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Causal link between lipid profile and bone mineral density: A Mendelian randomization study

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ABSTRACT

The level of serum lipids is associated with bone mineral density (BMD), an important skeletal trait. Yet the causality has not been determined. Here we performed a Mendelian randomization (MR) analysis to test potential causal links between BMD and lipid profile, i.e., low-density lipoprotein cholesterol (LDC-c), total cholesterol (TC), triglyceride (TG) and high-density lipoprotein cholesterol (HDL-c). We observed causal effect of LDL-c, TC and TG to BMD, and reversely the effect of BMD to HDL-c. We further explored the effect of body mass index (BMI) in these causalities and found that the effect of LDL-c, TC and TG to BMD is independent of BMI. Our findings provided useful information in the clinical relevance of blood lipids on BMD variation and osteoporosis risk.

1. Introduction

Serum lipids are important complex traits for a number of metabolic diseases and are highly inheritable [1]. It is estimated that 28.5 million (a prevalence of 11.9%) US adults of 20 years or older have a serum total cholesterol (TC) level ≥240 mg/dL [2]. Long-term exposure to even modestly elevated cholesterol levels can lead to coronary heart disease (CHD) later in life [3] and high cholesterol (≥190 mg/dL or ≥5.0 mmol/L) has become a global public health problem, causing 2.6 million deaths (4.5% of total deaths) annually worldwide [2]. High cholesterol is also associated with a spectrum of other adverse outcomes, such as metabolic syndrome [4], cardiovascular disease (CVD) [3] and low bone mineral density (BMD) [5–8], a critical risk factor of osteoporosis.

Osteoporosis is a common bone metabolic disease among the elderly, characterized by low bone mass, micro-architectural deterioration of bone tissue and an increased risk to fracture [9]. Fifteen percent of white people over 50 years may suffer osteoporotic fracture in their remaining lifetime, and the projected related costs may exceed $25 billion in the US by 2025 [10]. BMD is a gold standard for osteoporosis diagnosis and is a highly heritable trait with a heritability of > 60% [11].

The association of BMD and serum lipids has been extensively investigated [5–7,12]. In some studies, a higher level of high-density lipoprotein cholesterol (HDL-c) was found to be associated with a lower BMD or an increased risk of osteoporosis [5–8,13,14]. However, in another study, higher HDL-c level was associated with higher BMD [15]. A non-association between serum lipids and BMD was also reported [16]. Other lipid traits, including, low-density lipoprotein cholesterol (LDL-c), TC, and triglyceride (TG) achieved similar conflicting

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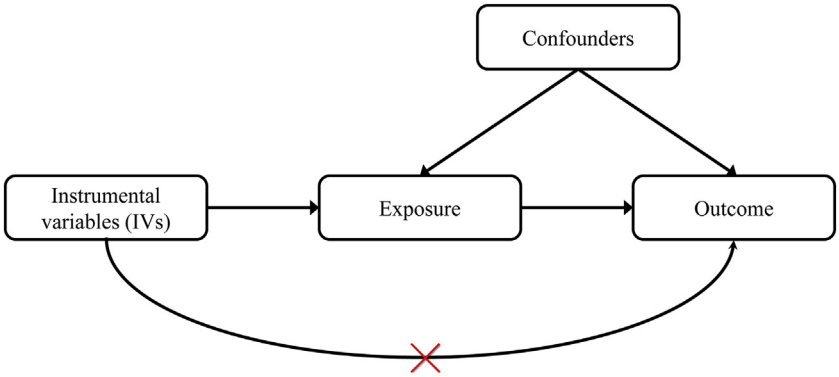

Fig. 1. The rational diagram for the Mendelian randomization causal inference.

results [5–8,12–15,17–19]. Controversial results were also reported towards the confounding role of body mass index (BMI) played in the association between BMD and lipids [17,20].

Given accumulating evidence for the potential relationship between lipid profile and BMD [5–8,12–20], a causal inference between lipid profile and BMD is needed. Randomized controlled trial (RCT) is a gold standard for establishing causality for an association. However, it is extremely time-consuming and expensive. As an alternative, Mendelian randomization (MR) is a powerful yet more convenient technique to perform causal inference.

