6c**) and 45 shared SNPs (**Fig. 6c**) in the SNP185 dataset or if $\sum_{j_h}^{m_h} \beta_{TGj_h} + \sum_{j_l}^{m_l} \beta_{TGj_l} < 0$ but $\sum_{j}^{m} \beta_{CADj} > 0$ or $\sum_{j_h}^{m_h} \beta_{TGj_h} + \sum_{j_l}^{m_l} \beta_{TGj_l} > 0$ but $\sum_{j}^{m} \beta_{CADj} < 0$, then $\beta_{TG} < 0$ in statistics due to negative pleiotropic effects of SNPs associated with HDL-c, like in the 116 shared SNPs in the SNP363 data (**Fig. 6b**).

Simulation breaks LD between SNPs j and k (no link between (β_{xj}, β_{CADj}) and (β_{xk}, β_{CADk})) and removes pleiotropy of SNPs between lipids x and y (no association between (β_{xj}, β_{CADj}) and (β_{yj}, β_{CADj})). Simulation tests for associations of LDL-c and HDL-c with risk for CAD in the SNP338 and SNP363 datasets in no noise and noise cases directly verified the conclusion above. For TG, the test SNPs consist of two groups: one group in which SNPs were associated with HDL-c and TG in the test data is similar to , as noted in the second regression model, $\beta_{TGj}$is referred to as β_{TGj_h} for SNP_j, and the other group in which SNPs were associated with LDL-c and TG in the test data, the β_{TGj} is referred to as β_{TGj_l}. If $\sum_{j=1}^{m_h} \beta_{TGj_h}$ and $\sum_{j=1}^{m_l} \beta_{TGj_l}$ are balanced to be zero, then β_{TG} = 0. The case can be seen in simulations using SNP338 and SNP363 datasets as test datasets. For the SNP185 dataset of Do et al[3], many SNPs associated with HDL-c were not selected due to selection bias so that HDL-c was not associated with risk for CAD. On the other hand, as shown in Figure 3g, TG had 24 SNPs associated with HDL-c only but just 8 SNPs associated with LDL-c only. Table 2 also shows that in SNP185 dataset, TG was negatively correlated with HDL-c (r = -0.30512, p < 0.0001) but not correlated with LDL-c (r = 0.034, p = 0.64). Therefore, in simulated data, $|\sum_{j=1}^{m_h} \beta_{TGj_h}| > |\sum_{j=1}^{m_l} \beta_{TGj_l}|$, leading to $\beta_{TG} < 0$ in statistics.

Supplementary Tables:

Table S1. Data sources and information

Data name	Risk factors or disease	Number of participates	SNP Number	Data sources or references
metabochip data (Mc)	LDL-c, HDL-c, TG	188577	120165	http://csg.sph.umich.edu/abecasis/public/lipids2013/
Joint GWAS and metabochip data (jointGwasMc)	LDL-c, HDL-c, TG	187167	2436375	http://csg.sph.umich.edu/abecasis/public/lipids2013/
CARDIoGRAMplusC4D	CAD	Cases: 63746 Controls: 130 681	2420360	http://www.cardiogramplusc4d.org/downloads/
Data of 185 SNPs of Do et al.(2013)	LDL-c, HDL-c, TG, and CAD	188577	185	http://www.nature.com/ng/journal/v45/n11/full/ng.2795.html

CAD, coronary artery disease; CARIoGRAMplusC4D: Coronary Artery Disease Genome-wide Replication and Meta-analysis plus Coronary Artery Disease Genetics; GLGC, Global Lipids Genetic Consortium; HDL-c, high-density lipoprotein cholesterol; LDL-C; low-density lipoprotein cholesterol; TG: triglycerides; SNP: single nucleotide polymorphism.

