

Original Article

Unveiling the Causal Relationship Between Osteoporosis and Circulating Metabolites from a Genetic Perspective

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Abstract

Objectives: Osteoporosis (OP) is a major public health concern characterized by increased bone fragility. This study aimed to investigate the causal relationship between circulating metabolites, particularly lipid-related metabolites, and OP using Mendelian Randomization (MR). **Methods:** A bidirectional two-sample MR approach was applied using summary statistics from large-scale Genome-Wide Association Studies (GWAS) comprising 484,598 individuals of European ancestry. Genetic variants associated with circulating metabolites were selected as instrumental variables. Causal effects were estimated using inverse variance weighting (IVW), weighted median, and MR-Egger methods. Sensitivity analyses were conducted to assess heterogeneity and pleiotropy. **Results:** MR analyses indicated a potential causal relationship between higher levels of monounsaturated fatty acids (MUFA) and a reduced risk of OP (OR = 0.997; 95% CI: 0.994–0.999; P = 0.013). Conversely, increased total lipids in lipoprotein particles were associated with a higher OP risk (OR = 1.002; 95% CI: 1.000–1.004; P = 0.031). In addition, OP was inversely associated with total lipids (OR = 0.269; 95% CI: 0.095–0.759; P = 0.013) and triglycerides (OR = 0.259; 95% CI: 0.090–0.745; P = 0.012) in chylomicrons and extremely large very-low-density lipoproteins. No evidence of pleiotropy or heterogeneity was detected. **Conclusion:** This study provides genetic evidence for causal links between lipid metabolism and OP, suggesting that circulating lipid metabolites may serve as potential biomarkers for risk stratification and prevention.

Keywords: Circulating Metabolites, Lipid Metabolism, Lipoprotein Particles, Mendelian Randomization, Osteoporosis

Introduction

Osteoporosis (OP) is a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, resulting in increased bone fragility and susceptibility to fractures¹. Globally, OP affects approximately 200 million people, predominantly postmenopausal women and older adults, and contributes substantially to morbidity, mortality, and healthcare

costs^{2,3}. Despite the availability of antiresorptive and anabolic therapies, OP often remains undiagnosed until fractures occur, underscoring the urgent need for early detection and preventive strategies⁴.

Circulating metabolites—small molecular compounds measurable in the blood, including lipids, amino acids, carbohydrates, and nucleic acid metabolites—play pivotal roles in bone metabolism and remodeling. These metabolites influence osteoblast and osteoclast activity and participate in inflammatory processes that indirectly affect bone turnover⁵. Alterations in metabolite concentrations reflect both physiological and pathological states. Specific lipid metabolites, such as glycerophospholipids and sphingolipids, are crucial in OP development. They not only directly modulate the activity of bone-forming and bone-resorbing cells but also regulate inflammatory responses and activate key signaling pathways, including Wnt/ β -catenin, PI3K/Akt, and MAPK, thereby contributing to OP progression^{6,7}.

The authors have no conflict of interest.

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Metabolomic studies have revealed significant differences in serum metabolic profiles between OP patients and healthy individuals, with distinct metabolite alterations associated with reduced bone density and increased fracture risk. These findings suggest that circulating metabolites may function both as biomarkers for OP and as mediators of its pathogenesis⁸.

Mendelian Randomization (MR) provides a robust framework for investigating causal relationships between circulating metabolites and OP⁹. By leveraging genetic variants as instrumental variables, MR helps to overcome confounding and reverse causation common in observational studies, thereby offering clearer insights into causality¹⁰. This approach is particularly valuable for elucidating the links between circulating metabolites and OP, advancing our understanding of its pathophysiology, and identifying potential biomarkers and therapeutic targets. Such knowledge is critical for improving early diagnosis, guiding preventive strategies, reducing fracture risk, and ultimately enhancing patient quality of life.

In this context, our study applies MR to systematically evaluate the causal effects of circulating metabolites on OP from a genetic perspective. The aim is to generate novel insights that may inform risk prediction, prevention, and clinical management strategies.

