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Causal association between body mass index and risk of rheumatoid arthritis: A Mendelian randomization study

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Abstract

Objective: This study aimed to examine whether body mass index (BMI) is causally associated with rheumatoid arthritis (RA).

Method: A two-sample Mendelian randomization (MR) analysis using the inverse-variance weighted (IVW), weighted median and MR-Egger regression methods was performed. We used the publicly available summary statistics data sets of genome-wide association studies (GWAS) meta-analyses for BMI in individuals of European descent (n = 322 154; GIANT consortium) as the exposure and a GWAS for noncancer illness code self-reported: RA from the individuals included in the UK Biobank (total n = 337 159; case = 7480, control = 329 679) as the outcome.

Results: We selected 68 single nucleotide polymorphisms at genome-wide significance from GWASs on BMI as the instrumental variables. The IVW method showed evidence to support a causal association between BMI and RA (beta = 0.003, SE = 0.001, $P = 0.033$). MR-Egger regression revealed that directional pleiotropy was unlikely to be biasing the result (intercept = −3.54E-05; $P = 0.736$), but it showed no causal association between BMI and RA (beta = 0.004, SE = 0.004, $P = 0.302$). However, the weighted median approach yielded evidence of a causal association between BMI and RA (beta = 0.006, SE = 0.002, $P = 0.004$). Cochran's Q test and the funnel plot indicated no evidence of heterogeneity and asymmetry, indicating no directional pleiotropy.

Conclusion: The results of MR analysis support that BMI may be causally associated with an increased risk of RA.

KEYWORDS
BMI, mendelian randomization, rheumatoid arthritis

1 | INTRODUCTION

Rheumatoid arthritis (RA)is a chronic autoimmune inflammatory disease that predominantly affects the synovial joints, causing significant morbidity, disability, a reduced quality of life and shortened life expectancy.[1] Although the aetiology of RA is not fully understood, environmental factors likely play an important role in the development of RA in genetically susceptible individuals.[2,3]

Adipose tissue is considered to be actively associated with inflammation and immunity.[4] It secretes pro-inflammatory and anti-inflammatory cytokines, and hormonally active substances and chemokines.[4] Overweight or obese individuals may have an increased risk of RA, and excess body weight has been considered as a potential contributor to the development of RA.[5] Excess body weight, measured by body mass index (BMI), corresponds to an abnormal accumulation of adipose tissue within the body.[6] Thus, it is considered to be a useful indicator for obesity. High BMI has been reported to be associated with a higher risk of RA in observational studies, suggesting that obesity may be a risk factor for RA.[5,7]

However, observational studies are prone to biases such as reverse causation and residual confounding,[8,9] thus limiting our understanding of the effect of BMI on RA.

Mendelian randomization (MR) is a technique that uses genetic variants as instrumental variables (IVs) to assess whether an observational association between a risk factor and an outcome is consistent with a causal effect.[10] A two-sample MR estimates causal effects where data on the exposure and outcome have been measured in different samples.[11] To the best of our knowledge, no previous study has used the MR approach to test the causal effect of BMI on the risk of RA. Thus, this study aimed to examine whether BMI is causally associated with the occurrence of RA, using a two-sample MR analysis.

2 | MATERIALS AND METHODS

2.1 | Data sources and selection of genetic variants

We searched the MR Base database (http://www.mrbase.org/), which houses a large collection of summary statistic data from hundreds of genome-wide association studies (GWASs). We used the publicly available summary statistics data sets of GWAS meta-analyses for BMI in individuals of European descent (n = 322 154; GIANT consortium)[12] as the exposure. A two-sample MR study of genetic variants associated with BMI was used as the IV to improve inference, based on a *P*-value threshold of 5.00E-08 (genome-wide significance). We obtained summary statistics (beta coefficients and standard errors) for 68 single nucleotide polymorphisms (SNPs) associated with BMI as the IVs from the GWASs on BMI. We used the publicly available summary statistic data sets of a GWAS for non-cancer illness code self-reported: RA from the individuals included in the UK Biobank (total n = 337 159; case = 7480, control = 329 679)[13,14] (http://www.nealelab.is/blog/2017/9/11/details-and-considerations-of-the-uk-biobank-gwas) as the outcome.