Table S2. Selection schemes of SNPs

Scheme A					Scheme B				
AIL	P_v	P_c	P_d	SNP#	AIL	P_v	P_c	P_d	SNP#
25000	5e-08	0.99	0.99	58	25000	5e-08	0.979	0.979	58
20000	5e-08	0.99	0.99	73	20000	5e-08	0.979	0.979	68
15000	5e-08	0.99	0.99	80	15000	5e-08	0.979	0.979	91
10000	5e-08	0.99	0.99	94	10000	5e-08	0.979	0.979	121
5000	5e-08	0.99	0.99	114	5000	5e-08	0.979	0.979	178
1000	5e-08	0.99	0.99	133	1000	5e-08	0.979	0.979	266
	5e-08	0.99	0.99	171		5e-08	0.979	0.979	338
	5e-08	0.98	0.98	265		5e-08	0.95	0.972	735
	5e-08	0.979	0.979	338					
	5e-08	0.972	0.972	582					
	5e-08	0.95	0.972	735					

P_v is a given threshold for minimum p-value (P_{vj}) of SNPs associated with LDL-c, HDL-c and TG; P_c , a given threshold for proportion (P_{cj}) of sum of sample size of SNP j over all causal variables to the max sum of sample sizes over all SNPs in data; P_d , a given threshold for proportion (P_{dj}) of sample size of SNP j in disease to the max sample sizes over all sNPs (See **Supplementary Note S2**).

Table S3. Correlation analysis between LDL-c, HDL-c and TG

from data	SNP #		LDL-c	HDL-c	TG
Mc-lipid-CAD	338	LDL-c	1	0.2114	<0.0001
		HDL-c	-0.06668	1	<0.0001
		TG	0.420036	-0.55972	1
jointGwasMc-lipid-CAD	363	LDL-c	1	0.090419	<0.0001
		HDL-c	-0.08952	1	<0.0001
		TG	0.330894	-0.6977	1
data of white et al (2016)	145	LDL-c	1	0.0719	0.5900
		HDL-c	-0.14991	1	<0.0001
		TG	-0.04512	-0.45708	1
data of Do et al (2013)	185	LDL-c	1	0.0526	0.6464
		HDL-c	-0.14312	1	<0.0001
		TG	0.034039	-0.30512	1

Note: correlation coefficients are under diagonal lines and corresponding p-values are above diagonal lines.

Table S4. Results of MR-PRESSO analysis of dataset SNP338

Exposure	MR Analysis	Causal Estimate	Sd	T-stat	P-value
ldl	Raw	0.3559716	0.03506907	10.150586	2.764653e-21
hdl	Raw	-0.3449137	0.03446413	-10.007903	8.423297e-21
tg	Raw	0.1604794	0.03392713	4.730118	3.312579e-06
ldl	Outlier-corrected	NA	NA	NA	NA
hdl	Outlier-corrected	NA	NA	NA	NA
tg	Outlier-corrected	NA	NA	NA	NA

MR-PRESSO results`$`Global Test`$RSSobs: 550.0842
MR-PRESSO results`$`Global Test`$`Pvalue: <0.001
MR-PRESSO results`$`Distortion Test`$`Outliers Indice: No significant outliers
MR-PRESSO results`$`Distortion Test`$`Distortion Coefficient: NA
MR-PRESSO results`$`Distortion Test`$`Pvalue: NA

Table S5. Results of MR-PRESSO analyses of datasets SNP363 and SNP360

data	Exposure	MR Analysis	Causal Estimate	Sd	T-stat	P-value
SNP338	ldl	Raw	0.42386	0.04038	10.496331	1.155620e-22
	hdl	Raw	-0.38128	0.05090	-7.490704	5.346223e-13
	tg	Raw	0.15585	0.05816	2.679619	7.709089e-03
	ldl	Outlier-corrected	0.51658	0.04571	11.301323	1.464482e-25
	hdl	Outlier-corrected	0.51658	0.04571	11.301323	1.464482e-25
	tg	Outlier-corrected	0.51658	0.04571	11.301323	1.464482e-25
SNP360 (3 SNPs were excluded from SNP338)	ldl	Raw	0.44025	0.03904	11.275608	1.978695e-25
	hdl	Raw	-0.37571	0.04913	-7.647783	1.916145e-13
	tg	Raw	0.15102	0.05609	2.692141	7.433924e-03
	ldl	Outlier-corrected	NA	NA	NA	NA
	hdl	Outlier-corrected	NA	NA	NA	NA
	tg	Outlier-corrected	NA	NA	NA	NA