Materials and Methods

Study Design

This study was conducted using a bidirectional two-sample MR design to investigate the causal relationships between circulating metabolites and OP. MR analyses were based on three core assumptions¹¹: (1) the selected single nucleotide polymorphisms (SNPs) are strongly associated with the exposure; (2) the selected SNPs are not associated with confounders of the exposure–outcome relationship; and (3) the SNPs influence the outcome only through the exposure, not via alternative pathways. The MR analyses were conducted in two stages: first, with circulating metabolites as the exposure and OP as the outcome; and second, with OP as the exposure and circulating metabolites as the outcome.

Data Sources

Summary statistics for OP were obtained from the publicly available GWAS Catalog (<https://gwas.mrcieu.ac.uk/>). The dataset included 484,598 individuals of European ancestry, comprising OP cases and healthy controls. Genetic association data for circulating metabolites were derived from large-scale metabolomic GWAS analyses of up to 115,078 individuals of European ancestry. The metabolites assessed encompassed 51 classes of small molecules, including lipids (e.g., monounsaturated fatty acids, triglycerides, phospholipids), amino acids, carbohydrates, and related derivatives.

Selection of Genetic Instrumental Variables

Instrumental variables (IVs) were selected based on genetic variants associated with OP. SNPs meeting the genome-wide significance threshold ($p < 5 \times 10^{-8}$) were included. When no genome-wide significant SNPs were available for specific exposures, a relaxed threshold of $p < 5 \times 10^{-6}$ was applied, in line with established MR practices. To ensure independence, variants were clumped using a linkage disequilibrium (LD) threshold of $r^2 < 0.001$.

Instrument strength was assessed using the TwoSampleMR package, which applies default quality control filters to retain SNPs with F-statistics > 10 , thereby minimizing weak instrument bias. In MR studies, SNPs with F-statistics above 10 are generally considered strong instruments¹².

MR Analysis

Mendelian Randomization (MR) analyses were performed using the TwoSampleMR R package (v0.5.7) to assess causal relationships between circulating metabolites and OP. Three complementary methods were applied: inverse variance weighting (IVW), weighted median, and MR-Egger regression¹³.

A finding was considered robust if the beta estimates were directionally consistent across all three MR methods (either all positive or all negative) and the IVW method reached statistical significance ($p < 0.05$). Forward MR analyses were conducted with circulating metabolites as exposures and OP as the outcome, while reverse MR analyses treated OP as the exposure and circulating metabolites as outcomes.

Sensitivity Analyses

To assess robustness, several sensitivity analyses were conducted. Heterogeneity was evaluated using the Cochran's Q test, and horizontal pleiotropy was assessed with the MR-Egger intercept¹⁴ and the MR-PRESSO framework¹⁵. When pleiotropy was detected, MR-PRESSO was used to identify and correct outlier variants; if pleiotropy persisted after correction, the corresponding analyses were excluded¹⁶.

The weighted median estimator was additionally applied, as it provides valid causal estimates even when up to 50% of instruments are invalid¹⁷. A leave-one-out analysis was performed by sequentially excluding each SNP to determine whether individual variants disproportionately influenced the results.

Interpretation of sensitivity analyses followed standard thresholds: $Q_pval > 0.05$ indicated no heterogeneity, and $pval > 0.05$ in pleiotropy tests indicated no horizontal pleiotropy. For analyses with evidence of heterogeneity, the IVW random-effects model was applied.

Results

Causal Relationships Involving SNPs Related to Osteoporosis

In the forward MR analysis, circulating metabolites were evaluated as exposures and OP as the outcome. The

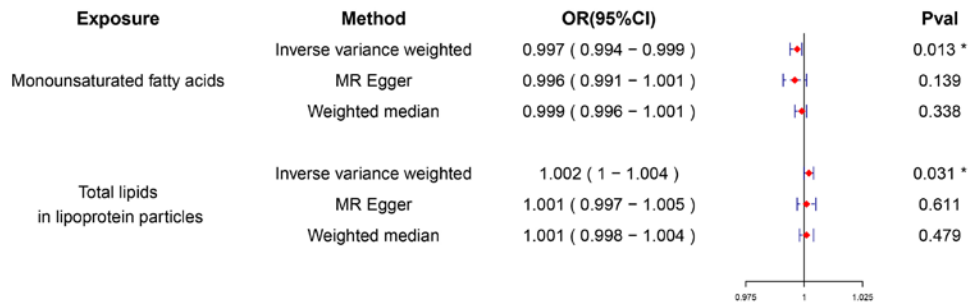


Figure 1. Two-sample Mendelian randomization (MR) analysis of monounsaturated fatty acids (MUFA) and total lipids in lipoprotein particles with osteoporosis (OP). Each row represents a different exposure–outcome association, showing the strength and direction of effect. Red squares indicate odds ratios (OR), horizontal lines indicate 95% confidence intervals (CI), and the far-right column reports the number of single nucleotide polymorphisms (SNPs).