2.2 | Statistical analysis for Mendelian randomization

Mendelian randomization analysis requires genetic variants to be related to, but not potential confounders of an exposure.[15] First, we assessed the independent association of SNPs with BMI. Second, we examined the association between each SNP and the risk of RA. Third, we combined these findings to estimate the uncompounded causal association between BMI and the risk of RA using MR analysis. We performed two-sample MR, a method used to estimate the causal effect of an exposure (BMI) on outcomes (RA) using summary statistics from different GWASs,[16] to assess the causal relationship between BMI and the risk of RA, using summary data from BMI and RA GWASs with 68 SNPs as IVs (Table 1).

The inverse-variance weighted (IVW) method uses a meta-analysis approach to combine the Wald ratio estimates of the causal effect obtained from different SNPs, and to provide a consistent estimate of the causal effect of the exposure on the outcome when each of the genetic variants satisfies the assumptions of an IV.[17] Although the inclusion of multiple variants in an MR analysis results in increased statistical power, it has the potential to include pleiotropic genetic variants that are not valid IVs.[16] To explore and adjust for pleiotropy, that is the association of genetic variants with more than one variable, the weighted median and MR-Egger regression methods were utilized. MR-Egger regression analysis, which is robust to invalid instruments, tests and accounts for the presence of unbalanced pleiotropy by introducing a parameter for this bias by incorporating summary data estimates of causal effects from multiple individual variants.[18] MR-Egger applies a weighted linear regression of the gene-outcome coefficients on the gene-exposure coefficients.[18] The slope of this regression represents the causal effect estimate, and the intercept can be interpreted as an estimate of the average horizontal pleiotropic effect across the genetic variants.[19] The weighted median estimator provides a consistent estimate of the causal effect, even when up to 50% of the information contributing to the analysis comes from genetic variants that are invalid IVs.[20] Compared to the MR-Egger analysis, the weighted median estimator has the advantage of retaining greater precision in the estimates.[20] Tests were considered statistically significant at $P < 0.05$. All MR analyses were performed in the MR Base platform (App version: 1.2.1 e646be [27 June 2018], R version: 3.5.0).[21]

2.3 | Heterogeneity and sensitivity test

We assessed the heterogeneities between SNPs using Cochran's Q-statistics[22] and I^2 statistic.[23,24] We also performed a "leave-one-out" analysis to investigate the possibility that the causal association was driven by a single SNP.

3 | RESULTS

3.1 | Studies included in the meta-analysis

3.1.1 | Instrumental variables for Mendelian randomization

We selected 68 independent SNPs from GWASs on BMI as the IVs. All of them are associated with BMI at genome-wide significance (Table 1, Figure 1). In total, 32 of the 68 SNPs were positively associated with RA, although they

TABLE 1 MR estimates from each method of assessing the causal effect of BMI on the risk of rheumatoid arthritis

MR method	Number of SNPs	Beta	SE	95% confidence interval	Association *P*-value	Cochran *Q* statistic	I^2	Heterogeneity *P*-value
IInverse-variance weighted	68	0.003	0.001	0.0002-0.005	0.033	65.98	0.015	0.512
MR Egger	68	0.004	0.004	−0.004-0.012	0.302	65.91	0.017	0.515
Weighted median	68	0.006	0.002	0.002-0.009	0.004	65.87	0.002	0.482

Beta, beta coefficient; MR, Mendelian randomization; SE, standard error; SNP, single nucleotide polymorphism.
[a]$I^2 = (Q - df)/Q$.[24]

were not statistically significant (Table 1; Table S1); 1.4% of variance in the exposure (value of R^2 statistic) was explained by the genetic variants serving as IVs. A *P*-value of 5.00E-08 corresponds to an *F* statistic >30 for each single variant.[15] A threshold of $F < 10$ has been used to define a "weak IV." Thus, weak instrument bias was negligible.

3.1.2 | Mendelian randomization results

The IVW method showed evidence to support a causal association between BMI and RA (beta = 0.003, SE = 0.001, $P = 0.033$; Table 1, Figures 1 and 2). The intercept represents the average pleiotropic effect across the genetic variants (the average direct effect of a variant with the outcome). An intercept that differs from zero (the MR-Egger test) is indicative of directional pleiotropy. MR-Egger regression revealed that directional pleiotropy was unlikely to be biasing the result (intercept = −3.54E-05; $P = 0.736$). The MR-Egger analysis showed no causal association between BMI and RA (beta = 0.004, SE = 0.004, $P = 0.302$; Table 1, Figures 1 and 2). However, the weighted median approach yielded evidence of a causal association between BMI and RA (beta = 0.006, SE = 0.002, $P = 0.004$; Table 1, Figure 2). The association between BMI and RA was not consistent between MR Egger and weighted median methods. The IVW and weighted median method suggest a causal effect of BMI on the risk of RA, whereas the MR-Egger method suggests a null causal effect. Considering that compared to the MR-Egger analysis, the weighted median estimator has the advantage of retaining greater precision in the estimates,[20] the results of the MR analysis may support a potential causal association between BMI and RA.

