

Causal Factors for Knee, Hip, and Hand Osteoarthritis: A Mendelian Randomization Study in the UK Biobank

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Objective. There is no curative treatment for osteoarthritis (OA), which is the most common form of arthritis. This study was undertaken to identify causal risk factors of knee, hip, and hand OA.

Methods. Individual-level data from 384,838 unrelated participants in the UK Biobank study were analyzed. Mendelian randomization (MR) analyses were performed to test for causality for body mass index (BMI), bone mineral density (BMD), serum high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels, type 2 diabetes, systolic blood pressure (BP), and C-reactive protein (CRP) levels. The primary outcome measure was OA determined using hospital diagnoses (all sites, $n = 48,431$; knee, $n = 19,727$; hip, $n = 11,875$; hand, $n = 2,330$). Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated.

Results. MR analyses demonstrated a robust causal association of genetically determined BMI with all OA (OR per SD increase 1.57 [95% CI 1.44–1.71]), and with knee OA and hip OA, but not with hand OA. Increased genetically determined femoral neck BMD was causally associated with all OA (OR per SD increase 1.14 [95% CI 1.06–1.22]), knee OA, and hip OA. Low systolic BP was causally associated with all OA (OR per SD decrease 1.55 [95% CI 1.29–1.87]), knee OA, and hip OA. There was no evidence of causality for the other tested metabolic factors or CRP level.

Conclusion. Our findings indicate that BMI exerts a major causal effect on the risk of OA at weight-bearing joints, but not at the hand. Evidence of causality of all OA, knee OA, and hip OA was also observed for high femoral neck BMD and low systolic BP. However, we found no evidence of causality for other metabolic factors or CRP level.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis in developed countries, representing an increasing health economic burden (1). Patients with knee or hip OA have excess all-cause mortality compared with the general population, and there is no curative treatment for OA (2). Besides age and sex, modifiable factors have been shown to be associated with OA risk, the highest level of evidence being for obesity and joint injury (3,4). Obesity is a major risk factor for OA incidence and progression at the knee, and to a lesser extent, at the hip (5). In addition, the role of obesity is strongly supported by findings of improvement of knee symptoms in patients undergoing weight loss (6,7).

Besides body mass index (BMI), other factors have been described as being associated with either prevalence, incidence or progression of OA. High bone mineral density (BMD) was

determined to be associated with increased risk of radiographic hip OA (8) or knee OA (9), and with total joint replacement (10). However, results from prospective studies of incident radiographic OA or OA progression are controversial (11). The concept of a “metabolic OA” phenotype was recently proposed (4). However, as metabolic factors are closely related to BMI, their BMI-independent contribution to the risk of OA is unknown. Previous studies have shown that the presence of the metabolic syndrome and many of its components are associated with the risk of hand and knee OA (12–14). Most associations with each of the metabolic syndrome components, however, become nonsignificant after adjustment for BMI (13,15). In addition, conflicting data regarding type 2 diabetes as a BMI-independent predictor of OA have been reported (16,17). The results from classic epidemiologic studies may be affected by residual confounding or reverse causation. Thus, there is an unmet need for a well-powered study

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Anonymized phenotype and genetic data are available from UK Biobank on application.

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to identify causal risk factors of OA. We hypothesized that causal associations may differ by OA site.

Mendelian randomization (MR) can be used to test for a causal association between a risk factor and a particular outcome (18). Two recent MR studies have demonstrated that overweight or high BMI is causally associated with increased risk of OA (19,20). Therefore, to reduce potential bias through genetic associations with confounders, MR analyses of other causal factors should include sensitivity analyses without genetic instrument variables also associated with BMI.

The present study aimed to identify causal risk factors for site-specific OA in the complete UK Biobank data set. Using genetic instrument variables from previously published genome-wide association study (GWAS) meta-analysis, the possible causality of BMI, BMD, serum high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels, type 2 diabetes, systolic blood pressure (BP), and C-reactive protein (CRP) levels in the risk of developing knee, hip, and hand OA was evaluated. The primary outcome measure was hospital diagnosis of OA. In secondary analyses, more severe cases of knee and hip OA, as identified by joint replacement, were also evaluated.

