The relationship between weight status and metabolic syndrome in patients with rheumatoid arthritis and spondyloarthritis

Charlotte Giraud, Céline Lambert, Frederic Dutheil, Bruno Pereira, Martin Soubrier, Anne Tournadre

Version of Record: https://www.sciencedirect.com/science/article/pii/S1297319X20301445
Manuscript_e054804ac717b7b74b6b92d4d4642ac9

The relationship between weight status and metabolic syndrome in patients with rheumatoid arthritis and spondyloarthritis

Charlotte Giraud[1,2] , Céline Lambert[3] , Frédéric Dutheil[4], Bruno Pereira[3], Martin Soubrier[1,2], Anne Tournadre[1,2]

[1] Rheumatology department, CHU Clermont-Ferrand, 63003 Clermont-Ferrand, France

[2] UNH-UMR 1019, INRA and University of Auvergne, 63003 Clermont-Ferrand, France

[3] Biostatistics unit (DRCI), CHU Clermont-Ferrand, 63003 Clermont-Ferrand, France

[4] Preventive and Occupational Medicine, CHU Clermont-Ferrand, 63003 Clermont-Ferrand, France

Corresponding author:

Pr Anne Tournadre

Rheumatology Department, Hopital G. Montpied

58 rue Montalembert BP69, 63003 Clermont-Ferrand Cedex 1, France

Tel (33) 473 751 488; Fax (33) 473 751 489

atournadre@chu-clermontferrand.fr

Abstract

Objectives: To compare the prevalence and correlates of metabolic syndrome (MetS) stratified by body mass index (BMI) categories in rheumatoid arthritis (RA) and spondyloarthritis (SpA).

Methods: The age- and sex-standardized prevalence of MetS was calculated by BMI categories and compared between RA and SpA patients before starting first biologic, and controls. The determinants of metabolic syndrome in patients without obesity were investigated.

Results: MetS was observed in 28 % of RA (21/75), 22.5 % of SpA (18/80), 19 % of controls (187/998). The age- and sex-standardized prevalence of MetS was not significantly different between RA 19% (95% CI: 11-27%), SpA 26% (95% CI: 16-36%) and controls 16% (95% CI: 14-18%). When stratified by BMI, the standardized prevalence of MetS was less frequent in obese RA patients (15%, 95% CI: 4-27%) compared to obese controls (48%, 95% CI: 40-55%) or to obese SpA (36%, 95% CI: 26-45%). In normal-weight RA patients, MetS standardized prevalence was 16% (95% CI: 7-25%) compared to 5% (95% CI: 0-11%) in SpA, and 6% (95% CI: 4-8%) in controls. In non-obese SpA, MetS was associated with abdominal obesity, visceral fat mass and cardiovascular risk. In non-obese RA patients with metabolic syndrome, body composition did not differ from metabolically healthy RA patients.

Conclusions: MetS is not uniform among patients with similar BMI. In RA, MetS was less frequent in obese patients, and unlike SpA, was not associated with body fat composition in non-obese patients. Differences between RA and SpA for metabolic health suggest various pathophysiological mechanisms.

key words: metabolic syndrome, obesity, rheumatoid arthritis, spondyloarthritis

Introduction

Patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA) have in common an increased cardiovascular (CV) mortality [1]. Traditional CV risk factors and inflammation that both promote atherosclerosis and exacerbate established CV risk factors may explain this increased risk [2–4]. In addition, inflammation promotes metabolic disorders. Patients with RA and SpA exhibit higher risk for metabolic syndrome [5–7] and altered body composition characterized by a decrease in lean mass while fat mass may be preserved or even increased regardless of changes in total body weight [8–10]. This phenotype also called "sarcopenic obesity" is associated with intramuscular fat accumulation [11,12] which promote insulin resistance and contribute to the alteration of muscle performances, inducing frailty and disability in RA patients, which in turn exacerbate muscle loss and fat deposition [13].

A BMI in the normal range associates with a decreased risk of cardio-metabolic disease and all-cause mortality in the general population [14]. However, this does not apply to all subjects with normal BMI: 20% of the normal-weight adults are metabolically unhealthy with a 3-fold higher risk of all-cause mortality and CV events [15]. In contrast, metabolically healthy obese subjects appear relatively resistant to cardio-metabolic disorders. Contrasting with the general population, low BMI associates with increased all-cause and CV mortality in RA which could be explained by an alteration in body composition and lean-to-fat mass ratio [16]. To date, the metabolic profile associated with body size phenotypes has not been explored in chronic inflammatory rheumatic diseases.

Therefore, the purpose of the present study was (1) to determine the prevalence of metabolic syndrome stratified by BMI categories among 75 RA and 80 SpA patients and to compare to the general population (2) to analyze in an exploratory study the characteristics of patients with metabolic syndrome (21 RA and 18 SpA) focusing on 16 RA and 12 SpA patients without obesity.

Methods

Patients.

Patients over 18 years-old with RA and SpA starting first biologic Disease-modifying anti-rheumatic drugs (DMARD) were included from 2014 in the longitudinal cohort of RCVRIC analyzing cardiovascular risk and chronic inflammatory rheumatism (PHRC RCVRIC AOI 2014 N° ID-RCB-A01847-40). The patients fulfilled the 2010 RA classification criteria [17], the ASAS classification criteria for axial [18] or peripheral [19] SpA. Patients with psoriatic arthritis (PsA) fulfilling the Caspar criteria were not included in the study and in the SpA group because of a too specific metabolic phenotype. Patients with pathologies or treatments which could interfere with metabolic syndrome or body composition (thyroid disease, kidneys and/or liver deficiency, pregnancy, chronic infections, active neoplasia, ethanol consumption of >30g a day) were excluded.

The study was approved by the local ethics committee of Clermont-Ferrand (Institutional Review Boards: AU 1161) and all the patients gave informed consent for participation.

Controls.

Controls were obtained among all workers undergoing annual work medical examination from occupational health services in the University Hospital of Clermont-Ferrand. Socio-demographic, occupational and clinical data were retrieved. People with a history of musculoskeletal disease were excluded as well as those for whom data to define the metabolic syndrome or necessary for age and sex standardization were not available. From the 10,805 participants, 998 controls were included for analysis. The study was approved by the local ethics committee of Clermont-Ferrand (Institutional Review Boards: 2015CE/70) and all the patients gave informed consent for participation.

