Increased Prevalence of Metabolic Syndrome Associated with Rheumatoid Arthritis in Patients without Clinical Cardiovascular Disease

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ABSTRACT. ***Objective.*** To examine whether patients with rheumatoid arthritis (RA) with no overt cardiovascular disease (CVD) have a higher prevalence of metabolic syndrome (MetS) than subjects without RA or CVD. We also examined whether RA disease characteristics are associated with the presence of MetS in RA patients without CVD.

Methods. Subjects from a population-based cohort of patients who fulfilled 1987 American College of Rheumatology criteria for RA between January 1, 1980, and December 31, 2007, were compared to non-RA subjects from the same population. All subjects with any history of CVD were excluded. Waist circumference, body mass index (BMI), and blood pressure were measured during the study visit. Data on CVD, lipids, and glucose measures were ascertained from medical records. MetS was defined using NCEP/ATP III criteria. Differences between the 2 cohorts were examined using logistic regression models adjusted for age and sex.

Results. The study included 232 RA subjects without CVD and 1241 non-RA subjects without CVD. RA patients were significantly more likely to have increased waist circumference and elevated blood pressure than non-RA subjects, even though BMI was similar in both groups. Significantly more RA patients were classified as having MetS. In RA patients, MetS was associated with Health Assessment Questionnaire Disability Index, large-joint swelling, and uric acid levels, but not with C-reactive protein or RA therapies.

Conclusion. Among subjects with no history of CVD, patients with RA are more likely to have MetS than non-RA subjects. MetS in patients with RA was associated with some measures of disease activity. (First Release Oct 15 2010; J Rheumatol 2011;38:29–35; doi:10.3899/jrheum.100346)

Key Indexing Terms:
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PREVALENCE

Persons with rheumatoid arthritis (RA) experience an excess burden of cardiovascular disease (CVD), and the mechanisms of this increased risk are not fully understood[1,2,3]. In addition to other traditional cardiovascular risk factors, metabolic syndrome (MetS) is considered to be a significant and independent determinant of increased risk of CVD, although its definition and utility are controversial[4,5]. The main difference in the various definitions involves the measure of central obesity, and a report on the efforts to reach a consensus definition was published recently[6]. MetS is a cluster of 3 or more of the following abnormalities: increased waist circumference, elevated triglycerides, reduced high density lipoprotein, elevated blood pressure, and elevated fasting glucose. Studies have examined the prevalence of MetS in subjects with RA and whether it is increased compared to subjects without RA, but the results have been inconsistent, perhaps due to differences in MetS definitions and in study populations[7,8,9,10]. Given the increased prevalence of CVD in RA subjects, an increased prevalence of MetS in these subjects would not be surprising. A more clinically relevant question is whether the prevalence of MetS is increased in RA subjects without overt CVD, as knowledge of such a relationship would present an opportunity for risk reduction interventions. The pur-

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pose of our study was to examine whether RA subjects with no history of CVD have a higher prevalence of MetS than subjects without RA and no history of CVD, and to examine whether RA disease characteristics are associated with the presence of MetS in RA subjects without CVD.

MATERIALS AND METHODS

Study subjects and design. This community population-based study of residents of Olmsted County, Minnesota, USA, was conducted using the resources of the Rochester Epidemiology Project (REP), a population-based medical records linkage system that allows ready access to complete medical records from all community medical providers[11]. An incidence cohort of all residents of Olmsted County aged ≥ 18 years who first fulfilled 1987 American College of Rheumatology classification criteria for RA between January 1, 1980, and December 31, 2007, was identified[12,13]. From among this incident RA cohort, we identified eligible subjects with RA, namely those alive and living in Olmsted County. For this study, we recruited 232 (58%) of the 401 eligible RA subjects without CVD.

A cross-sectional study comparing these RA subjects to subjects from a community population-based cohort of subjects without RA was performed[14]. The institutional review boards of the Mayo Foundation and the Olmsted Medical Center approved this study. All subjects provided written informed consent prior to participation.

