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The Causal relationship of adipokines with rheumatoid arthritis among European populations: a two-sample Mendelian randomization study

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Abstract

Background

Adipokines played an important role in the pathogenesis of rheumatoid arthritis (RA). However, observational studies have indicated an inconsistent association between adipokines (adiponectin, resistin and leptin) and RA. Therefore, we tried to explore the causal effects of genetically predicted adipokines on RA by two-sample Mendelian randomization (MR) study.

Methods

Summary statistics of RA were obtained from a genome-wide association study (GWAS) of European descent, including 14,361 RA cases and 43,923 controls. Based on three additional GWAS, we selected genetic variants as instrumental variables (IVs) that were related to adiponectin, resistin and leptin. The two-sample MR study was conducted to estimate causality between adipokines and RA by the inverse-variance weighted (IVW) method and weighted-median method. In addition, we applied MR-Egger regression, MR-PRESSO and leave-one-out analysis to evaluate the potential pleiotropy effects.

Results

We screened a total of 12 single nucleotide polymorphisms (SNPs) for adipokines (7 SNPs for adiponectin, 3 SNPs for resistin and 2 SNPs for leptin). We found that resistin was positively related to risk of RA (the IVW method: OR: 1.28, 95% CI: 1.07-1.53, *P*-value = 0.007; the weighted median: OR: 1.25, 95% CI: 1.02-1.54, *P*-value = 0.035). However, based on the IVW method and weighted median, there was little evidence to support the causal relationship between adiponectin, leptin and RA. MR-Egger regression, MR-PRESSO and leave-one-out analysis did not indicate horizontal pleiotropy.

Conclusions

Our MR study indicates that genetically predicted resistin is causally associated with risk of RA. However, there was little evidence to support the causality of adiponectin and leptin on RA, tentatively.

Background

Rheumatoid arthritis (RA) is a common and chronic autoimmune disease, characterized by synovial inflammation, pannus formation and joint destruction, eventually leading to joint dysfunction and decreased quality of life[1, 2]. Previous epidemiological surveys demonstrated that the global incidence of RA is 0.5-1%[1]. Mortality risk among the RA population is 1.5-fold higher than that in the general population in a 15-year prospective cohort study[3]. Although the pathogenesis of RA remains complex and unclear, it is certain that these factors, including genetics, smoking, obesity and immune system, play a crucial part in its development[4].

Adipokines, a type of bioactive proteins produced by adipocytes, have emerged as important modulators of inflammatory and immune responses. They play a vital role in numerous rheumatic diseases[5]. Over the past years, the relationship between adipokines (adiponectin, resistin and leptin) and RA has attracted increased attention of researchers. However, epidemiologic results remained conflicting. In RA patients, increased levels of adiponectin were observed in the synovial fluid and circulating blood, associated with disease activity and joint destruction[6-8]. However, another observational study found patients with RA had lower circulating levels of adiponectin compared with healthy controls[9]. Consistent with adiponectin, the association of resistin and leptin with RA was also incompatible. RA patients had a higher leptin concentration, whereas levels of resistin were similar to healthy controls[10, 11]. On the contrary, Fadda SM *et al*[12] found resistin levels were remarkably increased in RA patients, compared with osteoarthritis patients. Therefore, the causal relationship between adipokines (adiponectin, resistin and leptin) and RA is still unknown. Besides, these conflicting findings may be disturbed by potential biases and reverse causation.

Depending on genome-wide association studies (GWAS), Mendelian randomization (MR) provides one method to evaluate the causality of exposure and outcome by using genetic variants as instrumental variables (IVs)[13]. Since genetic variants are randomly assigned before birth, MR analysis can get rid of the influence of lifestyles and environmental factors[14]. Therefore, compared with traditional observational epidemiological studies, MR study is able to avoid the confusion caused by various underlying biases, confounders and reverse causation[14]. To enhance the effectiveness of study, two-sample MR investigated the associations of IVs-exposure and IVs-outcome from two independent samples by the openly available GWAS database.

AS far to our knowledge, no MR analysis was performed to test the potential causal relationship between adipokines and RA among European populations. Therefore, we aimed to estimate the causal effects between three adipokines (adiponectin, leptin and resistin) and RA by two-sample MR study.

Methods

Data sources

Figure 1 illustrated the general idea of the whole study. The summary statistics of RA were obtained from a previous GWAS meta-analysis with a total of more than 100,000 individuals of European and Asian ancestries, covering ~10 million single nucleotide polymorphisms (SNPs)[15]. As this study was primarily targeted at European individuals, we selected genetic data of European ancestries (14,361 RA cases and 43,923 controls). According to the description of original manuscripts, all cases met the 1987 criteria of the American College of Rheumatology (ACR) for RA diagnosis. Besides, we identified genetic variants associated with adiponectin at a meta-analysis from 16 GWAS with 29,347 individuals of European ancestry[16]. One GWAS with 32,161 subjects of European descent was employed to select IVs related to leptin[17], one genomic atlas of the human plasma proteome from the INTERVAL study for resistin[18]. Thereinto, the genetic variants of leptin were adjusted for blood mass index (BMI). Ethical

approval and consent to participants were not necessary as the MR study was based on openly available databases and published studies.

