

Adipokines and risk of rheumatoid arthritis: a Mendelian randomization study

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Abstract

Background: Circulating adipokines levels have been reported to be associated with the risk of rheumatoid arthritis (RA). However, it is still unclear whether these associations are causal or biased by reverse causation or residual confounding. This study aimed to assess potential causal roles of five adipokines (namely, adiponectin, leptin, resistin, chemerin, and retinol-binding protein 4 [RBP4]) in the occurrence of RA.

Methods: We conducted a two-sample Mendelian randomization analysis to investigate these associations. We used summary-level data from genome-wide association studies (GWASs) for adipokines in individuals of European ancestry as the exposure, and a separate large-scale meta-analysis of a GWAS which included 14,361 RA cases and 43,923 controls of European ancestry as the outcome. Genetic variants were selected as instrumental variables if robustly genome-wide significant in their associations with adipokines. The causal effects were estimated using the inverse-variance weighted method in the primary analysis. Sensitivity analyses were performed to warrant that bias due to genetic pleiotropy was unlikely.

Results: The circulating resistin was found to be the only adipokinetic factor having statistical significance, with higher levels causally associated with the risk of RA (odds ratio: 1.28; 95% confidence interval: [1.07, 1.53] per unit increase in the natural log-transformed resistin). In contrast, associations of adiponectin, leptin, chemerin, and RBP4 with risk of RA were not statistically significant. The MR assumptions did not seem to be violated. Sensitivity analyses yielded consistent findings.

Conclusions: Genetically predicted circulating resistin levels were positively associated with RA risk. Our analysis suggested that resistin may play a notable causal role in RA pathogenesis. It would be beneficial for the development of clinical as well as public health strategies that target appropriate levels of resistin for future RA intervention.

Introduction

Rheumatoid arthritis (RA) is a chronic multisystem disease marked by symmetrical inflammatory polyarthritis, which usually spreads from small joints to larger joints [1]. It accounted for 3.5 million disability-adjusted life-years globally according to a recent report on the Global Burden of Diseases [2]. Although the definitive causes of RA remain unknown, the reams of evidence point to the immune-mediated etiology related with chronic inflammation and articular destruction [3].

Adipokines are a class of multifunctional molecules secreted by adipose tissue, which could effectively regulate inflammation via autocrine/paracrine and endocrine pathways [4]. Since adipokines have the potential to modulate target tissues and cells in bone, synovium, cartilage and various immune cells [5], they may play an important role in RA pathogenesis. To date, a large number of case-control studies have been undertaken to explore the association between circulating adipokines and risk of RA, but inconsistent results were reported. Some studies showed that RA patients had higher circulating levels of adipokines compared with healthy controls [6–8], while some others found either no association or a significant association in the opposite direction [9–11]. The conflicting findings may be attributed to the small study sample sizes, clinical heterogeneity, or the use of different adipokines measurements for assessment. Besides, the association established in those observational studies cannot be equated to a causal relationship without further evidence, as bias due to reverse causation and/or residual confounding may occur.

Free of the limitations of traditional observational studies, Mendelian randomization (MR) is a novel method that uses genetic variants as instrumental variables (IVs) or 'proxies' for exposures of interest to test the potential causal effect of a modifiable risk factor on the outcome [12–14]. In particular, two-sample MR has been widely considered in situations when measuring the exposure and outcome in the same set of individuals is infeasible [15]. The present research applies the two-sample MR approach to investigate whether there exists a genuine association between circulating adipokines and risk of RA. Following the Mendel's second law that alleles are independently isolated and randomly assigned from parents to offspring during gamete formation, MR can avoid the influence of potential confounding factors [14]. Moreover, it overcomes the problem of reverse causation, as genotype is basically fixed since conception and consequently precedes the diseases process [14].

In this paper, we assess the causal associations between several genetically predicted adipokines and RA risk using the two-sample MR approach along with sensitivity analyses. Based on the genetic IVs from several published genome-wide association studies (GWASs), potential causal effects of key adipokines, namely, adiponectin, leptin, resistin, chemerin, and retinol-binding protein 4 (RBP4), on the risk of developing RA are examined.

Materials And Methods

Data sources

We downloaded genetic data for five adipokines (adiponectin, leptin, resistin, chemerin and RBP4) as well as RA from the IEU GWAS database (<https://gwas.mrcieu.ac.uk>), which provide a large collection of GWAS summary statistics. Specifically, the genetic data for circulating adiponectin levels were obtained from a meta-analysis of GWASs in 39,883 individuals of European ancestry [16], and the genetic data for circulating leptin levels adjusted for body mass index (BMI) from 23 population based GWAS with 32,161 individuals of European ancestry [17]. The published meta-analysis of GWASs identified several loci associated with circulating chemerin levels in 2,791 individuals of European descent from 3 independent studies [18]. The genetic data for resistin and RBP4 were acquired from a recent GWAS in 3,301 individuals of European descent [19]. Our investigation is carried out based on publicly available data; therefore, no additional ethical approval would be required.