Measurements.

- Patient disease assessment.

Standard demographic data, disease and imaging characteristics, cardio-metabolic profile of patients were recorded at inclusion. The duration, extra articular manifestations, the presence of rheumatoid factor and/or anti-CCP antibodies, HLAB27 status, and biological markers of inflammation (erythrocyte sedimentation rate (ESR; mm/h) and circulating concentration of C-reactive protein (CRP; mg/l)) were recorded. Disease activity was evaluated by the DAS 28ESR/CRP, the BASDAI and ASDAS-CRP. Radiographic erosions were recorded at baseline feet and hands. Sacroiliitis was recorded on radiographs and MRI of the sacroiliac joints. All treatments were registered: conventional DMARDs, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs).

- Cardio-metabolic profile.

Weight, height, waist circumference, blood pressure, cholesterol-lowering, antihypertensive, antidiabetic drugs were collected in all patients. BMI was calculated as weight (in kg) divided by height (in m^2). Subjects were categorized in different BMI strata: normal weight BMI <25kg/m², overweight BMI 25-29.9 kg/m² and obese BMI ≥30kg/m². Patients were questioned for common cardiovascular risk factors including age, sex, family or personal history of cardiovascular disease, such as stroke, myocardial infarction or sudden death, type 2 diabetes or impaired fasting glucose, past and current smoking, history of hypertension, dyslipidemia (plasma LDL-C, HDL-C and TG), familial dyslipidemia. Ten-year CVD risk was calculated using the Systematic COronary Risk Evaluation (SCORE) equation (10) adapted for patients with RA by a 1.5 multiplication factor [20].

Metabolic syndrome was defined according the WHO criteria [21]. Three abnormal findings out of 5 would qualify a person for the metabolic syndrome: elevated waist circumference (≥94cm for men, ≥80cm for women), elevated triglycerides ≥150 mg/dl, reduced HDLc <50mg/dl for women and <40mg/dl for men or drug treatment, elevated blood pressure or

antihypertensive medication, elevated fasting glucose ≥1g/l or type 2 diabetes mellitus. Arterial stiffness, a marker of the cardiovascular risk, was measured by augmentation of pulse wave velocity (PWV) using the Sphygmocor apparatus (Atcor Medical, Sydney,Australia) as previously described [22].

- Body composition.

All subjects underwent total body DXA scanning (HOLOGIC Discovery A S/N 85701). Fat, lean, and bone mass for the total body and per region (arms, legs, and trunk) were measured and analyzed using the manufacturer's validated software (version 4.02 HOLOGIC APEX). Daily quality control and calibration procedures were performed using the manufacturer's standard. Body fat percentage was calculated as the proportion of total fat mass to total mass. Appendicular fat and lean masses were computed as the sum of the tissue compartment (fat or lean) of both arms and legs. Skeletal muscle mass index (SMI) was calculated as appendicular lean mass divided by height^2, fat mass index (FMI) as total fat mass divided by height^2. The trunk-peripheral fat ratio, a measure of "android" fat was calculated using fat of the body trunk divided by the peripheral (legs and arms) fat. Separation of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) were performed by two blinded readers inside a region of interest using a new software developed on DXA with a validated method [10].

Statistical analysis.

Statistical analysis was performed using Stata software (version 13, StataCorp, College Station, TX). All tests were two-sided, with a type I error set at 5%. Categorical parameters were expressed as frequencies and associated percentages, and continuous data as mean ± standard deviation or as median [interquartile range], according to statistical distribution. The age- and sex-standardized prevalence of metabolic syndrome was calculated by BMI categories (normal weight BMI<25kg/m², overweight BMI 25-29.9 kg/m² and obese BMI ≥30kg/m²) using direct standardization with the age and sex distribution of the French

population between the ages of 20 and 80 as the standard (according to INSEE estimates at the January, 1st2017). The prevalence are expressed with 95% confidence intervals (CI). Then, quantitative variables were compared between independent groups (metabolically healthy patients vs. metabolically unhealthy patients) by Student t-test or Mann-Whitney test, as appropriate. The Gaussian distribution was verified by the Shapiro-Wilk test and homoscedasticity by the Fisher-Snedecor test. For categorical variables, comparisons between groups were done by the chi-squared test or by the Fischer exact test. The results were expressed as effect-size (ES) and 95% confidence interval. Effect-size bounds were defined as follows [23] : small (ES: 0.2), medium (ES: 0.5) and large (ES: 0.8, "grossly perceptible and therefore large").

Results

Characteristics of the study participants

Characteristics of patients with RA, SpA and controls are summarized table 1.

Seventy-five RA patients were included (73% women, mean age of 59.2±11.0 years). RA was active (DAS 28 CRP 4.24 ± 1.13) with a median duration of 2.5 years [0.5–10.0]. The majority of patients were RF-positive or anti-CCP positive (84%). Current conventional DMARD was noted in 68 patients (93%), of these 54 (86%) took methotrexate. Steroids were noted in 38 patients (54%). Among RA patients, 34 (45%) had normal weight, 28 (37%) were overweight and 13 (17%) obese. Metabolic syndrome was reported in 21 patients (28%); of these 9 had normal weight (43%), 7 overweight (33%) and 5 obesity (24%).

Eighty SpA patients were included (55% women, mean age 45.9±12.7 years). Sixty-four (80%) were classified as axial SpA. HLAB27 positivity was noted in 48 patients (61%), and sacroiliitis on radiographs or MRI in 45 (57%). Mean BASDAI and ASDAS-CRP were respectively 54.6 ± 17.5 and 3.14 ± 0.72. Treatment with NSAIDs was noted in 52 patients (71%). Among SpA, 32 patients (40%) had normal weight, 31 (39%) were overweight and 17

(21%) obese. Metabolic syndrome was reported in 18 patients (22.5%); of these 3 had normal weight (17%), 9 overweight (50%) and 6 obesity (33%).