MR-PRESSO results`$`Global Test`$RSSobs: 672.9603
MR-PRESSO results`$`Global Test`$`Pvalue: <0.001
MR-PRESSO results`$`Distortion Test`$`Outliers Indice: No significant outliers
MR-PRESSO results`$`Distortion Test`$`Distortion Coefficient: NA
MR-PRESSO results`$`Distortion Test`$`Pvalue: NA

Table S6. R^2 of SNP datasets

		LDL-c	HDL-c	TG
SNP338	**total**	0.067658	0.020118	0.010047
	shared	0.118296	0.372035	0.135062
	unique	0.158198	0.071825	0.170607
SNP363	**total**	0.058397	0.004520	0.030580
	shared	0.036203	0.116992	0.082518
	unique	0.114813	0.047842	0.080932
SNP173(1)		0.069171	0.021500	0.037258
SNP173(2)		0.065374	0.018952	0.033582
SNP185		0.015385	0.162740	0.028591
SNP145		0.038207	0.328188	0.038345

Table S7. Results [a] of simulation MVMR analysis of lipid risk for coronary artery disease using SNP338 data as test data and Mc-lipid-CAD data as mother data

		SNP number found					LDL-c		HLD-c		TG	
Pc	Pd	Total	LDL-c	HDL-c	TG	FDR	beta	p-value	beta	p-value	beta	p-value
null p-value is distributed from 1e-07 to 1												
0.9	0.9	394	101	148	148	0.0	0.430	3.83E-14	-0.392	2.40E-16	-0.034	0.35993
0.9	0.98	319	76	124	122	0.0	0.462	1.76E-11	-0.394	2.98E-13	-0.031	0.40845
0.9	0.99	212	50	84	79	0.0	0.451	5.15E-08	-0.401	1.10E-09	0.020	0.58740
0.95	0.9	339	85	128	129	0.0	0.426	6.93E-12	-0.382	4.55E-12	-0.026	0.43788
0.95	0.98	278	64	109	108	0.0	0.455	1.95E-09	-0.389	4.81E-10	-0.026	0.46385
0.95	0.99	183	42	74	69	0.0	0.439	7.63E-06	-0.397	9.90E-08	0.023	0.47068
0.97	0.9	292	73	109	112	0.0	0.435	9.41E-10	-0.379	1.46E-09	-0.028	0.43603
0.97	0.98	241	56	94	94	0.0	0.464	4.89E-08	-0.381	2.41E-08	-0.027	0.49519
0.97	0.99	160	37	65	60	0.0	0.439	5.01E-05	-0.396	4.42E-06	0.011	0.37889
0.98	0.9	239	60	88	92	0.0	0.445	1.32E-08	-0.380	3.76E-08	-0.036	0.31616
0.98	0.98	197	46	75	77	0.0	0.478	6.62E-07	-0.384	5.78E-07	-0.034	0.31816
0.98	0.99	129	30	51	49	0.0	0.443	0.00896	-0.400	5.42E-05	0.005	0.16253
0.99	0.9	219	56	81	85	0.0	0.451	7.97E-08	-0.369	1.31E-06	-0.039	0.29322
0.99	0.98	181	43	69	71	0.0	0.482	3.34E-06	-0.372	2.50E-05	-0.039	0.35592
0.99	0.99	119	28	47	45	0.0	0.444	0.01441	-0.393	0.00015	-0.007	0.19769
Min		119	28	47	45	0.0	0.426	3.83E-14	-0.401	2.4E-16	-0.039	0.16253
Max		394	101	148	148	0.0	0.482	0.01441	-0.369	0.00015	0.023	0.5874
mean		233	56	90	90	0.0	0.449	0.00156	-0.387	1.6E-05	-0.018	0.37879
null p-value is distributed from 1e-12 to 1												
0.9	0.9	456	102	149	147	0.136	0.224	0.00692	-0.199	0.00098	-0.0303	0.54951
0.9	0.95	433	102	149	147	0.088	0.227	0.00622	-0.199	0.00099	-0.0283	0.53214
0.9	0.97	416	102	149	147	0.053	0.229	0.00662	-0.202	0.00078	-0.0296	0.50381
0.9	0.98	328	77	125	120	0.024	0.237	0.00717	-0.191	0.00580	-0.0232	0.48904
0.95	0.9	390	87	129	128	0.126	0.227	0.00526	-0.203	0.00183	-0.0492	0.40744
0.95	0.95	371	87	129	128	0.081	0.230	0.00402	-0.204	0.00208	-0.0473	0.40318
0.95	0.97	358	87	129	128	0.047	0.231	0.00421	-0.205	0.00202	-0.048	0.39936
0.95	0.98	284	66	108	105	0.021	0.236	0.00899	-0.196	0.00905	-0.0409	0.44766
0.97	0.9	339	78	113	112	0.115	0.227	0.00686	-0.203	0.00591	-0.0606	0.38646
0.97	0.95	324	78	113	112	0.074	0.230	0.00552	-0.204	0.00508	-0.0586	0.40456
0.97	0.97	314	78	113	112	0.045	0.230	0.00608	-0.206	0.00581	-0.0597	0.39458
0.97	0.98	250	60	95	93	0.02	0.231	0.02614	-0.197	0.01790	-0.0571	0.41751
0.98	0.9	280	66	94	92	0.107	0.217	0.02392	-0.213	0.01216	-0.036	0.60610
0.98	0.95	268	66	94	92	0.071	0.220	0.02001	-0.213	0.01066	-0.034	0.57882
0.98	0.97	260	66	94	92	0.038	0.220	0.02133	-0.216	0.01075	-0.0354	0.56723
0.98	0.98	208	51	78	77	0.019	0.221	0.03510	-0.208	0.04489	-0.0323	0.53354
0.99	0.9	255	60	86	85	0.102	0.215	0.01770	-0.223	0.00903	-0.0351	0.50215
0.99	0.95	245	60	86	85	0.065	0.217	0.01486	-0.222	0.01003	-0.033	0.49443
0.99	0.97	238	60	86	85	0.038	0.216	0.01641	-0.226	0.00877	-0.0348	0.49136