We extracted the RA information from a separate large-scale meta-analysis of trans-ethnic GWAS, including a total of > 100,000 participants of European and Asian ancestries [20]. In this instance, performing a two-sample MR analysis would be suitable to estimate the causal effects [15]. To mitigate the risk of bias induced by population stratification, only summary-level data from 58,284 subjects of European ancestry (14,361 RA cases and 43,923 controls) were used in the present analysis. The following genetic information was collected, including the rs ID for single nucleotide polymorphisms (SNPs), beta coefficient with corresponding standard error, effect allele, non-effect allele, effect allele frequency, name of the phenotype, physical position of SNPs (chromosome and position), sample size, association *p*-value, and units in which the effects are presented. All RA cases had been diagnosed by a board-certified rheumatologist or met the 1987 diagnosis criteria of the American College of Rheumatology for RA [21]. Details of the study protocols of above the mentioned GWASs are available from the previous publications [16–20].

Selection Of Instrumental Variables

We chose SNPs that are robustly associated with adipokines at the genome-wide significance level ($P < 5 \times 10^{-8}$). To ensure the selected SNPs being mutually independent, we estimated the linkage disequilibrium (LD) between the SNPs using European samples from the 1000 Genome Project as the reference panel. A smaller association p -value indicates a stronger adipokine-SNP association; we selected the SNPs that reached the LD threshold ($r^2 > 0.001$) with relatively small association p -values. For any specifically requested SNPs that were not found in the RA GWAS, we used SNPs in strong LD ($r^2 > 0.8$) to substitute the requested SNPs. We further eliminated SNPs that lacked necessary information and/or linked with intermediate allele frequencies.

Statistical analysis

Validity of the causal estimates obtained from the MR approach relies on three key assumptions of an IV: 1) The genetic variants were strongly associated with circulating adipokine levels; 2) The genetic variants were not related to potential confounding factors of the adipokine-RA association; 3) The genetic variants must only affect the risk of RA through the adipokines rather than any other pathway (no potential pleiotropic effects) [22]. These assumptions apply for all the analyses below. Figure 1 is an illustrative diagram showing how these assumptions are accommodated in the present study.

Two-sample MR analysis was performed to estimate the causal effects, as the summary statistics for exposure and outcome had been extracted from different GWASs. We calculated R^2 and the F statistics to estimate the proportion of variance in adipokines explained by the IV (each selected SNP) and to assess the strength of instruments. In the main analysis, we calculated the causal effect estimates obtained from different SNPs based on the Wald ratio method [23], applying the fixed-effects inverse-variance weighted (IVW) method, with each selected genetic variant satisfying the three assumptions of an IV [24]. Including multiple variants in an MR analysis may introduce pleiotropic genetic variants that are invalid IVs [23]. Sensitivity analyses were then performed to ensure that potential pleiotropy on the MR causal estimates is unlikely. In particular, weighted-median (WM) method can relax the assumptions of MR: even if nearly half of the genetic variants were invalid instruments, the WM method can still provide a robust and consistent estimate of the causal effect [22]. Additionally, MR-Egger regression analysis was used to account for the presence of directional pleiotropy according to its intercept term ($P < 0.05$); the slope of this regression also helped examine the consistency of a causal estimate, while taking into account the pleiotropic effects [25]. Of note, the MR-Egger regression analysis has the limitation of generating estimates with low precision, and may be influenced by outlying genetic variants [25]. We used the MR pleiotropy residual sum and outlier (MR-PRESSO) method to further test the presence of pleiotropy. Causal estimates in our analysis were thus obtained after outlier correction [26]. Cochran Q test was employed to assess the statistical heterogeneity between SNPs in IVW estimates, with $P < 0.05$ considered as significantly heterogeneous. We also implemented the random-effects IVW method [27, 28] to account for possible heterogeneity between IV estimates. To investigate the reliability of the causal association, we performed the “leave-one-out” analysis: each SNP was excluded in turn to explore the potential impact of individual SNP on the summary causal estimates.