Data collection. Study participation for subjects in both the RA and non-RA cohorts was identical except that RA subjects were asked additional questions pertaining to their RA disease. Subjects in both cohorts completed a cardiovascular risk factor and medication usage questionnaire, underwent a physical examination [including measurement of blood pressure, waist circumference, and body mass index (BMI)], and provided a blood sample. Medical records were reviewed to ascertain diagnoses of CVD and to obtain recent measures of lipids and glucose. For each patient, the available laboratory measurements were performed after fasting and the measurements closest to the study visit within the period from 5 years prior to 1 year after the study visit (median 2.3 yrs prior, interquartile range 0.9–3.6 yrs prior to study visit) were obtained. Lipid measures were not available in 21 RA and 324 non-RA subjects, and glucose measures were not available in 35 RA and 284 non-RA subjects. History of CVD was defined as physician diagnosis prior to the study visit of any of the following: angina pectoris, coronary artery disease, myocardial infarction, or coronary revascularization procedures (i.e., bypass grafting, percutaneous coronary intervention). MetS was defined using the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) criteria as affirmed and slightly modified by the American Heart Association and the National Heart, Lung and Blood Institute[15]. The MetS definition requires any 3 of these 5 criteria: increased waist circumference (≥ 102 cm in non-Asian men, ≥ 88 cm in non-Asian women, ≥ 90 cm in Asian men, ≥ 80 cm in Asian women), elevated triglycerides (≥ 150 mg/dl or treatment with fibrates or nicotinic acid), reduced high-density cholesterol (HDL < 40 mg/dl in men or < 50 mg/dl in women or treatment with fibrates or nicotinic acid), elevated blood pressure (≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or treatment for hypertension) or elevated fasting glucose (≥ 100 mg/dl or treatment for elevated glucose). In addition, these criteria are identical to those recently published in a joint interim statement for MetS[6]. However, the statement suggested another set of waist circumference thresholds for Europeans (≥ 94 cm in men, ≥ 80 cm in women) and recommended evaluation of both sets of thresholds in US populations until a consensus is reached. Therefore, additional analyses using these lower thresholds were performed.

For individuals in the RA cohort, rheumatoid factor (RF), anticitrullinated protein antibodies (ACPA), C-reactive protein (CRP), interleukin 6 (IL-6), and uric acid levels were measured using the sample obtained at the study visit. RF testing was performed by nephelometry (latex enhanced assay; Behring Nephelometer II, Dade Behring, Newark, DE, USA). ACPA and IL-6 testing were performed by enzyme immunoassay (Inova Diagnostics, San Diego, CA; R&D Systems, Minneapolis, MN, USA, respectively). CRP testing was performed by immunoturbidimetric assay (CRPLX reagent, Roche, Indianapolis, IN, USA). Uric acid testing was performed by Photometric, Uricase/Quinone-Imine Dye Formation (Roche). Medical records were reviewed to obtain RA disease duration and the presence of radiographic erosions based on radiographs obtained during clinical care. The questionnaire included the Health Assessment Questionnaire (HAQ) disability score and RA medication usage at the time of the study visit, including systemic glucocorticoids, disease-modifying antirheumatic drugs (DMARD), biologic agents, and nonsteroidal antiinflammatory drugs (NSAID). Systemic glucocorticoid use included either oral or intravenous forms (e.g., prednisone, methylprednisolone, hydrocortisone, and/or dexamethasone); DMARD included methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, and/or azathioprine; and biologic agents included tumor necrosis factor inhibitors, anakinra, abatacept, and/or rituximab. RA medication usage at the study visit was verified with subjects' pill bottles and by reviewing the most recent medication list in the medical record for discrepancies.

Statistical methods. Descriptive statistics were used to summarize the demographics and the criteria for MetS for both cohorts, as well as the RA disease characteristics for the RA cohort. Descriptive statistics in the non-RA cohort were adjusted to the age and sex distribution of the RA cohort to allow comparison. Differences between the 2 cohorts were tested using linear and logistic regression models adjusted for age and sex. Two-way interactions between cohort and age and sex were examined. Logistic regression models were also used to examine the association between MetS and RA disease characteristics, adjusting for age, sex, and RA disease duration. Chi-square and t tests were used to examine differences between characteristics of patients with RA who participated in the study and those who did not participate.

RESULTS

The study included 232 subjects with RA (mean age 58.8, SD 12.8 yrs; 75% women) and 1241 subjects without RA (mean age 63.9, SD 9.2 yrs; 55% women). Subjects with any history of CVD were excluded from both cohorts. Baseline characteristics for both cohorts are reported in Table 1. Both cohorts were predominantly White (93% in RA vs 92% in non-RA group). The difference in racial distribution ($p < 0.001$) was due to the higher percentage of Asians in the RA cohort (3% in RA vs 0.4% in non-RA) and the higher percentage of persons of unknown race in the non-RA cohort. BMI, smoking, and the use of statins were similar in both cohorts.

