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Effect of blood lipids and lipid-lowering therapies on osteoarthritis risk: A Mendelian randomization study

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Background: We aimed to investigate the effects of blood lipids and lipid-lowering agents on osteoarthritis (OA) risk.

Materials and methods: We performed Mendelian randomization (MR) analyses to estimate the causal effect of blood low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels on knee and hip OA. Single nucleotide polymorphisms (SNPs) were selected from large genome-wide association studies (GWASs) of individuals of European ancestry as genetic instruments for blood lipid levels. The associations of selected genetic instruments with knee and hip OA were estimated in a recent GWAS of the UK Biobank and arcOGEN datasets. Univariate and multivariate MR analyses were performed to detect and adjust for potential pleiotropy. Furthermore, genetic instruments in *HMGCR*, *NPC1L1*, and *PCSK9* regions were used to mimic LDL-C-lowering effects of statin, ezetimibe, and evolocumab, respectively.

Results: Genetically determined LDL-C increments led to reduced risks of both knee OA (OR = 0.91 per 1-SD increment, 95% CI: 0.86–0.95, $P = 6.3 \times 10^{-5}$) and hip OA (OR = 0.92, 95% CI: 0.85–0.99, $P = 0.027$). Multivariate MR analysis proved that the effect was independent of HDL-C, TG, and body mass index. TG increment was associated with reduced risks of hip OA in the univariate MR analysis; however, this was not supported by the multivariate MR analysis. Genetically proxied LDL-C-lowering effects of statins are related to increased risks of knee OA but not hip OA.

Conclusions: The findings suggested that LDL-C increments have independent protective effects on both knee and hip OA. LDL-C-lowering effects of statins may increase the risk of knee OA.

KEYWORDS

osteoarthritis, statins, Mendelian randomization, ezetimibe, blood lipid

Introduction

Osteoarthritis (OA) is the most common form of arthritis; it affects more than 5% of people worldwide, and its prevalence is growing (1). OA is characterized by articular cartilage degeneration, chronic pain, joint deformities, and eventual disability (2). Although the etiology of OA is not well-understood, it is considered a metabolic syndrome-associated disease rather than a purely age- or weight-related disease (3). Experimental studies and a recent meta-analysis of observational studies showed that dyslipidemia is involved in OA pathophysiology (4, 5). However, the causal effect of blood lipid profile, particularly low-density lipoprotein cholesterol (LDL-C), on the risk of developing OA remains unclear.

Statins, inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), are the most frequently prescribed cholesterol-lowering drugs. These drugs are recommended as first-line therapy to reduce the risk of atherosclerotic cardiovascular disease (ASCVD) (6). To date, the effects of statins on OA have aroused great interest from researchers; however, results are conflicting and vary from reduced risk to no effect or even an increased risk of OA (3, 7). Nevertheless, the current evidence is limited to observational studies and is inevitably affected by confounding factors, making it difficult to clarify the causal relationship. In recent years, in addition to statins, newer lipid-lowering agents acting on different mechanisms, including ezetimibe or anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (evolocumab), have been widely used to achieve LDL-C targets in the secondary prevention of ASCVD (8). However, the effects of these drugs on OA have not been reported.

Therefore, we aimed to use a Mendelian randomization (MR) approach to investigate the effect of blood lipid profiles and lipid-lowering agents on OA risk. Because MR employs genetic variants associated with the target of cholesterol-lowering agents, which are random with respect to potential confounding factors, our study will help clarify the causal relationship among blood lipids, lipid-lowering agents, and OA.

Materials and methods

This study was performed according to the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) (9).

Genetic instruments for blood lipids

Single nucleotide polymorphisms (SNPs) for plasma LDL-C, high-density lipoprotein cholesterol (HDL-C), and

triglyceride (TG) were selected as instrumental variables. Data on these variables were obtained from the genome-wide association studies (GWASs) of the Global Lipids Genetics Consortium (10), which included 188,578 individuals with European ancestry and excluded those receiving lipid-lowering treatment. The included SNPs need to be significantly associated with the trait at the genome-wide level ($P < 5 \times 10^{-8}$) and independent of each other ($r^2 < 0.001$). Among the included SNPs, 81, 89, and 55 were associated with LDL-C, HDL-C, and TG, respectively (Supplementary Tables S1–S3).