Among the 998 controls analyzed for metabolic syndrome (61% of women, mean age 42.7±9.4 years), 632 (64%) had normal weight, 263 (26%) were overweight and 103 (10%) obese. Metabolic syndrome was observed in 187 controls (19%); of these 46 had normal weight (25%), 81 overweight (43%) and 60 obesity (32%).

Prevalence of metabolic syndrome among BMI categories

The age- and sex-standardized prevalence of metabolic syndrome was not significantly different between RA, 19% (95% CI: 11% to 27%), SpA 26% (95% CI: 16% to 36%) and controls 16% (95% CI: 14% to 18%).

When stratified by BMI categories, the age- and sex-standardized prevalence of metabolic syndrome differed between the three groups (Figure 1). In contrast to controls and in a lesser extent to SpA, the prevalence of metabolic syndrome did not increase with bodyweight in RA. In normal-weight patients, metabolic syndrome was 16% (95% CI: 7% to 25%) in RA, as compared to 5% (95% CI, 0% to 11%) in SpA, and 6% (95% CI: 4% to 8%) in controls. By contrast, in obese population, metabolic syndrome was less frequent in RA patients (15%, 95% CI: 4% to 27%) compared to controls (48%, 95% CI: 40% to 55%, p=0.03) or to SpA (36%, 95% CI: 26% to 45%, p=0.06).

Comparison between metabolically healthy and unhealthy patients

RA patients with metabolic syndrome (n=21) were not different from metabolically healthy RA (n=54) patients for weight, waist circumference, body composition (Table 2). Others components of the metabolic syndrome were significantly different between healthy and unhealthy patients: elevated triglycerides (p<0.001), elevated glycemia (p=0.02), reduced HDLc (p<0.001) (Table 2). Contrasting with RA, BMI (p=0.02), waist circumference

(p<0.001), troncular (p=0.008) and visceral (p=0.004) fat, as well as markers of CV risk (SCORE p=0.003 and PWV p=0.005) were increased in SpA with metabolic syndrome (n=18) compared to metabolically healthy patients (n=62).

Then we investigated the factors associated with metabolic syndrome focusing on patients without obesity which corresponds to 16 RA and 12 SpA patients (Table 3 and Figure 2). Both in non-obeses (BMI <30kg/m²) RA and SpA patients, elevated triglycerides and reduced HDLc had the higher correlation with metabolic syndrome as assessed with the effect size. Only for non-obese SpA patients but not for RA patients, body fat composition (total fat mass, fat mass index, troncular, visceral and subcutaneous fat mass) was associated with metabolic syndrome. Cardiovascular risk assessed with the SCORE equation and arterial stiffness were also significantly associated with metabolic syndrome. Conversely, non-obese RA patients with metabolic syndrome did not differ for the body composition from metabolically healthy non-obese RA patients.

Discussion

When standardized on age and sex, the prevalence of metabolic syndrome was similar between RA (19%), SpA (26%) and controls (16%). The prevalence of metabolic syndrome among the three different populations is consistent with the literature. A great variability exists according to the sex, age, ethnic origin of the studied populations and the criteria used for the estimation of the metabolic syndrome. In RA, the overall pooled prevalence of metabolic syndrome varied from 14.3% to 37.8% based upon the diagnostic criteria used and the mean age [5]. In axial SpA, less data are available and the estimated prevalence of metabolic syndrome varied from 27% to 45.8% [24–26]. In the general French population, a survey of 1,856 participants (The French Nutrition and Health Survey 2006-2007) reported a prevalence of metabolic syndrome between 14.6 % and 21.1%, increasing with age and lower

than in most industrialized countries [27]. In our study, 54% of RA, 60% of SpA and 36% of controls were overweight or obese which is similar to the 60%, 59% and 43% reported in the literature [28–30].

Our results extend prior observations as we observed different distribution of the metabolic syndrome in normal-weight and obese persons. In RA patients, metabolically healthy obesity was more frequent compared to controls, and metabolically unhealthy normal-weight was paradoxically not associated with body fat composition. Conversely, whether in overall SpA or in non-obese SpA, metabolic syndrome was associated with abdominal obesity, visceral fat mass and CV risk. As expected, RA received more often corticosteroids than SpA, especially since these are mainly axial SpA. However, in RA, corticosteroid therapy does not seem to be associated with metabolic health whether in the total population or in non-obese patients. Very few patients with SpA received systemic steroids, and this therefore could not explain that metabolic syndrome was associated with body fat composition.

The higher prevalence of metabolically healthy obesity among RA patients supports the so-called “obesity paradox”. This term refers to the protective effect of overweight and obesity in such patients [31–33]. If obesity and metabolic syndrome are well recognized risk factors for CV diseases and all-cause mortality [14,34], recent studies reported that cardio metabolic abnormalities may not be uniform among the body size phenotypes [15,35]. This led to the identification of metabolically unhealthy normal-weight individuals and by opposition metabolically healthy obese individuals. Interestingly, highest risk of all-cause mortality and CV events was noted in metabolically unhealthy normal-weight persons [36]. The different pathophysiological mechanisms leading to elevated blood glucose, blood lipids, and blood pressure values in lean subjects are not currently identified [15]. They may include the variability in body fat distribution. Visceral fat has been identified as key actor in the development of dyslipemia, insulin resistance, hypertension, atherosclerosis and cardiovascular events [34]. Other localized fat depots around the heart, including pericardial

and epicardial fat, have also been shown to be associated with coronary events in the general population independent of traditional risk factors. The muscular accumulation of toxic lipid mediators also called lipotoxicity promote insulin resistance, anabolic muscular resistance and mitochondrial dysfunction [37,38]. During chronic inflammation, decreased capacity of fat storage in adipose tissue can lead to accumulation of ectopic fat in non-adipose tissue such as liver, muscle, heart [39]. At the opposite, lower-body subcutaneous adipose tissue included the leg regions is associated with a lower cardiac risk factor burden and may be protective by acting as a metabolic buffer [34]. Sex differences related to estrogens and testosterone impact the distribution of fat as well as genetic factors. In addition, lifestyle and reduced physical activity contribute to the occurrence of metabolic syndrome in normal-weight individuals [35,40]. Although RA and SpA have in common increased CV mortality and insulin resistance, differences between RA and SpA for metabolic health by body size phenotype, and for the correlation with body fat suggest various pathophysiological mechanisms leading to metabolic syndrome. This hypothesis will require future studies including exploration of ectopic fat in muscle or heart tissues, lifestyle changes (physical activity, sedentary behaviors, diet), comorbidities such as anxiety or depression and treatments. In addition, studies comparing RA and PsA which is considered to be more related to metabolic comorbidities than RA due to the high prevalence of obesity and type 2 diabetes [41], could explore different inflammatory and metabolic pathways.

