RHEUMATOLOGY

Rheumatology 2018;57:2145–2148
doi:10.1093/rheumatology/key229
Advance Access publication 4 August 2018

Concise report

Genetic association between adiposity and gout: a Mendelian randomization study

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Abstract

Objective. To investigate whether overall obesity (as measured by BMI) and abdominal obesity (as measured by waist-to-hip ratio adjusted for BMI) are associated with gout risk and serum urate concentrations using Mendelian randomization.

Methods. Single nucleotide polymorphisms associated with BMI ($n = 97$) and waist-to-hip ratio adjusted for BMI ($n = 49$) were analysed for association with gout risk in 2115 gout cases and 67 259 controls, and with serum urate concentrations in 110 347 individuals from the Global Urate Genetics Consortium.

Results. Genetically higher BMI, but not waist-to-hip ratio adjusted for BMI, was positively associated with risk of gout and serum urate concentrations. Each standard deviation (about 4.6 kg/m^2) increase in genetically predicted BMI was associated with an odds ratio of gout of 2.24 (95% CI 1.70, 2.95; $P = 8.4 \times 10^{-9}$) and with a 0.30 mg/dl (95% CI 0.25, 0.35; $P = 1.6 \times 10^{-36}$) increase in serum urate concentrations.

Conclusion. These findings provide support that overall obesity may be a risk factor for gout and is associated with higher serum urate concentrations.

Key words: adiposity, body mass index, gout, Mendelian randomization, obesity, urate

Rheumatology key messages

- Genetically higher BMI was positively associated with gout risk and serum urate concentrations.
- Genetically higher waist-to-hip ratio was not associated with gout risk or serum urate concentrations.
- These results provide support that overall but not abdominal obesity is associated with an increased gout risk.

Introduction

Gout is a form of inflammatory arthritis caused by the crystallization of uric acid within the joints [1]. The disease inflicts substantial morbidity by causing severe pain and is associated with an increased risk of death, primarily from cardiovascular disease [2]. The global burden of gout is considerable and several studies have suggested that the incidence and prevalence of gout have been increasing since the 1990s [3–5]. In the US, the prevalence of gout is around 10% among adults over 70 years of age [4]. The rise in gout has paralleled overweight and obesity trends [6], suggesting that excess adiposity may be a risk factor for gout. A positive association of adiposity with risk of gout has been found in observational studies [7] and some but not all studies have shown beneficial effects of weight loss on gout attacks [8]. It is unclear, however, whether the association is causal and independent of other possible risk factors, such as purine-rich and Western diets, sugar-sweetened beverages, alcohol consumption, renal disease, and the use of diuretics and antihypertensive drugs [1, 3, 4, 9]. A recent systematic review concluded that available studies of the effect of weight loss on gout attacks and serum uric acid concentrations are of low methodological quality and that there is a need for rigorous prospective studies, preferably randomized controlled trials [8].

An alternative approach to infer causality is to use Mendelian randomization, a method in which genetic variants that influence the modifiable exposure of interest (e.g. body weight) are used as proxy measures to determine whether the exposure causes the disease (e.g. gout). Mendelian randomization exploits Mendel's second law, which implies that the inheritance of any particular trait should be independent of other characteristics [10]. The Mendelian randomization study design is analogous to a randomized controlled trial.

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Submitted 20 April 2018; revised version accepted 21 June 2018

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CLINICAL SCIENCE

Here we used the Mendelian randomization framework to investigate the associations of overall obesity (as measured by BMI) and abdominal obesity [waist-to-hip ratio (WHR) adjusted for BMI] with gout risk and serum urate concentrations.

Methods

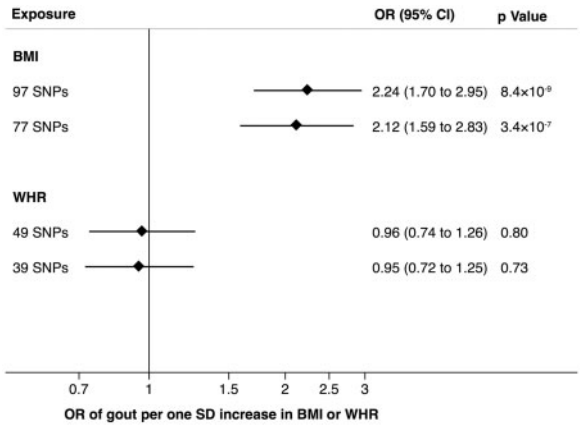
Selection of genetic variants and data sources