Selection of instrumental variables

In the present study, SNPs were defined as IVs. To obtain the effective estimate, IVs must meet the below hypotheses[19]: (i) IVs are robustly associated with exposure; (ii) IVs are independent of potential confounding factors; (iii) IVs affect outcome exclusively via exposure. Furthermore, SNPs concerned with adiponectin and resistin were identified at genome-wide significance threshold (*P*-value < 5×10^{-8}), without linkage disequilibrium (LD) (pairwise r^2 < 0.001, window size = 10000kb). To detect more independent SNPs which were associated with leptin, the significance threshold was relaxed to *p*-value < 1×10^{-6}. If the requested SNPs are unavailable in RA GWAS, we used proxy SNPs with strong LD (r^2 > 0.8) to subscribe for the requested SNPs.

In the study, we evaluated the power of the selected SNPs depending on F statistics and R^2. F statistics is calculated by R^2 at the online mRnd power tool (http://cnsgenomics.com/shiny/mRnd/)[20]. R^2 is expressed as $2 \times MAF \times (1 - MAF) \times \beta^2$, where MAF is the minor allele frequency, β is the effect size on adipokines [21]. The IVs with F statistics >10 were considered powerful enough to estimate the causality.

Statistical analyses

In our study, the inverse variance-weighted (IVW) method, the primary analysis, was conducted to evaluate the causal association between adipokines and RA[22]. The IVW method provides consistent estimate of the causal effect if the selected IVs are valid[23]. A fixed-effect IVW model was chosen when *P*-value for the Cochran'Q test > 0.05; otherwise, a random-effect model was selected. Additionally, we used the weighted median as the supplement of the IVW method. The weighted median provided valid estimate if more than 50% of the weight was effective IVs[24].

In terms of sensitivity analyses, we performed MR-Egger regression, MR pleiotropy residual sum and outlier test (MR-PRESSO) method and leave-one-out analysis to test the presence of horizontal pleiotropy[22]. The intercept of the MR-Egger regression reflects the average pleiotropic effect[25]. The MR-PRESSO detects pleiotropy and reassesses the effect estimates after excluding the outlying SNPs[26]. Besides, to rule out the influence of other confounders (e.g. body mass index, smoking, serum triglycerides, etc), we explored the potential pleiotropy of each selected SNPs (*P*-value < 5×10^{-8}) by the PhenoScanner V2 database (http://www.phenoscanner.medschl.cam.ac.uk/)[27].

All estimates were 2-sided, and differences were considered as statistical significance (*P* < 0.05), unless noted. Statistical analysis was conducted by using the TwoSampleMR (V 0.5.6)[28] and MR-PRESSO (V 1.0)[26] packages in R software (4.1.0).

Results

Supplemental Table S1 provided the summary statistics of the selected SNPs for adipokines. We eliminated 2 SNPs (rs7964945 for adiponectin, rs10487505 for leptin) because of palindrome with intermediate allele frequencies. In the end, 7 SNPs were taken as IVs for adiponectin, 3 SNPs for resistin and 2 SNPs for leptin. All above SNPs did not have LD (r^2 < 0.001). The selected SNPs explained 0.710% for adiponectin, 3.301% for resistin, and 0.072% for leptin, respectively. The F statistics for them ranged from 15.46 to 210.80, which were higher than the conventional threshold of 10, indicating that there were no weak IVs.

As shown in Figure 2, Cochran'Q test suggested significant heterogeneity of the selected SNPs was absent (*P*-value = 0.342 for adiponectin, *P*-value = 0.926 for resistin, *P*-value = 0.802 for leptin). Therefore, we applied the fixed-effect IVW model. Among three adipokines, resistin was the only adipokines which was positively correlated to risk of RA based on the IVW method (adiponectin: OR: 1.15, 95% CI: 0.86-1.55, *P*-value = 0.352; resistin: OR: 1.28, 95% CI: 1.07-1.53, *P*-value = 0.007; leptin: OR: 1.67, 95% CI: 0.50-5.57, *P*-value = 0.402) (Figure 2). The weighted median also supported the above results (adiponectin: OR: 1.17, 95% CI: 0.82-1.66, *P*-value = 0.391; resistin: OR: 1.25, 95% CI: 1.02-1.54, *P*-value = 0.035) (Figure 2). Besides, there was little evidence for horizontal pleiotropy assessed by MR-Egger regression and MR-PRESSO methods (MR-Egger: $P_{intercept}$ = 0.515 for adiponectin, $P_{intercept}$ = 0.833 for resistin; MR-PRESSO: *P*-value = 0.434 for adiponectin). Likewise, leave-one-out analysis revealed the robustness of the causal effect in this MR study (Supplementary Figure S1). As a complementary approach, we also did not find potential pleiotropy of each selected SNPs by searching the PhenoScanner V2 database. Scatter plots, forest plots and funnel plots were presented in Supplementary Figure S2-S4.

