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# Body-size phenotypes and cardiometabolic risk in Rheumatoid Arthritis (Short Title: Subgroups of obesity in RA)

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## ABSTRACT

**Objectives:** Obesity is a significant contributor to metabolic complications. However, such complications are not uniform in people with similar body-size. The existence of normal-weight individuals with and obese individuals without metabolic complications has been described in the general population and is important in the context of cardiovascular disease (CVD). This has not been investigated in rheumatoid arthritis (RA), a condition associated with increased cardiometabolic risk. This study aims to identify the prevalence and predictors of body-size phenotypes in RA and investigate their associations with CVD risk. **Methods:** Body mass index (BMI: kg/m$^2$), body fat (BF) and fat free mass (FFM), RA characteristics and CVD risk factors were assessed in 363 (262 female) volunteers with RA. Abnormal cardiometabolic status was defined as the presence of >1 of the following: hypertension, increased triglycerides or increased Low or reduced High Density Lipoprotein, high glucose, insulin resistance. **Results:** Among normal-weight, overweight, and obese participants, 25%, 45.8%, 57.1% respectively were metabolically abnormal. Old age (B= 1.032, err=0.011; p= 0.005), waist circumference (B= 1.057, err= 0.011; p= 0.000), and smoking cessation (B= 1.425, err= 0.169; p=0.036) were significant predictors for metabolic abnormality. **Conclusions:** A significant number of RA patients present with different body-size and metabolic phenotypes. Body Mass Index alone is not a sufficient indicator of cardiometabolic risk in RA; this may have significant implications in their CVD risk evaluation. Body fat distribution seems to be a significant contributor to such abnormalities. Further research is needed, focusing on the metabolic properties of specific adipose depots of RA patients.

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## INTRODUCTION

Obesity associates with cardiometabolic abnormalities, such as reduced insulin sensitivity, hyperlipidaemia and hypertension, and leads to high risk for the development of cardiovascular disease (CVD). However, these abnormalities are not uniform within the various body-weight categories.[1,2] Investigations in body-size phenotypes have revealed two distinct groups: the first exhibits high body mass index (BMI) and body fat (BF) but no cardiometabolic abnormalities; this is often termed "uncomplicated obesity or metabolically healthy obesity".[3] The second consists of normal-weight individuals who exhibit cardiometabolic abnormalities, and is known as "metabolically obese normal-weight".[4,5]

Rheumatoid Arthritis (RA), the most common inflammatory arthritis, associates with increased cardiovascular morbidity and mortality[6] and a high prevalence of obesity (>50% of RA patients).[7] In these patients, obesity has been shown to protect against joint damage[8, 9] and CVD death[10] while at the same time associates with increased disease activity,[11] presence of CVD risk factors[12] and reduced quality of life.[13] The reasons for such seemingly conflicting findings in the existing literature is not clear.[14] The different body-size phenotypes might partly explain this discrepancy. The aims of the present study were: 1) to estimate the prevalence of body-size phenotypes among patients with RA; 2) to investigate the associations of phenotypes with disease characteristics, inflammation, and body composition; and 3) to identify predictors of metabolic abnormalities within the various phenotypes.

## MATERIALS AND METHODS

### Participants

Patients from the Dudley Rheumatoid Arthritis Co-morbidity Cohort (DRACCO) were included in this study. The project had Research Ethics Committee approval from the Black Country Ethics Committee and patients provided informed consent prior to participation. Patient characteristics have been previously described in detail.[15] Out of the 400 patients in the cohort, 363 (262 female) had complete assessments for BMI, glucose, insulin sensitivity, hypertension, and blood lipids; these patients were included in the analyses.

### Definition of body-size phenotypes

For this study, we have adopted the definition of Wildman et al.[1] for the classification of body size phenotypes, which is currently considered as the optimum set of criteria for this. It classifies body size phenotypes based on BMI (normal-weight: BMI<25kg/m$^2$, over-weight: BMI<25-29.9kg/m$^2$, obese: BMI>30kg/m$^2$) and the presence of cardiometabolic abnormalities (high blood pressure, high triglycerides, low levels of high density lipoprotein-HDL, high fasting glucose, and insulin resistance). Patients with 0 or 1 cardiometabolic abnormalities were considered metabolically healthy, while patients with 2 or more were considered metabolically abnormal **(Table 1)**. The use of 2 rather than 3 cardiometabolic abnormalities (as in the definition of the metabolic syndrome) allows for earlier identification of patients potentially at risk for developing CVD.[1] Due to the systemic inflammation associated with RA, we decided not to include C-reactive protein (CRP) as a cardiometabolic abnormality, since almost 100% of our participants would be positive for this. All patient characteristics according to phenotype allocation are presented in **Table 2**.