Assessment of knee and hip OA

The associations between the selected genetic instruments and knee and hip OA were estimated in a recent GWAS meta-analysis of the UK Biobank and Arthritis Research UK Osteoarthritis Genetics (arcOGEN) datasets (77,052 cases and 378,169 controls) (11), which also included individuals with European ancestry. The UK Biobank is a cohort based on 22 assessment centers in the UK that includes 500,000 participants aged 40–69 years and recruited from 2006 to 2010 (12). The diagnosis of hip and knee OA was based on self-reports and hospital records in the UK Biobank. The arcOGEN dataset includes unrelated UK-based knee and hip OA cases from the ArcOGEN Consortium (13). Knee and hip OA were diagnosed if the individual underwent total joint replacement or had radiographic evidence of OA (Kellgren–Lawrence grade ≥ 2).

Two-sample MR

We conducted two-sample MR analysis using the “TwoSampleMR” package in the R software (version 4.1.2). First, we performed a harmonization process to ensure that the effect alleles of SNPs were the same for exposure and outcome. Palindromic SNPs were aligned if the minor allele frequency was < 0.3 . As a result, two LDL-C SNPs and three HDL-C SNPs were excluded because they were palindromic with intermediate allele frequencies. To estimate the individual effect of each SNP, the Wald ratio was calculated by dividing the SNP-outcome association by the SNP-exposure association. We primarily estimated the causal effect of blood lipids on OA using the random-effect inverse variance-weighted (IVW) method. Estimates of causal effects were reported as odds ratios (ORs) per one standard deviation (SD) increase in LDL-C, HDL-C, and TG. The weighted median, MR-Egger regression, weighted mode, and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) outlier-corrected methods were used for additional sensitivity analyses. The weighted median method can provide an unbiased estimate

TABLE 1 Univariate Mendelian randomization analysis results.

Exposure	Outcome	Methods	Number of SNPs	OR (95% CI)	P-value
LDL-C	Knee OA	Inverse variance weighted	79	0.91 (0.86–0.95)	6.3×10^{-5}
		MR Egger	79	0.92 (0.86–0.99)	0.022
		Weighted median	79	0.91 (0.85–0.97)	0.003
		Weighted mode	79	0.90 (0.85–0.96)	9.4×10^{-4}
		MR-PRESSO outlier-corrected	79 (1 outlier SNP)	0.91 (0.87–0.95)	1.3×10^{-4}
LDL-C	Hip OA	Inverse variance weighted	79	0.92 (0.85–0.99)	0.027
		MR Egger	79	0.89 (0.79–0.99)	0.038
		Weighted median	79	0.90 (0.83–0.97)	0.006
		Weighted mode	79	0.90 (0.84–0.96)	0.003
		MR-PRESSO outlier-corrected	79 (3 outlier SNPs)	0.91 (0.85–0.97)	0.006
HDL-C	Knee OA	Inverse variance weighted	86	0.99 (0.90–1.09)	0.835
		MR Egger	86	1.10 (0.93–1.30)	0.277
		Weighted median	86	0.99 (0.90–1.08)	0.793
		Weighted mode	86	1.05 (0.96–1.14)	0.309
		MR-PRESSO outlier-corrected	86 (6 outlier SNPs)	1.01 (0.94–1.09)	0.771
HDL-C	Hip OA	Inverse variance weighted	86	1.00 (0.92–1.08)	0.968
		MR Egger	86	1.08 (0.93–1.26)	0.313
		Weighted median	86	1.13 (1.02–1.25)	0.025
		Weighted mode	86	1.09 (0.98–1.22)	0.112
		MR-PRESSO outlier-corrected	86 (2 outlier SNPs)	1.02 (0.95–1.10)	0.585
TG	Knee OA	Inverse variance weighted	55	0.94 (0.86–1.02)	0.135
		MR Egger	55	0.96 (0.84–1.11)	0.584
		Weighted median	55	0.88 (0.80–0.96)	0.005
		Weighted mode	55	0.93 (0.86–1.02)	0.136
		MR-PRESSO outlier-corrected	55 (3 outlier SNPs)	0.93 (0.87–1.00)	0.072
TG	Hip OA	Inverse variance weighted	55	0.91 (0.84–0.98)	0.017
		MR Egger	55	0.91 (0.80–1.03)	0.149
		Weighted median	55	0.91 (0.81–1.02)	0.106
		Weighted mode	55	0.89 (0.80–1.00)	0.053
		MR-PRESSO outlier-corrected	55 (0 outlier SNPs)	0.91 (0.84–0.98)	0.021