SUBJECTS AND METHODS

UK Biobank study subjects and ethics approval. In this study, conducted using the UK Biobank resource (<http://www.ukbiobank.ac.uk/>), 502,647 individuals between the ages of 37 and 76 years were recruited from across the UK from 2006 to 2010 (21). Participants provided a range of information regarding health status, demographics, and lifestyle via questionnaires and interviews. In addition, they were physically examined for anthropometric measurements, BP readings, and an estimation of BMD of the heel using a noninvasive method. The full data set was downloaded in April 2018. We included 384,838 unrelated participants of white European descent with valid data on the outcome measure and relevant covariates (age, sex, BMI). Pairs of individuals up to third-degree relatives were identified using the robust estimated kinship coefficients from the King software (22). The UK Biobank has ethical approval from the North West Multi-Centre Research Ethics Committee, and informed consent was obtained from all participants. The present research was approved by the UK Biobank Research and Access Committee (application no. 26952).

Outcome measure definitions. The outcome measure was obtained from the UK Biobank database downloaded in April 2018. The primary outcome measure in the present study was OA as defined by hospital diagnoses (<http://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=2022>) using the International Classification of Diseases, Ninth Revision (ICD-9) codes or the Tenth Revision (ICD-10) for all OA ($n = 48,431$), knee OA ($n = 19,727$), hip OA ($n = 11,875$), and hand OA ($n = 2,330$) (see Supplementary

Table 1, available on *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40928/abstract>). Of the total of 48,731 all OA cases, 11 were identified with ICD-9 codes and 48,420 with ICD-10 codes. In secondary analyses, we evaluated self-reported OA from the UK Biobank questionnaires and more severe cases of OA defined by a history of knee replacement or hip replacement. Patients with valid information from operative procedures summary information for knee replacement (W40-42) or hip replacement (W37-39), according to the Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4 (<http://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=2025>), were included. We excluded patients who had a concomitant diagnosis of chronic inflammatory arthritis or aseptic osteonecrosis at the time of intervention. For hip replacement, we further excluded patients who had concomitantly self-reported hip fracture (Supplementary Table 1, <http://onlinelibrary.wiley.com/doi/10.1002/art.40928/abstract>). In the UK Biobank, the hospital admissions registers began in 1981 and were updated until February 29, 2016. The last OA case date registered in our data set was February 25, 2016.

As expected, there was a substantial overlap between the different OA outcomes (Supplementary Table 2, <http://onlinelibrary.wiley.com/doi/10.1002/art.40928/abstract>). Interestingly, among the 11,875 individuals with a hospital diagnosis of hip OA, only 4,445 (37%) were identified in the self-reported OA questionnaire. Therefore, we selected outcome measure definitions using hospital diagnoses for our primary analyses.

Causal associations using MR. To assess causal associations between risk markers and OA, we performed MR analyses. We used genetic instrument variables obtained from selected GWAS as proxies for BMI (23), femoral neck BMD and lumbar spine BMD (24), serum HDL cholesterol, LDL cholesterol, and triglyceride levels (25), type 2 diabetes (26), systolic BP (27), and CRP levels (28) (Supplementary Table 3, <http://onlinelibrary.wiley.com/doi/10.1002/art.40928/abstract>). As genetic variants are randomly distributed at birth, they are unaffected by confounders. We then regressed the association of these single-nucleotide polymorphisms (SNPs) on the outcome measure, weighing their effect by the magnitude of their effect upon the corresponding exposure.

Our primary MR method was the 2-sample inverse-variance weighting, using the effect estimates for the exposure from the corresponding GWAS. Sensitivity analyses were performed using the MR-Egger method to preclude pleiotropy (29) (Supplementary Figure 1, <http://onlinelibrary.wiley.com/doi/10.1002/art.40928/abstract>), the weighted median MR method, and the penalized weighted median MR method. When the exposure parameter was available (for BMI, type 2 diabetes, and systolic BP), we also performed 1-sample MR methods using the effect estimates for exposure in the UK Biobank. Power analyses were performed for each exposure and OA outcome (Supplementary Table 4,

<http://onlinelibrary.wiley.com/doi/10.1002/art.40928/abstract>). Early on we identified a robust causal effect of BMI on the risk of OA and therefore for other candidate causal traits, we performed additional MR sensitivity analyses excluding genetic instrument variables that are also associated ($P < 0.05$) with BMI (Supplementary Tables 5–13, <http://onlinelibrary.wiley.com/doi/10.1002/art.40928/abstract>). Detailed methods for MR studies are described in Supplementary Methods, <http://onlinelibrary.wiley.com/doi/10.1002/art.40928/abstract>.