Selected as instrumental variables were single-nucleotide polymorphism (SNPs) associated with the adiposity measures at genome-wide significance ($P < 5 \times 10^{-8}$) in the Genetic Investigation of Anthropometric Traits Consortium, which included 339 224 individuals (~95% of European ancestry) for BMI [11] and 224 459 individuals (~94% of European ancestry) for WHR adjusted for BMI [12]. We only included independent SNPs (i.e. not in linkage disequilibrium, $r^2 < 0.05$) within each trait, and only considered the SNPs with the strongest effect on each adiposity measure for use as instrumental variables (supplementary Table S1, available at *Rheumatology* online). Summary-level (i.e. aggregated) data for the SNP–outcome associations were obtained from the Global Urate Genetics Consortium, which included 2115 gout cases and 67 259 controls of European ancestry and 110 347 European-ancestry individuals for serum urate from 48 studies [13]. The BMI- and WHR-related SNPs were all available in the Global Urate Genetics Consortium and no proxies were used. Individual studies participating in the consortia received approval from relevant institutional review boards or ethics committees, and participants gave informed consent.

Statistical analysis

The conventional inverse variance weighted method [14] was used to estimate the associations of genetically predicted 1 SD increase in each adiposity measure with odds ratio of gout and serum urate concentrations (in mg/dl). The weighted median and Mendelian randomization-Egger (MR-Egger) regression methods were used as sensitivity analyses [14]. The weighted median method provides consistent estimates if at least 50% of the weight comes from valid instrumental variables [14]. The MR-Egger method can be used to identify and adjust for directional pleiotropy [14, 15]. Bias caused by pleiotropy is analogous to small study bias in a meta-analysis, where small studies with less precise estimates tend to report larger estimates than larger studies with more precise estimates. Heterogeneity between SNPs was tested by using the I^2 statistic and Cochran's Q test [16]. A threshold of statistical significance of $P < 0.0125$ ($P = 0.05/4$) was used to reflect testing of two adiposity measures (BMI and WHR adjusted for BMI) and two outcomes (gout and serum urate concentrations). Stata (version 14.1; StataCorp, College Station, TX, USA) was used for all analyses.

FIG. 1 Associations of genetically predicted BMI and WHR adjusted for BMI with OR of gout



OR: odds ratio; SNPs: single-nucleotide polymorphisms; WHR: waist-to-hip ratio.

Results

Adiposity-associated SNPs

The number of independent SNPs associated with the adiposity measures was 97 for BMI (77 in European sex-combined analysis) [11] and 49 for WHR adjusted for BMI (39 in European sex-combined analysis) [12]. Summary statistics data for the SNP–exposure and SNP–outcome associations are presented in supplementary Table S1, available at *Rheumatology* online.

Gout results

Genetically predicted BMI was positively associated with risk of gout (Fig. 1 and supplementary Fig. S1, available at *Rheumatology* online). Using data from all 97 BMI-associated SNPs, the odds ratio of gout per 1 SD (about 4.6 kg/m^2) increase in BMI was 2.24 (95% CI 1.70, 2.95; $P = 8.4 \times 10^{-9}$), without heterogeneity among SNPs (I^2 = 0%, $P = 0.87$). A consistent association was found when using information from 77 SNPs associated with BMI in the European sex-combined meta-analysis (Fig. 1). Results were also similar in sensitivity analyses using the weighted median and MR-Egger methods, but the MR-Egger estimate was less precise (Table 1). There was no evidence of directional pleiotropy (intercept 0.009, 95% CI −0.009, 0.027; $P = 0.31$). Genetically predicted WHR adjusted for BMI was not associated with gout (Fig. 1).

Serum urate results

BMI was also positively associated with serum urate concentrations, with a 0.30 mg/dl (95% CI 0.25, 0.35; $P = 1.6 \times 10^{-36}$) higher serum urate concentration per SD increase in genetically predicted BMI ($n = 97$ SNPs). There was no association between WHR adjusted for BMI and serum urate concentration (0.05 mg/dl, 95% CI −0.02, 0.11; $P = 0.17$).