Finally, our results highlight the inability of BMI and anthropometric to capture cardiometabolic risk especially in RA patients.

Strengths of the study include the comparison of three different populations for the distribution of metabolic syndrome by body size phenotypes. Age and sex are important confounding factors for the development of metabolic abnormalities. Then, the age and sex-standardized prevalence of having metabolic syndrome calculated by direct standardization with the age and sex distribution of the French population as the standard, was used to

compare RA, SpA and controls. The age and sex differences between RA, SpA due to the disease characteristics did not allow for a satisfactory matching with same control group.

Limits include the lack of assessment of others potential risk factors for metabolic syndrome, such as lifestyle changes (diet, physical activity), socioeconomic status. We analyzed the factors associated with metabolic syndrome focusing on non-obese (BMI<30 kg/m^2) due to the limited number of RA and SpA subjects with metabolic syndrome and normal-weight. The small number of patients in this exploratory study allows to detect "grossly perceptible and therefore significant" differences with an effect size of around 0.8 between non-obese patients who are metabolically healthy and unhealthy. It should be noted that this small number of subjects could not detect more detailed differences.

Finally, although obesity and fat mass are strongly linked to metabolic abnormalities, the prevalence of metabolic syndrome is not uniform among patients with similar BMI, and differ according disease's characteristics. In RA, metabolic syndrome was less frequent in obese patients, and not associated with body fat composition in non-obese patients. Further studies are required to determine the effect and mechanisms involved in this metabolic heterogeneity.

Competing interests: None.

Patient consent Obtained.

Ethics approval: Institutional Review Boards: AU 1161.

Funding statement: None

References

[1] Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008;59:1690–7.

[2] Mathieu S, Motreff P, Soubrier M. Spondyloarthropathies: an independent cardiovascular risk factor? Jt Bone Spine Rev Rhum 2010;77:542–5.

[3] Zhang J, Chen L, Delzell E, Muntner P, Hillegass WB, Safford MM, et al. The association between inflammatory markers, serum lipids and the risk of cardiovascular events in patients with rheumatoid arthritis. Ann Rheum Dis 2014;73:1301–8.

[4] Choy E, Ganeshalingam K, Semb AG, Szekanecz Z, Nurmohamed M. Cardiovascular risk in rheumatoid arthritis: recent advances in the understanding of the pivotal role of inflammation, risk predictors and the impact of treatment. Rheumatol Oxf Engl 2014;53:2143–54.

[5] Hallajzadeh J, Safiri S, Mansournia MA, Khoramdad M, Izadi N, Almasi-Hashiani A, et al. Metabolic syndrome and its components among rheumatoid arthritis patients: A comprehensive updated systematic review and meta-analysis. PLoS ONE 2017;12. https://doi.org/10.1371/journal.pone.0170361.

[6] Malesci D, Niglio A, Mennillo GA, Buono R, Valentini G, La Montagna G. High prevalence of metabolic syndrome in patients with ankylosing spondylitis. Clin Rheumatol 2007;26:710–4.

[7] Sidiropoulos PI, Karvounaris SA, Boumpas DT. Metabolic syndrome in rheumatic diseases: epidemiology, pathophysiology, and clinical implications. Arthritis Res Ther 2008;10:207.

[8] Giles JT, Bartlett SJ, Andersen RE, Fontaine KR, Bathon JM. Association of body composition with disability in rheumatoid arthritis: Impact of appendicular fat and lean tissue mass. Arthritis Care Res 2008;59:1407–15.

[9] Giles JT, Allison M, Blumenthal RS, Post W, Gelber AC, Petri M, et al. Abdominal adiposity in rheumatoid arthritis: association with cardiometabolic risk factors and disease characteristics. Arthritis Rheum 2010;62:3173–82.

[10] Tournadre A, Pereira B, Dutheil F, Giraud C, Courteix D, Sapin V, et al. Changes in body composition and metabolic profile during interleukin 6 inhibition in rheumatoid arthritis. J Cachexia Sarcopenia Muscle 2017:n/a-n/a. https://doi.org/10.1002/jcsm.12189.

[11] Kramer HR, Fontaine KR, Bathon JM, Giles JT. Muscle density in rheumatoid arthritis: Associations with disease features and functional outcomes. Arthritis Rheum 2012;64:2438–50.

[12] Baker JF, Von Feldt J, Mostoufi-Moab S, Noaiseh G, Taratuta E, Kim W, et al. Deficits in Muscle Mass, Muscle Density, and Modified Associations With Fat in Rheumatoid Arthritis. Arthritis Care Res 2014;66:1612–8.

[13] Baker JF, Mostoufi-Moab S, Long J, Zemel B, Ibrahim S, Taratuta E, et al. Intramuscular Fat Accumulation and Associations with Body Composition, Strength and Physical Functioning in Rheumatoid Arthritis. Arthritis Care Res 2018. https://doi.org/10.1002/acr.23550.

[14] Global BMI Mortality Collaboration null, Di Angelantonio E, Bhupathiraju S, Wormser D, Gao P, Kaptoge S, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet Lond Engl 2016;388:776–86.

[15] Stefan N, Schick F, Häring H-U. Causes, Characteristics, and Consequences of Metabolically Unhealthy Normal Weight in Humans. Cell Metab 2017;26:292–300.

[16] Wolfe F, Michaud K. Effect of body mass index on mortality and clinical status in rheumatoid arthritis. Arthritis Care Res 2012;64:1471–9.