Discussion

In this study, we estimated the causal relationship between three adipokines (adiponectin, resistin and leptin) and RA by collecting genetic variants from available GWAS datasets of European populations. We revealed that resistin was positively associated with risk of RA. However, there was no evidence supporting causal relationship between adiponectin, leptin levels and RA at present by two-sample MR analysis. Sensitivity analysis also demonstrated the robustness of our findings.

Compared with healthy controls or osteoarthritis, resistin levels in serum or synovial fluid were higher in RA patients[12]. Besides, increased resistin concentration was positively correlated with C-reactive protein (CRP), disease activity score-28 (DAS-28) and predicted more rapid joint destruction during 5-year follow-up[29, 30]. A previous meta-analysis also suggested that serum resistin levels were significantly elevated in patients with RA by summarizing eight relevantly clinical studies[31]. Experimental researches have demonstrated that resistin could stimulate the production of pro-inflammatory cytokines and the angiogenesis of synovium in joints. In vitro, resistin also stimulated the expression of interleukin (IL)-6, IL-1 and tumor necrosis factor (TNF)-α in human peripheral mononuclear blood cells (PMBC) and synovial fluid leukocytes through NF-κB dependent pathway[32], and upregulated the production of chemokine (CXCL8 and CCL2) by fibroblast-like synoviocytes (FLSs)[33]. Besides, resistin promoted endothelial

progenitor cells homing into the synovium by stimulating the expression of vascular endothelial growth factor (VEGF)[34]. Therefore, resistin could be an important risk factor for RA.

Adiponectin is an adipokine with both pro-and anti-inflammatory effects. Numerous clinical studies and meta-analyses suggested adiponectin levels were markedly higher in RA patients[7, 35]. Adiponectin also could promote the progression by increasing the production of TNF-α, IL-6 and IL-8 and the activity of osteoclasts to resorb bone tissue[36]. Although it was generally accepted that adiponectin stimulated chronic inflammation of RA, it also had anti-inflammatory effects by supporting M2 macrophages activation and promoting the production of anti-inflammatory cytokines (IL-10)[37]. Experimental studies indicated that leptin could upregulate expression of the vascular cell adhesion molecule (VCAM)-1, IL-6 and IL-8[5]. Although increased leptin levels were observed in RA patients, positively related to disease activity and joint erosion[10, 38, 39], there was little evidence to support the association between leptin and bone destruction after normalization by body fat mass[7]. Therefore, the discrepancies between different results may be explained by the lack of leptin correction by BMI or fat mass.

Our MR study also found genetically predicted adiponectin and leptin might have nothing to do with risk of RA based on present GWAS database. This discrepancy might result from several biases or confounders, such as a small sample size, the heterogeneity of the populations studied and selection biases. For instance, obesity is an important confounder, decreasing the odds of achieving remission in RA[40] and increasing the release of adiponectin and leptin[41]. Therefore, traditional investigational studies likely did not control for the confounding effects of obesity or BMI.

Our study has several strengths. As far as we know, this study is the first MR analysis that explores whether genetically predicted adipokines levels are causally related to RA based on open GWAS database. Besides, to decrease the population bias, we selected European individuals as the research subjects in this MR study. Furthermore, we chose two-sample MR study to reduce false positive results as far as possible.

Meanwhile, this MR study had the following shortcomings. Firstly, our study was based on openly available genetic data, and we cannot perform an in-depth subgroup analysis, such as the presence/absence of antibodies to citrullinated peptides or rheumatic factors. Secondly, since the subjects of this study were European, it is hard to generalize our conclusion to other populations. In the end, the selected SNPs only explained 0.710%, 0.072% for adiponectin and leptin, respectively. Therefore, we cannot completely exclude the causal relationship between adiponectin, leptin and risk of RA. Furthermore, it is necessary to carry out GWAS study with a larger sample size, which is related to adiponectin and leptin.

Conclusions

In conclusion, our MR study indicates that genetically predicted resistin is causally associated with risk of RA. However, there was little evidence to support causal relationship between adiponectin, leptin and RA,

tentatively. More researches are required to explore the causal association between adipokines (adiponectin, resistin and leptin) and RA.