3.2 | Heterogeneity and sensitivity test

Cochran's *Q* test indicated no evidence of heterogeneity between IV estimates based on the individual variants (Table 1). Heterogeneity is the variability in the causal estimates obtained for each SNP (ie how consistent is the causal estimate across all SNPs). Low heterogeneity suggests increased reliability of MR estimates. Our results of I^2 values showed low heterogeneity, indicating increased reliability of MR estimates (Table 1). Results from the "leave-one-out" analysis demonstrated that no single SNP was driving the IVW point estimate. Asymmetry in the funnel plot indicates directional horizontal pleiotropy, which can bias MR methods; however, the funnel plot and MR Egger regression test showed no evidence of asymmetry (Figure 3).

4 | DISCUSSION

Obesity has been considered as a risk factor for the development of RA.[5] However, it is uncertain whether obesity has a causal relationship with RA. We carried out three different estimating methods (inverse-variance weighted method, weighted median method and MR-Egger regression) for MR analyses. Our study indicated that the associations between BMI and RA may be causal. Although the MR estimates using IVW, MR Egger and weighted median analysis were not consistent, IVW and weighted median analysis support a causal association between BMI and RA. Considering that compared to the MR-Egger analysis, the weighted median estimator has the advantage of retaining greater precision in the estimates,[20] this MR analysis indicates a potential causal role of BMI in the risk of RA. Thus, our study corroborates the association found in previous observational studies.

A meta-analysis showed that obese or overweight individuals had a 31% and 15% increased risk for RA, respectively, in comparison with the corresponding risks in individuals of normal weight.[7] There are plausible mechanisms by which BMI may potentially affect the occurrence of RA. First, obesity is associated with increased levels of inflammatory cytokines, including tumour necrosis factor-alpha and interleukin-6, and pro-inflammatory adipokines such as leptin.[25] Leptin plays an important role in regulating neuroendocrine and immune responses.[26] It activates monocyte/macrophage cells, increases the production of inflammatory cytokines and directs T-cell differentiation to Th1 phenotype.[27] Both leptin and inflammatory cytokines may contribute to the development of RA. Second, altered sex hormonal metabolism in obese individuals may be involved in the occurrence of RA. Moreover, obese