TABLE 1 Associations of genetically predicted BMI and WHR adjusted for BMI with gout using different methods

Exposure	SNPs	Method	OR (95% CI)[b]	*P*-value	MR-Egger[a]	
					Intercept (95% CI)	*P*-value
BMI	97	IVW	2.24 (1.70, 2.95)	8.4×10^{-9}		
BMI	97	WM	2.13 (1.38, 3.28)	0.001		
BMI	97	MR-Egger	1.63 (0.84, 3.19)	0.15	0.009 (−0.009, 0.027)	0.31
BMI	77	IVW	2.12 (1.59, 2.83)	3.4×10^{-7}		
BMI	77	WM	2.12 (1.32, 3.41)	0.001		
BMI	77	MR-Egger	1.96 (0.96, 4.00)	0.06	0.003 (−0.018, 0.023)	0.81
WHR	49	IVW	0.97 (0.74, 1.27)	0.80		
WHR	49	WM	1.04 (0.73, 1.48)	0.84		
WHR	49	MR-Egger	1.11 (0.41, 2.30)	0.83	−0.005 (−0.035, 0.026)	0.77
WHR	39	IVW	0.95 (0.72, 1.25)	0.73		
WHR	39	WM	1.04 (0.72, 1.49)	0.84		
WHR	39	MR-Egger	2.04 (0.60, 7.01)	0.26	−0.025 (−0.065, 0.015)	0.21

[a]The MR-Egger intercept quantifies the effect of directional pleiotropy. Values significantly different from zero provide evidence that the exposure-associated SNPs may influence the outcome through other pathways than through the exposure. [b]ORs are per SD increase in each adiposity measure. IVW: inverse variance weighted; WHR: waist-to-hip ratio; WM: weighted median; SNPs: single-nucleotide polymorphisms; OR: odds ratio; MR-Egger: Mendelian randomization-Egger.

Discussion

This genetic study provides evidence that higher BMI, but not WHR adjusted for BMI, is causally associated with risk of gout independent of other risk factors and is also associated with higher serum urate concentrations. Each SD increase in genetically predicted BMI was associated with an over 2-fold increased risk of gout and 0.3 mg/dl increase in serum urate concentrations.

Our results confirm those from conventional observational studies which have found that BMI is positively associated with gout risk [7]. A meta-analysis of 10 prospective studies with 27 944 gout cases and 215 739 participants showed that each 5 kg/m^2 increment in BMI was associated with a 55% elevated risk of gout [7]. Available evidence from longitudinal observational studies, with low methodological quality and low precision, also suggests that weight loss provides a beneficial effect on serum urate concentrations and gout attacks [8]. In addition, results from a previous Mendelian randomization study have shown that the BMI-increasing alleles of variants in the *FTO*, *MC4R* and *TMEM18* gene regions are associated with higher serum urate concentrations [17]. These known BMI-increasing loci [11] have also been found to be associated with body fat percentage, but with larger effects (expressed in SD per allele) on BMI than on body fat percentage [18].

The fact that abdominal adiposity as measured by WHR adjusted for BMI was not associated with either serum urate concentration or gout strengthens the conceivable causal relationship between overall obesity and the development of gout. The association of BMI but not WHR adjusted for BMI with gout risk suggests that excess body weight rather than central location of body fat is more important in increasing serum urate concentrations and the risk of gout.

Important strengths of this study include the large sample sizes for both the gout and serum urate analyses. In addition, because genetic variants are not influenced by disease, reverse causation bias was avoided. Potential confounding by dietary and lifestyle factors was reduced as genetic variants are randomly allocated during meiosis and thus are independent of self-selected behaviours that may be confounders of the BMI–gout relationship.

As in any Mendelian randomization study, the possibility that pleiotropy (i.e. the genetic association with the outcome is through a different causal pathway and not through the exposure of interest) may have influenced the results cannot entirely be ruled out. However, the genetic association between BMI and risk of gout was similar in sensitivity analyses and there was no evidence of pleiotropy. Bias due to population stratification is unlikely to explain the observed associations because BMI was positively associated with gout and serum urate concentrations in analyses restricted to data from 77 SNPs associated with BMI in European-ancestry individuals. A shortcoming is that we could not assess the associations of adiposity with gout and serum urate concentrations separately for men and women, with potentially different fat accumulation in different locations.

In summary, findings from this genetic study provide strong support that overall obesity as measured by BMI increases the risk of gout. The association may, at least in part, be mediated by higher serum urate concentrations.

Acknowledgements

The authors would like to thank the Genetic Investigation of Anthropometric Traits Consortium and the Global Urate Genetics Consortium for providing summary-level data for these analyses.

Funding: No specific funding was received from anybody in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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