The criteria for MetS are reported in Table 2. RA subjects were significantly more likely to have an increased waist circumference than non-RA subjects (age and sex-adjusted odds ratio 2.3, 95% CI 1.7, 3.1; $p < 0.001$). This difference was even more pronounced after additional adjustment for BMI (OR 4.7, 95% CI 3.0, 7.5; $p < 0.001$). RA subjects were also more likely to have elevated blood pressure (OR 1.5, 95% CI 1.1, 2.1; $p = 0.02$). The proportion of subjects with elevated triglycerides, reduced HDL, and elevated fasting glucose was similar in both groups ($p > 0.25$).

The prevalence of MetS was higher in RA subjects (33%) compared to non-RA subjects (25%; Table 2). This difference was more pronounced after adjustment for age and sex (OR 1.6, 95% CI 1.2, 2.2; $p = 0.004$) and was similar for

Table 1. Descriptive characteristics in subjects with and without RA who did not have cardiovascular disease.

Characteristic	RA, n = 232	Non-RA, n = 1241	p
Age, yrs, mean ± SD	58.8 ± 12.8	63.9 ± 9.2	< 0.001
Female, n (%)	174 (75)	681 (55)	< 0.001
Race, n (%)			< 0.001
White	218 (93)	1146 (92)	
Asian/Pacific Islander	6 (3)	5 (0.4)	
Other*	3 (1)	17 (1)	
Unknown	5 (2)	73 (6)	
Smoking (current or former), n (%)	105 (45)	547 (44)	0.74
Body mass index, kg/m^2, mean ± SD	28.5 ± 5.8	28.3 ± 5.4	0.52
Use of statins, n (%)	42 (18)	272 (22)	0.20

* Includes Native American, Black, and subjects reporting more than one race.

Table 2. Criteria for metabolic syndrome (MetS) in subjects with and without RA who did not have cardiovascular disease.

Criteria†	RA (n = 232), n (%)	Non-RA (n = 1241), n (%*)	Odds Ratio (95% CI) Adjusted for Age and Sex	p
Increased waist circumference	127 (54)	432 (35/40)	2.3 (1.7, 3.1)	< 0.001
Elevated triglycerides or treatment**	64 (30)	321 (35/28)	0.8 (0.6, 1.2)	0.26
Reduced HDL or treatment**	50 (24)	198 (22/16)	1.2 (0.8, 1.7)	0.43
Elevated blood pressure or treatment	135 (58)	725 (58/47)	1.5 (1.1, 2.1)	0.02
Elevated fasting glucose or treatment***	64 (32)	355 (37/28)	1.0 (0.7, 1.4)	0.96
Metabolic syndrome (≥ 3 of 5 criteria)	76 (33)	316 (25/20)	1.6 (1.2, 2.2)	0.002

† MetS was defined using the national Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria as affirmed and slightly modified by the American heart Association (AHA) and the National Heart, Lung and Blood Institute (NHLBI)[14]. MetS definition requires any 3 of 5 criteria: increased waist circumference (≥ 102 cm in non-Asian men, ≥ 88 cm in non-Asian women, ≥ 90 cm in Asian men, ≥ 80 cm in Asian women), elevated triglycerides (≥ 150 mg/dl or treatment with fibrates or nicotinic acid), reduced high-density cholesterol (HDL < 40 mg/dl in men or < 50 mg/dl in women or treatment with fibrates or nicotinic acid), elevated blood pressure (≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or treatment for hypertension), or elevated fasting glucose (≥ 100 mg/dl or treatment for elevated glucose). * Non-RA percentages are presented raw and adjusted to age and sex distribution of RA subjects. ** Lipid measures were not available in 21 RA and 324 non-RA subjects. *** Glucose measures were not available in 35 RA and 284 non-RA subjects. HDL: high-density lipoprotein cholesterol.

both sexes (interaction p = 0.87). Among women, the prevalence of MetS was 32% in RA subjects compared to 25% in non-RA subjects. Among men, the prevalence of MetS was 36% in RA subjects compared to 26% in non-RA subjects. While the prevalence of MetS in both groups increased with age, the difference in prevalence between the RA and non-RA cohorts did not change significantly with age (interaction p = 0.18). When subjects without laboratory measures were removed from both groups, results were similar, with a higher prevalence of MetS among the 183 RA subjects (38%) compared to the 889 non-RA (34%; adjusted for age and sex to the RA cohort, 21%) with complete data. However, this difference no longer achieved statistical significance (OR 1.3, 95% CI 0.94, 1.9; p = 0.11). Of note, comparisons of subjects with and without laboratory measures in both groups indicated subjects without laboratory measures were younger and less likely to be hypertensive (p < 0.001 for both). Due to differences in the racial distribution of the 2 cohorts, analyses were performed excluding non-White subjects from each group, and revealed results identical to those for the full dataset.