### Assessments

All assessments have been previously described in detail.[15] Briefly, standing height and weight were assessed and BMI was calculated (kg/m$^2$); waist circumference was also assessed. Cut-offs for increased waist circumference were >102cm for males or >88cm for females.[16] Body composition (body fat and fat free mass) was assessed by Bioelectrical Impedance (Tanita BC-418 MA Segmental Body Composition Analyzer, Tanita Corporation, Tokyo, Japan).

Inflammation was assessed by the erythrocyte sedimentation rate (ESR) and CRP. The Disease Activity Score-28 (DAS28) was used to assess clinical disease activity.[17] The anglicised version of the Stanford Health Assessment Questionnaire (HAQ)[18] was used to measure functional disability. Disease duration and RA medication were assessed by review of patients' clinical notes.

Blood pressure (BP) was assessed as previously described.[15] Briefly, BP was assessed, after at least 5min rest, on the right arm with the patient in a seated position. Reported value is the mean of three measurements taken at 5min intervals. Blood lipids, glucose and insulin were assessed in venous blood collected in the fasting state. Insulin sensitivity was evaluated with the Homeostasis Model Assessment of insulin resistance (HOMA =[Glucose x Insulin]/22.5)[19] and the Quantitative Insulin sensitivity Check Index (QUICKI =1/[logInsulin+logGlucose]).[20] Smoking status was recorded by patient self-report.

### Data Management and Analyses

The Kolmogorov-Smirnov test of normality was used to assess dispersion of the data. Dispersion is reported as mean (standard deviation) or median (interquartile range). Results of the logistic models are reported as odds ratio with 95% confidence intervals (OR, 95% CI). Statistical significance was set at $p<0.05$.

The frequency of occurrence of each phenotype was examined in the descriptive statistics of the sample. Cross-tabulations with $\chi^2$ analyses were performed to identify differences in the prevalence of cardiometabolic abnormalities between body sizes. Analysis of

**Table 1.** Body-size phenotype grouping criteria

| **Groups** | Criteria |
|---|---|
| Normal weight, metabolically healthy | BMI<25.0<br><2 cardiometabolic abnormalities |
| Normal weight, metabolically unhealthy | BMI<25.0<br>≥2 cardiometabolic abnormalities |
| Overweight, metabolically healthy | BMI 25.0-29.9<br><2 cardiometabolic abnormalities |
| Overweight, metabolically unhealthy | BMI 25.0-29.9<br>≥2 cardiometabolic abnormalities |
| Obese, metabolically healthy | BMI≥30.0<br><2 cardiometabolic abnormalities |
| Obese, metabolically unhealthy | BMI≥30.0<br>≥2 cardiometabolic abnormalities |
| **Cardiometabolic abnormalities**<br>1) High blood pressure: ≥140mmHg systolic, or ≥90mmHg, or on anti-hypertensive medication<br>2) High triglycerides: >1.7mmol/L<br>3) Low HDL (high density lipoprotein): <1.03mmol/L<br>4) High glucose: >5.5mmol/L<br>5) Insulin Resistance: HOMA≥2.5, or QUICKI≤0.333, or diagnosis for diabetes, or anti-diabetic medication | |

Variance (ANOVA) was used to test for differences between the various phenotypes in disease characteristics and inflammation. Finally, regression analyses were used to identify predictors of dysmetabolism (i.e., presence of 2 or more out of 5 metabolic abnormalities as defined above) among the various phenotypes. The initial models included the following as covariates: age, gender, smoking, BMI, body fat (BF), waist circumference, ESR, RA duration, RA medication (NSAIDs, methotrexate, steroids, and biologics). Variables with the least contribution to the model were eliminated until only significant variables remained.

## RESULTS

### Prevalence of body-size phenotypes in RA

In the total sample, 44% of the patients were metabolically unhealthy (i.e., had ≥2 cardiometabolic abnormalities). The prevalence of metabolic abnormality was 54.5% for males and 40.5% for females (p=0.011). Among normal-weight, 25% were metabolically unhealthy. Gender specific prevalence was 36.8% for males and 22.2% for females. In overweight patients, 45.8% had metabolic complications, 56% of males and 40.8% of females. Finally, 57.1% of obese individuals were metabolically unhealthy. Again, male participants had a higher prevalence of metabolic abnormalities (62.5%) compared to females (55.2%).

