Body Mass Index and the Risk of Rheumatic Disease: Linear and Nonlinear Mendelian Randomization Analyses

Torgny Karlsson,* Fatemeh Hadizadeh,* Mathias Rask-Andersen, Åsa Johansson, and Weronica E. Ek

**Objective.** Although the association between obesity and risk of rheumatic disease is well established, the precise causal relation has not been conclusively proven. Here, we estimate the causal effect of body mass index (BMI) on the risk of developing 5 different rheumatic diseases.

**Methods.** Linear and nonlinear mendelian randomization (MR) were used to estimate the effect of BMI on risk of rheumatic disease, and sex-specific effects were identified. Analyses were performed in 361,952 participants from the UK Biobank cohort for 5 rheumatic diseases: rheumatoid arthritis (n = 8,381 cases), osteoarthritis (n = 87,430), psoriatic arthropathy (n = 933), gout (n = 13,638), and inflammatory spondylitis (n = 4,328).

**Results.** Using linear MR, we found that 1 SD increase in BMI increases the incidence rate for rheumatoid arthritis (incidence rate ratio [IRR] 1.52 [95% confidence interval (95% CI) 1.43–1.55]), osteoarthritis (IRR 1.49 [95% CI 1.43–1.55]), psoriatic arthropathy (IRR 1.80 [95% CI 1.31–2.48]), gout (IRR 1.73 [95% CI 1.56–1.92]), and inflammatory spondylitis (IRR 1.34 [95% CI 1.14–1.57]) in all individuals. BMI was found to be a stronger risk factor in women compared to men for psoriatic arthropathy (P for sex interaction = 3.3 × 10⁻⁶) and gout (P for sex interaction = 4.3 × 10⁻³), and the effect on osteoarthritis was stronger in premenopausal compared to postmenopausal women (P = 1.8 × 10⁻⁵). Nonlinear effects of BMI were identified for osteoarthritis and gout in men, and for gout in women. The nonlinearity for gout was also more extreme in men compared to women (P = 0.03).

**Conclusion.** Higher BMI causes an increased risk for rheumatic disease, an effect that is more pronounced in women for both gout and psoriatic arthropathy. The novel sex- and BMI-specific causal effects identified here provide further insight into rheumatic disease etiology and mark an important step toward personalized medicine.

**INTRODUCTION**

Rheumatic diseases, including rheumatoid arthritis, osteoarthritis, psoriatic arthropathy, gout, and inflammatory spondylitis, constitute a heterogeneous group of diseases with unique clinical manifestations (1). Commonly, they are chronic and progressive, produce pain and weakness, can cause disability, and may significantly decrease the patient’s quality of life (2,3). Several risk factors have been linked to the development of rheumatic diseases of which some are modifiable, like obesity (4).

Body mass index (BMI) is a convenient measure of overall body mass and obesity (5). A number of observational studies have found a positive association between BMI and different rheumatic diseases (6). However, an observational study can neither control for unmeasured or unknown confounders, nor can it generally be conducted to determine the direction of the association, unless the design ensures a strict temporal and causal ordering between exposure and outcome. Therefore in most observational studies on obesity and rheumatic disease, it is unclear if obesity increases the risk for disease or if a person with a rheumatic disease is more likely to become obese (reversed causation). It is also possible that the association between obesity and rheumatic disease is only caused by an underlying lifestyle or environmental factor that increases the risk of both obesity and rheumatic disease (confounding).

Mendelian randomization (MR) is a powerful method, specifically developed to control for bias introduced by reversed causation and unmeasured confounding. It employs the instrumental variable technique and uses genetic variants associated with the exposure as instruments for the exposure. Since genetic variants...
are randomly allocated at conception and cannot be altered by disease status, they are not affected by either reversed causation or by confounders (7,8). In this capacity, MR may therefore be considered as an alternative to randomized controlled trials when this type of study is not possible to conduct (Supplementary Figure 1, available on the Arthritis & Rheumatology website at https://onlinelibrary.wiley.com/doi/10.1002/art.42613). Hereafter, we refer to an MR estimate as an estimate of the causal effect. In order for MR to yield consistent causal effect estimates, a genetic variant must be valid as an instrumental variable and should satisfy 3 core assumptions (9) as follows: 1) the variant must be strongly associated with the exposure (BMI), 2) the variant must not be associated with any measured, unmeasured, or unknown confounders of the relation of interest, and 3) the variant must be associated with the outcome (rheumatic disease) only through the exposure and not via other independent pathways (Supplementary Figure 2). The presence of weak instruments is a violation of the first assumption, while the second and third assumptions are violated by the presence of horizontal pleiotropy. Any violation of these 3 assumptions may result in biased estimates (10). MR investigations are commonly designed as 1- or 2-sample studies. In the 1-sample design, the effect of the instrument on both exposure and outcome are estimated in the same sample, while in the 2-sample design, the effect on exposure and on outcome are estimated separately in 2 non-overlapping samples. A 3-sample design is also possible but less common, due to the requirement of 3 independent samples. There are advantages and drawbacks for employing each design, and the choice may depend on the data available (11). For further discussion, see the Supplementary Material, https://onlinelibrary.wiley.com/doi/10.1002/art.42613.