Using the lower waist circumference thresholds for Europeans, a higher percentage of each cohort met criteria for increased waist circumference: 71% of RA and 62% of non-RA, but the significant difference in the prevalence of increased waist circumference among RA subjects compared to non-RA subjects persisted (OR 1.8, 95% CI 1.3, 2.4; p < 0.001). In addition, the prevalence of MetS increased minimally in each cohort (35% in RA and 31% in non-RA compared to the original values of 33% in RA and 25% in non-RA) and the significant difference in prevalence of MetS in RA subjects compared to non-RA subjects persisted (OR 1.5, 95% CI 1.1, 2.0; p = 0.013).

In a secondary analysis, each RA subject was matched to

3 non-RA subjects with similar age and sex. Conditional logistic regression analyses revealed the prevalence of MetS was significantly increased in RA compared to non-RA subjects (OR 2.2, 95% CI 1.5, 3.1; p < 0.001).

Characteristics of subjects with RA are summarized in Table 3. The median duration of RA was 7.0 years (interquartile range 4.1–12.8 yrs), 69% were RF-positive, and 40% were ACPA-positive. About one-half of RA subjects had erosive disease on radiography, with 97% having at least one radiographic assessment. The median HAQ score was 0.4 (IQR 0–0.8). Current medications for RA subjects at the time of the study visit included methotrexate (56%), hydroxychloroquine (32%), other DMARD (11%), biologic agents (16%), glucocorticoids (25%) and NSAID (60%).

Age was significantly associated with MetS (OR 1.5 per 10-yr increase, 95% CI 1.2, 1.9), but no significant association between RA disease duration and MetS was apparent (p = 0.18; Table 3). HAQ score and history of large-joint swelling were significantly associated with MetS (OR 3.2 per 1-unit of HAQ, 95% CI 1.9, 5.7; and OR 2.5, 95% CI 1.2, 5.3, respectively). There were no significant associations with MetS for inflammatory markers (i.e., CRP, IL-6), RF positivity, ACPA positivity, presence of erosions, or medication use. Cumulative steroid dose was also examined and was found not to be associated with MetS (p = 0.73). However, the use of glucocorticoids was significantly associated with increased waist circumference (OR 2.1, 95% CI 1.1, 3.9). Finally, there was a strong association between MetS and uric acid (OR 1.6 per 1 mg/dl, 95% CI 1.3, 2.1).

Additional analyses were performed to examine the differences between patients with RA who chose to participate in the study and those who declined to participate in order to determine whether participation bias may influence the results (Table 4). No differences were found in age, sex, duration of RA, RF positivity, or marital status. Participants were significantly less likely to have smoked and achieved a higher level of education compared to nonparticipants. No differences were found for other cardiovascular risk factors (obesity, hypertension, diabetes mellitus, and dyslipidemia).

DISCUSSION

RA patients without CVD are more likely to have MetS than non-RA subjects without CVD. Of MetS-related characteristics, patients with RA particularly have a higher prevalence of abdominal obesity and elevated blood pressure compared to non-RA subjects. After adjusting for age, sex, and BMI, patients with RA were more than 4 times as likely to have increased waist circumference compared to non-RA subjects. The presence of MetS in RA patients was asso-

Table 3. Characteristics of RA subjects and association with metabolic syndrome.