OA, Osteoarthritis; SNP, single nucleotide polymorphisms; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier.

of the causal effect even if half of the SNPs exhibit pleiotropy (14). The MR-Egger method adds a non-zero intercept to allow directional horizontal pleiotropy (15). It makes the assumption that horizontal pleiotropic effects are independent of SNP-exposure effects, which is also known as the InSIDE assumption. In addition, the MR-Egger regression intercept value was used to estimate the degree of horizontal pleiotropic effects. The weighted mode method groups SNPs according to the similarity of their effects and estimates the causal effect based on the largest cluster of SNPs. Therefore, it can provide an unbiased causal effect estimate as long as the largest cluster of SNPs is valid (16). The MR-PRESSO method can reduce the heterogeneity of the estimate by correcting the effects of outlier SNPs (17). We conducted MR-PRESSO analysis using the MR-PRESSO R package and set the number of

distributions to 10,000 and the significance threshold to 0.05. For additional sensitivity analyses, we used forest plots for visual inspection of potential pleiotropy. Cochran's Q statistics were calculated to assess the extent of heterogeneity, with P -values < 0.05 indicating significant heterogeneity. The causal direction between exposure and outcome was determined using the Steiger test, which compares the extent of outcome variance and exposure variance explained by instrumental variables (16).

Multivariable MR

As the included instrument SNPs may be associated with multiple lipid fractions and body mass index (BMI), we

performed multivariable MR to estimate the independent effect of each lipid. Multivariable MR analysis was conducted using the IVW method. Instrumental SNPs for BMI were selected from a GWAS meta-analysis of European ancestry conducted by the Genetic Investigation of ANthropometric Traits (GIANT) Consortium (18) (Supplementary Table S4).

Estimating the effect of lipid-lowering therapy on OA risk

Three sets of SNPs within the *HMGCR*, Niemann-Pick C1-Like 1 (*NPC1L1*), and *PCSK9* genes were used to mimic the LDL-C-lowering effect of statins, ezetimibe, and evolocumab, respectively, as used in previous studies (10, 19–23) (Supplementary Table S5). Because some SNPs were not completely independent (r^2 value for linkage disequilibrium <0.3), we estimated the causal effect of lipid-lowering therapy on OA using the random-effect IVW method that accounted for the correlation among variants, provided by the Mendelian Randomization R package (24). The linkage disequilibrium matrix for SNPs was extracted from the European 1,000 genome data (25).

Results

Causal effects of blood LDL-C on OA risk

IVW MR suggested that LDL-C increment was associated with reduced risks of knee OA (OR = 0.91, 95% CI: 0.86–0.95, $P = 6.3 \times 10^{-5}$) and hip OA (OR = 0.92, 95% CI: 0.85–0.99, $P = 0.027$). The MR-Egger, weighted median, weighted mode, and MR-PRESSO outlier-corrected methods yielded similar results (Table 1). The Cochrane Q statistic suggested significant heterogeneity (knee OA, $Q = 113.77$, $P = 0.005$; hip OA, $Q = 180.24$, $P < 0.001$). The MR-Egger regression showed no evidence of horizontal pleiotropy for knee OA (Egger intercept = -0.001 , $P = 0.589$) or hip OA (Egger intercept = 0.003 , $P = 0.410$) (Figures 1A,D). Visual inspection of the funnel plots revealed no signs of horizontal pleiotropy (Supplementary Figures S1, S2). The MR-PRESSO analysis identified one outlier and three outliers for knee and hip OA, respectively. However, these outliers did not influence the effect estimates for knee OA (MR-PRESSO distortion test P -value = 0.846) or hip OA ($P = 0.708$). In addition, the Steiger test demonstrated a causal relationship between exposure and outcome ($P < 0.001$).

