Word count: up to 600 words; Tables/illustrations: maximum 1 table/figure; References: maximum 6

**Body fat composition and risk of rheumatoid arthritis: a Mendelian randomisation study**

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Observational studies have repeatedly demonstrated obesity (defined using BMI) to be a risk factor for rheumatoid arthritis (RA), but its causal role remains unclear. Dramatic weight loss following bariatric surgery did not reduce RA risk [1]. Obesity is also paradoxically associated with reduced mortality among RA patients [2]. These inconsistencies may be due to biases inherent in observational designs or the limitations of BMI as a measure of adiposity. BMI is unable to distinguish between fat from fat-free (lean) mass. Excess fat mass promotes the proinflammatory state hypothesised to influence the RA disease process, whereas lean mass should improve the metabolic profile. There are additional challenges from confounding (e.g., obesity is related to lifestyle factors such as diet and smoking) and reverse causation (chronic inflammation can induce changes to body composition). Mendelian randomisation (MR) uses genetically predicted levels of the exposure to study its causal relationship with the outcome, in a way that is more robust to these sources of bias. In a recent MR study, genetically predicted BMI was causally linked with RA risk, but body mass distribution (waist to hip ratio) was not [3]. This study was unable to distinguish causal roles of fat and lean mass. We used two-sample MR to investigate the causal roles of body fat composition on risk of RA.

GWAS summary data were derived as follows. Body fat percentage, whole-body fat mass, whole-body fat-free mass (i.e., muscle and internal organs) and appendicular lean mass (i.e., predominantly skeletal muscle) were assessed using bioelectrical impedance in ~0.5 million individuals in the UK biobank [4]. The appendicular lean mass GWAS was adjusted for appendicular fat mass [5]. To provide context, we also used a GWAS meta-analysis of BMI from 681,275 individuals [6]. Single nucleotide polymorphisms (SNPs) were selected as instrumental variables using genome-wide significance threshold (p<5x10-8), excluding those in linkage disequilibrium (r2<0.01). GWAS summary statistics for RA was from 14,361 individuals (fulfilling 1987 ACR criteria or diagnosed by a rheumatologist) and 43,923 controls. All summary data were for those of European decent. We used inverse-variance weighted two-sample MR for the main analysis, supported by a panel of sensitivity analyses (MR Egger, median, mode, and outliers-removed approaches). Fat mass and fat-free mass were adjusted for each other using multivariable MR.

Additional details of each GWAS, genetic instruments, and results of sensitivity analyses are provided in online supplementary materials. F statistics ranged from 55 to 97, indicating good instrument strength (typically considered as F>10) for each exposure. Each standard deviation (SD) increase in whole-body fat mass (9.6kg) and body fat percentage (8.5%) was causally associated with higher odds of RA (OR 1.41; 95%CI 1.09, 1.84; and OR 1.68; 1.31, 2.16; respectively) (**Figure 1**). By contrast, whole-body fat-free mass and appendicular lean mass were not significantly associated with RA risk. There was no significant indication of horizontal pleiotropy as per MR Egger intercept, nor did removal of outlier SNPs (those contributing disproportionately to heterogeneity) change the effect sizes.

Using genetically predicted measures of body fat composition, we showed a significant causal relationship between fat mass (assessed using bioelectrical impedance) and RA risk, but not fat-free mass. These results are more robust to traditional observational methods that may be influenced by reverse causation. Proinflammatory states created by excess adiposity increases RA risk and represents a target for intervention in those deemed at high risk. The main strength of this study is the range of body composition measures assessed in a large population. However, data were limited to a European population and findings may not be directly extrapolatable to other populations. Interpretation may not be extrapolatable to effects of reduced adiposity on RA disease activity or treatment response. Bioelectrical impedance has strong correlation (r=0.83) with the gold standard of dual X-ray absorptiometry, and showed no evidence of heterogeneity when GWASs using both methods were meta-analysed [7]. In summary, this MR study showed a causal relationship between fat mass and RA risk but not fat-free mass.

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**Figure 1**. Causal effect estimates of each body composition measure and rheumatoid arthritis.



Effect sizes shown as per standard deviation (indicated in parentheses) of the exposure. \*fat mass effect size adjusted for fat-free mass and vice versa. \*\*Appendicular lean mass was adjusted for appendicular fat mass in the original GWAS. WB, whole body; BMI, body mass index.