Characteristic	RA, n = 232	Odds Ratio (95% CI) Adjusted for Age, Sex and RA Duration	p
Age, yrs, median (IQR)	58 (50, 68)	1.5 (1.2, 1.9) per 10 years	< 0.001
Female, n (%)	174 (75)	1.1 (0.6, 2.2)	0.81
RA duration, yrs, median (IQR)	7.0 (4.1, 12.8)	0.7 (0.5, 1.2) per 10 years	0.23
RF-positive, n (%)	159 (69)	1.2 (0.6, 2.2)	0.60
ACPA-positive, n (%)	92 (40)	1.0 (0.5, 1.7)	0.90
CRP, mg/l, median (IQR)	2.1 (0.8, 4.6)	1.0 (0.95, 1.04)	0.85
Interleukin 6, pg/ml, median (IQR)	2.3 (1.4, 4.4)	1.0 (0.97, 1.03)	0.95
Uric acid, mg/dl, median (IQR)	4.8 (4.0, 5.8)	1.6 (1.3, 2.1)	< 0.001
Erosions/ destructive changes on radiographs, n (%)	119 (51)	0.8 (0.5, 1.5)	0.54
HAQ score, median (IQR)	0.4 (0.0, 0.8)	3.2 (1.9, 5.7)	< 0.001
History of large-joint swelling	177 (76)	2.5 (1.2, 5.3)	0.02
Medication usage, n (%)*			
Methotrexate	131 (56)	1.1 (0.6, 2.0)	0.69
Hydroxychloroquine	75 (32)	0.9 (0.5, 1.6)	0.69
Other DMARD	25 (11)	1.6 (0.6, 3.7)	0.33
Biologics	38 (16)	1.2 (0.6, 2.6)	0.59
Glucocorticoids (systemic)	59 (25)	1.0 (0.6, 2.0)	0.89
NSAID	140 (60)	0.7 (0.4, 1.2)	0.17

* At time of study visit. Systemic glucocorticoids included either oral or intravenous forms (e.g., prednisone, methylprednisolone, hydrocortisone, dexamethasone). Other DMARD included sulfasalazine, leflunomide, azathioprine. Biologics included tumor necrosis factor inhibitors, anakinra, abatacept, rituximab. RF: rheumatoid factor; CRP: C-reactive protein; IQR: interquartile range; HAQ: Health Assessment Questionnaire; DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drugs. ACPA: anticitrullinated protein antibodies.

Table 4. Descriptive characteristics in subjects with RA who participated in the study compared to nonparticipants.

Characteristic	Participants, n = 232	Nonparticipants, n = 169	p
Age, yrs, mean ± SD	58.8 ± 12.8	60.3 ± 15.2	0.27
Female, n (%)	174 (75)	132 (78)	0.47
Race, n (%)			0.51
White	218 (93)	148 (88)	
Asian/Pacific Islander	6 (3)	9 (5)	
Other*	3 (1)	5 (3)	
Unknown	5 (2)	7 (4)	
Ever married	209 (90)	154 (91)	0.73
Education level			< 0.001
< High school	4 (2)	16 (10)	
High school	65 (28)	65 (39)	
Technical school/college	145 (63)	77 (46)	
Graduate school	17 (7)	10 (6)	
Duration of RA, yrs, mean ± SD	8.8 ± 6.2	9.8 ± 7.5	0.13
RF-positive, n (%)	151 (65)	111 (66)	0.90
Smoking (current or former), n (%)	101 (44)	99 (59)	0.003
Ever BMI > 30 kg/m^2, n (%)	114 (49)	82 (49)	0.90
Hypertension, n (%)	194 (84)	145 (86)	0.55
Diabetes mellitus, n (%)	27 (12)	28 (17)	0.16
Dyslipidemia, n (%)	163 (70)	110 (65)	0.27

* Native American, Black, and subjects reporting more than one race. BMI: body mass index; RF: rheumatoid factor.

ciated with higher HAQ scores and large-joint swelling, but no significant associations with RA therapies were found.

Due to exclusion of patients with CVD, our estimates of the prevalence of MetS in RA were lower than in other studies of RA, which reported prevalences of 40%–50%[9,10]. Similarly, our estimated 25% prevalence of MetS in non-RA subjects was lower than the 34% reported by the National Health and Nutrition Examination Surveys (NHANES) for the general population[16]. Additional analyses including subjects with and without CVD who had available laboratory measures revealed the prevalence of MetS was 40% in RA and 35% in non-RA subjects, similar to the prevalences reported by others. Dessein, *et al* reported a lower prevalence of MetS (only 19%) in patients with RA, but patients taking glucose or lipid-lowering agents were excluded from their study[8].

Studies comparing the prevalence of MetS in RA and non-RA subjects have shown conflicting results. Karvounaris, *et al* reported 44% of their study cohort of Mediterranean patients with RA met NCEP/ATP III criteria for MetS, but found this to be no different than the 41% prevalence of MetS in their non-RA cohort[9]. However, their control group had an unusually high prevalence of abdominal obesity (83%) and elevated blood pressure (78%). In contrast, Chung, *et al* reported a significant increase in prevalence of MetS in RA patients, especially those with long-standing RA (30% in patients with early RA, 42% in patients with long-standing RA, and 22% in non-RA subjects)[10].

