Table 1. Power calculation for all the MR analyses conducted in the current study.

	Exposure		Outcome		Number of genetic instruments	Proportion of variance explained by the genetic instruments on exposure	Power (%)	F-statistics
	Disease or trait	**Sample size**	**Disease or trait**	**Sample size**				
1	LDL-C	188,577	TB-BMD (overall)	66,628	76	0.064	84	4,556.76
1a	*LDL-C*	*188,577*	*TB-BMD (Age: 15 or less)*	*11,807*	*75**	*0.064*	*24*	*808.32*
1b	*LDL-C*	*188,577*	*TB-BMD (Age: 15 to 30)*	*4,180*	*76*	*0.064*	*11*	*286.81*
1c	*LDL-C*	*188,577*	*TB-BMD (Age: 30 to 45)*	*10,062*	*76*	*0.064*	*21*	*689.00*
1d	*LDL-C*	*188,577*	*TB-BMD (Age: 45 to 60)*	*18,805*	*76*	*0.064*	*35*	*1,286.81*
1e	*LDL-C*	*188,577*	*TB-BMD (Age: 60 or above)*	*22,504*	*76*	*0.064*	*40*	*1,539.74*
2	HDL-C	188,577	TB-BMD (overall)	66,628	86	0.059	93	4,178.53
3	Triglycerides	188,577	TB-BMD (overall)	66,628	51	0.046	25	3,213.67
4	TB-BMD (overall)	66,628	LDL-C	188,577	68	0.061	100	12,251.48
5	LDL-C	188,577	eBMD	142,487	76	0.064	99	9,743.70
6	HDL-C	188,577	eBMD	142,487	86	0.059	100	8,934.83
7	Triglycerides	188,577	eBMD	142,487	51	0.046	46	6,871.44
8	eBMD	142,487	LDL-C	188,577	221	0.075	100	15,397.62

	Exposure		Outcome		Number of genetic instruments	Proportion of variance explained by the genetic instruments on exposure	Power (%)	F-statistics
	Disease or trait	**Sample size**	**Disease or trait**	**Sample size**				
9	LDL-C	188,577	Fracture	37,857 cases 227,116 controls	76	0.064	100	18,118.81
10	TB-BMD (overall)	66,628	CAD	71,602 cases 260,875 controls	68	0.061	100	21,599.61
11	CAD	71,602 cases 260,875 controls	TB-BMD (overall)	66,628	294	Remarks		
12	eBMD	142,487	CAD	71,602 cases 260,875 controls	214	0.073	100	26,183.12
13	CAD	71,602 cases 260,875 controls	eBMD	142,487	297	Remarks		

The MR analyses of LDL-C level on age-stratified TB-BMD were shown in italic.

* One genetic instrument cannot be matched with TB-BMD GWAS meta-analysis for the age group of 15 or less. No proxy can be identified.

Remarks: mRnd could not calculate the power of MR analysis that involved binary exposure and continuous outcome. We could not determine whether the detected null effect was due to the absence of real causal effect, or due to insufficient power.

Table 2. Demographic characteristics of NHANES III and HKOS participants.

	NHANES III			HKOS		
N	3638			1128		
Age (years)	57.1	±	12.7	59.9	±	10.5
Female (%)	1878		53.7%	878		77.8%
Ethnicity/Race						
Non-hispanic white (%)	1917		80.8%	NA		
Non-hispanic black (%)	803		8.2%	NA		
Mexican-American (%)	766		3.2%	NA		
Other (%)	152		7.8%	NA		
Southern Chinese (%)	NA			1128		100%
Height (cm)	167.4	±	9.9	158.3	±	8
Weight (kg)	76.3	±	17.1	58.6	±	10.6
BMD at femoral neck (g/cm^2)	0.763	±	0.147	0.7	±	0.126
BMD at lumbar spine (g/cm^2)	NA			0.925	±	0.164
BMI (kg/m^2)	27.15	±	5.31	23.52	±	6.34
Serum LDL (mmol/L)	3.53	±	0.94	2.86	±	0.81
Serum HDL (mmol/L)	1.31	±	0.4	1.64	±	0.46
Serum triglycerides (mmol/L)	1.6	±	0.8	1.25	±	0.66

Data are presented as mean±SD for continuous variables and N±%. for categorical variables.

Table 3. Comparison of observational and causal estimates for BMD (in SD) per 1 SD decrease of LDL-C.

Analysis	Beta	95% CI		P-value
		Lower	Upper	
Observational				
BMD at femoral neck*				
NHANES III	0.045	0.009	0.081	0.015
HKOS	0.039	-0.011	0.089	0.123
BMD at lumbar spine*				
HKOS	0.083	0.03	0.135	0.002
Mendelian Randomization approach to evaluate causality of LDL-C on TB-BMD				
76 SNPs				
Conventional IVW	0.038	0.002	0.074	0.038
Multivariable IVW	0.033	-0.004	0.070	0.083
Weighted median	0.018	-0.026	0.063	0.416
MR-Egger	0.011	-0.045	0.068	0.694
MR-Egger intercept	0.002	-0.001	0.005	0.235
68 SNPs [Sensitivity analysis after exclusion of 8 genetic instruments associated with potential confounders (BMI or / and diabetes)]				
Conventional IVW	0.038	-1.7×10^{-4}	0.076	0.051
Multivariable IVW	0.036	-0.004	0.075	0.077
Weighted median	0.018	-0.029	0.066	0.445
MR-Egger	0.002	-0.056	0.059	0.957
MR-Egger intercept	0.003	-5×10^{-4}	0.006	0.099
Mendelian Randomization approach to evaluate causality of LDL-C on eBMD				
76 SNPs				
Conventional IVW	0.076	0.042	0.111	1.20×10^{-5}
Multivariable IVW	0.083	0.047	0.118	4.39×10^{-6}
Weighted median	0.065	0.04	0.09	3.59×10^{-7}
MR-Egger	0.052	-0.002	0.106	0.059
MR-Egger intercept	0.002	-0.001	0.005	0.257
68 SNPs [Sensitivity analysis after exclusion of 8 genetic instruments associated with potential confounders (BMI or / and diabetes)]				
Conventional IVW	0.063	0.027	0.099	5.78×10^{-4}
Multivariable IVW	0.067	0.029	0.105	0.001
Weighted median	0.034	0.007	0.060	0.012
MR-Egger	0.043	-0.012	0.098	0.122
MR-Egger intercept	0.001	-0.002	0.005	0.351