A causal effect of BMI on rheumatoid arthritis (12), osteoarthritis (13), and gout (14,15) have been identified in previous MR studies. However, a possible causal effect of BMI on psoriatic arthropathy and inflammatory spondylitis has not yet been investigated. A previous MR study on psoriasis identified a causal effect for BMI; however, that study did not specifically investigate the effect of BMI on psoriatic arthropathy (16). Furthermore, although the prevalence of rheumatic diseases is known to differ between sexes (17,18), no study has, to the best of our knowledge, investigated sex-stratified effects of BMI on rheumatic disease using MR. Due to the possible modifying effect of sex hormones, the effect of BMI on rheumatic disease in connection to menopausal status is also crucial to explore. Finally, the changes in risk of disease for a given increase in BMI may not necessarily be the same in lean and in obese individuals. Characterizing such nonlinear effects of BMI on rheumatic disease is of great importance for personalized risk assessment and remains to be addressed.

Based on data from the UK Biobank (UKB), we estimated both sex-combined and sex-stratified causal effects of BMI on rheumatoid arthritis, osteoarthritis, gout, psoriatic arthropathy, and inflammatory spondylitis using linear MR. To investigate the potential influence of menopausal status, we also estimated the effect of BMI before and after menopause in women. Finally, we utilized nonlinear MR to test whether there exists a nonlinear effect of BMI on any of the 5 rheumatic diseases investigated.

PATIENTS AND METHODS

Study cohort, genotype data, exposure, and outcome measures. The UKB is a population-based cohort, with both a prospective and retrospective study design and includes over half a million individuals (N = 502,682) recruited from across the UK. Participants were 37–73 years of age at time of baseline assessment, 2006–2010. Baseline data from physical examinations, including weight and height measures, verbal interviews, and several touchscreen questionnaires on diet, lifestyle, and disease history were obtained for all participants. Blood samples were also collected from all participants at recruitment and utilized for blood biochemistry measurements, such as urate levels. Genome-wide genotyping was performed on all participants, including a total of 820,967 directly genotyped single nucleotide polymorphisms (SNPs) and >90 million imputed variants. To reduce potential bias from population stratification in the MR estimates, only White British participants identified through genetic principal components analysis were included, resulting in 361,952 individuals.

Diagnoses of rheumatic diseases were extracted from a curated data set (category 1712) of first occurrences of a large number of disease outcomes. Diagnosis codes from primary care, hospital in-patient, death register, and self-reported data were mapped to 3-digit International Classification of Diseases, 10th revision (ICD-10) codes before first-occurrence data were collected. Disease definitions and their comorbidity matrix are listed in Supplementary Tables 1 and 2, https://onlinelibrary.wiley.com/doi/10.1002/art.42613. Four-digit ICD-10 codes were also available from in-patient hospitalization and death registers, and based on these, we excluded individuals with diagnoses that represent secondary and posttraumatic disease. In most analyses, end of follow-up was set to December 31, 2019, and individuals were censored at death. In the analysis of premenopausal women, however, participants were either followed until age at menopause or until age at assessment, whichever came first (Supplementary Material). Exposure and covariate data for BMI, sex, year of birth, age at assessment, menopausal status, age at menopause, bilateral oophorectomy, age at bilateral oophorectomy, year of death, and genetic principal components were obtained from related data fields (Supplementary Table 3). Disease onset in relation to menopause is summarized in Supplementary Table 4, https://onlinelibrary.wiley.com/doi/10.1002/art.42613.