### Association of phenotypes with disease characteristics, inflammation, and body composition

Patients with metabolic abnormalities were compared to metabolically healthy patients within the same BMI categories. No statistically significant differences between groups were detected by ANOVA for any of the disease characteristics or markers of inflammation assessed (**Table 2**). However, patients with metabolic abnormalities tended to score slightly higher in all of these assessments.

Similarly, no statistically significant differences for measures of body composition were found between groups, apart from normal-weight patients, where metabolically healthy patients had significantly smaller waist circumference compared to metabolically unhealthy patients (84cm±7.5 vs. 90.5cm±8.5 respectively; p=0.007). Moreover, there was a tendency for higher waist circumference in all metabolically abnormal patients compared to their metabolically healthy counterparts.

### Predictors of metabolic abnormalities

Among the various different models used, regression analyses identified 3 significant predictors for metabolically unhealthy patients among all body sizes: older age (B= 1.032, err=0.011; p= 0.005), ex-smoker (B= 1.425, err= 0.169; p=0.036), and larger waist circumference (B= 1.057, err= 0.011; p= 0.000).

**Table 2.** Participants' characteristics by body-size phenotype

| | | Metabolically Healthy | | | Metabolically Abnormal | | |
|---|---|---|---|---|---|---|---|
| | Total | Normal Weight | Over-weight | Obese | Normal Weight | Over-weight | Obese |
| Prevalence (%, N) | 100 (362) | 18.7 (68) | 22.9 (83) | 14 (51) | 6.3 (23) | 19.3 (70) | 18.7 (68) |
| **Demographics** | | | | | | | |
| Female (%) | 72.2 | 80.4 | 73.5 | 76.5 | 71.6 | 65 | 70.6 |
| Age, years | 61 (12.1) | 59.5 (13.5) | 60.1 (12.4) | 55.8 (11.3) | 65.4 (12.7) | 62.2 (10.5) | 63.6 (10.7) † |
| Smoking (%) | | | | | | | |
| Current | 16.9 | 25.4 | 18.3 | 4 | 17.4 | 20.9 | 11.9 |
| Former | 37.9 | 22.4 | 34.1 | 34 | 43.5 | 41.8 | 55.2 |
| **Adiposity** | | | | | | | |
| BMI (kg/m$^2$) | 28.2 (4.7) | 22.6 (1.4) | 27.1 (1.4) | 33.2 (3.1) | 23.1 (1.1) | 27.1 (1.4) | 34 (3.1) |
| Body Fat (%) | 35.7 (8) | 29.5 (7.1) | 35.2 (6.8) | 41.9 (6) | 33.7 (5.6) | 33.6 (7) | 40.6 (7.2) |
| FFM (kg) | 48.4 (10.3) | 42.3 (8.6) | 47.5 (9.7) | 51.6 (9.1) | 41.8 (6.9) | 49.4 (10.1) | 54.2 (10.5) |
| Waist (cm) | 98.5 (12.5) | 84 (7.5) | 96.4 (6.3) | 106.8 (10) | 90.5 (8.5)* | 99.3 (8.2) | 111 (10.6) |
| **Cardiometabolic Factors** | | | | | | | |
| Systolic BP (mmHg) | 141.7 (20.2) | 131.1 (18.4) | 139.2 (18.4) | 138.6 (21.8) | 143.1 (16.2) | 145.1 (19.2) | 152.3 (19.8)† |
| Diastolic BP (mmHg) | 79 (11.3) | 75.1 (11.1) | 79.7 (9.9) | 79.3 (10.9) | 77.2 (13.7) | 80.5 (11.4) | 81 (11.6) |
| Hypertension (%) | 69.7 | 32.4 | 63.9 | 52.9 | 95.7* | 92.9# | 94.1† |
| Triglycerides (mmol/L) | 1.4 (0.7) | 1.2 (0.4) | 1.2 (0.4) | 1.1 (0.3) | 1.6 (0.6) | 1.8 (0.9) # | 1.8 (0.8)† |
| High Triglycerides (%) | 30 | 7.4 | 6 | 5.9 | 52.2* | 50# | 60.3† |
| HDL (mmol/L) | 1.6 (0.4) | 1.7 (0.5) | 1.7 (0.4) | 1.6 (0.4) | 1.7 (0.4) | 1.4 (0.5)# | 1.4 (0.4) † |
| Low HDL (%) | 9.6 | 2.9 | 0 | 3.9 | 8.7* | 24.3# | 17.6† |
| Glucose (mmol/L) | 5.2 (1.4) | 4.8 (0.1) | 4.7 (0.4) | 4.9 (0.4) | 5.6 (0.3) | 5.8 (1.5) | 5.7 (1.5) |
| High Glucose (%) | 17.6 | 1.5 | 1.2 | 5.9* | 21.7* | 32.9# | 45.6† |
| HOMA | 1.9 [2] | 1.2 [1] | 1.5 [1.1] | 1.6 [1] | 2.5 [2.7]* | 3.3 [3.8]# | 3.5 [3.6] † |
| QUICKI | 0.35 (0.05) | 0.38 (0.04) | 0.37 (0.03) | 0.37 (0.03) | 0.33 (0.04)* | 0.32 (0.04)# | 0.31 (0.03) † |
| Insulin resistance (%) | 38 | 8.8 | 6 | 7.8 | 69.6* | 71.4# | 83.8† |
| **RA characteristics** | | | | | | | |
| Disease Duration (years) | 12.5 (10.5) | 13.3 (10.1) | 13.2 (10.7) | 10.1 (7.3) | 13.4 (10.9) | 13.3 (10.6) | 11.7 (10) |
| ESR (mm/H) | 20 [28] | 16 [30] | 18 [25] | 22 [22] | 19 [22] | 22.5 [22] | 24.5 [30] |
| CRP (mg/L) | 8 [15] | 7 [13] | 8 [10] | 11 [15] | 8.5 [20] | 9 [17] | 10.5 [19] |
| HAQ | 1.4 (0.9) | 1.3 (0.9) | 1.3 (0.9) | 1.4 (0.9) | 1.4 (0.9) | 1.5 (0.95) | 1.6 (0.87) |
| DAS | 4.2 (1.4) | 3.9 (1.4) | 4.1 (1.3) | 4.2 (1.4) | 4.4 (1.6) | 4.3 (1.3) | 4.4 (1.5) |