*Model was adjusted for age, sex, ethnicity/race, weight, height, serum HDL-C levels, and serum triglycerides levels.

Table 4. Genetic correlation among traits

	Trait 1	Trait 2	Genetic correlation (95% CI)	P-value
1	TB-BMD	eBMD	0.5918 (0.5553 to 0.6283)	5.4657×10^{-59}
2	LDL-C	TB-BMD	-0.0792 (-0.1065 to -0.0519)	0.0038
3	LDL-C	eBMD	-0.0821 (-0.1045 to -0.0597)	0.0003
4	HDL-C	TB-BMD	-0.0383 (-0.0616 to -0.015)	0.0996
5	HDL-C	eBMD	-0.0724 (-0.0949 to -0.0499)	0.0013
6	Triglycerides	TB-BMD	-0.0103 (-0.0377 to 0.0171)	0.7085
7	Triglycerides	eBMD	0.0334 (0.0053 to 0.0615)	0.2340
8	TB-BMD	CAD	0.0137 (-0.0166 to 0.044)	0.6512
9	eBMD	CAD	0.0669 (0.0416 to 0.0922)	0.0082
10	LDL-C	Fracture	0.024 (-0.0187 to 0.0667)	0.5735

Table 5. Causal estimates for LDL-C (in SD) per 1 SD decrease of BMD.

Mendelian Randomization approach to evaluate causal effects of TB-BMD on LDL-C				
Analysis	**Beta**	**95% CI**		**P-value**
		Lower	**Upper**	
68 SNPs				
Conventional IVW	0.035	0.003	0.066	0.034
Multivariable IVW	0.037	0.011	0.063	0.006
Weighted median	0.043	-0.001	0.087	0.055
MR-Egger	0.004	-0.087	0.095	0.927
MR-Egger intercept	0.002	-0.003	0.006	0.486
Mendelian Randomization approach to evaluate causal effects of eBMD on LDL-C				
Analysis	**Beta**	**95% CI**		**P-value**
		Lower	**Upper**	
221 SNPs				
Conventional IVW	0.025	-0.007	0.058	0.128
Multivariable IVW	0.016	-0.016	0.049	0.326
Weighted median	0.023	-0.013	0.057	0.211
MR-Egger	0.006	-0.065	0.077	0.867
MR-Egger intercept	0.001	-0.002	0.004	0.547

Table 6. Causal estimates for BMD or fracture (in SD) per 1 SD decrease of LDL-C caused by LDL-C-lowering drugs.

Gene encoding molecular target of LDL-C-lowering therapy	Number of genetic instruments	Beta	95% CI		P-value
			Lower	Upper	
Mendelian Randomization approach to evaluate the LDL-C-lowering effects on TB-BMD					
HMGCR	3	0.180	0.044	0.316	9.600×10^{-3}
NPC1L1	2	0.080	-0.138	0.298	0.472
PCSK9	1	0.006	-0.107	0.118	0.919
ABCG5/G8	1	0.037	-0.113	0.187	0.628
LDLR	1	0.018	-0.064	0.101	0.667
Mendelian Randomization approach to evaluate the LDL-C-lowering effects on eBMD					
HMGCR	3	0.143	0.062	0.223	5.165×10^{-4}
NPC1L1	2	-0.051	-0.176	0.074	0.427
PCSK9	1	0.039	-0.011	0.089	0.125
ABCG5/G8	1	0.037	-0.049	0.123	0.396
LDLR	1	0.024	-0.022	0.070	0.305
Mendelian Randomization approach to evaluate the LDL-C-lowering effects on fracture					
HMGCR	3	-0.090	-0.285	0.104	0.363

Table 7. Causal estimates for CAD per 1 SD decrease of BMD.

Mendelian Randomization approach to evaluate causality of TB-BMD on CAD				
68 SNPs				
Analysis	**Odds Ratio**	**95% CI**		**P-value**
		Lower	**Upper**	
Univariable MR analysis				
Conventional IVW	0.963	0.912	1.017	0.180
Weighted median	0.969	0.906	1.037	0.368
MR-Egger	1.059	0.911	1.231	0.453
MR-Egger intercept	0.995	0.987	1.003	0.186
Multivariable IVW				
LDL-C, HDL-C, triglycerides, diabetes and BMI as related risk factors	0.980	0.925	1.039	0.504
Mendelian Randomization approach to evaluate causality of eBMD on CAD				
214 SNPs				
Analysis	**Odds ratio**	**95% CI**		**P-value**
		Lower	**Upper**	
Univariable MR analysis				
Conventional IVW	0.949	0.903	0.998	0.042
Weighted median	0.973	0.921	1.027	0.320
MR-Egger	0.966	0.869	1.075	0.529
MR-Egger intercept	0.999	0.995	1.003	0.709
Multivariable IVW				
LDL-C, HDL-C, triglycerides, diabetes and BMI as related risk factors	0.962	0.916	1.011	0.123