MR is a method to assess whether the association between exposure and outcome is causal using genetic variant as instrumental variable (IV) for the exposure [21]. Comparing with traditional observational studies, MR represents a better alternative for testing whether associations are causal. MR designs rely on three basic assumptions: i) The genetic instruments (IVs) used in analysis should be associated with exposure (i.e., a risk factor); ii) The genetic instruments should not be associated with any confounders of exposure; iii) The association of genetic instruments with outcome should be only through exposure (i.e., no horizontal pleiotropic effect) (Fig. 1).

Here we adopted a newly developed approach, generalized summary data-based MR (GSMR) [22], to explore the causative link between lipid profile and BMD under a MR framework using genome-wide association study (GWAS) summary statistics. We used reverse GSMR to investigate the bidirectional causal relationship. We also performed MR analysis conditioning on BMI (which is associated with both lipid profile and BMD) to test the confounding effect of BMI on the BMD-lipid relationship.

2. Methods

2.1. Data sources

We collected several publicly available GWAS datasets as described below. Each study included was approved by the local institutional review board (IRB) and ethics committee, and all participants provided written informed consent.

1. The Global Lipids Genetics Consortium (GLGC) GWAS: including 188,577 individuals of primarily European ancestry (18,678 non-European) [23], four phenotypes including TC, TG, HDL-c and LDL-c, and ~2,447,000 genotyped and imputed SNPs. All of above lipid traits are publicly available on GLGC website (http://csg.sph.umich.edu/willer/public/lipids2013/).
2. UK Biobank (UKB) GWAS for BMD: including 426,824 participants of European descent from the UKB (http://www.gefos.org/?q=content/data-release-2018). The dataset contains BMD data and ~14,000,000 genotyped and imputed SNPs [24].
3. GIANT + UKB GWAS for BMI: including ~700,000 subjects of European ancestry with genotyped and imputed 16,652,994 SNPs [25], retrieved from the GWAS catalog (https://www.ebi.ac.uk/gwas/).

2.2. LDSC analysis

Linkage disequilibrium score regression (LDSC) analysis was performed on the GWAS summary results to evaluate genetic architecture of each trait. The method takes GWAS summary statistics as input and partitions them into the fraction attributable to polygenic architecture and the fraction due to cryptic relatedness and population stratification [26]. The analysis also estimates the genetic heritability attributable to GWAS SNPs. Reference linkage disequilibrium (LD) scores for the European population were downloaded from the software website (https://github.com/bulik/ldsc).

Through LDSC based analysis of GWAS summary results of lipid profile and BMD, we also inferred genetic correlation between a lipid trait and BMD [27]. The method is an extension of single trait LD score regression and is robust to sample overlap.

2.3. SNP selection

From GWAS summary results, we conducted a series of quality control (QC) steps to select eligible instrumental SNPs. First, we extracted genome-wide significant SNPs ($p < 5 \times 10^{-8}$) (i.e., the instrument SNPs) that are associated with lipid profile or BMD. Second, ambiguous SNPs with non-concordant alleles (e.g., A/G vs. A/C) and palindromic SNPs with ambiguous strand (i.e., A/T or G/C) were excluded from the above selected instrument SNPs. Third, SNPs with minor allele frequency (MAF) < 0.01 were removed. Finally, SNPs with a large frequency difference when compared with the reference sample (> 0.2) and poor imputation score (< 0.8) were excluded. These stringently selected SNPs were used as the final instrumental SNPs for subsequent MR analysis. A set of independent SNPs were clumped with PLINK ($r^2 < 0.05$ and window size = 1 Mb) [28].

2.4. Effect size estimate

All the GWAS summary results were based on standardized phenotypes (i.e., with mean 0 and standard deviation 1). Therefore, individual SNP effect size was estimated as the explainable variance with the formula $2f(1-f)\beta^2$, where f is allele frequency and β is regression coefficient.

2.5. Power assessment

The power to detect causal effect was calculated using an online tool mRnd [29] (http://cnsgenomics.com/shiny/mRnd/). This method uses a non-centrality parameter to calculate statistical power of a continuous

outcome inferred with a two sample MR approach. A non-centrality parameter derived from general equation needs several parameters to estimate. The first is the proportion of phenotypic variation explained by IV SNPs, which was estimated on the original GWAS studies. The second is the effect size of the exposure to the outcome at the epidemiological level, which was estimated from another independent observational cohort [6]. Addition parameters include sample size and standard deviation of exposure and outcome [6].