* Significantly different to metabolically healthy normal weight ($p<0.05$)
# Significantly different to metabolically healthy overweight ($p<0.05$)
† Significantly different to metabolically healthy obese ($p<0.05$)
BMI: body mass index; BP: blood pressure; CRP: C-reactive protein; DAS: disease activity score 28; ESR: erythrocyte sedimentation rate; FFM: fat free mass; HAQ: health assessment questionnaire; HDL: high density lipoprotein; HOMA: homeostasis model assessment of insulin resistance; LDL: low density lipoprotein; N: number; QUICKI: quantitative insulin sensitivity check index.

## DISCUSSION

The aim of this study was to investigate the prevalence of metabolic complications in different body-size phenotypes in RA patients, to test their associations with disease activity, and to identify potential predictors of such metabolic complications in these phenotypes. To our knowledge, this is the first study to investigate this in RA.

We were able to identify 6 different body-size phenotypes among patients with RA. Most importantly, we identified several normal-weight patients with metabolic abnormalities as well as overweight and obese patients without any such abnormalities. In the general population,[1] the prevalence of normal-weight individuals with metabolic abnormalities is very similar to that reported here for RA (23.5% vs 25%, respectively). This is also the case for overweight patients (51.3% vs 45.8%), However, there seems to be a large difference in the percentage of obese patients with RA that exhibit cardiometabolic complications compared to the general population: in our RA population, 57.1% of the obese participants had such complications, compared to almost 70% reported in the general population. We need to note that a large percentage of our population is female (>60%) and, as we have shown in our results, females tend to have less metabolic complications compared to males (55.2% vs 62.5% respectively in our sample). In a sample with more male participants, prevalence of metabolic complications could be higher but still, based on our findings, lower than that of the general population.

In the present study, we used the general BMI categorisation instead of our previously published RA specific BMI cut-off points (i.e., 23kg/m$^2$ and 28kg/m$^2$ for overweight and obesity respectively),[7] so that our findings can be directly comparable to that of the existing literature in other populations. However, the use of RA-specific BMI cut-off points yields similar results for the subgroups (i.e., 22.4%, 48.9%, 60.1% among normal-weight, overweight and obese exhibit metabolic complications). Thus, the use of these cut-off points does not change the essence of our findings.