We evaluated 9 candidate causal risk factors, and for all these traits, we first evaluated the association with all OA, as this was the outcome measure with the highest power for the 2-sample inverse-variance weighting method (required Bonferroni-corrected P value < 0.0056 [$P = 0.05/9$]). If this threshold was met for all OA, a nominal P value of 0.05 was required for the site-specific analyses of knee, hip, or hand OA. Therefore, 95% confidence intervals (95% CIs) for all OA are presented before and after adjustment for multiple comparisons ($n = 9$).

Comorbidities and covariates. For BMI, we used the calculated measures of weight/height² available in the anthropometrics data at recruitment. Two measures of systolic BP were obtained at the inclusion interview. We used the mean value of the 2 available measures for each individual. Information on the use of antihypertensive medication was collected during the same visit. For the population description at baseline, individuals with prevalent type 2 diabetes were identified using self-reported diabetes at recruitment in combination with a hospital diagnosis of type 2 diabetes by ICD-10 code (E11). For the MR analyses, we included prevalent and incident cases of type 2 diabetes, using any diagnosis of type 2 diabetes by ICD-10 codes in the database. Information on current smoking status (yes or no) was collected at the time of the interview.

RESULTS

The mean age of the 384,838 unrelated individuals of European descent included in the present study was 56.8 years. Patient characteristics and main comorbidities at recruitment are presented in Table 1. Our primary analyses were inverse-variance weighting by 2-sample MR for all OA, and after adjustment for multiple comparisons (9 traits; $P < 0.0056$), causal evidence was observed for high BMI ($P = 3.0 \times 10^{-24}$), high femoral neck BMD ($P = 3.0 \times 10^{-4}$), and low systolic BP ($P = 2.3 \times 10^{-6}$), as shown in Figure 1 (also see Supplementary Table 14, <http://onlinelibrary.wiley.com/doi/10.1002/art.40928/abstract>). For all OA, there was no clear evidence of pleiotropy, and the MR-Egger intercept demonstrated no significance for any of the tested exposures.

Evidence of a causal association of BMI with knee and hip OA, but not hand OA. The 2-sample MR revealed that an increase in genetically determined BMI was causally associated with all OA (odds ratio [OR] per SD increase 1.57 [95%

Table 1. Participant characteristics and main comorbidities at recruitment*

All subjects at recruitment	
Age, years	56.8 ± 8.0
Female sex, no. (%)	207,789 (54.0)
Body mass index, kg/m ²	27.4 ± 4.8
Cholesterol-lowering medication users, no. (%)	66,379 (17.3)
Prevalent type 2 diabetes, no. (%)	10,170 (2.6)
Prevalent and incident type 2 diabetes, no. (%)	16,946 (4.4)
Antihypertensive medication users, no. (%)	79,081 (20.6)
Systolic BP, mm Hg	138.0 ± 18.6
Systolic BP, excluding antihypertensive medication users, mm Hg	136.2 ± 18.3
Current smokers, no. (%)	39,840 (10.4)
OA	
All locations combined, no. (%)	
All OA	48,431 (12.6)
Self-reported OA	34,229 (8.9)
Knee, no. (%)	
Knee OA	19,727 (5.1)
Knee replacement	9,716 (2.6)
Hip, no. (%)	
Hip OA	11,875 (3.1)
Hip replacement	9,932 (2.6)
Hand OA, no. (%)	2,330 (0.6)

* The n value for each variable was 384,838, except as follows: for cholesterol-lowering medication users and antihypertensive medication users, $n = 384,468$; for systolic blood pressure (BP), $n = 384,515$; for systolic BP, excluding antihypertensive medication users, $n = 305,170$; for current smokers, $n = 383,470$; for knee replacement, $n = 379,840$; and for hip replacement, $n = 379,197$. Except where indicated otherwise, values are the mean ± SD. OA = osteoarthritis.