2.6. Bidirectional Mendelian randomization

We conducted MR analyses to identify the causality of association between lipid profile (i.e., HDL-c, LDL-c, TC and TG) and BMD using GSMR under a MR framework [22]. We performed GSMR implemented in GCTA using the largest GWAS datasets for lipid profile [23] and BMD [24]. This approach uses GWAS summary data to establish causal association between a putative risk factor and an outcome using quality-controlled SNPs as IVs. We also switched the exposure and outcome to explore the reverse causation in reverse GSMR analysis.

The estimated causal effect coefficient (b_{xy}) is the change in the number of standard deviations of the outcome per one standard deviation change of the exposure.

For estimation of allele frequency and LD level, we selected the reference sample formed by the European ancestral individuals from the 1000 genomes project (http://www.internationalgenome.org/) [30].

2.7. Sensitivity analysis

Causal relationship inference may be confounded by pleiotropic SNPs, which influence both exposure and outcome jointly. In contrast, if there are multiple independent (or nearly independent) SNPs associated with exposure and the effect of exposure on outcome is causal, the effects of exposure-associated SNPs are expected to be identical in absence of pleiotropy [31]. Hence, in order to exclude the influence of pleiotropic effects, we applied the HEIDI-outlier method to detect pleiotropic SNPs [22]. A significant pleiotropic SNP was declared at $p < 0.01$ based on the chi-squared statistic generated from the causal model being built, and was discarded from subsequent analyses. All remaining SNPs were used as non-pleiotropic IVs to estimate the causal effect of exposure to outcome.

2.8. Conditional analysis

BMI is a potential mediator in the causal relationship between lipid profile and BMD. To account for the effect of BMI, we performed additional MR analysis conditioning on BMI with mtCOJO [22]. The method estimates the marginal effect of exposure on outcome while accounting for multiple covariates. The analysis is equivalent to a two-step analysis with the first step to adjust both exposure and outcome with a covariate (BMI) and the second step to estimate the effect of adjusted exposure on adjusted outcome. As the estimate is not confounded by sharing environment and genetics that are correlated with instrument variables, it is free of collider bias as described in Aschard et al. [32]. We performed conditional analysis (conditioning on BMI) for lipid profile and BMD separately and then re-analyzed the lipid-BMD relationship using GSMR.

3. Results

We estimated heritability of each trait and genetic correlation between each lipid trait and BMD (Table 1). All traits have a moderate heritability ranging from 0.21 to 0.36 (Table 1). Of the above traits, we observed that all but one pair that are negatively correlated, where all correlation coefficients are small (< 8%). Notably, for the lipid traits, a total of 188,577 participants were included in the GWAS summary statistics, of which only 9.9% were non-Europeans. We did not expect that this small fraction of non-European individuals had a significant influence on our results.

We incorporated all independent SNPs ($r^2 < 0.05$) clumped by PLINK as IV SNPs. There were n = 179, 150, 176 and 113 IV SNPs (Table 1) for HDL-c, LDL-c, TC and TG, respectively, to be used to estimate the causal effect to BMD. These IVs are close to genes identified by previous study [23,24,33]. For example, more than half (53.5%) genes neighboring the IVs that were used for causal inference of BMD to HDL-c overlap with the genes identified from BMD GWAS studies (Supplementary Table 1) [24,33]. With a large sample size of (18,000-42,000) subjects and a large number of IVs (71–1697), we have sufficient statistical power to detect true causal effect with a regression coefficient between −0.04 and −0.02 (with a type I error rate of 0.05) (Fig. 2).

The causal effects between each of the four lipid traits and BMD are shown in Table 1. Family-wise error rate (FWER) was controlled at 0.05 by Bonferroni correction accounting for 8 tests ($P_{adj} = 6.25 \times 10^{-3}$). Under this stringent significance threshold, we observed 7 significant causal associations, representing ubiquitous bidirectional causal effects between lipid profile and BMD.