Selection of original set of genetic variants of BMI for downstream MR analyses. To identify genetic
MR analyses. To estimate the linear causal effect of BMI on rheumatic disease, we used a generalization of the random effects inverse variance weighting (IVW) method (19) on summary data of individual SNPs. The method employs generalized least squares to account for heteroskedastic errors and linkage disequilibrium between the SNPs via the variance–covariance matrix (20). Pairwise linkage disequilibrium was estimated in Plink using data from all 361,952 UKB participants. For consistency with the nonlinear analysis, we used a 1-sample design for the main linear MR. Weak-instrument bias was specifically controlled for, partly by using SNPs strongly associated with BMI (see Supplementary Table 5 for \( F \) statistics, https://onlinelibrary.wiley.com/doi/10.1002/art.42613), and partly by re-estimating the SNP effects on BMI in non-disease controls only (21). A further discussion on advantages and disadvantages of the different MR designs can be found in the Supplementary Material. All participants who were not excluded and who did not have an event registered for a specific rheumatic disease before the end of follow-up were defined as controls for that disease.

To enable inclusion of time-to-event data, the effect of each SNP on each rheumatic disease was estimated through Poisson regression with an offset term and robust standard errors (Supplementary Material). The same covariates were adopted as for the estimation and re-estimation of the SNP effects on BMI (Supplementary Material). Results from the linear analyses are presented as incidence rate ratios (IRRs) per 1 SD increase in BMI.

The nonlinear MR analysis was based on the method implemented in the nlmr package version 2.0 in R (22). This method computes linear MR estimates, called local averaged causal effects (22,23), in a number of quantiles, or strata, of the exposure (BMI). The method employs a 1-sample MR design with a polygenic score as instrument. The effect of the instrument on BMI was estimated in controls only, i.e., individuals who were not diagnosed during follow-up as having the specific disease under investigation, similar to the linear analyses (see Supplementary Table 6 for \( F \) statistics, https://onlinelibrary.wiley.com/doi/10.1002/art.42613). To avoid overfitting (24), UKB participants were divided into 2, non-overlapping subsamples of 180,976 individuals each. Nonlinear MR was performed separately in each subsample, such that the SNPs included in the polygenic score for each analysis were identified in the other subsample. The 2 MR estimates were then combined using fixed-effect meta-analysis for each BMI stratum (Supplementary Materials). For the meta-analyzed result, the mean BMI of each stratum was calculated as the average of the mean BMI of that stratum from the 2 subanalyses.

Instead of logistic regression, which is the default model for binary disease data in nlmr (22), we used Poisson regression with an offset term and robust standard errors, and applied the same covariates as in the linear MR analysis (Supplementary Material). In both the sex-combined and the sex-stratified analyses, we divided BMI values into 10 quantiles. Results from the nonlinear analyses are presented as IRRs per 1 SD increase in BMI for each stratum of BMI.

Secondary and sensitivity analyses. We conducted a series of secondary and sensitivity analyses to evaluate the robustness of our findings, as described in detail in the Supplementary Material. We performed both 2- and 3-sample MR analyses to quantify the magnitude of weak-instrument bias and winner’s curse, which act toward the null in these designs (11).

Horizontal pleiotropy was addressed by applying the weighted median method, which was specifically developed to be more robust against pleiotropic outliers than the IVW method (25), and by identifying potentially pleiotropic outliers using the modified second-order Cochran’s Q statistic (26). Identified statistical outliers were then removed prior to effect estimation, which was performed by the IVW method, as in the main analysis. Furthermore, we tested whether the use of robust standard errors induced bias in the downstream MR estimates by instead adopting a variance–covariance matrix with regular Poisson standard errors. Finally, we also tested whether the inclusion of low-linkage disequilibrium SNPs could introduce bias and examined the linearity between the instrument and exposure in the nonlinear MR.

Statistical methods. In the linear analyses, tests of equality of effect between women and men (sex interaction), were performed by Z test while the quadratic test was used to assess overall linearity in the nonlinear analyses (22). We fitted a parametric, nonlinear function to the local averaged causal effects data to test the equality of the variation in effect across BMI between sexes, which was designed as a Welch’s \( t \)-test of unequal variances (Supplementary Material). Corresponding 95% confidence intervals of the adopted function fits were calculated using the bootstrap method with 400 bootstrap samples.