CI 1.44–1.71; adjusted for 9 comparisons 1.39–1.77]), as shown in Figure 1 and Supplementary Table 14. As individual-level data were available and as the UK Biobank was well-powered for the outcome of all OA, we performed stratified analyses to compare the causal association of BMI in different subgroups. The causal association of genetically determined BMI with all OA was robust and similar in young individuals (below the median age of cases) and older individuals (above the median age of cases), in males and females, as well as in subpopulations stratified by smoking status or type 2 diabetes (Figure 2). Causal associations for BMI were also found at weight-bearing joints (OR per SD increase 1.76 [95% CI 1.56–1.99] in knee OA and 1.52 [95% CI 1.31–1.78] in hip OA), but not at the hand (OR 1.00 [95% CI 0.76–1.31]). Similar results were obtained with the other 2-sample MR methods and 1-sample MR methods (see Supplementary Tables 14–17, <http://onlinelibrary.wiley.com/doi/10.1002/art.40928/abstract>).

Evidence of a causal association of BMD with knee and hip OA. Genetically determined femoral neck BMD was causally associated with all OA (OR per SD increase 1.14 [95% CI 1.06–1.22; adjusted for 9 comparisons 1.03–1.25]; Figure 1). The causal association was found to be of similar magnitude at the knee (OR 1.18 [95% CI 1.05–1.32]) and

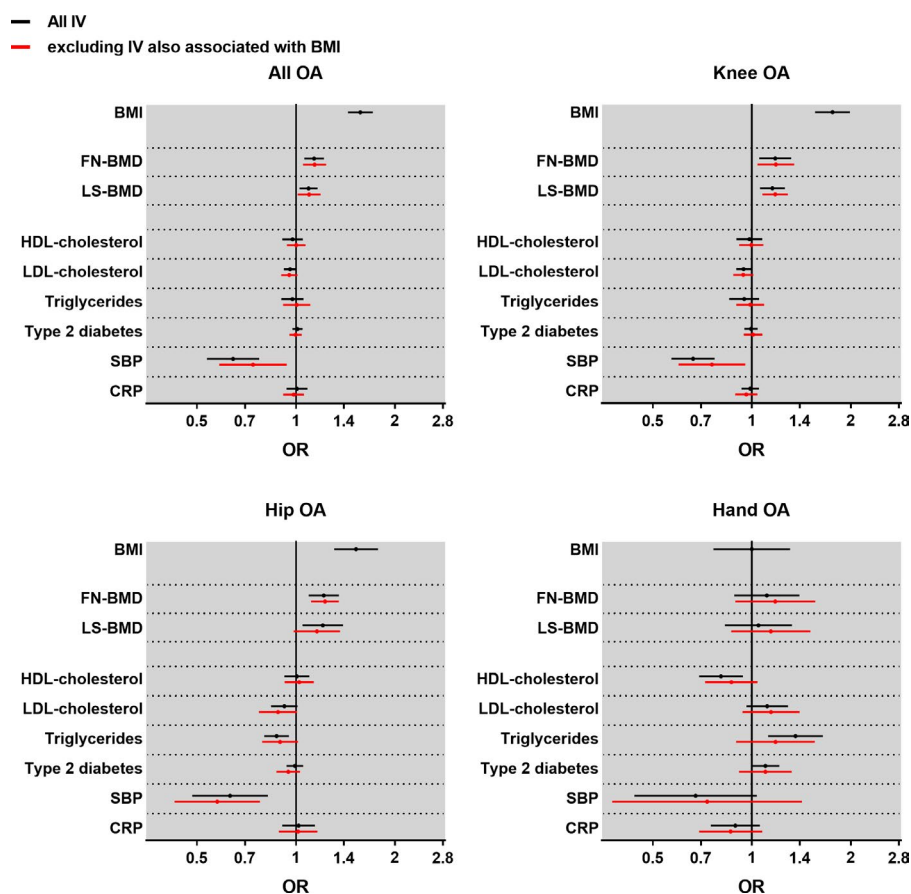


Figure 1. Causal associations between genetically determined risk factors and osteoarthritis (OA) by site. For each site, the odds ratio (OR) and 95% confidence interval for the risk of OA are represented for each factor, as determined using the 2-sample Mendelian randomization inverse-variance weighting method for body mass index (BMI; per SD increase), femoral neck bone mineral density (FN-BMD; per SD increase), lumbar spine BMD (LS-BMD; per SD increase), serum levels of high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride (per SD increase), systolic blood pressure (SBP; per SD increase), C-reactive protein (CRP) level (per $\ln[\text{mg/liter}]$ increase), or presence of type 2 diabetes. The total number of subjects is 384,838, with 48,431 all OA, 19,727 knee OA, 11,875 hip OA, and 2,330 hand OA cases. IV = instrument variable.