[17] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.
[18] Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777–83.
[19] Rudwaleit M, van der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2011;70:25–31.
[20] Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJL, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis 2017;76:17–28.
[21] Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–5.
[22] Mathieu S, Pereira B, Dubost J-J, Lusson J-R, Soubrier M. No significant change in arterial stiffness in RA after 6 months and 1 year of rituximab treatment. Rheumatol Oxf Engl 2012;51:1107–11.
[23] Cohen J. Statistical Power Analysis for the Behavioral Sciences. Academic Press; 2013.
[24] Papadakis JA, Sidiropoulos PI, Karvounaris SA, Vrentzos GE, Spanakis EK, Ganotakis ES, et al. High prevalence of metabolic syndrome and cardiovascular risk factors in men with ankylosing spondylitis on anti-TNFalpha treatment: correlation with disease activity. Clin Exp Rheumatol 2009;27:292–8.
[25] Maia DG, Augusto KL, Bezerra MC, Rodrigues CEM. Metabolic syndrome in patients with ankylosing spondylitis receiving anti-TNFα therapy: association with predictors of cardiovascular risk. Clin Rheumatol 2017;36:2371–6.
[26] Malesci D, Niglio A, Mennillo GA, Buono R, Valentini G, La Montagna G. High prevalence of metabolic syndrome in patients with ankylosing spondylitis. Clin Rheumatol 2007;26:710–4.
[27] Vernay M, Salanave B, de Peretti C, Druet C, Malon A, Deschamps V, et al. Metabolic syndrome and socioeconomic status in France: The French Nutrition and Health Survey (ENNS, 2006–2007) n.d.:10.
[28] Stavropoulos-Kalinoglou A, Metsios GS, Koutedakis Y, Kitas GD. Obesity in rheumatoid arthritis. Rheumatol Oxf Engl 2011;50:450–62.
[29] Maas F, Arends S, van der Veer E, Wink F, Efde M, Bootsma H, et al. Obesity Is Common in Axial Spondyloarthritis and Is Associated with Poor Clinical Outcome. J Rheumatol 2016;43:383–7.
[30] Feral-Pierssens A-L, Carette C, Rives-Lange C, Matta J, Goldberg M, Juvin P, et al. Obesity and emergency care in the French CONSTANCES cohort n.d.:12.
[31] Sparks JA, Chang S-C, Nguyen U-S, Barbhaiya M, Tedeschi SK, Lu B, et al. Weight Change During the Early Rheumatoid Arthritis Period and Risk of Subsequent Mortality in Women With Rheumatoid Arthritis and Matched Comparators. Arthritis Rheumatol 2018;70:18–29.

[32] Baker JF, Billig E, Michaud K, Ibrahim S, Caplan L, Cannon GW, et al. Weight Loss, the Obesity Paradox, and the Risk of Death in Rheumatoid Arthritis: WEIGHT LOSS AS A PREDICTOR OF DEATH IN RA. Arthritis Rheumatol 2015;67:1711–7.
[33] Kremers HM, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis. Arthritis Rheum 2004;50:3450–7.
[34] Neeland IJ, Poirier P, Després J-P. Cardiovascular and Metabolic Heterogeneity of Obesity: Clinical Challenges and Implications for Management. Circulation 2018;137:1391–406.
[35] Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). Arch Intern Med 2008;168:1617–24.
[36] Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. Ann Intern Med 2013;159:758–69.
[37] Guillet C, Delcourt I, Rance M, Giraudet C, Walrand S, Bedu M, et al. Changes in basal and insulin and amino acid response of whole body and skeletal muscle proteins in obese men. J Clin Endocrinol Metab 2009;94:3044–50.
[38] Fabbri E, Chiles Shaffer N, Gonzalez-Freire M, Shardell MD, Zoli M, Studenski SA, et al. Early body composition, but not body mass, is associated with future accelerated decline in muscle quality. J Cachexia Sarcopenia Muscle 2017;8:490–9.
[39] Liu L, Mei M, Yang S, Li Q. Roles of Chronic Low-Grade Inflammation in the Development of Ectopic Fat Deposition. Mediators Inflamm n.d.:8.
[40] Scheen AJ. Progression of the prevalence of metabolic syndrome in normal-weight US subjects. Arch Intern Med 2009;169:636–7; author reply 637.
[41] Ferguson LD, Siebert S, McInnes IB, Sattar N. Cardiometabolic comorbidities in RA and PsA: lessons learned and future directions. Nat Rev Rheumatol 2019;15:461–74.

Table 1. Characteristics of the study participants. Data are presented as frequencies (associated percentages), as mean ± standard deviation, or as median [interquartile range].

	RA (n=75)	**SpA** (n=80)	**Controls** (n=998)
Female	55 (73%) *	44 (55%)	604 (61%)
Age (years)	59.2 ± 11.0 ***	45.9 ± 12.7 *	42.7 ± 9.4
BMI (kg/m²)	26.0 ± 5.0 **	27.0 ± 5.4 ***	24.4 ± 4.5
Normal weight	34 (45%)	32 (40%)	632 (64%)
Overweight	28 (37%)	31 (39%)	263 (26%)
Obese	13 (17%)	17 (21%)	103 (10%)
Waist circumference (cm)	93.3 ± 12.7 ***	94.0 ± 13.9 ***	85.5 ± 12.7
Triglycerides (g/l)	1.07 [0.79-1.38] ***	0.91 [0.60-1.39]	0.88 [0.64-1.24]
HDLc (g/l)	0.62 ± 0.17	0.56 ± 0.16	0.62 ± 0.65
LDLc (g/l)	1.20 ± 0.33	1.18 ± 0.42	1.26 ± 0.36
Glycemia (g/l)	0.90 ± 0.19	0.87 ± 0.25	0.89 ± 0.36
Blood hypertension	28 (37%) *	12 (15%) *	255 (26%)
Smoking	22 (31%)	29 (37%)	-
SCORE %	1.5 [0.0-3.0]	0.0 [0.0-1.0]	-
Disease duration (years)	2.5 [0.5-10.0]	1.0 [0.3-5.5]	-
DAS 28 CRP	4.24 ± 1.13	-	-
BASDAI	-	54.6 ± 17.5	-
ASDAS CRP	-	3.14 ± 0.72	-
HAQ	0.75 [0.50-1.12]	0.75 [0.37-1.12]	-
CRP (mg/l)	7.4 [2.9-17.2]	4.6 [2.9-15.4]	-
antiCCP or RF seropositivity	42/50 (84%)	-	-
Axial spA		64/80 (80 %)	
HLA B27 positivity	-	48/79 (61%)	-
Sacroiliitis (Radiographs or MRI)	-	45/79 (57%)	-
current NSAIDs	15/54 (28%)	52/73 (71%)	-
current steroids	32 (43%)	2 (3 %)	-
prednisone mg/day	5.0 [5.0; 7.5]	8.5 [7; 10]	
steroids for more than 6 months	28/32 (88%)	2/2 (100 %)	
current cDMARD	68/73 (93%)	23/79 (29%)	-