0.99	0.98	191	47	72	70	0.021	0.218	0.03019	-0.218	0.03649	-0.0323	0.50339
Min		191	47	72	70	0.019	0.215	0.00402	-0.226	0.00078	-0.061	0.38646
Max		456	102	149	147	0.136	0.237	0.03510	-0.191	0.04489	-0.023	0.60610
mean		310	74	110	108	0.064	0.225	0.01367	-0.207	0.01005	-0.040	0.48061

[a] Results in the table are averaged over 10 repeat simulations. P_c is a given criterion for proportion of sum of sample sizes of a SNP over all given causal variables to the largest sum of sample sizes over all SNPs in a simulated dataset and P_d , given criterion for proportion of sample size of a SNP in a disease to the largest sample size over all SNPs in the disease in a simulated dataset.

Table S8. Results [a] of simulation MVMR analysis of lipid risk for coronary artery disease using dataset SNP185 of Do et al as test data and Mc-lipid-CAD data as mother data

		Number of SNPs found					LDL-c		HDL-c		TG	
		total	LDL	HDL	TG	FDR	beta	p-value	beta	p-value	beta	p-value
Pc	Pd	**null p-value is distributed from 1e-07 to 1**										
		238	82	96	60	0	0.391	2.98E-15	-0.129	0.01489	-0.298	0.00018
0	0.7	223	77	90	57	0	0.391	2.42E-14	-0.126	0.02124	-0.328	0.00015
0	0.9	155	53	63	39	0	0.392	3.75E-08	-0.113	0.09856	-0.308	0.01696
0	0.915	143	49	58	36	0	0.385	1.52E-07	-0.114	0.09327	-0.314	0.01541
0	0.93	128	45	51	33	0	0.365	0.001954	-0.109	0.12561	-0.282	0.0999
0.7	0	237	82	96	60	0	0.391	3.32E-15	-0.129	0.01495	-0.298	0.00018
0.7	0.7	222	77	90	56	0	0.391	3.00E-14	-0.125	0.02125	-0.329	0.00016
0.7	0.9	154	53	63	39	0	0.391	5.97E-08	-0.113	0.09825	-0.308	0.01705
0.7	0.915	142	49	58	36	0	0.384	2.06E-07	-0.113	0.09306	-0.315	0.01553
0.7	0.93	128	45	51	33	0	0.365	0.001954	-0.109	0.12564	-0.283	0.09989
0.9	0	204	71	83	52	0	0.394	2.71E-12	-0.131	0.03048	-0.305	0.00136
0.9	0.7	191	66	77	49	0	0.393	1.04E-10	-0.126	0.04899	-0.332	0.00108
0.9	0.9	132	46	54	33	0	0.391	2.38E-07	-0.100	0.18609	-0.294	0.09471
0.9	0.915	122	43	50	30	0	0.386	6.31E-07	-0.100	0.18839	-0.317	0.07237
0.9	0.93	109	39	44	27	0	0.366	0.003088	-0.094	0.20085	-0.285	0.14139
0.915	0	196	68	79	50	0	0.402	7.55E-10	-0.126	0.03853	-0.297	0.00314
0.915	0.7	183	64	74	47	0	0.402	1.40E-09	-0.121	0.05929	-0.322	0.00327
0.915	0.9	126	44	51	32	0	0.4	2.70E-07	-0.094	0.18848	-0.28	0.11201
0.915	0.915	116	41	47	29	0	0.395	7.06E-07	-0.093	0.20179	-0.302	0.09169
0.915	0.93	104	37	42	26	0	0.374	0.006387	-0.09	0.20142	-0.264	0.16553
0.93	0	187	65	75	47	0	0.399	7.33E-10	-0.135	0.03407	-0.301	0.00282
0.93	0.7	175	62	70	44	0	0.4	1.97E-09	-0.130	0.05223	-0.316	0.00349