hip (OR 1.22 [95% CI 1.09–1.35]), but not at the hand (OR 1.11 [95% CI 0.88–1.39]; Figure 1 and Supplementary Table 14). Sensitivity analyses, excluding BMI-associated SNPs (Figure 1), as well as analyses using other MR methods, revealed similar results (Supplementary Table 14). For lumbar spine BMD, the causal association with all OA was less pronounced and only nominally significant. Site-specific analyses demonstrated a causal association of lumbar spine BMD at the knee (OR 1.15 [95% CI 1.06–1.26]), which remained after the exclusion of genetic instrument variables also associated with BMI (Supplementary Table 14).

Evidence of a causal association of systolic BP with hip OA. Systolic BP was causally inversely associated with all OA (OR per SD increase 0.64 [95% CI 0.54–0.77; adjusted for 9 comparisons 0.50–0.83]), knee OA (OR 0.66 [95% CI 0.57–0.77]), and hip OA (OR 0.63 [95% CI 0.48–0.82], Figure 1 and Supplementary Table 14). The associations remained unchanged when subjects receiving antihypertensive medication were excluded

from the analyses (see Supplementary Figure 2, <http://onlinelibrary.wiley.com/doi/10.1002/art.40928/abstract>). Similar results were obtained in sensitivity analyses excluding BMI-associated SNPs, and with other MR methods (Supplementary Tables 14–17, <http://onlinelibrary.wiley.com/doi/10.1002/art.40928/abstract>).

No evidence of a causal association of other tested metabolic markers or CRP level with OA. No other tested candidate traits (HDL cholesterol, LDL cholesterol, triglyceride level, type 2 diabetes, or CRP level) demonstrated any evidence of a causal association with all OA, knee OA, hip OA, or hand OA that remained after exclusion of genetic instrument variables also associated with BMI or correction for multiple comparisons (Figure 1). Although failing to pass our prespecified threshold for adjustment for multiple comparisons, weak causal inverse associations between LDL cholesterol level and risk of knee OA and hip OA were observed (for knee OA, OR per SD increase 0.94 [95% CI 0.90–0.99] for all SNPs and OR 0.94 [95% CI 0.88–1.01] without BMI SNPs; for hip OA, OR per SD increase 0.92 [95% CI