BMI=Body Mass Index; SCORE=Systematic COronary Risk Evaluation equation; DMARD= Disease-modifying anti-rheumatic drugs

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, between RA and controls or SpA and controls

Table 2. Factors associated with metabolic syndrome in RA and SpA patients. Data are presented as frequencies (associated percentages), as mean±standard deviation, or as median [interquartile range].

	RA		*p value*	SpA		*p value*
	Metabolically healthy n=54	**Metabolically Unhealthy n=21**		**Metabolically healthy n=62**	**Metabolically Unhealthy n=18**	
Female	39 (72%)	16 (76%)	0.73	37 (60%)	7 (39%)	0.12
Age (years)	58 ± 12	62 ± 8.5	0.08	45.4 ± 12.4	47.6 ± 13.9	0.52
BMI (kg/m²)	25.8 ± 4.9	26.6 ± 5.2	0.53	26.3 ± 5.3	29.5 ± 5.3	***0.02***
Waist circumference (cm)	91.9 ± 12.7	96.7 ± 12.4	0.16	90.9 ± 12.9	103.5 ± 12.9	***<0.001***
Triglycerides (g/l)	0.99 ± 0.32	1.51 ± 0.52	***<0.001***	0.88 ± 0.41	1.97 ± 0.89	***<0.001***
HDLc (g/l)	0.67 ± 0.16	0.50 ± 0.11	***<0.001***	0.60 ± 0.15	0.45 ± 0.14	***<0.001***
LDLc (g/l)	1.18 ± 0.31	1.27 ± 0.38	0.29	1.14 ± 0.36	1.29 ± 0.57	0.32
Blood hypertension	19 (35%)	9 (43%)	0.54	6 (10%)	6 (33%)	***0.02***
Glycemia (g/l)	0.85 ± 0.11	1.02 ± 0.29	***0.02***	0.83 ± 0.15	1.04 ± 0.44	***0.01***
Smoking	17 (33%)	5 (25%)	0.50	21 (34%)	8 (44%)	0.44
SCORE %	0.8 [0.0-2.3]	1.5 [0.0-4.5]	0.11	0.0 [0.0-1.0]	1.0 [0.0-1.0]	***0.003***
PWV (m/sec)	10.90 ± 1.80	11 ± 3	0.96	9.70 ± 1.87	11.20 ± 1.93	***0.005***
Disease duration (years)	3.0 [0.8-10.5]	2.0 [0.3-8.5]	0.46	1.0 [0.3-6.5]	1.3 [0.3-4.0]	0.86
DAS 28 CRP	4.36 ± 1.10	3.97 ± 1.18	0.20			
BASDAI				55.5 ± 18.7	51.3 ± 12.1	0.12
ASDAS CRP				3.12 ± 0.77	3.21 ± 0.53	0.64
HAQ	0.75 [0.50-1.25]	0.75[0.50-1.00]	0.77	0.75 [0.31-1.12]	0.75 [0.37-1.12]	0.62
CRP (mg/l)	8.9 [3.0-17.3]	5.1 [2.9-11.7]	0.09	3.6 [2.9-13.7]	10.5 [3.1-19.0]	0.08
antiCCP or RF seropositivity	34/41(83%)	8/9 (89%)	1.00			
Axial spA				51 (82%)	13 (72 %)	0.57
HLA B27 positivity				36 (59%)	12 (67%)	0.56
Sacroiliitis (Radiographs or MRI)				36 (59%)	9 (50%)	0.50
current NSAIDs	13/35 (37%)	2/19 (11%)	***0.04***	41/56 (73%)	11/17 (65%)	0.55
current steroids	23 (43%)	9 (43%)	0.98	2 (3%)	0 (0%)	1.00
prednisone mg/day	20/23 (87%)	8/9 (89%)	1.00	2/2 (100%)		
steroids for more than 6 months	5.0 [5.0; 10.0]	5.0 [4.0; 6.0]	0.20	8.5 [7.0; 10.0]		
current cDMARD	48/53 (91%)	20/20 (100%)	0.31	16/61 (26%)	7/18 (39%)	0.30
Body composition (DXA) :						
Total fat mass (g)	24 626 ± 8 109	24 918 ± 7,878	0.97	23 545 ± 9,823	28 789 ± 6 997	***0.01***
Total lean mass (g)	47 290 ± 11,102	46 808 ± 9 167	0.77	49 709 ± 10 638	58 435 ± 13 440	***0.01***
Body fat (%)	34.1 ± 8.3	34.6 ± 6.7	0.83	31.7± 9.8	33.2 ± 5.0	0.39
FMI (kg/m²)	9.2 ± 3.3	9.5 ± 3.4	0.70	8.6 ± 4.1	9.9 ± 2.6	0.11
SMI (kg/m²)	6.85 ± 1.38	6.91 ± 1.32	0.61	7.2 ± 1.4	8.1 ± 1.7	0.05
Trunk/peripheral fat	0.99± 0.28	1.07± 0.25	0.26	0.96 ± 0.27	1.23 ± 0.36	***0.008***
VAT (cm²)	100.6 ± 55.8	114.5± 60.9	0.38	87.2 ± 44.0	143.4 ± 82.3	***0.004***
SAT (cm²)	298.7± 128.0	306.5 ± 117.0	0.94	297.1 ± 160.8	337.0 ± 87.8	0.08

BMI=Body Mass Index; SCORE=Systematic COronary Risk Evaluation equation; PWV=pulse wave velocity; FMI= fat mass/height^2; SMI=Appendicular (4 limbs) lean mass/ height$^{2;}$ VAT= visceral adipose tissue; SAT= Subcutaneous adipose tissue

Table 3. Factors associated with metabolic syndrome in non-obese RA and SpA patients. Data are presented as frequencies (associated percentages), as mean ± standard deviation, or as median [interquartile range].