Causal effects of blood HDL-C on OA risk

IVW MR revealed no evidence of the association between HDL-C levels and OA risk (Table 1). The Cochrane Q statistic suggested significant heterogeneity (knee OA: $Q = 273.34$, $P < 0.001$; hip OA: $Q = 142.05$, $P < 0.001$). The MR-Egger regression showed no evidence of horizontal pleiotropy for knee OA (Egger intercept = -0.006 , $P = 0.157$) or hip OA (Egger intercept = -0.004 , $P = 0.223$) (Figures 1B,E). Visual inspection of funnel plots revealed no horizontal pleiotropy (Supplementary Figures S3, S4). The MR-PRESSO analysis revealed six outliers and two outliers for knee and hip OA, respectively. However, these outliers did not influence the effect estimates for knee OA ($P = 0.132$) and hip OA ($P = 0.201$).

Causal effects of blood TG on OA risk

IVW MR revealed that TG increment was associated with reduced risks of hip OA (OR = 0.91, 95% CI: 0.84–0.98, $P = 0.017$) but not knee OA (OR = 0.94, 95% CI: 0.86–1.02, $P = 0.135$) (Table 1). The effect of TG on hip OA was reproduced using the MR-PRESSO method (OR = 0.91, 95% CI: 0.84–0.98, $P = 0.021$). Weighted mode MR also showed a trend toward reduced risks of hip OA (OR = 0.89, 95% CI: 0.80–1.00, $P = 0.053$). However, the MR-Egger regression and weighted median MR did not show any association. The Cochrane Q statistic suggested significant heterogeneity in the association between TG and knee OA ($Q = 125.11$, $P < 0.001$) but not between TG and hip OA ($Q = 64.85$, $P = 0.148$). The MR-Egger regression showed no evidence of horizontal pleiotropy for knee OA (Egger intercept = -0.002 , $P = 0.635$) and hip OA (Egger intercept = 0 , $P = 0.994$) (Figures 1C,F). Visual inspection of funnel plots revealed no horizontal pleiotropy (Supplementary Figures S5, S6). The MR-PRESSO analysis identified three outliers for knee OA. However, these outliers did not influence the effect estimates ($P = 0.930$). In addition, the Steiger test demonstrated a causal relationship between exposure and outcome ($P < 0.001$).

Multivariable MR

Multivariable MR revealed a protective effect of LDL-C increment on the risk of knee OA (OR = 0.93, 95% CI: 0.87–0.99, $P = 0.021$) and hip OA (OR = 0.91, 95% CI: 0.84–0.98, $P = 0.009$) independent of HDL-C, TG, and BMI (Table 2). The estimated OR was comparable to that obtained using univariate MR analyses (Figure 2). Multivariable MR analysis revealed that neither HDL-C nor TG level was associated with OA risk.