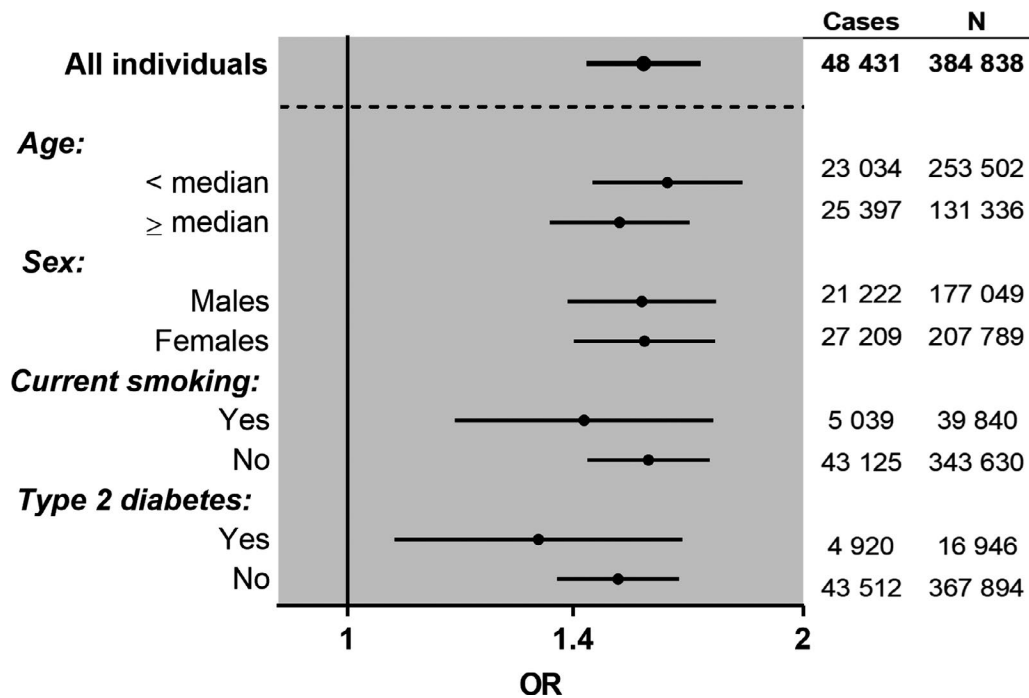


Figure 2. Stratified analyses of the causal associations of body mass index (BMI) with all osteoarthritis (OA). Odds ratios (ORs) and 95% confidence intervals are shown for the causal associations between BMI (per SD increase) and the risk of all OA, as determined using the 2-sample Mendelian randomization inverse-variance weighting method in analyses stratified by age (median of cases), sex, current smoking status, or type 2 diabetes.

0.84–1.01] for all SNPs and OR 0.88 [95% CI 0.77–1.01] without BMI SNPs (Supplementary Table 14).

Secondary analyses using knee and hip joint replacement as definitions of severe OA. We repeated the analyses using knee or hip replacement definitions of severe OA and found causal associations for genetically determined high BMI (knee replacement: OR per SD increase 2.30 [95% CI 1.93–2.75]; hip replacement: OR per SD increase 1.65 [95% CI 1.41–1.92]), and high femoral neck BMD (knee replacement: OR per SD increase 1.27 [95% CI 1.09–1.48]; hip replacement: OR per SD increase 1.17 [95% CI 1.05–1.31]). Systolic BP was causally inversely associated with joint (knee replacement: OR per SD increase 0.64 [95% CI 0.50–0.83]; hip replacement: OR per SD increase 0.64 [95% CI 0.48–0.85]), which was in accordance with the findings from our primary analyses using hospital diagnoses (Figure 3 and Supplementary Tables 14–17, <http://onlinelibrary.wiley.com/doi/10.1002/art.40928/abstract>).

DISCUSSION

This study used the largest known data set to date with individual-level clinical, genetic, and outcome data to assess causal factors for OA. In the UK Biobank setting, we found 3 factors (high BMI, high femoral neck BMD, and low systolic BP) that were causally associated with increased risk of OA. High BMI was shown to be causal for knee OA and hip OA, but not hand OA. We

also report the first clear evidence of a causal role of high femoral neck BMD, predominantly reflecting cortical bone mass, on the risk of knee OA and hip OA. The most novel finding from this study is that low systolic BP was causally associated with all OA, knee OA, and hip OA. In contrast, the other metabolic factors and CRP levels were not causally associated with the risk of developing OA, after exclusion of the genetic instrument variables that are also associated with BMI.

Weight loss is reported to reduce knee OA symptoms and structural damage (7,30). The causal role of BMI in both knee and hip OA has recently been demonstrated in a previous study using first-release data from the UK Biobank (19). In this study, we replicated these causal BMI associations at weight-bearing joints. In addition, because in the current well-powered study we had access to individual-level data, we also performed stratified analyses, demonstrating that the causal effect of BMI on OA was robust and similar in young and old individuals, in males and females, as well as in subpopulations stratified by smoking status or type 2 diabetes. Importantly, we observed no evidence of a causal effect of BMI on the risk of hand OA. Collectively, these findings demonstrate that it is the body weight-induced loading of the joints that causes the increased risk of OA observed at weight-loaded, but not non-weight-loaded OA sites.