To control for multiple testing and account for 5 rheumatic diseases and 2 types of analyses, i.e., linear and nonlinear MR,
Table 1. Baseline characteristics and number of rheumatic disease cases in the UK Biobank

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants (%)</td>
<td>194,797 (53.8)</td>
<td>167,155 (46.2)</td>
<td>361,952 (100)</td>
</tr>
<tr>
<td>Age at assessment, median (1st–3rd quartile)*</td>
<td>58 (51–63)</td>
<td>59 (51–64)</td>
<td>58 (51–63)</td>
</tr>
<tr>
<td>Age at end of follow-up, median (1st–3rd quartile)**</td>
<td>69 (61–74)</td>
<td>69 (62–74)</td>
<td>69 (61–74)</td>
</tr>
<tr>
<td>BMI, mean ± SD kg/m²</td>
<td>27.03 ± 5.14</td>
<td>27.84 ± 4.23</td>
<td>27.41 ± 4.76</td>
</tr>
<tr>
<td>Z-transformed BMI offset‡</td>
<td>5.26</td>
<td>6.58</td>
<td>5.76</td>
</tr>
<tr>
<td>Urate level, mean ± SD mmol/liter</td>
<td>270.79 ± 65.99</td>
<td>354.45 ± 71.62</td>
<td>309.45 ± 80.33</td>
</tr>
<tr>
<td>Rheumatic disease, no. cases/controls§</td>
<td>5,595/189,201</td>
<td>2,786/164,369</td>
<td>8,381/353,570</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>51,692/142,552</td>
<td>35,738/130,842</td>
<td>87,430/273,394</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>490/194,274</td>
<td>443/166,697</td>
<td>933/360,971</td>
</tr>
<tr>
<td>Psoriatic arthropathy</td>
<td>2,073/192,717</td>
<td>11,565/155,568</td>
<td>13,638/348,285</td>
</tr>
<tr>
<td>Gout</td>
<td>2,433/192,245</td>
<td>1,895/165,037</td>
<td>4,328/357,316</td>
</tr>
</tbody>
</table>

* Age at assessment was the age when evaluated for the first time at an assessment center.
† Age at end of follow-up in the main analyses was the age at death or December 31, 2019, whichever came first.
‡ The offset in z-transformed body mass index (BMI) was calculated as the mean BMI divided by the SD of BMI.
§ All participants that were not identified as having each respective disease were used as controls. Secondary and posttraumatic cases (Supplementary Table 1, https://onlinelibrary.wiley.com/doi/10.1002/art.42613) were set to missing; therefore, the total number of cases and controls do not necessarily equal the total number of participants.

The significance level was set to 0.005, obtained by dividing 0.05 by 10, in all main sex-combined analyses. This means that a P value less than 0.005 was considered significant.

Ethics approval and data availability. The UKB study was approved by the National Research Ethics Committee (REC reference no. 11/NW/0382). All participants in the UKB study gave informed consent. An application for using data from UKB has been approved (application no. 15479). The UKB analysis performed in this study was approved by the Swedish Ethical Review Authority (approval no. dnr 2020-04415).

Data used for this study are available for bona fide researchers from the UKB resource (http://www.ukbiobank.ac.uk) and can be accessed by an application to the UKB.

RESULTS

Baseline characteristics of the study cohort are summarized in Table 1. More detailed information for each rheumatic disease investigated is presented in Supplementary Table 7, https://onlinelibrary.wiley.com/doi/10.1002/art.42613.

Linear MR of BMI on rheumatic disease. In the linear sex-combined MR analysis, a genetic predisposition to higher BMI was shown to significantly increase the relative risk of all 5 rheumatic diseases investigated (Figure 1 and Table 2). In a secondary analysis, we also applied 2- and 3-sample MR. All effect estimates were significant (P < 0.05) and consistent with the main results (Table 2). However, we noted that the 2- and 3-sample MR analyses tended to generate weaker effects and larger P values (Table 2). This could potentially indicate the presence of weak-instrument bias in these analyses or in the results of the main analysis, despite our efforts to eliminate this bias. In particular, the result for inflammatory spondylitis was relatively weak and should be interpreted with care (Figure 1 and Table 2).