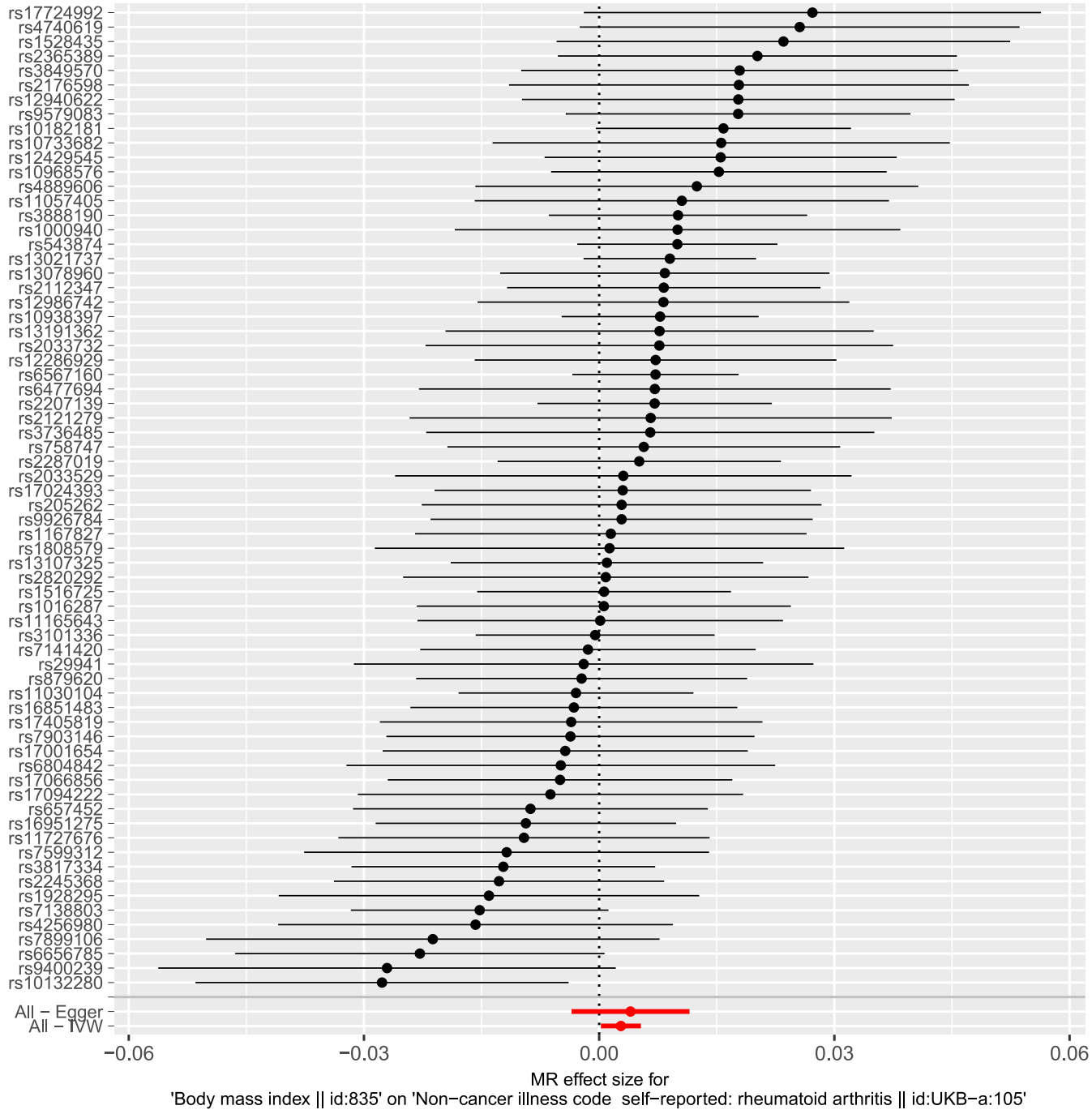

FIGURE 1 Forest plot of the causal effects of single nucleotide polymorphisms associated with body mass index on rheumatoid arthritis. The significance of red lines are MR results of MR-Egger test and IVW method

individuals have higher levels of estrogens and androgens,[28] which may play a role in the development of RA. Third, involvement of the hypothalamus has been suggested in both obesity and RA reports.[4] Increased inflammatory response in hypothalamus produces insulin and leptin resistance contributing to the pathogenesis of obesity susceptibility,[4] and there is a link between the activation of hypothalamic inflammation and cytokine production, which involved in the pathogenesis of RA.[5] Several of the SNPs associated with high BMI used in this study are linked to signalling in the hypothalamus, suggesting a possible role of the hypothalamus involvement in relationship between RA and obesity. However as many RA patients are not obese, the issue of causality of BMI also could be questioned.

Mendelian randomization minimizes the possibility of bias inherent to observational studies.[29] However, MR studies are susceptible to bias from pleiotropy (association

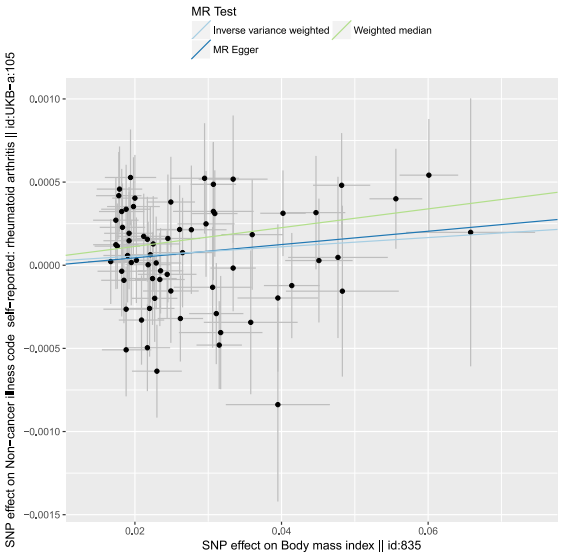

FIGURE 2 Scatter plots of genetic associations with body mass index against the genetic associations with rheumatoid arthritis. The slopes of each line represent the causal association for each method. The blue line represents the inverse-variance weighted estimate, the green line represents the weighted median estimate, and the dark blue line represents the Mendelian randomization-Egger estimate