analysis identified potential causal associations between monounsaturated fatty acids (MUFA) and total lipids in lipoprotein particles with OP. Specifically, higher MUFA levels were associated with a reduced risk of OP (OR = 0.997, 95% CI: 0.994–0.999, $P = 0.013$), while increased total lipids in lipoprotein particles were associated with a higher risk of OP (OR = 1.002, 95% CI: 1.000–1.004, $P = 0.031$) (Figure 1).

These associations were significant in the IVW method and directionally consistent across the MR-Egger and weighted median approaches. An OR below 1 suggests a protective effect of MUFA against OP, whereas an odds ratio above 1 indicates that higher levels of total lipids in lipoprotein particles may act as risk factors for OP.

Scatter plots and forest plots (Figures 2A, B and 3A, B) further supported the observed associations, while funnel plots (Figures 2C and 3C) showed no evidence of horizontal pleiotropy or heterogeneity, reinforcing the robustness of the findings.

Causal Relationships Involving SNPs Related to Circulating Metabolites

When OP was treated as the exposure and circulating metabolites as outcomes, MR analysis revealed potential causal associations with total lipids (OR = 0.269, 95% CI: 0.095–0.759, $P = 0.013$) and triglycerides (OR = 0.259, 95% CI: 0.090–0.745, $P = 0.012$) in chylomicrons and extremely large very-low-density lipoproteins (VLDL) (Figure 4). These results were consistent across IVW, MR-Egger, and weighted median methods.

Scatter and forest plots (Figures 5A, B and 6A, B) further supported the associations, while funnel plots (Figures 5C and 6C) indicated no evidence of horizontal pleiotropy or heterogeneity, confirming the robustness of the findings.

The ORs below 1 indicate negative correlations, suggesting that higher OP liability is associated with lower

levels of total lipids and triglycerides in chylomicrons and extremely large VLDL. This finding implies that OP may exert a protective effect against elevated lipid and triglyceride levels in these lipoprotein fractions.

Discussion

This study used MR to investigate causal relationships between circulating metabolites and OP. We found that higher levels of MUFA were causally associated with reduced OP risk, whereas greater total lipid content in lipoprotein particles was associated with increased OP risk. In reverse analyses—treating OP as the exposure—higher OP liability was associated with lower circulating levels of total lipids and triglycerides in chylomicrons and extremely large VLDL. Collectively, these findings provide genetic evidence for a link between lipid metabolism and bone health and support the hypothesis that dysregulated lipid metabolism contributes to OP pathogenesis.

We also observed an inverse association between OP liability and lipid levels (total lipids and triglycerides) in chylomicrons and extremely large VLDL, with no evidence of pleiotropy or heterogeneity, and no causal effects for other tested metabolites¹⁸. Broadly, circulating metabolites—including lipids, amino acids, and carbohydrates—regulate bone metabolism via multiple mechanisms that affect both formation and resorption. MUFA, a key component of several healthy dietary patterns, has been reported to modulate inflammatory markers, promote osteoblast proliferation and differentiation, inhibit osteoclast activity, and enhance calcium handling, thereby supporting bone health^{19,20}. Our MR results are consistent with a potential protective association between MUFA and OP; however, the effect size was small (OR = 0.997), and its clinical relevance is uncertain. These results should be viewed as preliminary genetic evidence that warrants mechanistic follow-up.