Differences in risk by sex and menopausal status. In the linear, sex-stratified MR analysis, higher BMI significantly increased the risk for all diseases in both sexes, except for the effect on psoriatic arthropathy in men and on inflammatory spondylitis in both women and men (Figure 1). A significantly larger effect of BMI on psoriatic arthropathy was detected in women compared to men (P = 3.3 × 10<sup>−5</sup>). Similarly, a significant sex interaction was also found for gout (Figure 1), with high BMI being a stronger risk factor in women compared to men (P = 4.3 × 10<sup>−3</sup>). When analyzing pre- and postmenopausal women separately (Supplementary Figure 3, https://onlinelibrary.wiley.com/doi/10.1002/art.42613), we identified a significantly larger effect of BMI on osteoarthritis in premenopausal women compared to postmenopausal women (P = 1.8 × 10<sup>−5</sup>).

Nonlinear MR analyses. The impact of a given increase in BMI on the risk of developing rheumatic disease may not necessarily be the same in lean as in obese individuals. In the sex-combined nonlinear MR analysis, strong evidence of a variation in effect of BMI between different BMI strata (quantiles) was found for gout (Table 3). The relative change in incidence rate of gout for 1 SD increase in BMI appeared to be largest for individuals with a BMI of 23–25 kg/m², while the effect in overweight and obese individuals was found to be smaller (Supplementary Figure 4, https://onlinelibrary.wiley.com/doi/10.1002/art.42613). This result suggests that the incidence rate of gout will not increase as much in already obese individuals who gain weight as it would in normal-weight individuals who gain weight. However, it should be noted that individuals with a high BMI have a higher baseline risk for gout compared to individuals with a lower BMI, since the IRR for gout is above unity for all BMI strata (Supplementary Figure 4). A
In the 3-sample MR, we used 96 genetic instruments (single-nucleotide polymorphisms [SNPs]) previously identified by the GIANT consortium.* Causal effects from the main, linear Mendelian randomization (MR) analysis presented in Figure 1.† In the 3-sample MR, the genome-wide genetic variants identified in each of the 2 UK Biobank (UKB) subsamples for the nonlinear MR (N = 180,976 each) were used as instruments (Supplementary Material, https://onlinelibrary.wiley.com/doi/10.1002/art.42613). Effects on rheumatic disease were estimated in the non-overlapping subsample. Here, weak-instrument bias and winner's curse both act in the direction of the null.‡ In the 3-sample MR, we used 96 genetic instruments (single-nucleotide polymorphisms [SNPs]) previously identified by the GIANT consortium (ref. 45), in cohorts that did not overlap with the UKB (Supplementary Material). The effects of the SNPs on BMI and on rheumatic disease were then independently re-estimated in the 2 non-overlapping subsamples of the UKB (N = 180,976 each). For a 3-sample MR design, any weak-instrument bias also acts in the direction of the null (ref. 11).§ Causal incidence rate ratios (IRRs) per 1 SD increase in BMI, with corresponding 95% confidence intervals (95% CIs) and P values. Two- and 3-sample MR estimates were calculated using fixed-effect meta-analysis (Supplementary Material) of the 2 independent results from each UKB subsample pair.

Table 2. Effects of BMI on rheumatic disease in the sex-combined analysis, using 1-sample, 2-sample and 3-sample MR

<table>
<thead>
<tr>
<th>Disease</th>
<th>IRR (95% CI)§</th>
<th>SE</th>
<th>P</th>
<th>IRR (95% CI)†</th>
<th>SE</th>
<th>P</th>
<th>IRR (95% CI)‡</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>1.52 (1.36–1.69)</td>
<td>0.055</td>
<td>3.3 × 10⁻⁴</td>
<td>1.44 (1.26–1.65)</td>
<td>0.069</td>
<td>1.3 × 10⁻⁷</td>
<td>1.36 (1.14–1.61)</td>
<td>0.088</td>
<td>4.8 × 10⁻⁷</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1.49 (1.43–1.55)</td>
<td>0.020</td>
<td>6.8 × 10⁻⁷</td>
<td>1.38 (1.32–1.43)</td>
<td>0.021</td>
<td>6.1 × 10⁻⁵</td>
<td>1.41 (1.33–1.49)</td>
<td>0.028</td>
<td>5.5 × 10⁻⁵</td>
</tr>
<tr>
<td>Psoriatic arthropathy</td>
<td>1.80 (1.31–2.48)</td>
<td>0.163</td>
<td>3.0 × 10⁻⁴</td>
<td>1.98 (1.37–2.87)</td>
<td>0.189</td>
<td>3.1 × 10⁻⁴</td>
<td>1.98 (1.21–3.25)</td>
<td>0.252</td>
<td>6.6 × 10⁻³</td>
</tr>
<tr>
<td>Gout</td>
<td>1.10 (0.84–1.43)</td>
<td>0.054</td>
<td>2.8 × 10⁻⁴</td>
<td>1.72 (1.54–1.93)</td>
<td>0.058</td>
<td>4.8 × 10⁻³</td>
<td>1.63 (1.34–1.75)</td>
<td>0.068</td>
<td>5.3 × 10⁻³</td>
</tr>
<tr>
<td>Inflammatory spondylitis</td>
<td>1.34 (1.14–1.57)</td>
<td>0.082</td>
<td>4.4 × 10⁻⁴</td>
<td>1.24 (1.02–1.49)</td>
<td>0.096</td>
<td>2.7 × 10⁻²</td>
<td>1.26 (1.02–1.56)</td>
<td>0.108</td>
<td>3.0 × 10⁻²</td>
</tr>
</tbody>
</table>