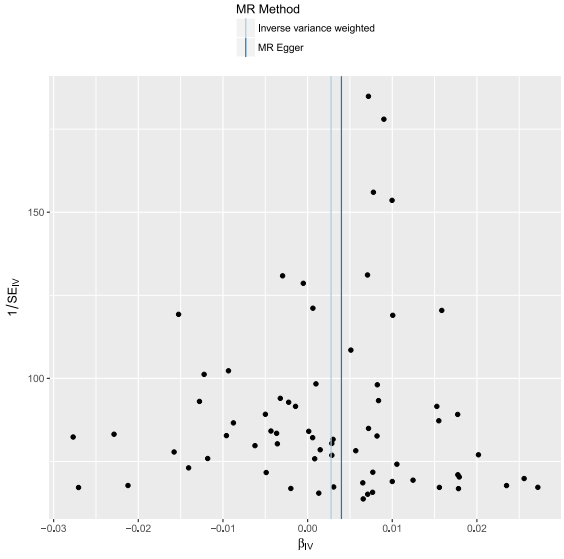

FIGURE 3 Funnel plot to assess heterogeneity. The blue line represents the inverse-variance weighted estimate, and the dark blue line represents the Mendelian randomization-Egger estimate

of genetic variants with more than one variable).[30] The genetic variant may be associated with multiple phenotypes, a phenomenon known as "pleiotropy," which may result in a confounded estimate from MR and may potentially lead to biased causal estimates.[31] Although the inclusion of multiple variants in MR analysis typically leads to increased statistical power, it also results in the potential inclusion of pleiotropic genetic variants that are not valid IVs.[32] Therefore, the approaches for the sensitivity analysis need to be applied to test the validity of conclusions drawn from the MR study. To eliminate pleiotropy, we employed a weighted median estimator, which provides valid estimates even if 50% of the SNPs are not valid instruments,[20] and we used MR-Egger regression to provide a test for unbalanced pleiotropy and a causal estimate of the influence of exposure on the outcome in its presence.[18] Our results were not consistent across all the three approaches. The MR-Egger method results in a loss of precision and power, and our weighted median estimator results were also similar to the IVW estimator results, thereby providing additional confidence for these associations. Our data support previous observational studies that have shown an association between BMI and RA. The current findings may provide an opportunity to determine the mechanisms underlying the effects of obesity on the risk of RA.

The present study has several limitations. First,genetic variants have only a modest effect on a given exposure (BMI), as they might explain only a very small proportion of variance in a particular exposure.[33] Our analysis might have had limited power to detect an association. Second, individuals with RA were classified by noncancer illness code: self-reported, which might cause potential bias, such as selection bias and information bias. Third, the studies on BMI and RA were based on participants of European ancestry. As causality may depend on ethnicity and selection bias, further MR studies are required for other populations. Fourth, suggestions exist about the change in the BMI cut-off points in RA based on the observations that RA may lead to rheumatoid cachexia.[1,2] However, available data did not permit us to perform the MR analysis according to the change in the BMI cut-off points. Fifth, there are inherited issues about BMI. Despite the success of the GWAS strategy, the established loci together explain <2% of the interindividual BMI variation.[1] In addition, sex and age are associated with differences in obesity and body composition. Women tend to store more fat subcutaneously rather than in visceral adipose tissue. Thus, women tend to carry more body fat than men at the same BMI.[2] Sixth, we performed MR exposing a second cohort of publically available SNP data from diagnosed RA patients with the instruments derived from the BMI study. However, we could not repeat our findings. Nevertheless, this meta-analysis has its strength. Although BMI has been studied as a potential risk factor for RA, an MR has been never performed. It is important that estimates of both the gene-exposure and the gene-outcome associations are available for each of these variants. To the best of our knowledge, this is the first such study on the causal relationship between BMI and RA.

In conclusion, the results of MR analysis support that BMI may be causally associated with an increased risk of

RA. Our findings suggest that obesity may play an important role in the development of RA. The current findings may provide an opportunity to determine the mechanisms underlying the effects of obesity on the risk of RA.

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CONFLICTS OF INTEREST

The authors have no financial or nonfinancial conflicts of interest to declare.

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SUPPORTING INFORMATION

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