To ensure that the above causal effect signals are free from pleiotropy, we performed HDIEI-outlier analysis on independent SNPs ($r^2 < 0.05$) (extracted from clumping analysis in PLINK) to eliminate potential SNPs with pleiotropic effect. When BMD is the outcome, there are 72, 48, 49 and 42 pleiotropic SNPs for HDL-c, LDL-c, TC and TG respectively. After removing pleiotropic effect SNPs, we repeated the MR analysis. Four causal associations remained significant (Table 2), which are LDL-c ➔ BMD, TC ➔ BMD, TG➔BMD and BMD ➔ HDL-c.

Specifically, LDL-c, TC and TG are negatively and causally associated with BMD (Table 2), suggesting an increase of these serum lipids may cause a decrease in BMD value. Reversely, BMD is negatively and causally associated with HDL-c (Table 2), suggesting that an increase in BMD may cause a decrease in HDL-c concentration.

We then analyzed the relationship of lipids, BMD and BMI using non-pleiotropic SNP IVs. The significance threshold was set at 0.005 (0.05/10) accounting for multiple testing. Overall, the causal effect is mutual between BMI and BMD, with BMI having a stronger and more significant effect on BMD ($b_{xy} = 0.167$, $p = 6.96 \times 10^{-202}$) than vice versa. Such mutual effects are also observed between BMI and lipid measures (Fig. 3, Table 3).

To adjust for BMI's influence on the causal link between BMD and lipid measures, we performed causal analysis using non-pleotropic IVs conditioning on BMI with Bonferroni corrected significance level of 0.01 (0.05/4). The results are listed in Table 4. Three causal associations (LDL-c ➔ BMD, TC ➔ BMD and TG➔ BMD) remained to be significant with the same negative association (Table 4), albeit slightly decreased effect size. For the BMD's causal effect on HDL-c, although the effect size remained similar (Tables 2 and 4), the p value has become non-significant at the Bonferroni-corrected level.

4. Discussion

We performed an MR-based causality analysis between lipid profile and BMD using several GWAS datasets that are among the largest GWAS cohorts in the field, rendering us a sufficient statistical power to detect the causality effect of even moderate effect size. Our findings provided evidence that serum lipids may be an important factor causally influencing BMD variation, BMD itself may also cause the change in HDL-c. In particular, although BMD was detected here to have a negative influence on HDL-c, no effect was observed for HDL-c on BMD, which may indicate that using HDL-c as a predictor for BMD may not be reasonable [34]. Notably, the negative regulation of TG to BMD and non-significant genetic correlation (95% CI: −0.004-0.088) indicate that TG and BMD might be negatively associated.

Previous studies disagreed on whether BMI may confound or

Table 1
Causal effects between lipid profile and BMD using all IV SNPs.

Exposure	Outcome	b_{xy} (s.e.)	IV SNPs	Partial h^2	R_g (s.e.)	H^2(s.e.)	P
HDL-c	BMD	−0.011(0.004)	179	0.13	−0.08 (0.02)	0.21 (0.03)	$\mathbf{3.6 \times 10^{-3}}$
LDL-c	BMD	−0.039(0.003)	150	0.15	−0.07 (0.02)	0.20 (0.03)	$\mathbf{3.30 \times 10^{-32}}$
TC	BMD	−0.044(0.003)	176	0.14	−0.07 (0.02)	0.21 (0.03)	$\mathbf{2.67 \times 10^{-36}}$
TG	BMD	−0.013(0.005)	113	0.08	0.04 (0.02)	0.21 (0.04)	$\mathbf{4.00 \times 10^{-3}}$
BMD	HDL-c	−0.041(0.007)	1777	0.26	−0.08 (0.02)	0.36 (0.02)	$\mathbf{7.49 \times 10^{-10}}$
BMD	LDL-c	−0.026(0.007)	1774	0.26	−0.07 (0.02)	0.36 (0.02)	$\mathbf{2.74 \times 10^{-4}}$
BMD	TC	−0.032(0.007)	1776	0.26	−0.07 (0.02)	0.36 (0.02)	$\mathbf{3.61 \times 10^{-6}}$
BMD	TG	0.013(0.006)	1774	0.26	0.04 (0.02)	0.36 (0.02)	0.05

Notes: b_{xy} is regression effect size; IV SNPs is the number of SNPs being used as instrumental variables; Partial h^2 is the proportion of phenotypic variation explained by IV SNPs; R_g is genetic correlation between exposure and outcome; H^2 is heritability explained by all SNPs. Significant p-values were marked in bold. s.e.: standard error.