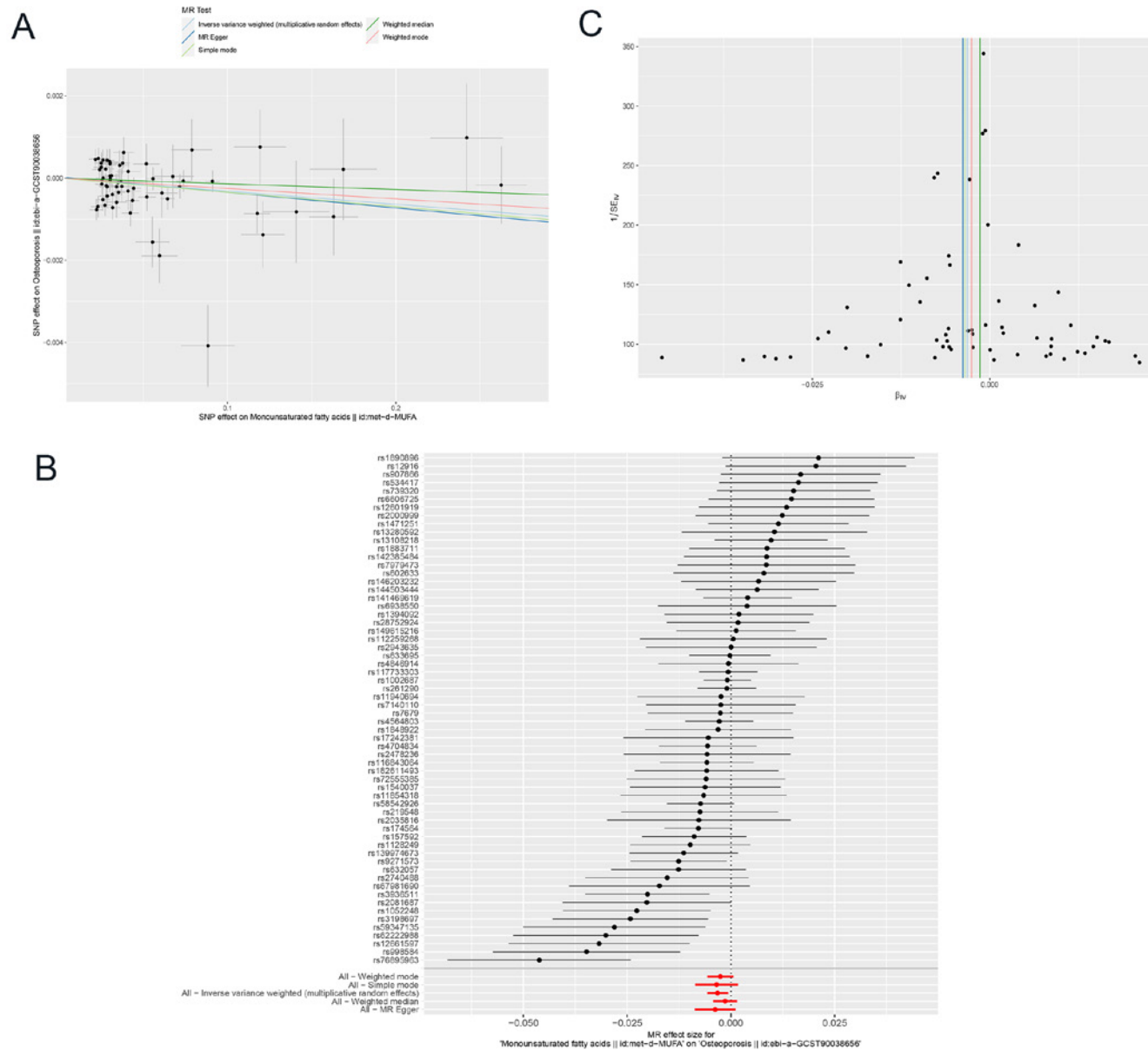


Figure 2. Mendelian randomization (MR) analyses of monounsaturated fatty acids (MUFA) and osteoporosis (OP). Each point represents a single nucleotide polymorphism (SNP). (A) Scatter plot. (B) Forest plot. (C) Funnel plot.