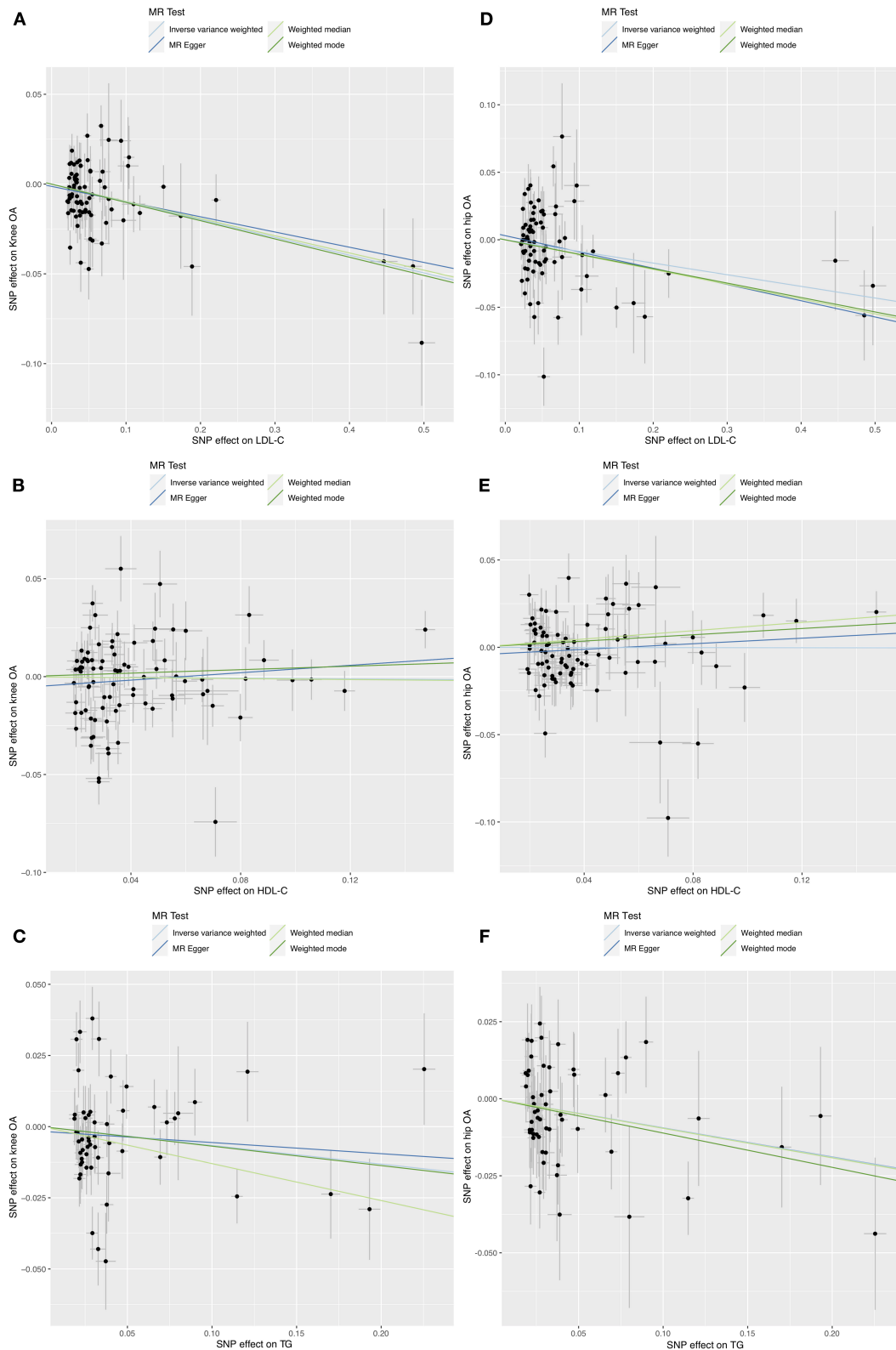
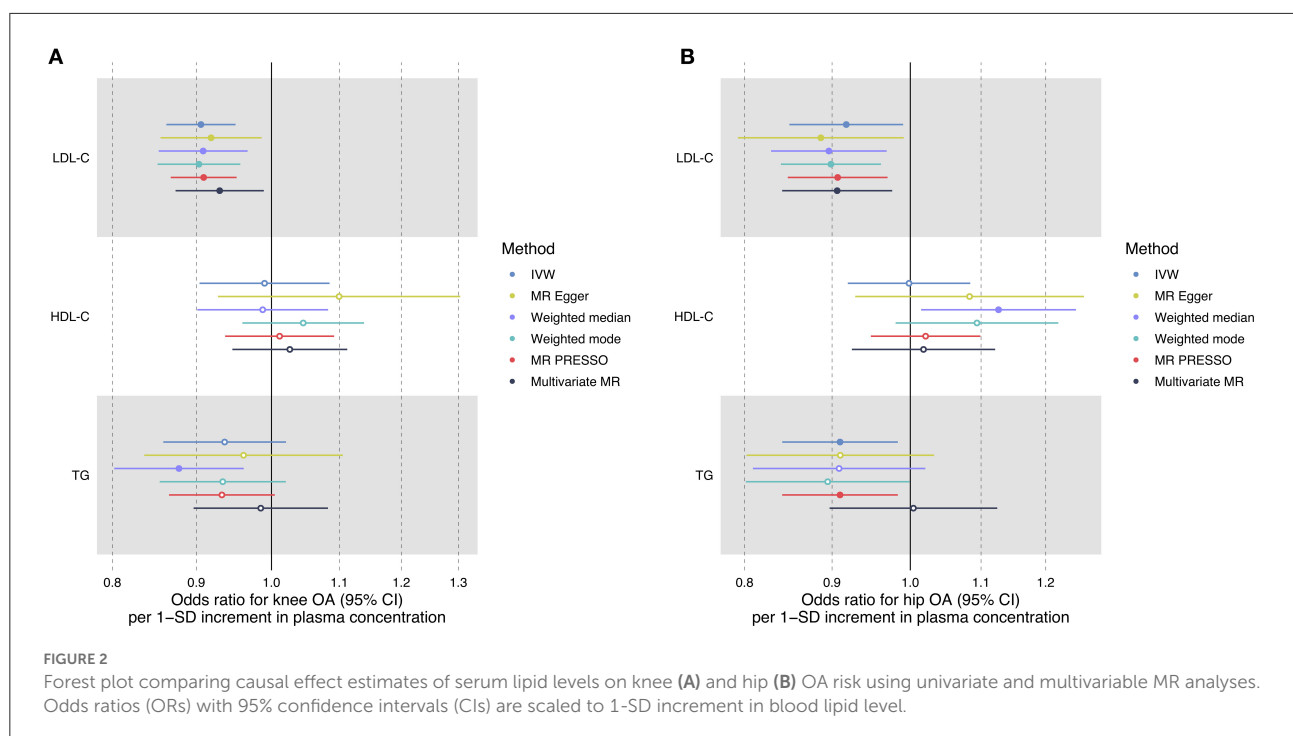