* Causal effects from the main, linear Mendelian randomization (MR) analysis presented in Figure 1.
† In the 2-sample MR, the genome-wide genetic variants identified in each of the 2 UK Biobank (UKB) subsamples for the nonlinear MR (N = 180,976 each) were used as instruments (Supplementary Material, https://onlinelibrary.wiley.com/doi/10.1002/art.42613). Effects on rheumatic disease were estimated in the non-overlapping subsample. Here, weak-instrument bias and winner's curse both act in the direction of the null.
‡ In the 3-sample MR, we used 96 genetic instruments (single-nucleotide polymorphisms [SNPs]) previously identified by the GIANT consortium (ref. 45), in cohorts that did not overlap with the UKB (Supplementary Material). The effects of the SNPs on BMI and on rheumatic disease were then independently re-estimated in the 2 non-overlapping subsamples of the UKB (N = 180,976 each). For a 3-sample MR design, any weak-instrument bias also acts in the direction of the null (ref. 11).§ Causal incidence rate ratios (IRRs) per 1 SD increase in BMI, with corresponding 95% confidence intervals (95% CIs) and P values. Two- and 3-sample MR estimates were calculated using fixed-effect meta-analysis (Supplementary Material) of the 2 independent results from each UKB subsample pair.

Figure 1. Results from the linear Mendelian randomization analysis used to estimate the effect of body mass index (BMI) on risk of rheumatic disease. Incidence rate ratios (IRRs) with corresponding 95% confidence intervals (95% CIs) and random-effect P values for the 5 rheumatic diseases evaluated are shown. In the sex-combined analysis, black diamonds denote the IRR for 1 SD increase in BMI. In the sex-stratified analyses, beige diamonds denote the corresponding effects for women while blue diamonds denote the effects for men. Significant sex interactions were found for psoriatic arthropathy and gout (denoted by asterisks). Main causal effects of BMI on psoriatic arthropathy and inflammatory spondylitis, as well as the 2 sex-interaction effects, were considered novel findings.
nonlinear effect was also observed for osteoarthritis. The other rheumatic diseases showed no significant evidence of nonlinearity (Table 3).

In the sex-stratified analysis, we detected significant differences in effects between BMI strata for gout in both women and men, and for osteoarthritis in men (Table 3, Supplementary Figure 5). The variation in effect on osteoarthritis across the range of BMI values for both sexes is illustrated in Figure 2A. Although a nonlinear effect was found for men but not for women (Table 3), a significant difference in effect variation between sexes was not detected for osteoarthritis ($P$ for interaction $> 0.05$). However, for gout, we detected a significant difference between men and women ($P = 0.03$) in effect variation (Figure 2B). The different shapes of the 2 curves in Figure 2B for gout indicate that the nonlinear effect was different between men and women. For men, the curve exhibited a peak in effect of BMI at $\approx 25$ kg/m$^2$. Hence, the relative increase in risk of gout per SD increase in BMI was smaller in men with a BMI either $< 25$ or $> 25$ kg/m$^2$ compared to men with a BMI at $\approx 25$ kg/m$^2$ who increased their BMI 1 SD unit. In women, the nonlinear response to 1 SD increase in BMI showed a consistent decrease in effect on gout toward higher BMI.