0.93	0.9	120	43	49	30	0	0.398	4.77E-07	-0.097	0.19502	-0.281	0.13618
0.93	0.915	111	40	46	27	0	0.392	1.04E-06	-0.097	0.20669	-0.306	0.1214
0.93	0.93	99	36	41	24	0	0.37	0.008527	-0.093	0.19999	-0.264	0.19548

Min		99	36	41	24	0	0.365	3.32E-15	-0.135	0.01495	-0.332	0.00016
Max		237	82	96	60	0	0.402	0.00853	-0.090	0.20669	-0.264	0.19548
mean		151	53	61	38	0	0.388	0.00099	-0.111	0.118379	-0.299	0.06336
null p-value is distributed from 1e-12 to 1												
0	0	352	82	96	61	0.324	0.384	2.79E-14	-0.1322	0.00778	-0.246	0.00170
0	0.7	329	77	90	57	0.322	0.382	5.63E-13	-0.1241	0.01499	-0.266	0.01155
0	0.9	224	53	62	37	0.317	0.394	7.45E-07	-0.1287	0.09683	-0.242	0.17330
0	0.915	206	49	58	34	0.316	0.401	3.55E-06	-0.1252	0.11716	-0.254	0.15864
0	0.93	185	44	53	31	0.314	0.411	2.16E-06	-0.1353	0.12906	-0.264	0.14943
0.7	0	350	82	95	60	0.323	0.384	2.77E-14	-0.1299	0.01172	-0.245	0.00183
0.7	0.7	327	76	89	57	0.324	0.383	5.53E-13	-0.1218	0.02256	-0.265	0.01201
0.7	0.9	222	53	62	37	0.315	0.396	6.97E-07	-0.1245	0.12675	-0.240	0.18122
0.7	0.915	204	49	58	34	0.314	0.402	3.37E-06	-0.1208	0.14668	-0.253	0.16470
0.7	0.93	184	44	52	31	0.31	0.412	2.01E-06	-0.131	0.15974	-0.261	0.14281
0.9	0	301	70	83	51	0.326	0.387	3.34E-11	-0.1372	0.02990	-0.238	0.02082
0.9	0.7	281	65	77	48	0.324	0.384	1.98E-10	-0.1285	0.04534	-0.266	0.01822
0.9	0.9	190	45	54	31	0.316	0.403	2.08E-06	-0.1254	0.14790	-0.263	0.14550
0.9	0.915	176	41	50	29	0.313	0.414	2.44E-05	-0.122	0.17048	-0.263	0.13492
0.9	0.93	158	37	45	26	0.31	0.422	2.43E-05	-0.1344	0.18013	-0.256	0.14131
0.915	0	292	68	80	49	0.325	0.393	1.80E-10	-0.1325	0.03306	-0.238	0.02454
0.915	0.7	272	64	75	46	0.327	0.392	5.14E-09	-0.123	0.05150	-0.265	0.02427
0.915	0.9	185	44	52	30	0.319	0.411	5.34E-06	-0.1183	0.15294	-0.257	0.19116
0.915	0.915	170	41	48	28	0.318	0.413	3.70E-05	-0.1141	0.17602	-0.257	0.17377
0.915	0.93	153	37	44	25	0.314	0.422	4.30E-05	-0.1345	0.18612	-0.248	0.17767
0.93	0	278	64	76	47	0.324	0.389	4.53E-10	-0.1319	0.03234	-0.210	0.12062
0.93	0.7	260	60	71	44	0.323	0.388	5.63E-08	-0.1234	0.04670	-0.236	0.10573
0.93	0.9	176	41	49	29	0.318	0.411	2.21E-05	-0.1228	0.14640	-0.204	0.22578
0.93	0.915	162	38	46	27	0.315	0.415	3.92E-05	-0.117	0.17288	-0.198	0.27816
0.93	0.93	146	34	42	24	0.315	0.421	0.000324	-0.1374	0.17824	-0.207	0.15736
Min		146	34	42	24	0.31	0.383	2.77E-14	-0.1374	0.01172	-0.266	0.00183
Max		350	82	95	60	0.327	0.422	0.000324	-0.1141	0.18612	-0.198	0.27816
mean		222	52	62	37	0.318	0.402	2.42E-05	-0.1268	0.11198	-0.245	0.12502