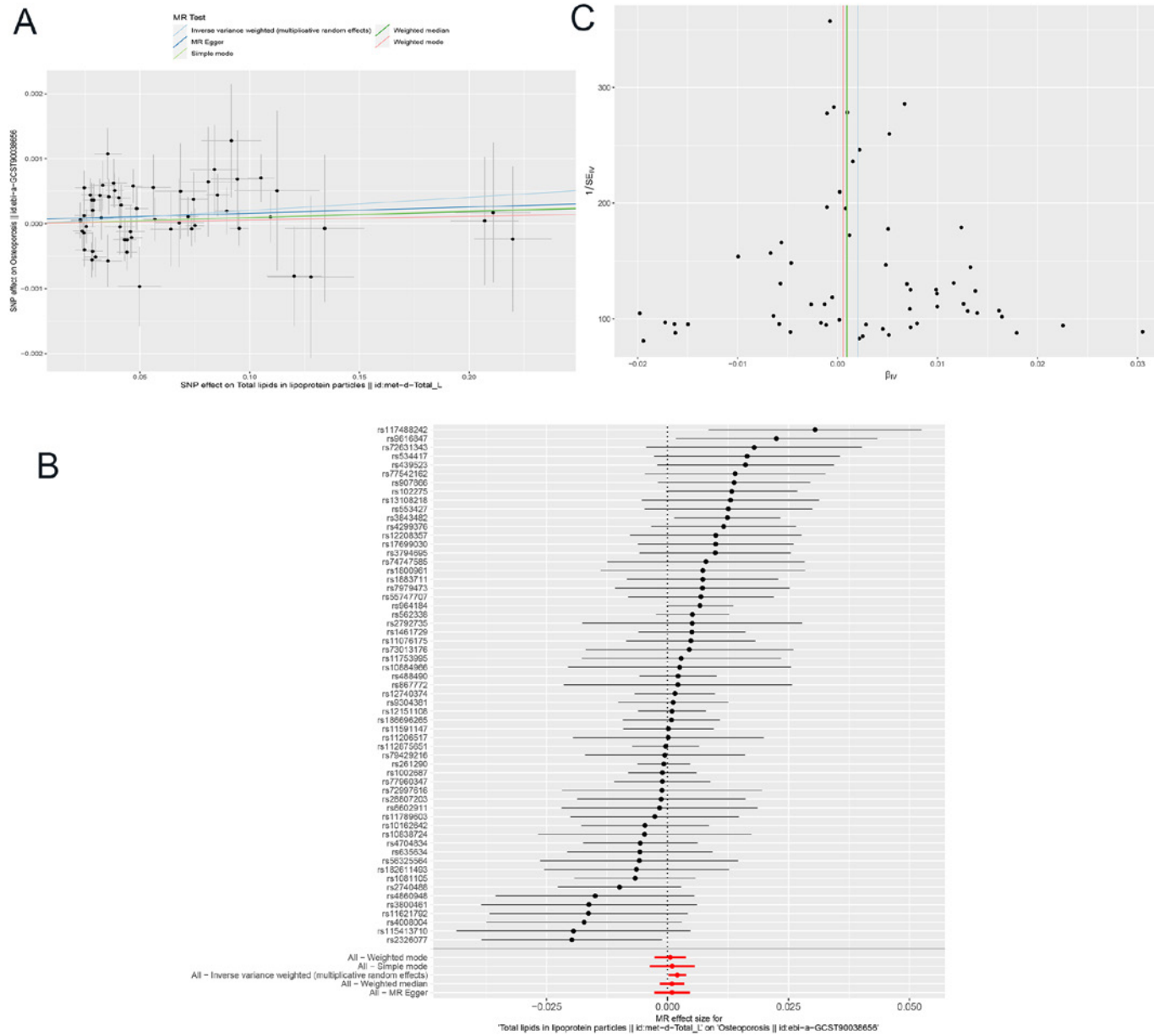


Figure 3. Mendelian randomization (MR) analyses of total lipids in lipoprotein particles and osteoporosis (OP). Each point represents a single nucleotide polymorphism (SNP). (A) Scatter plot. (B) Forest plot. (C) Funnel plot.