In the existing literature, a protective effect of obesity in RA, both in terms of disease activity[8,9] and cardiovascular risk[10] has been reported. Our data, similarly to observations in the general population,[21] does not support this: metabolic complications are more prevalent in obese than in overweight or normal-weight patients. However, they do support the notion that obesity may have a lesser impact - at least in terms of metabolic complications - in RA, compared to the general population.[22] In general, obese individuals exhibit, in absolute terms, larger fat-free mass compared to leaner individuals. In RA, loss of fat-free mass, and especially muscle mass, is very common[23] and is mostly observed in normal-weight patients, while excessive body weight seems to be accompanied by a relative preservation of fat-free mass.[24] Since the muscle is where most of the metabolic activity occurs, increased muscle mass may counteract some of the negative effects of obesity and help some obese RA patients maintain a healthier metabolism than their counterparts in the general population.

In the present study, we were unable to find any significant differences in disease characteristics and inflammation between body-size phenotypes. However, metabolically healthy patients tended to have smaller waist circumference compared to metabolically unhealthy. Central adiposity is a well-established risk factor for CVD and its assessment is included in several of the definitions for the metabolic syndrome.[25] Excess abdominal adiposity is considered to be one of the main causes of metabolic complications; enlarged adipose tissue secretes a number of bioactive molecules called adipokines.[26] These participate in a number of metabolic processes which can inhibit the expression of several genes (such as GLUT4 and PPARγ) associated with transportation of glucose or production and sensitisation of insulin; they also promote lipolysis and thus increase the levels of circulating free fatty acids, while they may also act directly on insulin signalling.[27] These mechanisms may reduce insulin action in the muscle, and cause endothelial dysfunction,[28,29] hypertension,[30] and eventually CVD.[31] The significance of central adiposity is further supported by the fact that body fat percentages were very similar between body-weight phenotypes; indicating that overall fat may be a lesser factor for the development of metabolic complications than body fat distribution. Moreover, the gender differences initially observed became insignificant when waist circumference was introduced in the models, as is indeed the case in the general population.[1] These observations highlight the importance for the assessment of central adiposity.

In addition to waist circumference, smoking cessation was identified as a significant predictor for metabolic complications. We have shown previously[32] that within RA, ex-smokers exhibit high body fat content and increased waist-circumference; both of which may contribute to metabolic complications. However, the fact that ex-smoking was an independent predictor of metabolic complication may indicate the existence of other mechanisms. Finally, old age was also an independent predictor of metabolic complications. Aging associates with a number of significant changes, including anthropometric and lifestyle alterations, neuro-hormonal variations, and increases in oxidative stress; resulting in reduced insulin sensitivity[33,34] which is implicated in a number of mechanisms leading to CVD.[35] This is also evident among our patients: metabolically healthy pa-

tients were significantly younger than their metabolically unhealthy counterparts.

This study proves that the assessment of obesity, in terms of BMI alone, is not a sufficient indicator of metabolic state.[36] This might partly explain the conflicting evidence for the impact of obesity on the health of RA patients. Studies investigating obesity in RA should try to stratify patients according to body-size phenotypes and analyse their data accordingly. Furthermore, the identified predictors of subtype allocation (i.e., older age, higher waist circumference, and smoking status) should be systematically included as potential confounders in analyses of such studies. Essentially, our findings point towards a combination of assessments for obesity. However, further studies are needed before we can propose specific methods for that purpose.

The results of this study should be interpreted with caution. This is a cross-sectional study and results do not provide definitive evidence for causality or directionality. Furthermore, comparisons with the general population are based on the existing literature and not directly on a local control group. Race, physical activity and diet - all significant aspects in the study of obesity - were not assessed. On the other hand, the size of the cohort and the prospective collection of data in a standardised, systematic manner are important strengths, as they minimised missing values and selection bias, and allowed adjustment for potentially important confounders. The method of classification in body size phenotypes, despite being widely used, does not allow for quantitative evaluation of the cardiometabolic abnormalities. In this way, a patient with a value just above the cut-off point (e.g., blood pressure of 140/90 mmHg) will be classified in the same group as a patient with a very high value (e.g., blood pressure 180/100 mmHg). However, this is the case for other classification methods, such as the metabolic syndrome, which serve primarily for identifying patients at risk for adverse effects and do not dictate medical interventions.[25]

In conclusion, within its limitations, this study identified a number of different body-size phenotypes among RA patients. One in 4 normal-weight patients has metabolic complications, while >40% of obese RA patients are metabolically healthy. Old age, waist circumference and smoking cessation are significant predictors for metabolic complications among the various body-sizes, whereas (current) inflammation or physical dysfunction do not appear to be as important. Yet, the underlying mechanisms by which these or other factors influence metabolism in RA are far from clear and require further investigation. Further research focusing on specific adipose depots and their metabolic properties should be conducted.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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