Results for the association between MetS and RA disease characteristics and medications varied widely. This variation is undoubtedly due, in part, to differing populations studied and study methodology. Whereas Chung, *et al*[10] report a strong association between MetS and RA disease duration, this association was not found by Karvounaris, *et al*[9] or in our study. While we did not have Disease Activity Score (DAS) measures in our cohort, we found MetS to be associated with higher HAQ scores and a history of large-joint swelling, which are both indicators of RA disease severity related to physical disability. However, Chung, *et al* found MetS was associated with the DAS and the erythrocyte sedimentation rate, but not with the HAQ[10]. Our findings of lack of association between MetS and other markers of inflammation (CRP and IL-6) in RA are in agreement with several studies[9,10,17], but differ from findings in patients with systemic lupus erythematosus (SLE) and in the general population[18,19,20,21]. Although the results of these studies are not consistent, an association between MetS and RA disease activity or severity seems likely and cannot be excluded[22].

We also noted an association between MetS and elevated uric acid levels, which was not examined in previous studies of MetS in RA patients, but has been associated with MetS in patients with SLE and in the general population[18,19,23]. In addition, Panoulas, *et al* reported uric acid is independently associated with hypertension in RA[24]. Evidence of a link between uric acid and cardiovascular risk is mounting, but treatment of asymptomatic hyperuricemia to reduce cardiovascular risk is not supported to date[25].

Our study found no significant associations between MetS and medication use, although glucocorticoids were associated with increased waist circumference. However, Chung, *et al*[10] reported a higher prevalence of MetS in patients taking glucocorticoids or hydroxychloroquine, but other medications such as methotrexate and biologic agents were not assessed. In contrast, several studies reported improvement of cardiovascular risk factors among patients using hydroxychloroquine[26,27]. Further, Karvounaris, *et al* reported a lower prevalence of MetS in patients taking glucocorticoids or biologic agents, but no significant association with methotrexate use[9]. Methotrexate use was associated with reduced prevalence of MetS by Toms, *et al*, who also found no association between MetS and glucocorticoid use[17,28]. The role of glucocorticoids is complex, as their use is associated with increased waist circumference, but their use may also be confounded with disease severity. As none of these studies were randomized trials, it is likely that confounding by indication plays a role in these conflicting results.

Increased waist circumference appears to play a bigger role in MetS in patients with RA compared to non-RA subjects, since RA patients are more than 4 times as likely to have increased waist circumference compared to non-RA subjects after adjustment for BMI. Although we did not measure body composition, this finding is consistent with Giles, *et al*, who found concomitant increased fat mass and decreased muscle mass was more common in RA patients than non-RA subjects, particularly among subjects with normal BMI[29]. Similarly, Stravropoulos-Kalinoglou, *et al* reported increased body fat in RA patients and recommended lower BMI thresholds for defining obesity in RA[30]. Concomitant increased fat mass and decreased muscle mass, also referred to as rheumatoid cachexia, is likely related to MetS in patients with RA[31].

Strengths of our study include its population-based design with a sizable RA cohort (> 200 subjects) and a large population-based comparison cohort (> 1000 subjects). In addition, comprehensive review of all inpatent and outpatient medical records from the community ensured accurate assessment of cardiovascular disease that was not subject to recall bias. A limitation of the study is that only 58% of eligible subjects agreed to participate. However, the participation rate among RA subjects was similar to that in the non-RA cohort, as was the finding that participants were better educated than nonparticipants, so participation bias is unlikely to have had a substantial effect on the comparisons between the cohorts[32]. Also, some subjects in each cohort had no available measures of lipids or glucose. However, analyses excluding subjects without these measures revealed similar results, albeit the difference in prevalence of MetS comparing RA with non-RA subjects no longer achieved statistical significance. The use of lipids/glucose measurements up to 5 years prior to the study visit is also potentially problematic as these values may have changed during the interval. However, the current primary care guidelines recommend measurement of lipids every 5 years[33,34]. Thus the closest lipids measurement in the past 5 years is representative of the information available clinically for risk assessment in these patients. Finally, the population of Olmsted County, Minnesota, is predominantly White, so the results may not be generalizable to other more diverse populations.

Among subjects without CVD, patients with RA have a higher prevalence of MetS than non-RA subjects. MetS in RA patients was associated with higher disability and a history of large-joint swelling, but not with RA therapy. More research is needed to understand the reasons for these metabolic changes in RA and the effects of MetS on development of CVD in patients with RA. Recognition of MetS in RA patients who have not yet developed CVD could provide a valuable opportunity for preventative intervention.

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