Since gout is caused by needle-shaped crystals of uric acid that build up in the joints, we also performed a corresponding nonlinear analysis for the variation in effect of BMI on urate levels across the range of BMI values. The similarities in variation between urate levels (Figure 2C) and gout (Figure 2B) were clearly evident, particularly for men.

As described in the Supplementary Material, several sensitivity analyses were performed (Supplementary Tables 8–10 and Supplementary Figure 6, https://onlinelibrary.wiley.com/doi/10.1002/art.42613), which did not indicate any severe bias and did not change our main results. However, 1 of the polygenic scores showed a weakly significant nonlinear relation with BMI, likely due to the presence of tenuous nonlinearity in the outermost BMI strata (Supplementary Figure 7). By performing a rank-based inverse normal transformation of BMI, this nonlinearity was substantially alleviated. The main nonlinear results remained unchanged (Supplementary Figure 8), except for osteoarthritis which was no longer significant. However, in contrast to this nonsignificant sex-combined result for osteoarthritis, the rank-based inverse normal transformation of BMI led to a slightly bigger and nominally significant difference in nonlinearity between sexes for osteoarthritis (Figure 2A).

**DISCUSSION**

This is the first MR study to demonstrate that a genetic predisposition to high BMI is causally linked to a higher risk of developing psoriatic arthropathy and inflammatory spondylitis. For psoriatic arthropathy and gout, we also found strong sex-specific effects, and for osteoarthritis the effect of BMI was significantly stronger in premenopausal compared to postmenopausal women. Furthermore, gout and osteoarthritis showed causal effects of BMI that varied across the BMI range, a variation that also differed between sexes for gout. Previously identified causal effects of BMI on risk of developing rheumatoid arthritis, osteoarthritis, and gout in all individuals were confirmed.

Observational studies have previously suggested that high BMI is associated with more severe symptoms in patients with ankylosing spondylitis (27–29), but MR studies on the subject are lacking. Inflammatory spondylitis is a broad term in the UKB that includes ankylosing spondylitis and other inflammatory spondyloarthropathies. Our result of a causal effect of BMI on inflammatory spondylitis agrees with a previous study that used a mouse model of spondylarthitis (30) and showed that persistent mechanical stress on the joints over time is positively associated with 2 common manifestations of inflammatory spondylitis, namely enthesitis and new bone formation. Excess joint loading in obese individuals could thus be a possible explanation for the observed causal relation.

Investigating sex-specific effects is crucial for the understanding of sex differences in rheumatic disease pathology. For psoriatic arthropathy, which is the most frequent comorbidity among psoriatic patients (31), we identified a large effect of increased BMI in women, in sharp contrast to the null effect in men. To our knowledge, this is the first study to find evidence of sex-specific effects of BMI on psoriatic arthropathy. Gout is

### Table 3. Nonlinear MR results for variation in effect of BMI on rheumatic disease*

<table>
<thead>
<tr>
<th>Disease</th>
<th>Sex-Combined</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>0.83</td>
<td>0.47</td>
<td>0.10</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>$2.0 \times 10^{-3}$</td>
<td>0.23</td>
<td>$7.0 \times 10^{-4}$</td>
</tr>
<tr>
<td>Psoriatic arthropathy</td>
<td>0.30</td>
<td>0.57</td>
<td>0.17</td>
</tr>
<tr>
<td>Gout</td>
<td>$9.6 \times 10^{-11}$</td>
<td>$4.3 \times 10^{-3}$</td>
<td>$6.9 \times 10^{-11}$</td>
</tr>
<tr>
<td>Inflammatory spondylitis</td>
<td>0.75</td>
<td>0.86</td>
<td>0.79</td>
</tr>
</tbody>
</table>

* $P$ values shown for variation in the effect of body mass index (BMI) on rheumatic disease among 10 BMI strata (quantiles) using a quadratic test (ref. 22). $P$ values in bold were significant for multiple testing. Sex-combined and sex-stratified nonlinear Mendelian randomization (MR) analyses showed evidence of a variation in effect of BMI across the BMI range for gout and osteoarthritis, suggesting differential increases in risk of disease per SD increase in BMI between normal-weight and obese individuals. The findings for osteoarthritis and gout were considered novel.
known to predominantly affect men (32). However, with regard to
obesity as a risk factor for gout, we observed a significantly larger
causal effect of increased BMI in women, although the effect was
significant in both sexes. This result confirms previous observa-
tional studies (33,34).