The importance of subchondral bone in the pathophysiology of OA has been extensively debated (31–34). So far, the supposed inverse association between osteoporosis and OA (35,36), and the observation that high bone mass is associated with

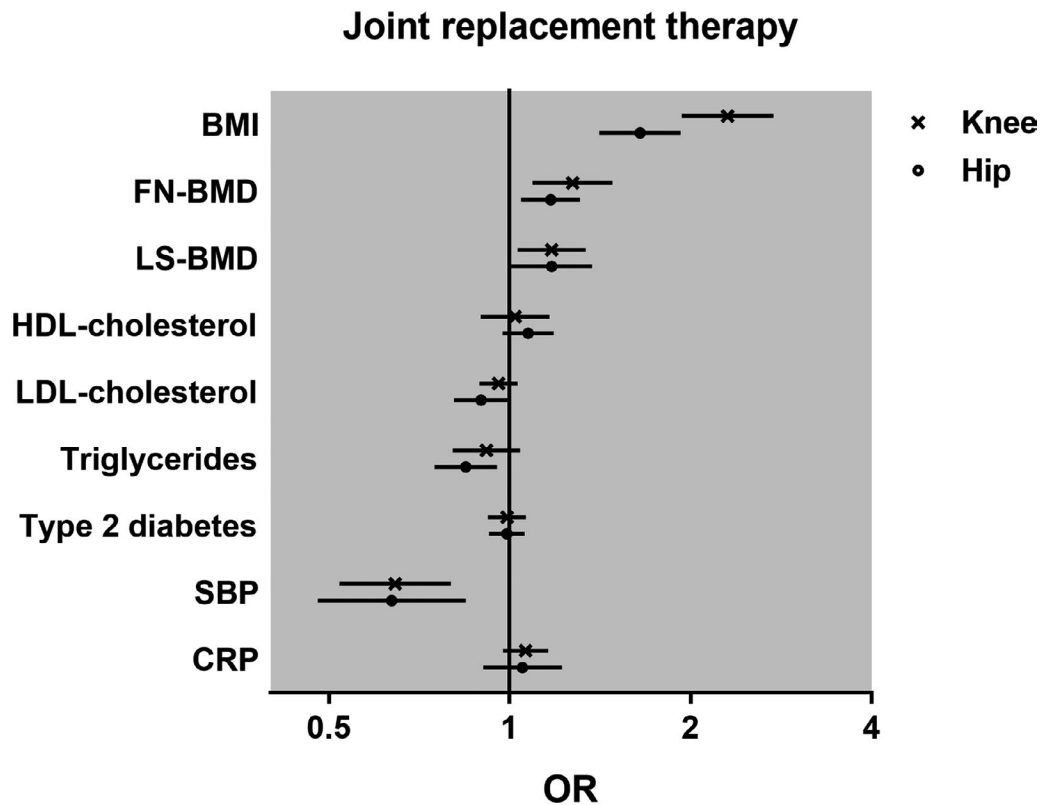


Figure 3. Causal associations between genetically determined risk factors and knee or hip replacement. For each joint replacement osteoarthritis (OA) definition, the odds ratio (OR) and 95% confidence interval for the risk of OA are represented for each factor, as determined using the 2-sample Mendelian randomization inverse-variance weighting method for body mass index (BMI; per SD increase), femoral neck bone mineral density (FN-BMD; per SD increase), lumbar spine BMD (LS-BMD; per SD increase), serum levels of high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride (per SD increase), systolic blood pressure (SBP; per SD increase), C-reactive protein (CRP) level (per ln[mg/liter] increase), or presence of type 2 diabetes. The total number of subjects is 384,838 (9,716 knee replacement and 9,932 hip replacement cases).

osteophyte volume (37), radiographic OA (8,9), and increased prevalence of joint replacement (10), led to the general hypothesis that increased BMD could be deleterious to the joint. The findings of these observational studies are in accordance with the results from the present MR analyses, which demonstrated a robust causal role of femoral neck BMD on knee and hip OA. We confirmed these associations in sensitivity analyses excluding the genetic instrument variables that were also associated with BMI, to preclude pleiotropy. Similarly, as previously described (19), we observed a modest causal association between lumbar spine BMD and knee OA. The previous lumbar spine BMD MR analyses, performed in an early-released subset of the UK Biobank, did not comply with the MR assumptions that genetic instrument variables should not be associated with the known confounder (BMI). In addition, the previous UK Biobank study was restricted by the phenotypes available in the MR-base platform (<http://www.mrbase.org/>), and therefore the most powerful lumbar spine BMD GWAS was not used. Also, the femoral neck BMD trait with the most robust causal association in the present study was not available for selection of genetic instrument variables (24).