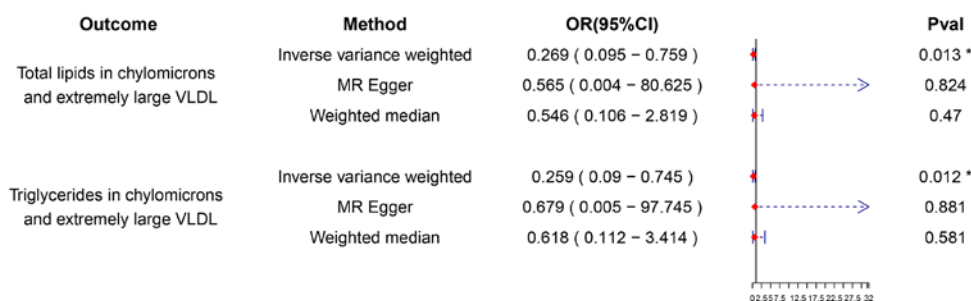


Figure 4. Two-sample Mendelian randomization (MR) analysis of osteoporosis (OP) with total lipids and triglycerides in chylomicrons and extremely large very-low-density lipoproteins (VLDL). Each row represents an exposure–outcome association. Red squares indicate odds ratios (OR), horizontal lines indicate 95% confidence intervals (CI), and the far-right column shows the number of single nucleotide polymorphisms (SNPs).

Elevated lipoprotein particle lipids (e.g., triglycerides, cholesterol) have been implicated in adverse effects on bone through vascular inflammation and oxidative stress, as well as possible perturbations of calcium metabolism²¹. Epidemiological studies have linked hyperlipidemia to higher fracture risk, particularly among older adults, with elevated low-density lipoprotein levels associated with lower bone mineral density and increased OP risk²². Taken together with our forward-direction MR results, these observations suggest that higher total lipids in lipoprotein particles may be bona fide risk factors for OP.

In the reverse direction, the observed inverse association between OP liability and lipids in chylomicrons and extremely large VLDL may reflect compensatory endocrine or metabolic adaptations rather than a direct lipid-lowering effect of OP *per se*. Chylomicrons and VLDL are the principal carriers of dietary and endogenous triglycerides²³. Prior work has associated higher triglyceride levels with increased OP risk²⁴. Hormonal and metabolic factors that change with OP—such as altered insulin sensitivity and glucose–lipid metabolism—can in turn influence bone remodeling^{25–27}. Estrogen, essential for maintaining bone density and regulating fat distribution, declines with age and postmenopause^{28,29}, while bone-derived hormones (e.g., osteocalcin) modulate glucose and lipid metabolism; reductions in osteocalcin with bone loss may therefore affect systemic lipid profiles³⁰. Reduced physical activity among individuals with OP could further lower energy expenditure and shift lipid handling^{31,32}. We hypothesize that distinct lipid components act on bone via different mechanisms before and after OP onset: elevated lipoprotein-transported lipids may promote bone loss (e.g., via oxidative stress and osteoclast activation) prior to disease, while established OP and altered bone–fat crosstalk may secondarily modify systemic lipid levels (e.g., via reduced osteocalcin). These endocrine and paracrine pathways offer a plausible

explanation for the inverse associations observed and support a complex, potentially bidirectional interaction between bone and lipid metabolism³³.

From a clinical perspective, our findings suggest a potential causal role of circulating lipid metabolites in OP risk and point to candidate biomarkers for risk assessment. Nevertheless, MR does not provide direct clinical validation of biomarkers; translation to practice will require prospective cohorts and experimental studies to determine whether lipid metabolites can reliably inform OP risk stratification and guide therapy.

Limitations

Strengths include the use of large GWAS datasets, a bidirectional MR framework, and extensive sensitivity analyses. Limitations include restriction to European ancestry—limiting generalizability—as well as the nature of MR estimates, which reflect lifelong genetic exposures and may not mirror short-term intervention effects. The absence of individual-level data precluded assessment of gene–environment interactions and comorbidities. Finally, several effect sizes were small (e.g., MUFA–OP, OR = 0.997), and their biological and clinical significance remains to be clarified.

Conclusions

This study provides genetic evidence supporting a causal relationship between circulating lipid metabolites and OP. While optimizing lipid metabolism may contribute to better bone health, current data do not support lipid-lowering agents as standalone OP treatments. Future randomized trials and mechanistic studies are needed to elucidate bone–lipid crosstalk and to evaluate integrated therapeutic strategies targeting both metabolic and skeletal systems.