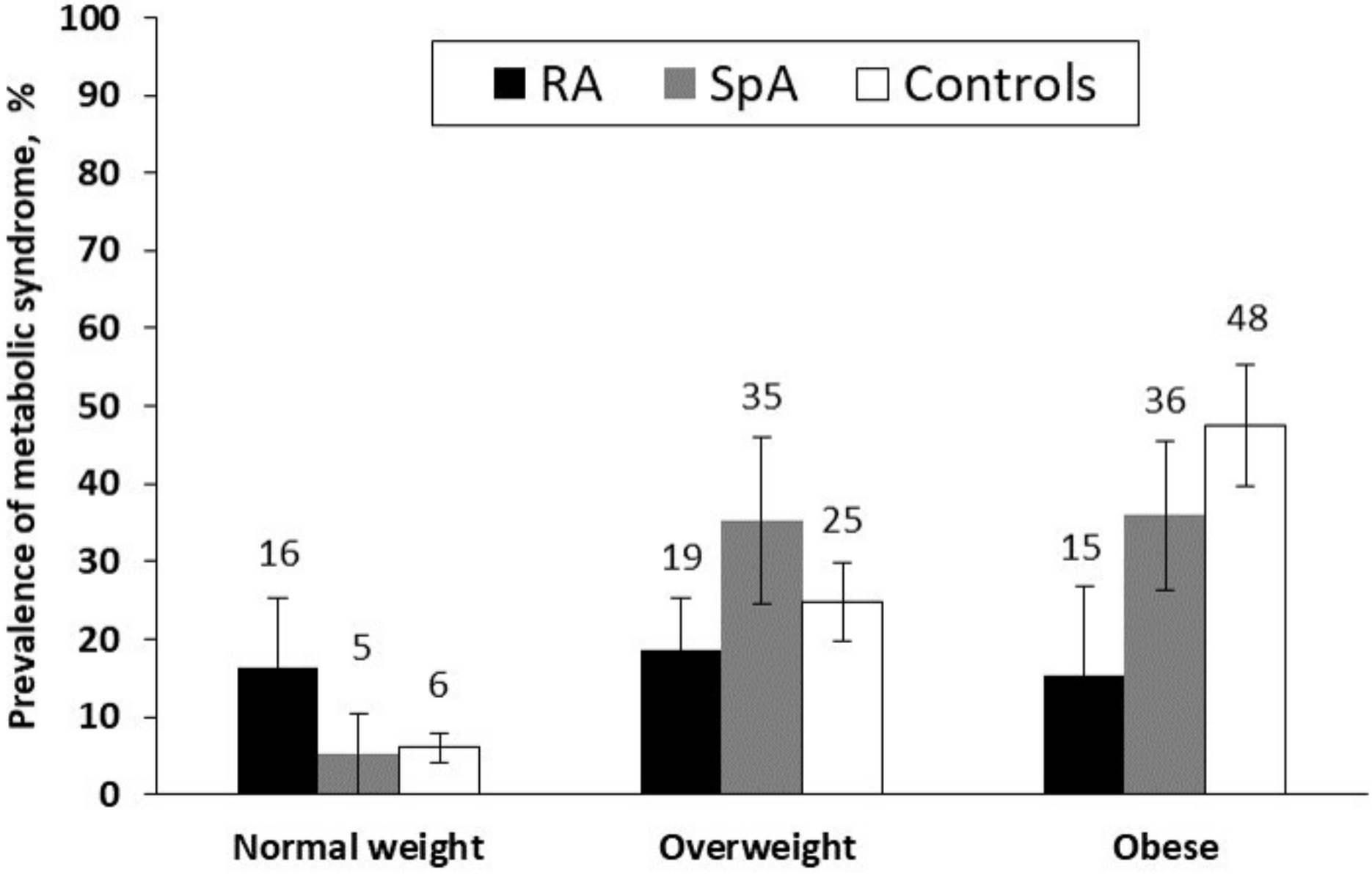
	Non obese RA (BMI<30)		*p value*	**Non obese SpA (BMI<30)**		*p value*
	Metabolically Healthy n=46	**Metabolically Unhealthy** n=16		**Metabolically Healthy** n=51	**Metabolically Unhealthy** n=12	
Female	32 (70%)	12 (75%)	0.76	29 (57%)	6 (50%)	0.67
Age (years)	57.0 ± 11.9	62.7 ± 9.3	0.09	44.6 ± 12.2	48.9 ± 15.8	0.40
BMI (kg/m²)	24.3 ± 3.3	24.6 ± 3.3	0.78	24.4 ± 2.9	26.9 ± 2.7	***0.006***
Waist circumference (cm)	88.4 ± 10.2	92.7 ± 10.8	0.23	87.7 ± 10.2	97.8 ± 9.6	***0.003***
Triglycerides (g/l)	0.99 ± 0.34	1.62 ± 0.52	***<0.001***	0.89 ± 0.43	1.85 ± 1.01	***<0.001***
HDLc (g/l)	0.66 ± 0.16	0.49 ± 0.10	***<0.001***	0.60 ± 0.16	0.49 ± 0.16	***0.03***
LDLc (g/l)	1.17 ± 0.33	1.25 ± 0.39	0.44	1.10 ± 0.34	1.34 ± 0.54	0.16
Blood hypertension	16 (35%)	7 (44%)	0.52	5 (10%)	4 (33%)	0.06
Glycemia (g/l)	0.85 ± 0.11	0.97 ± 0.23	0.10	0.83 ± 0.15	1.07± 0.50	***0.03***
Smoking	16 (37%)	4 (27%)	0.46	17 (34%)	4 (33%)	1.00
SCORE %	0.0 [0.0-1.5]	2.3 [0.8-5.6]	***0.01***	0.0 [0.0-1.0]	1.0 [0.0-1.0]	***0.01***
PWV (m/sec)	10.85 ± 1.86	11.10 ± C54.30	0.81	9.80 ± 1.90	11.30 ± 2.0	***0.02***
Disease duration (years)	3.5 [1.0-10.5]	3.5 [0.5-10.0]	0.82	1.0 [0.3-6.0]	1.0 [0.4-3.8]	0.91
DAS 28 CRP	4.35 ± 1.09	3.84 ± 1.1	0.13	-	-	
BASDAI	-	-		53.5 ± 19.1	53.1 ± 11.9	0.48
ASDAS CRP	-	-		3.11 ± 0.77	3.17 ± 0.63	0.80
HAQ	0.75 [0.50-1.25]	0.75 [0.50-1.00]	0.74	0.66 [0.25-1.12]	0.62 [0.37-1.12]	0.83
CRP (mg/l)	8.0 [2.9-17.3]	5.0 [2.9-9.2]	0.15	3.0 [2.9-16.4]	5.5 [3.1-33.5]	0.18
antiCCP or RF	30/35 (86%)	5/5 (100%)	1.00	-	-	
Axial spA				43 (84%)	8 (67%)	0.32
HLA B27 positivity	-	-		30/50 (60%)	7/12 (58%)	1.00
Sacroiliitis (Radiographs or MRI)	-	-		30/50 (60%)	7/12 (58%)	1.00
current NSAIDs	11/29 (38%)	1/14 (7%)	0.07	35/47 (75%)	7/11 (64%)	0.47
current steroids	20 (43%)	8 (50%)	0.65	1 (2%)	0 (0%)	1.00
prednisone mg/day	17/20 (85%)	7/8 (88%)	1.00	1/1 (100%)	-	
steroids for more than 6 months	5.0 [5.0; 7.5]	5.0 [4.0; 6.5]	0.47	10	-	
current cDMARD	41/45 (91%)	15/15 (100%)	0.56	15/50 (30%)	4/12 (33%)	1.00
Body composition (DXA) :						
Total fat mass (g)	22 124 ± 5 910	22 975 ± 4 458	0.60	20 404 ± 6,508	26 278 ± 5 727	***0.01***
Total lean mass (g)	46 149 ± 10 494	45 393 ± 9 674	0.92	48 677 ± 10 065	54 079 ± 3 015	0.16
Body fat (%)	32.6 ± 7.9	33.9 ± 5.1	0.48	29.6 ± 8.6	33.1 ± 5.4	0.16
FMI (kg/m²)	8.2 ± 2.6	8.6 ± 1.7	0.53	7.3 ± 2.5	9.1 ± 1.7	***0.02***
SMI (kg/m²)	6.6 ± 1.2	6.5 ± 1.1	1.00	6.9 ± 1.3	7.4 ± 1.4	0.24
Trunk/peripheral fat	0.98 ± 0.29	1.06 ± 0.26	0.31	0.93 ± 0.28	1.17 ± 0.41	***0.04***
VAT (cm²)	90.7 ± 47.1	112.0 ± 56.2	0.21	75.5 ± 36.4	121.2 ± 71.6	***0.03***
SAT (cm²)	266.4 ± 109.7	278.5 ± 59.7	0.62	247.9 ± 109.2	315.6 ± 77.6	***0.04***

