Data S1

Methods for causal effect of BMI on PAI-1

To further investigate our findings on the negative direction of effect of PAI-1 on BMI, which runs counter to some prior evidence,[1] we explored the causal effect of BMI on PAI-1. Locke *et al.* reported 77 independent genome-wide significant loci associated with BMI in 322,154 individuals of European ancestry.[2] We applied the MR approach using all 77 loci as an instrumental variable (IV) using the inverse variance weighted (IVW) method described in our main article. Two sensitivity analyses were further adopted to examine potential pleiotropic effects of the selected IV. In the first sensitivity analysis, we used the MR-Egger method.[3] In this method, an Egger regression, which is commonly used to detect small study bias, was used to detect the potential bias of pleiotropic effects in the MR. The beta coefficient in the MR-Egger is considered as a causal effect after correcting for pleiotropic effects. The intercept of the Egger regression provides information on the directional pleiotropic effect in the IV (right panel in **Table S3**).[3] In the second sensitivity analysis, we investigated whether the causal effect was consistent when only 50% of the SNPs are assumed to be valid in the IV, an approach known as weighted median estimator.[4]

Results for causal effect of BMI on PAI-1

We found that increasing 1 unit of BMI was causally associated with a 0.21 unit increase of log-transformed PAI-1 (beta, 0.21, 95% CI, 0.13, 0.29; **Table S3**). The result was consistent when the MR-Egger method was applied (beta, 0.21, 95% CI, 0.02, 0.41; **Table S3**), with little influence of pleiotropic effect as indicated by the intercept (beta, -0.0002, P-value, 0.949). The median estimator was also in agreement with the other two analyses (beta, 0.22, 95% CI, 0.09, 0.36; **Table S3**). Taken together, our results support a robust positive causal effect of BMI on PAI-1.

Table S1. Publications included in the observational meta-analysis

Study	PMID	Adjustment in the multiple-variable model
Thögersen *et al*, 1998[5]	9826309	Age, sex, diabetes, smoking, hypertension, BMI, Cholesterol, and ApoA-1.
Cushman *et al*, 1999[6]	10073948	Hypertension, smoking status, race (white or nonwhite), diabetes, and body mass index.
Söderberg *et al*, 1999[7]	10583712	BMI, hypertension, history of diabetes, daily smoking habits, cholesterol levels, leptin, apo A-1, apo B, and insulin.
Folsom *et al*, 2001[8]	11304480	Age, race, and sex, smoking status (never, former, current), total cholesterol, HDL cholesterol, systolic blood pressure, use of antihypertensive medication, and diabetes.
Thøgersen *et al*, 2004[9]	15167204	N/A (dichotomous analysis).
Smith *et al*, 2005[10]	16286603	Age, sex, race, hypertension, diabetes mellitus, total cholesterol, HDL, cigarette smoking and alcohol intake.
Aleksic *et al*, 2009[11]	18342864	Age, sex, race, hypertension, diabetes mellitus, total cholesterol, HDL, cigarette smoking and alcohol intake.
Thøgersen *et al*, 2009[12]	19357504	Age, smoking, CRP, t-PA, creatinine.
Luc *et al*, 2010[13]	19823188	Diabetes, hypertension, smoking status, total and high-density lipoprotein (HDL) cholesterol and triglycerides.
Meltzer *et al*, 2010[14]	20413657	Age, HDL and total cholesterol, triglycerides, BMI, and diabetes.
Yano *et al*, 2013[15]	23551722	Sex, body mass index, history of diabetes, history of hyperlipidemia, and 24-hour pulse rate, high levels of high-sensitivity C-reactive protein, prothrombin fragment 1+2.
De Luca *et al*, 2013[16]	24004495	Duration of time between the date of samples and the analysis time, age, total cholesterol, HDL.

Knudsen *et al*, 2014[17]	24566095	Viral load and a high (Data collection on Adverse events of Anti-HIV Drugs) D:A:D risk score.
Tofler *et al*, 2016[18]	26896607	Age, sex, systolic blood pressure, anti-hypertensive therapy, BMI, diabetes, cigarette smoking, total cholesterol, HDL cholesterol, and triglycerides.

Table S2. SNPs involved in the genetic risk scores as instrumental variable for PAI-1

SNPid	Chr:position(hg19)	Risk/Other alleles	Allele freq in PAI-1*	Allele freq in CHD*	Effect on PAI-1**	Effect on CHD***
SNPs involved in the single locus instrumental variable						
rs2227631	chr7:100,769,538	A/G	0.592	0.563	0.076 (0.010)	0.008 (0.009)
rs2075756	chr7:100,466,441	A/G	0.282	0.279	0.058 (0.010)	0.027 (0.010)
rs12672665	chr7:100,483,731	A/G	0.479	0.474	0.047 (0.009)	0.012 (0.009)
rs757718	chr7:100,792,810	T/C	0.093	0.118	0.081 (0.016)	-0.013 (0.017)
SNPs involved in the multi locus instrumental variable						
rs2227631	chr7:100,769,538	A/G	0.592	0.563	0.076 (0.010)	0.008 (0.009)
rs6976053	chr7:100,512,119	T/C	0.479	0.476	0.054 (0.009)	0.019 (0.009)
rs6486122	chr11:13,361,524	T/C	0.689	0.638	0.051 (0.009)	0.034 (0.010)
rs11128603	chr3:12,385,828	A/G	0.898	0.870	0.086 (0.016)	-0.001 (0.014)

* Allele freq in PAI-1 and CHD reported the allele frequency of the risk allele in the study samples for PAI-1 and CHD respectively.

** Effect of SNPs on PAI-1 is reported as beta coefficient (with standard error) from Huang *et al*, 2012.[19]

*** Effect of SNPs on CHD is reported as log-transformed Odds ratio (with standard error) from Nikpay *et al*, 2015.[20]

Table S3. Causal effect of BMI on PAI-1

	Causal effect of BMI on PAI-1			Directional pleiotropic effect	
Method	Beta	95% CI	P-value	Beta	P-value
Primary MR analysis					
IVW approach	0.21	0.13, 0.29	4.31E-07	N/A	N/A
Sensitivity analysis					
MR_Egger	0.21	0.02, 0.41	0.034	-0.0002	0.949
Weighted median estimator	0.22	0.09, 0.36	0.001	N/A	N/A

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