To eliminate the effects of known confounding factors on causality, we extracted relevant phenotypes of the selected SNPs in GWAS catalog (<https://www.ebi.ac.uk/gwas>). These MR analyses were repeated after excluding SNPs associated with secondary phenotype at the genome-wide significance threshold ($P < 5 \times 10^{-8}$). Since SNPs near the ADIPOQ locus were closely related to the coding of circulating adiponectin [29], we restricted SNPs in ADIPOQ gene to further evaluate the causal association between adiponectin and risk of RA.

All statistical analyses were conducted using RStudio version 3.6.3 with “TwoSampleMR” R packages. Two-sided P values were computed, with $P < 0.05$ considered as statistically significant.

Results

We identified 10 independent SNPs associated with adiponectin, 4 associated with leptin, 3 associated with resistin, 1 associated with chemerin, and 1 associated with RBP4 as IVs. Supplementary Table 1 summarises the information of the SNPs used as the IVs. All selected SNPs were strongly associated with adipokines and, by contrast, not associated with RA. The F statistics for all SNPs > 10 , suggesting that the analysis is unlikely to be affected by weak instrument bias.

As presented in Table 1, resistin was found as the only adipokinetic factor positively associated with the risk of RA. The casual odds ratio (OR) was 1.28 (95% confidence interval (CI): 1.07, 1.53; $P = 0.007$) per unit increase in natural log-transformed resistin levels using the IVW method, and 1.25 (95% CI: 1.02, 1.54; $P = 0.031$) using the WM method. This causal association became statistically insignificant along with a wider 95% CI in the MR-Egger regression analysis, which may be attributed to inadequate statistical power. Furthermore, the intercept of the MR-Egger regression model did not suggest a horizontal pleiotropy effect across the genetic variants ($P = 0.833$). Cochran’s Q test did not indicate heterogeneity between Wald ratio estimates based on individual SNPs. Due to the limited number of SNPs for resistin, we were unable to conduct a MR-PRESSO test to further detect the presence of pleiotropy. There was little evidence of causal associations between adiponectin, leptin, chemerin as well as RBP4 with risk of RA. Scatter plots, forest plots and funnel plots for adiponectin, leptin as well as resistin are presented in Supplementary Fig. 1–3. We note that the causal estimates of individuals SNP for chemerin and RBP4 were reported in Table 2, and thus would not be repeated duplicately in plots. Since only one SNP associated with chemerin and RBP4 each, we were unable to perform leave-one-out analysis and Cochran’s Q test. For these reasons, the supplementary figures visualise analysis results for three adipokines only.

Table 1
MR estimates of the causal effects of five adipokine on the risk of RA

Exposure	MR method	Number of SNPs	OR	95% CI	Association <i>p</i> -value	Cochran's Q Statistic	Heterogeneity <i>p</i> -value	MR Egger intercept (<i>p</i> -value) ^a
Adiponectin	IVW	10	1.20	0.93, 1.56	0.164	10.15	0.338	
	WM	10	1.26	0.90, 1.76	0.185			
	MR Egger	10	1.21	0.77, 1.90	0.436			-0.0002 (0.984)
	MR PRESSO ^b	10	1.24	0.98, 1.57	0.107			
Leptin	IVW	4	1.88	0.80, 4.44	0.148	0.56	0.905	
	WM	4	1.59	0.60, 4.20	0.353			
	MR Egger	4	0.41	3.02e-09, 5.65e+07	0.935			0.036 (0.888)
	MR PRESSO ^b	4	1.25	0.73, 2.13	0.462			
Resistin	IVW	3	1.28	1.07, 1.53	0.007	0.15	0.926	
	WM	3	1.25	1.02, 1.54	0.031			
	MR Egger	3	1.39	0.74, 2.60	0.493			-0.015 (0.833)
Chemerin	Wald ratio	1	1.58	0.81, 3.07	0.180			
RBP4	Wald ratio	1	1.13	0.78, 1.64	0.530			
<p>Abbreviations: MR, Mendelian randomization; RA, rheumatoid arthritis; SNP, single nucleotide polymorphism; RBP 4, retinol-binding protein 4; OR, odds ratio; CI, confidence interval; IVW, Inverse variance weighted; WM, weighted median; MR PRESSO, MR Pleiotropy RESidual Sum and Outlier.</p> <p>^a Beta coefficient for the MR Egger intercept estimate.</p> <p>^b Insignificant outliers.</p>								

In the leave-one-out analysis, not a single SNP was found to substantially drive the overall risk estimates of adipokins on the risk of RA (Supplementary Fig. 4). After searching the secondary phenotypes of the SNPs used as IVs in the GWAS catalog, we found that several SNPs were also associated with obesity-related traits, including

triglyceride, cholesterol levels, waist-hip ratio and body fat percentage with genome-wide significance (Supplementary Table 2). Similar results were obtained after excluding the pleiotropic SNPs potentially related to obesity. In sensitivity analyses where we restrict SNPs in ADIPOQ gene to further evaluate the causal role of adiponectin on RA, similar null association was found.