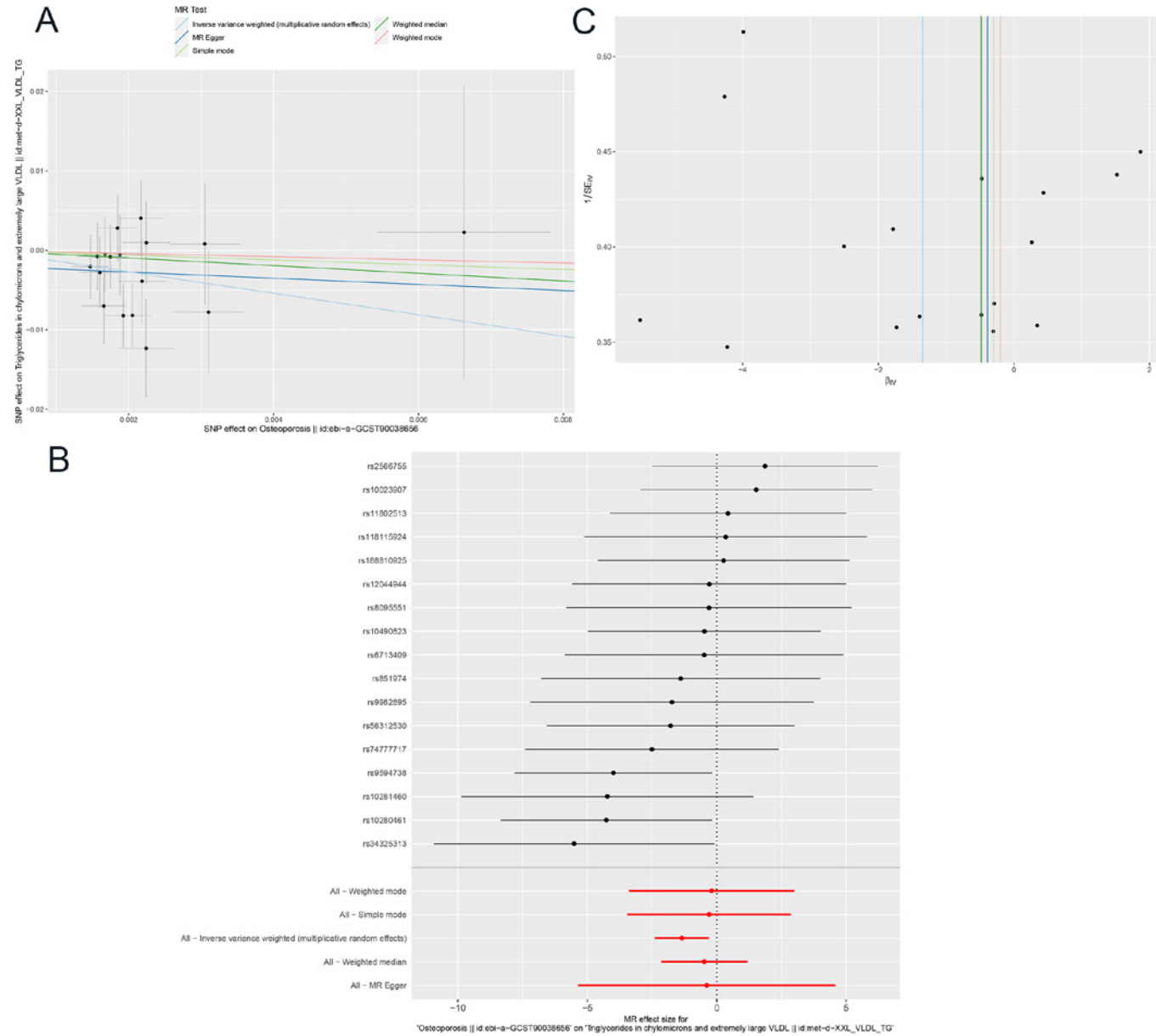


Figure 5. Mendelian randomization (MR) analyses of osteoporosis (OP) and total lipids in chylomicrons and extremely large very-low-density lipoproteins (VLDL). Each point represents a single nucleotide polymorphism (SNP). (A) Scatter plot. (B) Forest plot. (C) Funnel plot.