[a] Results in table are averaged over 10 repeat simulations. P_c is a given criterion for proportion of sum of sample sizes of a SNP over all given causal variables to the largest sum of sample sizes over all SNPs in a simulated dataset and P_d, given criterion for proportion of sample size of a SNP in a disease to the largest sample size over all SNPs in the disease in a simulated dataset.

Table S9. Results [a] of simulation MVMR analysis of lipid risk for coronary artery disease using SNP363 data as test data and Mc-lipid-CAD data as mother data

		Number of SNPs found					LDL-c		HDL-c		TG	
Pc	Pd	total	LDL-c	HDL-c	TG	FDR	beta	pvalue	beta	p-value	beta	p-value
null p-value is distributed from 1e-12 to 1												
0	0	612	151	239	109	0.19	0.2705	2.85E-06	-0.2144	2.50E-03	-0.0661	0.254342
0	0.7	601	151	239	109	0.175	0.2717	2.65E-06	-0.2167	2.74E-03	-0.0668	0.263725
0	0.9	566	151	239	109	0.124	0.2743	9.56E-07	-0.223	2.15E-03	-0.0679	0.267804
0	0.93	554	151	239	109	0.105	0.2741	1.38E-06	-0.2248	2.18E-03	-0.0708	0.273109
0.5	0	604	151	239	109	0.179	0.2706	2.55E-06	-0.2158	1.99E-03	-0.0674	0.244669
0.5	0.7	594	151	239	109	0.165	0.2725	1.93E-06	-0.2176	2.76E-03	-0.068	0.245366
0.5	0.9	562	151	239	109	0.117	0.2748	8.46E-07	-0.2242	2.12E-03	-0.0694	0.262287
0.5	0.93	551	151	239	109	0.1	0.2744	1.15E-06	-0.225	2.11E-03	-0.0716	0.264578
0.7	0	478	145	232	105	0	0.2839	1.05E-06	-0.2316	1.81E-03	-0.0750	0.252553
0.7	0.7	478	145	232	105	0	0.2839	1.05E-06	-0.2316	1.81E-03	-0.0750	0.252553
0.7	0.9	478	145	232	105	0	0.2839	1.05E-06	-0.2316	1.81E-03	-0.0750	0.252553
0.7	0.93	478	145	232	105	0	0.2839	1.05E-06	-0.2316	1.81E-03	-0.0750	0.252553
min		478	145	232	105	0	0.2705	8.46E-07	-0.2316	0.00181	-0.0750	0.244669
max		612	151	239	109	0.19	0.2839	2.85E-06	-0.2144	0.00276	-0.0661	0.273109
mean		546	149	237	108	0.096	0.2765	1.543E-06	-0.2240	0.00215	-0.0707	0.2571743

[a] Results in table are averaged over 10 repeat simulations. P_c is a given criterion for proportion of sum of sample sizes of a SNP over all given causal variables to the largest sum of sample sizes over all SNPs in a simulated dataset and P_d, given criterion for proportion of sample size of a SNP in a disease to the largest sample size over all SNPs in the disease in a simulated dataset.