Discussion

In this paper, we explored the genetic association between adipokines and the development of RA, finding that per one unit increase in natural log-transformed resistin levels could be causally associated with 28% increased risk of RA occurrence. Whereas, little evidence supported causal associations of genetically predicted adiponectin, leptin, chemerin or RBP4 levels with the RA risk. Our analysis results indicate that regulating the circulating resistin to appropriate levels may lower the incidence of RA, which could be useful in future clinical practice. To the best of our knowledge, this is the first MR study to evaluate the potential causal association between circulating adipokine levels and risk of RA.

A large number of observational epidemiological studies have been undertaken to investigate the role of adipokines in the occurrence and progression of RA. Two recent meta-analyses of case-control studies demonstrated that circulating adiponectin levels could be significantly higher in the RA patients than those in the health controls [30, 31]. However, it was also reported separately that adiponectin levels were not related to RA activity [30, 32]. Meanwhile, the findings from meta-analyses consistently indicated that patients with RA may have higher circulating leptin levels compared with the control group [33–35]. Two of these studies further established a correlation between leptin levels and RA activity [34, 35]. Several case-control studies have also suggested associations of chemerin and RBP4 concentrations with RA [36, 37]. However, our MR results suggested that genetically predicted levels of adiponectin, leptin, chemerin or RBP4 were not causally associated with risk of RA. The inconsistency between our MR analysis and the previous observational studies may be attributed to the following reasons. Firstly, the previously published results are mostly based on retrospective case-control studies with a small sample size, which are particularly prone to recall and selection biases. This thereby leads to an even weaker causal argument. Secondly, residual confounding (e.g., the adipokines may be correlated with other factors that impact on RA risk) and reverse causation (e.g., RA may have resulted in high or low circulating adipokine levels) may further limit the ability of causal inference in the traditional observational studies. Thirdly, MR studies provide causal estimates of the impact of lifetime adipokines levels on RA, which might diverge from the short-term effects as assessed in traditional observational studies.

For resistin, our MR results were broadly compatible with the findings of the previous meta-analysis outcomes [38]. Several biological mechanisms have been proposed to interpret the potential effect of resistin on the pathogenesis of RA. It is widely recognized that RA is a persistent inflammatory disease, which is related to several inflammatory cytokines [39]. Šenolt et al. reported that resistin was expressed in different inflammatory cells of RA synovial tissue, including macrophages (CD68), B lymphocytes (CD20) and plasma cells (CD138) [40]. Those authors speculated that resistin was involved in the activation of these cells as a signaling molecule in RA. Subsequently, a case-control study found a positive association of serum resistin with C-reactive protein levels in RA patients, further supporting the potential pro-inflammatory effects of resistin in this disease. Furthermore, synovial liquid resistin levels have been claimed to be significantly associated with rheumatoid factor and anti-citrullinated protein antibody [41], both of which are markers of RA. Cellular analysis suggested that resistin down-regulates the expression of microRNA 206 via protein kinase C delta (PKC- δ /AMPK) signaling pathway to promote endothelial

progenitor cell (EPC) migration and RA angiogenesis. In addition, resistin induced the vascular endothelial growth factor (VEGF) expression, which was also associated with EPC migration and tube formation [42]. Therefore, resistin plays an important role in the pathogenesis of RA and may be a potential target for RA intervention.

Our investigation has some potential limitations. Firstly, it is known that genetic variants only explain a relatively small proportion of variation in adipokines, which may lead to inadequate power to detect causal associations in studies with small sample sizes [43]. Secondly, pleiotropy is considered to be the most challenging limitation of MR analysis. Even though none of the performed MR analyses showed an indication of pleiotropy, we were unable to completely rule out the possibility that pleiotropy had affected the results. Thirdly, our MR analyses were conducted using participants of European ancestry. While restricting the investigation to racially homogeneous populations reduces the population stratification bias, our findings may not be applicable to other populations for different genetic backgrounds. Finally, for the use of summary-level data, we were unable to perform subgroup analyses to address study-specific factors, e.g., age, sex and other RA risk factors.

In conclusion, the present MR study indicates that genetically predicted circulating resistin levels are positively associated with risk of RA. This can be beneficial for the development of clinical as well as public health strategies. Nevertheless, we encourage further prospective studies and MR analyses with more genetic instruments and longitudinal studies, which follow up RA patients over time monitoring the risk factors and outcome, to be conducted to confirm the results.