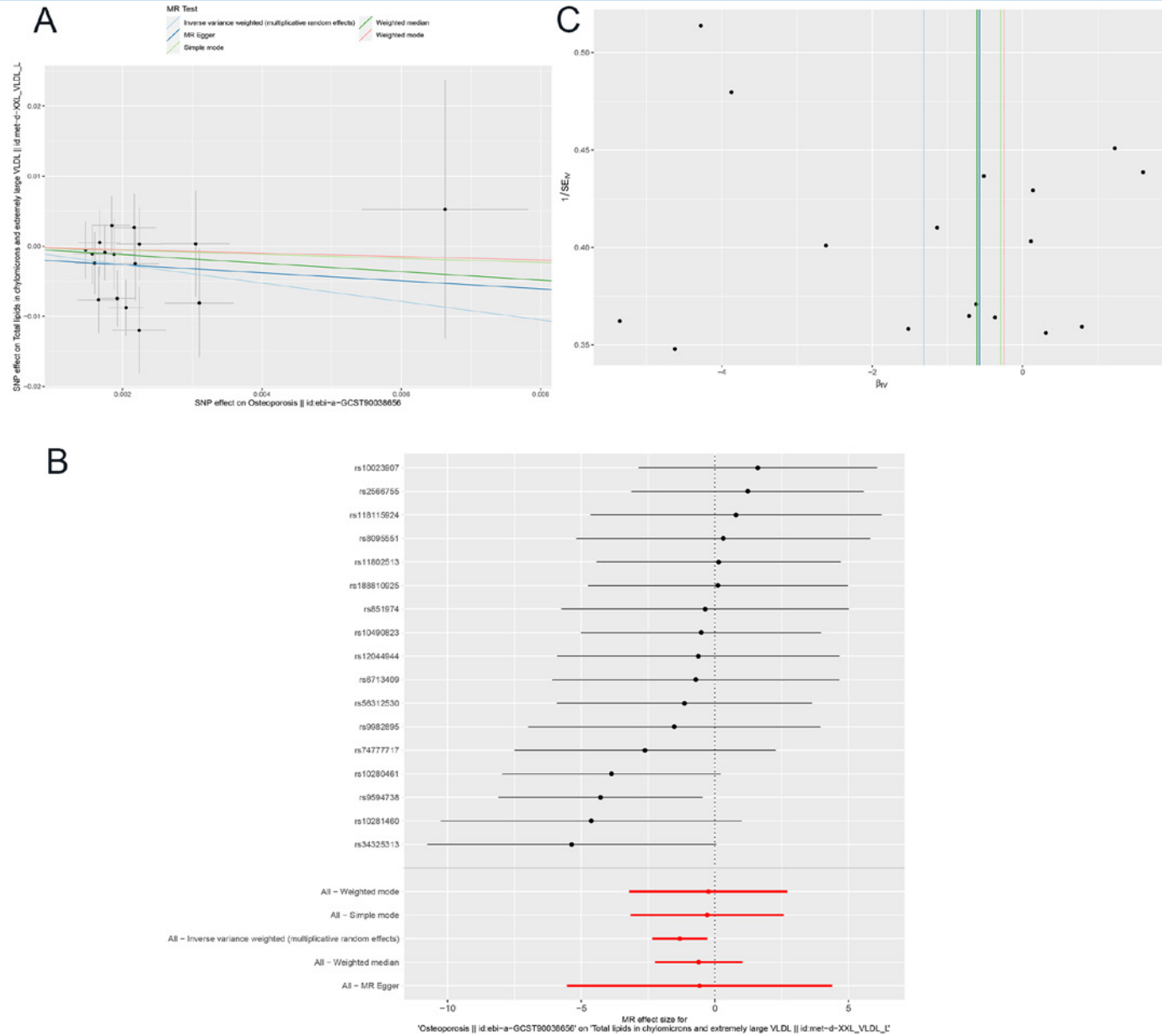


Figure 6. Mendelian randomization (MR) analyses of osteoporosis (OP) and triglycerides in chylomicrons and extremely large very-low-density lipoproteins (VLDL). Each point represents a single nucleotide polymorphism (SNP). (A) Scatter plot. (B) Forest plot. (C) Funnel plot.

Ethics approval

Ethics approval was not required for this study because it used publicly available, de-identified summary statistics from GWAS. All contributing GWAS had prior approval from their local institutional review boards/ethics committees, and all participants provided written informed consent. No new data were collected and no individual-level data were accessed.

Authors' contributions

PW designed the study and drafted the manuscript. YZ was responsible for the collection and analysis of the experimental data. Both authors revised the manuscript critically for important intellectual content. Both authors read and approved the final manuscript.

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