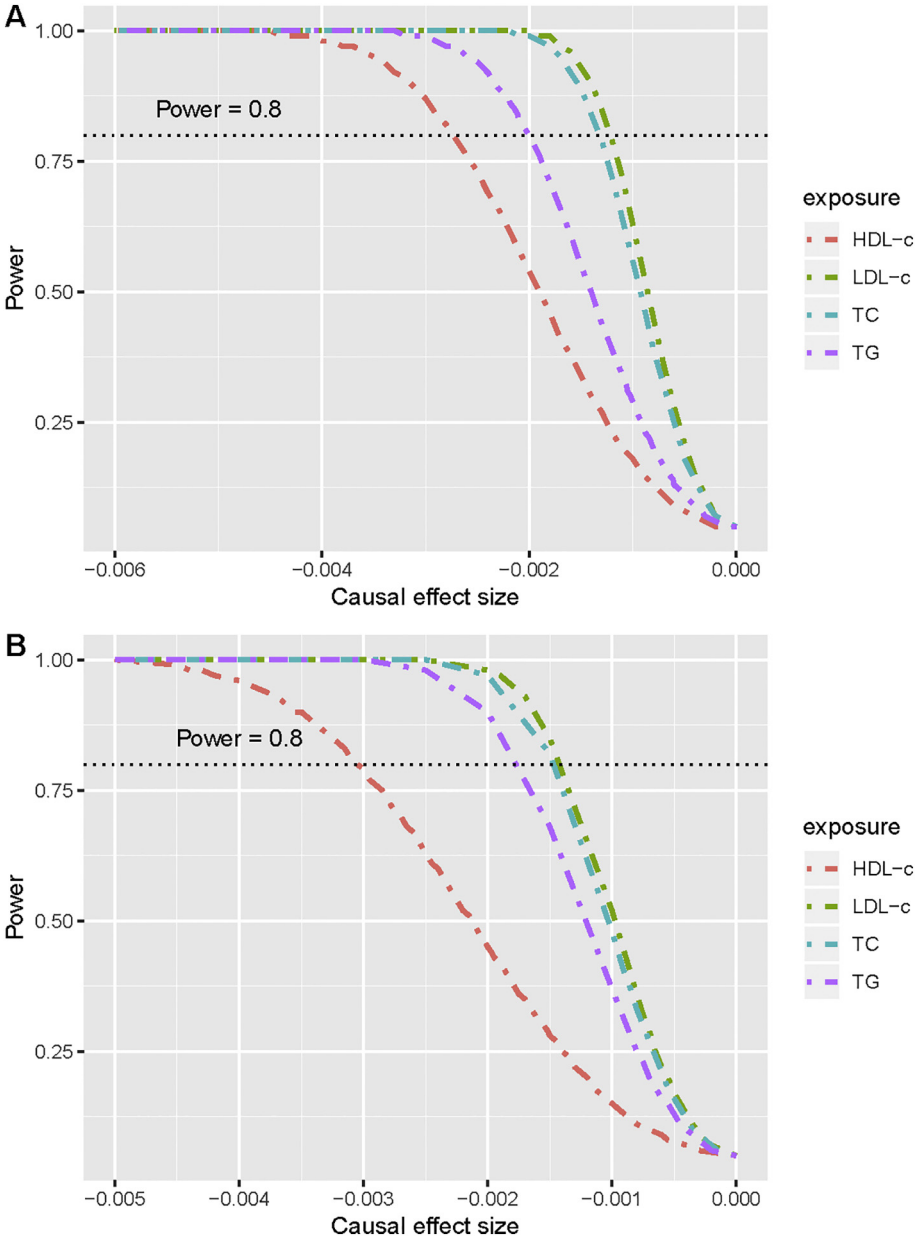

Fig. 2. Power estimate for the Mendelian randomization causal inference.
Fig. 2A is power estimate for causal inference of lipid profile to BMD; Fig. 2B is for causal inference of BMD to lipid profile. Different traits were marked in different colors. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Causal effects between lipid profile and BMD using non-pleiotropic IV SNPs.