Our present finding that low systolic BP is causally associated with OA is novel. Previous limited observational studies have evaluated the association between hypertension, defined as a combination of antihypertensive medication use and high BP, and OA. Hypertension was associated with increased risk of radiographic knee OA both in a prospective analysis in the Framingham Osteoarthritis Study (15) and in a large cross-sectional South Korean study (38). However, after adjustment for BMI, hypertension was not significantly associated with incident OA in the Framingham Osteoarthritis Study. It is possible that earlier prospective studies have been underpowered to identify systolic BP as a BMI-independent predictor of OA. Further studies are needed to confirm the causal link between low systolic BP and OA, and to identify the underlying mechanisms.

The previous MR study, which used a less powered subsample from the UK Biobank, indicated that some metabolic factors may display modest, but significant, causal associations with OA (19). However, BMI-associated SNPs were not excluded in those analyses, which therefore most likely were confounded by pleiotropic effects related to the known strong causal effect of BMI on OA. The present study, performing sensitivity analy-

ses with BMI-associated SNPs excluded, did not identify any causal association of metabolic risk factors except for systolic BP. The absence of a causal association for type 2 diabetes on OA in the present study indicates that the results of the previous observational association studies could be biased by remaining confounding factors or by reverse causation. Indeed, low physical activity caused by impaired mobility with knee or hip OA may increase insulin resistance. Finally, the lack of evidence of a causal role of lipids in knee or hip OA is supported by the results of 2 studies that showed no beneficial effect of statin use on OA risk or OA progression (39,40). However, a recent MR analysis in the Malmö Diet and Cancer Study showed that genetically determined increased LDL cholesterol was causally associated with reduced risk of OA (41). This latter MR analysis also confirmed that high BMI is causally associated with increased risk of OA. Although low-grade inflammation has been associated with increased risk of severe OA in observational studies (13), no causal effect of CRP levels was observed in the present study, which is in accordance with the negative results of intervention studies targeting inflammatory cytokines (42).

The major strength of the present study is its large sample size with individual-level data available. With respect to the second and third MR assumptions, we considered possible pleiotropy in sensitivity analyses in addition to the MR-Egger method, by excluding instrument variables that were also associated with BMI, since BMI was early shown to be a strong causative factor for knee and hip OA. We also performed detailed power calculations to ascertain the interpretation of negative results. Finally, we replicated our main analyses using other definitions for severe OA cases, using a joint replacement register that was independent of the ICD-9 and ICD-10 codes and found very similar results.

However, this study has some limitations. As we used hospital diagnoses, we could not assess any radiographic structural progression or pain as is recommended for clinical trials (43). While MR as an approach is appealing to address concerns about confounding, we cannot fully exclude the possibility that the null findings for some of the MR analyses could be due to misclassification of the diagnosis. This limitation may mostly affect hand OA, for which we acknowledge an underestimation of cases. Moreover, for knee OA, post-traumatic OA may be overrepresented when using hospital diagnosis. A hospital contact could also impact the chance of being classified as an OA case. However, we consider that our case definitions, being classified by hospital physicians, reflect symptomatic cases. ICD-10 code validation was not conducted in the present study using the UK Biobank; however, previous validation studies in other cohorts showed good positive predictive value (44,45). Another limitation is that the impact of physical activity could not be analyzed in this study, as no large published GWAS met our criteria to be used as a source of genetic instrument variables. Finally, our conclusions can only apply to a white European population.

In conclusion, BMI exerts a major causal effect on the risk of OA at weight-bearing joints, but not at the hand. Evidence of causality of knee OA and hip OA was observed for high femoral neck BMD and low systolic BP. These results should be considered in the future research of OA and for the elaboration of prevention or therapeutic strategies for the different OA sites.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Funck-Brentano had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Funck-Brentano, Nethander, Ohlsson.

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Analysis and interpretation of data. Funck-Brentano, Nethander, Movérare-Skrtic, Richette, Ohlsson.

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