FIGURE 1 Scatter plots of MR analyses for the causal effect of LDL-C, HDL-C, and TG on knee (A–C) and hip (D–F) OA risk.

TABLE 2 Multivariate Mendelian randomization analysis results.

Exposure	Outcome	Number of SNPs	OR (95% CI)	P-value
LDL-C	Knee OA	38	0.93 (0.87–0.99)	0.021
HDL-C	Knee OA	50	1.03 (0.95–1.11)	0.532
TG	Knee OA	27	0.99 (0.90–1.08)	0.755
BMI	Knee OA	360	2.14 (1.95–2.34)	6.4×10^{-61}
LDL-C	Hip OA	38	0.91 (0.84–0.98)	0.009
HDL-C	Hip OA	50	1.02 (0.92–1.12)	0.717
TG	Hip OA	27	1.00 (0.90–1.12)	0.942
BMI	Hip OA	360	1.54 (1.38–1.72)	5.3×10^{-15}

OA, Osteoarthritis; SNP, single nucleotide polymorphisms; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; BMI, body mass index.



Causal effects of lipid-lowering therapy on OA risk

LDL-C increment determined by six SNPs in the *HMGCR* region was significantly associated with a reduced risk of knee OA (OR = 0.76, 95% CI: 0.60–0.96, $P = 0.024$) but not hip OA (OR = 1.00, 95% CI: 0.75–1.34, $P = 0.994$) (Table 3, Figure 3), suggesting that the LDL-C-lowering effect of statins is related to increased risks of knee OA. In contrast, the LDL-C-lowering effect of ezetimibe and evolocumab had no influence on OA risk (Table 3). There was some evidence of heterogeneity across the effects of SNPs in the *NPC1L1* region ($P = 0.013$).

Discussion

We performed this two-sample MR study to investigate the effects of blood lipids and cholesterol-lowering agents on the risk of knee and hip OA. We found that an increase in LDL-C levels was associated with reduced risks of both knee and hip OA. Multivariate MR analysis proved that this effect was independent of HDL-C level, TG level, and BMI. There was some evidence (from IVW and MR-PRESSO method) that TG increment was associated with reduced risks of hip OA; however, this was not reproduced in the multivariate MR. Another important finding was that the genetically proxied LDL-C-lowering effect of statins was related to increased risks of knee OA but not hip OA.

TABLE 3 Estimates of the effect of LDL-C on OA risk using SNPs in specific genes.