BMI=Body Mass Index; SCORE=Systematic COronary Risk Evaluation equation; PWV=pulse wave velocity; FMI= fat mass/height^2; SMI=Appendicular (4 limbs) lean mass/ height$^{2;}$ VAT= visceral adipose tissue; SAT= Subcutaneous adipose tissue

Figure 1. Age- and sex- standardized prevalence of metabolic syndrome by BMI categories.

Figure 2. Factors associated with metabolic syndrome in non-obese RA and SpA patients. Forest plot showing effect sizes and 95% confidence intervals for variables associated with metabolic syndrome in non-obese RA and SpA patients.

BMI=Body Mass Index; SCORE=Systematic COronary Risk Evaluation equation; PWV=pulse wave velocity; FMI= fat mass/height^2; SMI=Appendicular (4 limbs) lean mass/ height$^{2;}$ VAT= visceral adipose tissue; SAT= Subcutaneous adipose tissue


RA
SpA
Controls
Prevalence of metabolic syndrome, %
100
90
80
70
60
50
40
30
20
10
0
16
5
6
19
35
25
15
36
48
Normal weight
Overweight
Obese

Effect size with 95% confidence interval

	RA SpA	p value
BMI	0.08 [-0.48; 0.64] 0.90 [0.26; 1.54]	0.78 **0.006**
Waist circumference	0.41 [-0.20; 1.01] 0.99 [0.33; 1.64]	0.23 **0.003**
Triglycerides	1.62 [0.93; 2.29] 1.69 [0.95; 2.42]	**<0.001** **<0.001**
HDLc	-1.16 [-1.75; -0.55] -0.71 [-1.35; -0.08]	**<0.001** **0.03**
Glycemia	0.77 [0.19; 1.35] 0.94 [0.27; 1.60]	0.10 **0.03**
SCORE	0.93 [0.34; 1.51] 0.74 [0.04; 1.43]	**0.01** **0.01**
PWV	0.09 [-0.49; 0.68] 0.75 [0.10; 1.38]	0.81 **0.02**
FMI	0. 15 [-0.42; 0.72] 0.74 [0.10; 1.37]	0.53 **0.02**
SMI	-0.10 [-0.67; 0.47] 0.37 [-0.26; 1.00]	1.00 0.24
Trunk/peripheral fat	0.30 [-0.27; 0.86] 0.80 [0.15; 1.43]	0.31 **0.04**
VAT	0.42 [-0.15; 0.99] 0.99 [0.34; 1.64]	0.21 **0.03**
SAT	0.12 [-0.45; 0.69] 0.64 [0.00; 1.28]	0.62 **0.04**