Supplementary Figures:

Figure S1. Scatter error-bar plots of lipoprotein-cholesterols versus coronary artery disease in the data of unique SNPs

Panels a, b, and c are respectively scatter error-bar plots of genetic associations of SNPs with LDL-c, HDL-c, and TG versus those with risk for CAD based on data of 255 unique SNPs in the data of 338 SNPs from Mc-lipid-CAD data and 247 unique SNPS in the data of 363 SNPs from jointGwasMc-lipid-CAD. Red solid line is a general liner regression line and green dash line is an MR-Egger regression line.

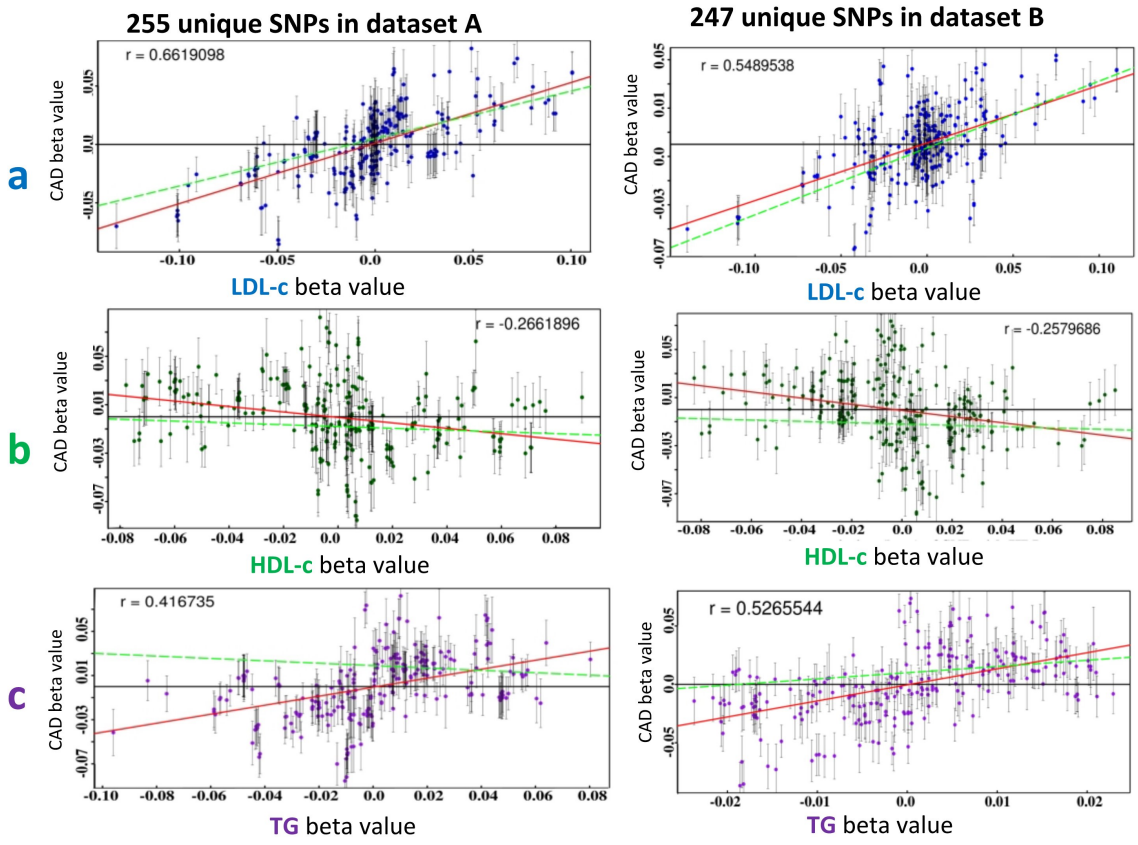
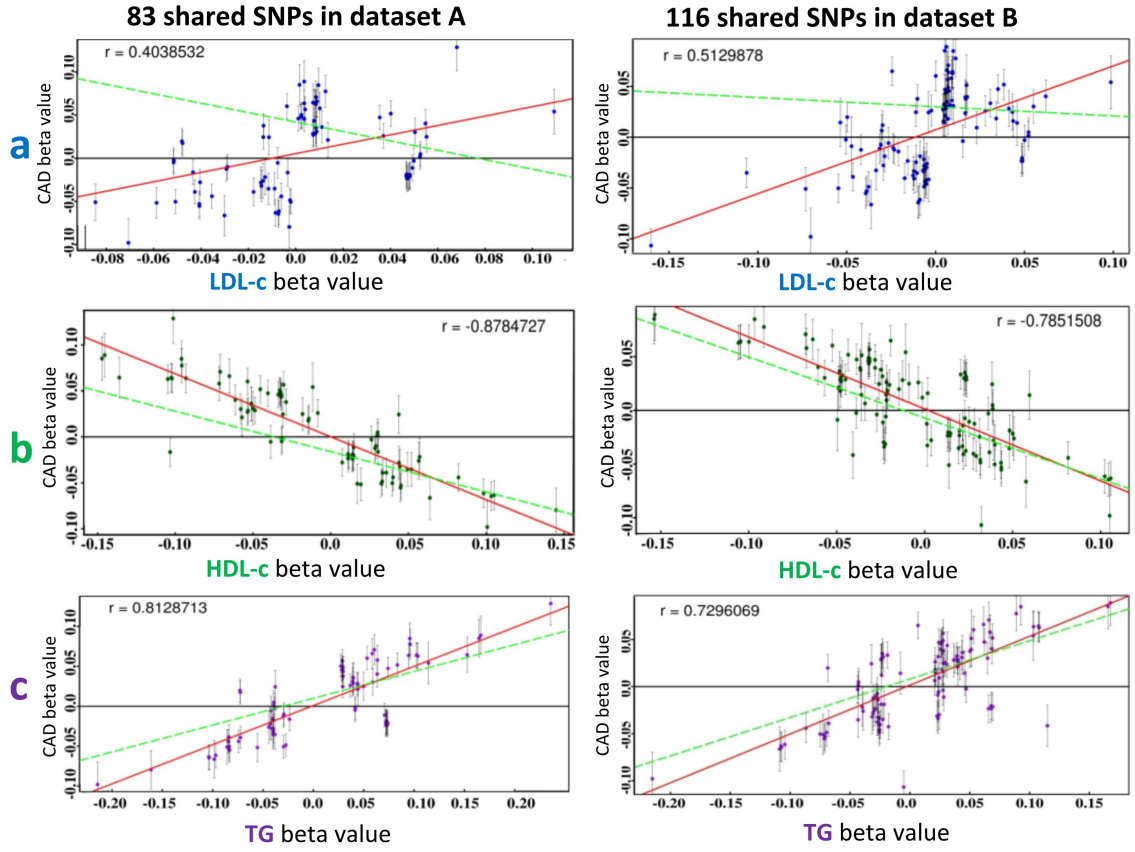


Figure S2. Scatter error-bar plots of lipoprotein-cholesterols versus coronary artery disease in the data of shared SNPs

Panels a, b, and c are respectively scatter errorbarplots of genetic associations of SNPs with LDL-c, HDL-c, and TG versus those with risk for CAD based on the data of 83 unique SNPs in the data of 338 SNPs from Mc-lipid-CAD data and 116 shared SNPS in the data of 363 SNPs from jointGwasMc-lipid-CAD. Red solid line is a general liner regression line and green dash line is an MR-Egger regression line.



Supplementary data (in Excel file with tabs for the following):

1. Dataset A: 338SNPs_lipid_CAD
2. Dataset B: 363SNPs_lipid_CAD
3. Dataset D1: 173 SNPs_lipid_CAD_Mc
4. Dataset D2: 173SNPs_lpid_CAD_jontGwasMC

Supplementary R code for implementing SNP selection, MVMR analysis, drawing forestplot, errorbarplot, and large-scale simulation MVMR analysis will be uploaded on Github.