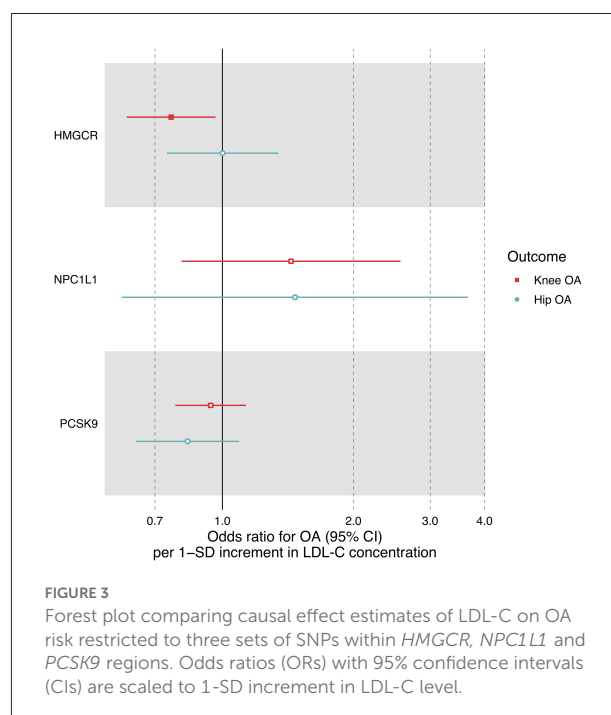
Gene	Outcome	Number of SNPs	OR (95% CI)	P-value	P for heterogeneity
HMGCR	Knee OA	6	0.76 (0.60–0.96)	0.024	0.610
NPC1L1	Knee OA	5	1.44 (0.81–2.56)	0.219	0.091
PCSK9	Knee OA	7	0.94 (0.78–1.13)	0.512	0.665
HMGCR	Hip OA	6	1.00 (0.75–1.34)	0.994	0.621
NPC1L1	Hip OA	5	1.47 (0.59–3.67)	0.411	0.013
PCSK9	Hip OA	7	0.83 (0.63–1.09)	0.184	0.226

OA, Osteoarthritis; SNP, single nucleotide polymorphisms; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; NPC1L1, Niemann-Pick C1-Like 1; PCSK9, proprotein convertase subtilisin/kexin type 9.

In contrast, the genetically proxied effects of ezetimibe and evolocumab had no influence on OA risk.

In the current study, we performed two-sample MR analyses using different methods under different assumptions, including MR-PRESSO and multivariate MR, which yielded consistent causal effect estimates. Previous studies also investigated the effect of increased LDL-C levels on OA risk using MR analyses (26–28). However, several major differences existed between these existing studies and the current study in terms of analyses and results. Hindy et al. (26) conducted one- and two-sample MR studies based on the Malmö Diet and Cancer Study (MDCS) cohort, which included ~30,000 adults. They found that increased LDL-C levels were associated with reduced overall OA risk (OR = 0.83). Gene-specific subgroup analysis revealed a trend toward reduced OA risk using SNPs within the *HMGCR* gene, but this did not reach statistical significance. However, their sample size was lower than that of the current study. In addition, they did not evaluate site-specific OA risk (26) unlike the present study, wherein we showed the different effects of statin on knee and hip OA. Gill et al. (27) performed a two-sample MR analysis and reported OR estimate for OA risk per 1-SD increment of LDL-C similar to our study (OR = 0.94); however, they did not adjust for other lipids, which could be potential sources of pleiotropy. In addition, they did not investigate site- and gene-specific OA risk. Recently, Meng et al. (28) conducted a two-sample MR analysis and demonstrated that LDL-C increment was associated with reduced risks of both knee OA (OR = 0.899) and hip OA (OR = 0.870). However, they used the same database to estimate SNP-exposure and SNP-outcome association, which could introduce bias in the two-sample MR owing to significant sample overlap (29). Therefore, we believe that our study provides a more robust and specific estimate of the causal effect than previous studies.

Although LDL-C plays a critical role in the pathogenesis of atherosclerosis, its role in OA has received relatively little attention. Since both obesity and hyperlipidemia are manifestations of metabolic syndrome and obesity is a well-recognized risk factor for OA, it is natural to assume that increased LDL-C is also a risk factor for OA (30). Evidence from animal experiments also supports this assumption. In



a hyperlipidemic mouse model, Gierman et al. (31) found that a high-cholesterol diet could lead to the development of both OA and atherosclerosis. Interestingly, administration of atorvastatin can suppress the development of both OA and atherosclerosis, whereas ezetimibe only has an effect on atherosclerosis. It was found that lipid deposits in osteoarthritic cartilage and chondrocytes at an early stage of OA, which may trigger the development of OA (32). In addition, oxidized LDL participates in cartilage destruction by activating synovial cells, thereby promoting the release of growth factors and proinflammatory cytokines (30). Nevertheless, our MR results provide an alternative hypothesis that genetically predicted lower LDL-C levels are associated with increased risks of OA. Further research is warranted to explain the discrepancies between animal and human genetic studies.