Abbreviations

RA: rheumatoid arthritis; MR: Mendelian randomization; GWAS: genome-wide association study; IVs: instrumental variables; IVW: inverse-variance weighted; MR-PRESSO: MR pleiotropy residual sum and outlier test; SNPs: single nucleotide polymorphisms; ACR: American College of Rheumatology; BMI: blood mass index; LD: linkage disequilibrium; OR: odds ratio; CI: confidence interval; CRP: C-reactive protein; DAS-28: disease activity score-28; IL: interleukin; TNF: tumor necrosis factor; PMBC: peripheral mononuclear blood cells; FLSs: fibroblast-like synoviocytes; VEGF: vascular endothelial growth factor; VCAM: vascular cell adhesion molecule.

Declarations

Acknowledgements

Summary statistics for the genetic related to RA, adiponectin, resistin and leptin were obtained from available GWAS by Okada Y et al, Dastani Z et al, Kilpelainen TO et al and Sun BB et al, respectively. We sincerely thank all above authors for providing the genetic information.

Authors' contributions

J.B. and S.F. conceived and designed the study. S.H. and M.W. conducted data analysis and wrote the manuscript. Y.H., F.H. and F.T. revised the manuscript critically. All authors read and consented for the final content.

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Data Availability statement

All data generated or analysed during this study are included in the supplementary information files of this article. The original genetic data that support the findings are available in MRC IEU Open GWAS project (https://gwas.mrcieu.ac.uk/).

Declarations

Ethics approval and consent to participate

Ethical approval and consent to participants were not necessary as the MR study was based on openly available databases and published studies. According to the relevantly original manuscripts, all

participants signed an informed consent, and the protocols were reviewed and approved by ethics committees at the involved institutions.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

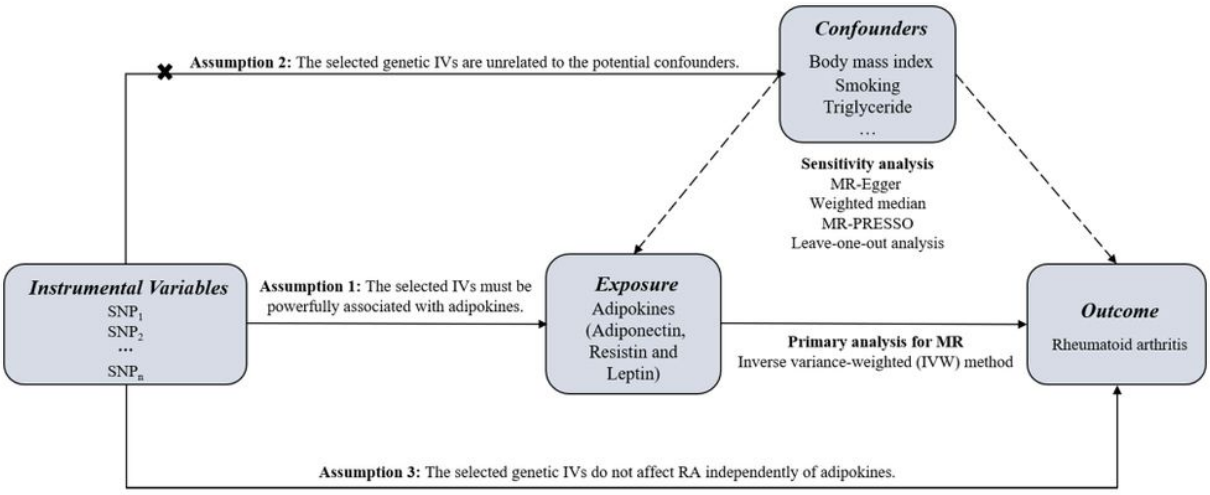

Figure 1

An overview of the MR study design.

Adipokines	Number of SNPs	OR	95% CI	P-value for association	P-value for Cochran'Q test	P-value for MR-Egger intercept
Adiponectin						
IVW	7	1.15	0.86-1.55	0.352	0.342	
Weighted median	7	1.17	0.82-1.66	0.391		
MR-Egger	7	1.3	0.82-2.05	0.314		0.515
MR-PRESSO	7	1.15	0.86-1.55	0.434		
Resistin						
IVW	3	1.28	1.07-1.53	0.007	0.926	
Weighted median	3	1.25	1.02-1.54	0.035		
MR-Egger	3	1.39	0.74-2.60	0.493		0.833
Leptin						
IVW	2	1.67	0.50-5.57	0.402	0.802	

Figure 2

Forest plot of MR analyses for the causality between adipokines and RA. Cochran'Q test suggested that there was no significant heterogeneity of the selected SNPs (P-value > 0.05), and there was little evidence for horizontal pleiotropy by MR-Egger regression and MR-PRESSO methods (P-value > 0.05). Resistin was positively related to risk of RA (the IVW method: OR: 1.28, 95% CI: 1.07-1.53, P-value = 0.007; Weighted median: OR: 1.25, 95% CI: 1.02-1.54, P-value = 0.035).

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