We identified a lower effect of BMI on the risk of osteoarthritis
in postmenopausal compared to premenopausal women. Previous
studies have delineated a potential protective effect for estradiol on
osteoarthritis, which could explain the increasing incidence of oste-
arthritis after menopause (35). One possible explanation for our
observation could therefore be related to the importance of estradiol
certainty in the emergence of osteoarthritis after menopause.
This additional risk due to low estradiol levels could potentially dilute
the underlying effect of BMI on osteoarthritis. A similar trend in pre-
and postmenopausal women was found for all the rheumatic dis-
eases investigated, except for inflammatory spondylitis. However,
a significant difference was only detected for osteoarthritis. This result needs further attention in future studies.

By conducting a non-linear MR analysis, we also detected a strong variation in the causal effect of increased BMI on gout between lean, normal-weight, and obese individuals, which implies a nonlinear exposure–outcome relation. The increase in incidence rate of gout for 1 SD increase in BMI was found to be lower in overweight individuals than in individuals with a BMI of \( \sim 25 \text{ kg/m}^2 \). This decline in effect toward high BMI was significantly steeper in men than in women, and data were de facto consistent with a near null effect of an additional increase in BMI in already obese men. Intriguingly, a corresponding analysis of the effect variation of BMI on urate levels indicates a very similar nonlinear response in both men and women as for gout risk. Given that gout is induced by deposits of uric acid crystals in the joints (32), this finding is consistent with the effect of BMI on gout being mediated by urate levels. However, a formal test could not be performed since nonlinear mediation analysis has yet to be implemented within the MR framework (36). The observed nonlinearity could partly be related to the strong association between obesity and insulin resistance (37,38). Glycosuria, a result of high blood glucose, can induce uricosuria, which would lead to reduced serum urate levels and a decreased risk of gout (39,40). Insulin resistance may thus have a regulating effect on the risk of gout at a population-wide level. Estrogen can induce renal clearance of uric acid, and may thus provide another avenue for regulating urate levels. This is a postulated mechanism to explain the low prevalence of gout among premenopausal women (32,41). There is also evidence for a causal link between BMI and gout via serum testosterone (42,43). Finally, apart from gout, a suggestive nonlinear effect of BMI on osteoarthritis was also detected. Although the effect was more pronounced in men than in women, a significant sex difference was not observed in the main analysis. We did not find evidence of nonlinear effects of BMI on rheumatoid arthritis, psoriatic arthropathy, or inflammatory spondylitis. This could, in part, be due to lack of power, and further analyses are warranted.

This study has a number of strengths. First, in contrast to most previous observational studies that make use of standard regression analysis, we applied the MR approach to investigate the causal relationship between study exposure and outcomes, which reduces potential confounding biases and effects of reversed causation. Second, we applied a contemporary nonlinear MR method to investigate the variation of effect on rheumatic disease across the BMI range and to probe sex-specific effects. Our study also has several limitations. First, it should be noted that an MR study is not equivalent to a randomized controlled trial (44). Second, non-random selection and population stratification are potential sources of bias that are not controlled for by MR. That said, a relative comparison, such as our sex-stratified analyses, may be less prone to such bias. Third, we took measures to minimize population stratification; however, this might affect the generalizability of the present findings to other nationalities and ethnicities, as we performed the analysis in White participants living in the UK. Fourth, horizontal pleiotropy and weak-instrument bias can affect MR results. However, our sensitivity analyses indicated that these potential biases were not major concerns in our study.

In summary, we carried out a series of MR analyses to estimate the unconfounded effect of BMI on 5 rheumatic diseases and showed that increased BMI is a significant risk factor for all rheumatic diseases investigated. This suggests that interventions which decrease BMI are likely to have beneficial effects on disease rates for all investigated rheumatic diseases. We also highlighted differences in the effect of BMI between men and women for several rheumatic diseases, in both the linear and nonlinear MR analyses. Such findings are of crucial importance for future precision health interventions.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content. All authors approved the final version to be published. Drs. Karlsson, Hadizadeh, and Ek had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Karlsson, Hadizadeh, Johansson, Ek.

Acquisition of data. Johansson, Ek.

Analysis and interpretation of data. Karlsson, Hadizadeh, Johansson, Raak-Andersen, Ek.

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