Abbreviations

BMI: Body mass index; EPC: Endothelial progenitor cell; GWAS: Genome-wide association study; IV: Instrumental variable; IVW: Inverse-variance weighted; LD: Linkage disequilibrium; MR: Mendelian randomization; MR-PRESSO: Mendelian randomization pleiotropy residual sum and outlier; RA: Rheumatoid arthritis; RBP4: Retinol-binding protein 4; SNP: Single nucleotide polymorphisms; WM: Weighted-median

Declarations

Ethics approval and consent to participate

Participating studies of the GWAS meta-analyses have received prior approval by relevant institutional review boards, and informed consent was obtained from each study participant. The current study was carried out based on publicly available data; therefore, no additional ethical approval would be required.

Consent for publication

Not applicable.

Availability of data and materials

RA summary statistics analysed during the current study are available at <https://gwas.mrcieu.ac.uk>.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors interpreted the data, critically revised the manuscript for important intellectual content, approved the final version of the manuscript, and agreed to be responsible for all aspects of the work.

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44. Legend.

Additional Files

Supplementary Table S1 Summary information on the SNPs used as genetic instruments for the five adipokines.

Supplementary Table 2 Potential secondary phenotypes of the genetic variants used for adipokines (from the GWAS catalog).

Supplementary Fig. 1 Scatter plots of causal associations between adipokines and risk of RA. The slope of each line represents the causal association using the corresponding MR analysis model.

Supplementary Fig. 2 Forest plots of individual and summary estimates for causal associations between adipokines and RA risk.

Supplementary Fig. 3 Funnel plots to detect heterogeneity, which show no evidence of asymmetry. Directional horizontal pleiotropy is suggested to be null.

Supplementary Fig. 4 Leave-one-out plot to assess if a single SNP drives association between adipokines with RA risk.

Figures

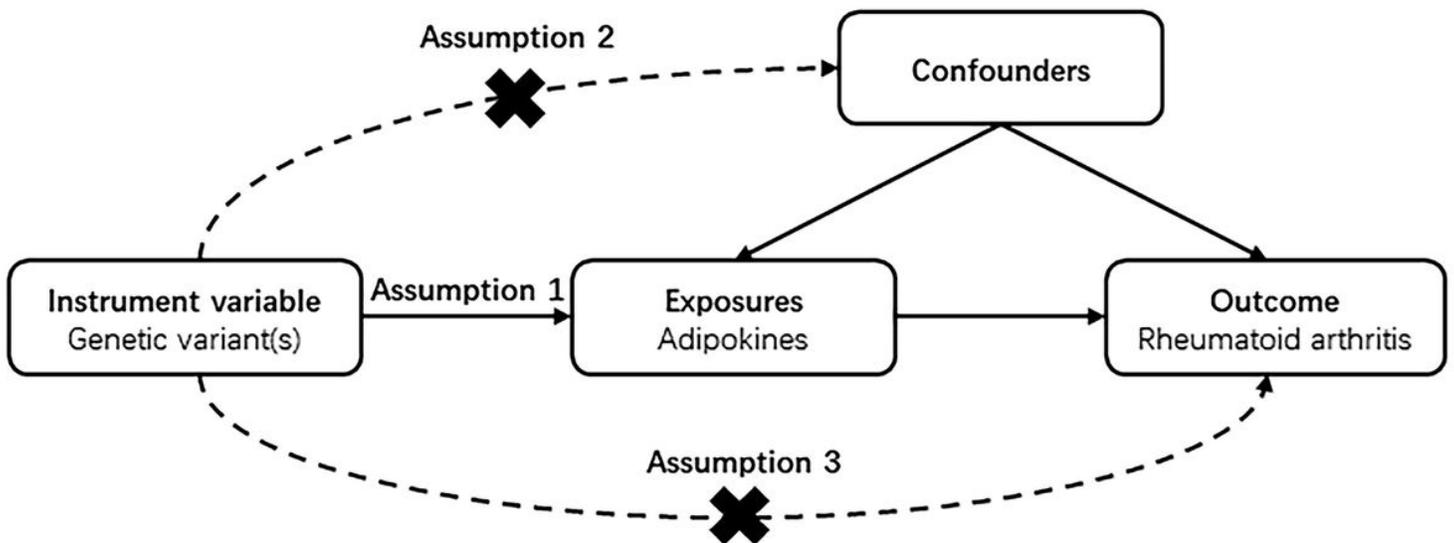


Figure 1

Supplementary Files

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- [SupplementaryFigureS4.tif](#)
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- [SupplementaryFigureS2.tif](#)
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