Exposure	Outcome	b_{xy} (s.e.)	IV SNPs	Partial h^2	R_g (s.e.)	H^2(s.e.)	P
HDL-c	BMD	−0.002(0.005)	107	0.09	−0.08 (0.02)	0.21 (0.03)	0.68
LDL-c	BMD	−0.023(0.004)	102	0.11	−0.07 (0.02)	0.20 (0.03)	**4.45×10^{-9}**
TC	BMD	−0.025(0.004)	127	0.11	−0.07 (0.02)	0.21 (0.03)	**1.19×10^{-10}**
TG	BMD	−0.044(0.006)	71	0.05	0.04 (0.02)	0.21 (0.04)	**4.65×10^{-14}**
BMD	HDL-c	−0.019(0.007)	1633	0.23	−0.08 (0.02)	0.36 (0.02)	**5.68×10^{-3}**
BMD	LDL-c	−0.005(0.007)	1697	0.25	−0.07 (0.02)	0.36 (0.02)	0.49
BMD	TC	−0.010(0.007)	1676	0.24	−0.07 (0.02)	0.36 (0.02)	0.15
BMD	TG	0.004(0.007)	1674	0.24	0.04 (0.02)	0.36 (0.02)	0.54

Notes: b_{xy} is regression effect size; IV SNPs is the number of SNPs being used as instrumental variables; Partial h^2 is the proportion of phenotypic variation explained by IV SNPs; R_g is genetic correlation between exposure and outcome; H^2 is heritability explained by all SNPs. Significant p-values were marked in bold. s.e.: standard error.

mediate the association between lipid profile and BMD [17,35,36]. We hence conducted analyses to investigate the potential influence of BMI on the causal link between lipid profile and BMD. We first estimated the causal associations between BMI and lipid profile and between BMI and BMD and observed multiple reciprocal causal effects. The results are supported by other studies [37–39]. We then further analyzed lipid-BMD associations conditioning on BMI to see whether the associations are indeed mediated by BMI. By comparing the change of effect sizes between analysis with and without conditioning (Table 4 vs. Table 2), the three causal effects (LDL-c ➔ BMD, TC ➔ BMD and TG➔ BMD) may be independent of BMI influence since the 3 associations conditioning on BMI are still significant (Table 4). Yet the causal effect of BMD on HDL-c may be mediated by BMI since the effect (BMD➔HDL-c) became non-significant under the conditional analysis (Table 4).

The causal link between BMD and HDL-c becomes non-significant after correcting by BMI. This phenomenon is due to the fact that the causal effect from BMD to HDL-c might be mediated by BMI, where the causal path is BMD➔BMI➔HDL-c. The first link between BMD and BMI might be explained by the fact that bone is one of the key components of body mass and hence an increased BMD may contribute to an increased BMI. For the 2nd link, the inverse relationship between BMI and HDL-c (i.e., a higher BMI may lead to a lower HDL-c), this may be explained by the commonly observed complication of obesity (a high BMI), the insulin resistance [40], which may result in a lowered level of HDL-c [41].

Multiple lines of evidence support a negative association between TG and BMD. For example, serum TG levels were positively associated with circulating levels of IL-6 [42] and TNF receptors [43], which are all key inflammatory factors leading to bone loss, and hence reduced BMD [44]. In addition, TG levels were also observed to be negatively associated with osteoprotegerin (OPG) [45], which is a decoy receptor that binds to RANKL and reduces bone resorption (and hence prevents from bone loss and increases BMD) [46]. The above observed associations may underlie a negative association between TG and BMD. Consistent with above, an increased TG levels were also observed to be associated with an increased fracture risk (i.e., an outcome of low BMD) [47].

Table 3
Causal effects among lipids, BMI and BMD using non-pleiotropic IVs.