In line with the effect of LDL-C on OA risk, our MR results suggested that the LDL-C-lowering effect of statins increased the

risk of knee OA. Many observational studies have investigated the association between statin use and OA risk; however, conflicting results have been reported (33–40). In a prospective cohort study of 5,674 women, Beattie et al. (33) found that statin use was associated with increased risks of incidental hip OA but not with the progression of hip OA. Eymard et al. (34) performed a *post-hoc* analysis of 336 patients from the SEKIOA trial and found an independent association between statin use and radiological progression of knee OA (OR = 1.49, $P = 0.010$) after adjusting for potential confounding factors. Makris et al. (35) conducted a 1:1 propensity score matching study that included 6,728 statin users and 6,728 non-users. They concluded that statin use led to an increased risk of non-traumatic arthritis (OR = 1.17, 95% CI: 1.09–1.25). In contrast, Clockaerts et al. (36) conducted a prospective cohort study of 2,921 participants and revealed that statin use led to a 50% reduction in overall knee OA progression, as assessed using the Kellgren and Lawrence score. Haj-Mirzaian et al. (37) conducted a retrospective cohort study stratifying participants based on the existence of Heberden nodes (HNs) and found a protective effect of statin use on the progression of radiographic knee OA in HN-positive participants. Other studies have found no effect of statin use on the risk or progression (38–40). A recent meta-analysis of observational studies found high heterogeneity among studies on the effect of statins on the progression of OA (7). Nevertheless, observational studies are inevitably affected by confounding factors, and more importantly, by indication bias (41), which has been well-discussed in studies evaluating statin use and colorectal cancer risk (42). Because of indication bias, observational studies may falsely show a protective effect of statins if hyperlipidemia is related to a lower risk of the disease, which is exactly the current situation since we proved that LDL-C increment was associated with reduced risks of knee and hip OA. According to Mendel's law of inheritance, alleles obtained by individuals in an SNP are random with respect to potential confounding factors. Using SNPs as instrumental variables, MR studies can mimic the effect of randomized controlled trials (43) and can thus provide causal effect estimation closer to the real situation. In addition to statins, ezetimibe and evolocumab are commonly used LDL-C-lowering drugs. However, to the best of our knowledge, no previous study has reported its effects on OA. Further studies need to compare the effects of statins, ezetimibe, and evolocumab on OA, which may overcome the potential indication bias of previous observational studies (44).

The limitations of this study are as follows. First, the MR methodology requires the absence of horizontal pleiotropy, and instrumental variables affect outcomes only through their effect on exposure. In the current study, potential pleiotropy may be due to the effect of instrumental SNPs on other lipids and body weight. Nevertheless, we conducted sensitivity MR analyses using different methods under different assumptions, including MR-Egger regression, which showed no evidence of directional

horizontal pleiotropy. We also performed multivariate MR wherein all the analyses yielded similar causal effect estimates. Second, the analyses were conducted based on European ancestry. Therefore, these results may not be applicable to other populations as well. Thirdly, estimates of causal effects were reported as OR per one SD increase in LDL-C, therefore, we could not assess the actual dose-response effect of increasing LDL-C levels and risk of OA. Fourthly, sex may modify the correlation between blood lipid and OA. Future study may stratify male and female individuals to identify this effect. Finally, we used SNPs within *HMGCR*, *NPC1L1*, and *PCSK9* to mimic the LDL-lowering effect of statins, ezetimibe, and evolocumab. There may be differences between the genetically proxied effect and the real drug effect. In addition, we could not compare the effects of different types of statins.

Conclusions

In conclusion, our MR study suggests that genetic predisposition to higher blood LDL-C levels may decrease the risk of both knee and hip OA. This effect was independent of HDL-C level, TG level, and BMI. The genetically proxied LDL-C-lowering effects of statins may increase the risk of knee OA but not hip OA. Further studies are needed to reveal the mechanisms underlying the effect of LDL-C and statin on OA and its potential role in treating and preventing OA.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: <https://www.mrbase.org/>.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the Local Legislation and Institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZW and YZ designed the study. ZW and ML performed statistical analyses and wrote the manuscript. All authors were involved in results interpreting and were involved in revising the article and approved the final version to be published.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmed.2022.990569/full#supplementary-material>

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