Exposure	Outcome	b_{xy} (s.e.)	IVSNPs	P
HDL-c	BMI	−0.016(0.005)	110	**6.76×10^{-4}**
LDL-c	BMI	−0.021(0.004)	111	**5.38×10^{-7}**
TC	BMI	−0.027(0.005)	129	**4.81×10^{-9}**
TG	BMI	−0.085(0.007)	57	**1.91×10^{-30}**
BMI	HDL-c	−0.259(0.011	848	**1.11×10^{-126}**
BMI	LDL-c	0.033(0.011)	868	**3.36×10^{-3}**
BMI	TC	−0.021(0.011)	865	0.06
BMI	TG	0.203(0.010)	847	**6.41×10^{-86}**
BMI	BMD	0.167(0.005)	636	**6.96×10^{-202}**
BMD	BMI	0.030(0.003)	907	**3.49×10^{-19}**

P values less than a significance threshold of 0.005 (0.05/10) are marked in bold.

Table 4
Causal effects between lipid profile and BMD conditioning on BMI.

Exposure	Outcome	b_{xy} (s.e.)	IV SNPs	P
LDL-c	BMD	−0.018(0.004)	101	**1.60×10^{-5}**
TC	BMD	−0.020(0.004)	129	**8.59×10^{-7}**
TG	BMD	−0.035(0.006)	77	**1.79×10^{-9}**
BMD	HDL-c	−0.015(0.007)	1511	0.04

P values less than a significance threshold of 0.01 (0.05/4) are marked in bold.

The unidirectional relationship of LDL-c to BMD and BMD to HDL-c was inferred by our data. Similar result for the LDL-c to BMD relationship was also achieved in another recent study [48], where a unidirectional effect between statin, a drug for lowering LDL-c, and BMD was observed. Consistent with our findings, previous studies demonstrated that LDL-c was involved in formation and extension of tartrate-resistant acid phosphatase multinucleated cells (osteoclast-like

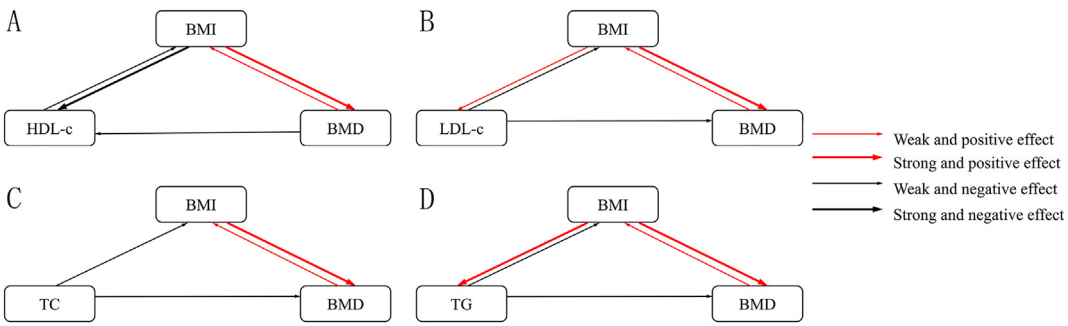

Fig. 3. Causal relationship inferred from the Mendelian randomization analyses.
Illustrative diagrams separately exhibit bidirectional causal associations between specific lipid trait, BMI and BMD.

cells) [49,50], which was abrogated with the depletion of LDL. Another supporting evidence is that oxidized LDL may boost osteoclast differentiation through inducing osteoclast-associated receptor in endothelial cells [51].

The mechanism underlying the unidirectional relationship of BMD to HDL-c still needs to be further clarified. Nevertheless, such a relationship might be explained by the observation where osteoblast-like cells are able to internalize and degrade certain subclasses of HDL particles. These cells also express scavenger receptor class B type I (SR-B1), scavenger receptor class B type II (SR-BII) and CD36 cell surface receptors, which are involved in uptake of cholesterol esters from HDL in other cell types [52,53].

In conclusion, using the state-of-the-art MR method and several GWAS datasets that are the largest in size in the field, we detected a causal link from three lipid traits, LDL-c, TC and TG, to BMD. The effects may be independent of BMI. Given BMD's importance to osteoporosis risk, controlling serum lipids including LDL-c, TC and TG, may alleviate risk to osteoporosis.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2019.05.037.

Declaration of Competing Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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