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BRIEF REPORT

Prevalence and Characteristics of Metabolic Syndrome Differ in Men and Women with Early Rheumatoid Arthritis

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Objective. Metabolic syndrome (MetS) prevalence in early rheumatoid arthritis (ERA) is conflicting. The impact of sex, including menopause, has not been described. We estimated the prevalence and factors associated with MetS in men and women with ERA.

Methods. A cross-sectional study of the Canadian Early Arthritis Cohort (CATCH) was performed. Participants with baseline data to estimate key MetS components were included. Sex-stratified logistic regression identified baseline variables associated with MetS.

Results. The sample included 1543 participants; 71% were female and the mean age was 54 (SD 15) years. MetS prevalence was higher in men 188 (42%) than women 288 (26%, $P < 0.0001$) and increased with age. Frequent MetS components in men were hypertension (62%), impaired glucose tolerance (IGT, 40%), obesity (36%), and low high-density lipoprotein cholesterol (36%). Postmenopausal women had greater frequency of hypertension (65%), IGT (32%), and high triglycerides (21%) compared with premenopausal women ($P < 0.001$). In multivariate analysis, MetS was negatively associated with seropositivity and pulmonary disease in men. Increasing age was associated with MetS in women. In postmenopausal women, corticosteroid use was associated with MetS. Psychiatric comorbidity was associated with MetS in premenopausal women. MetS status was not explained by disease activity or core RA measures.

Conclusion. The characteristics and associations of MetS differed in men and women with ERA. Sex differences, including postmenopausal status, should be considered in comorbidity screening. With this knowledge, the interplay of MetS, sex, and RA therapeutic response on cardiovascular outcomes should be investigated.

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SIGNIFICANCE & INNOVATIONS

- Metabolic syndrome (MetS) is common in patients with early rheumatoid arthritis, affecting 30% of patients at baseline
- Men have a higher prevalence of MetS (42%) and higher frequencies of individual MetS components (hypertension, impaired glucose tolerance, obesity, and low high-density lipoprotein levels) compared with women
- Postmenopausal women have a MetS profile similar to men and should equally be considered high risk for cardiovascular disease (CVD) development
- Baseline demographic and clinical factors associated with MetS differed among men and women, suggesting sex-specific variations are important considerations for comorbidity screening and surveillance of CVD outcomes

INTRODUCTION

Rheumatoid arthritis (RA) is associated with premature development of cardiovascular disease (CVD), which remains the leading cause of death in RA (1). Metabolic syndrome (MetS) is a clustering of CVD risk factors (hypertension, dyslipidemia, obesity, and impaired glucose tolerance [IGT]) that, when combined, substantially increases the risk of CVD morbidity and mortality (2). MetS is disproportionately higher in established RA compared with the general population; it is often characterized by other biochemical abnormalities (eg, renal dysfunction), high disease activity, and has been negatively associated with certain therapies (eg, corticosteroids) and favorably associated with others (methotrexate) (2,3). However, a wide variation in the prevalence of MetS in RA has been reported in the literature. This may be explained by differences in the MetS definition used, demographics, and disease course (early RA [ERA] versus established RA) (3).

In the general population, there is a lower prevalence of MetS in women compared with men, but prevalence rises after menopause (4,5). In addition, CVD risk in women with MetS may actually exceed that of men with MetS (4). In RA, the majority of studies has not found significant differences in MetS prevalence between men and women (3). These have largely focused on patients with established RA, and results may not be generalizable to ERA where initial disease activity, RA management algorithms, and screening/management of comorbidity may be different (6). The few studies exploring this topic in ERA have focused estimates of MetS in comparison with non-RA controls only and have not explored sex-specific variations in MetS components and associated factors (7–9). Furthermore, no study has explored menopause and its impact on MetS for women with ERA. Understanding sex-related variations in MetS—especially in RA with a clear female predominance—will help inform whether customized CVD risk assessment and management for men and women with ERA may be justified. To address this knowledge gap, the objectives of our study were to 1) estimate the frequency of MetS and its components among men and women with ERA, 2) determine the relationship between menopausal status and MetS in ERA, and 3) identify factors associated with MetS stratified by sex and menopausal status.

METHODS

Study Design and Participants. We performed a cross-sectional study using data from the Canadian Early Arthritis Cohort (CATCH) from inception in January 2007 through March 2017. CATCH is a multicenter, prospective, observational study of early inflammatory arthritis (6). Participants underwent standardized assessments at fixed intervals, including disease activity measures, medication review, and comorbidity profiling (by physician and self-report). Laboratory testing of metabolic parameters are encouraged but are left to the discretion of the rheumatologist. Management is not protocolized, however study centers generally followed a treat-to-target approach. The present study included CATCH patients with confirmed ERA (according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism or 1987 ACR RA classification criteria) and 2 or more of the required parameters for calculating MetS prevalence at baseline.

The local Ethics Committee of participating CATCH sites approved the study protocol, and written informed consent was obtained from all patients.

Definitions. Several different MetS criteria exist, and no one definition is considered the "gold standard." In routine clinical practice, measurements such as waist-to-hip ratio and fasting glucose levels may not be uniformly collected and/or available. Furthermore, it has been cautioned that there should be no obligatory component for MetS and that rather all individual components should be considered equally important (10). Thus, in order to maximize the number of data elements collected as part of routine clinical care in the CATCH cohort, we created a modified MetS definition incorporating elements of the World Health Organization definition, International Diabe-

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tes Foundation, and Hypertension Canada's guidelines (10,11). Our MetS definition required 2 or more of the following: central obesity defined as body mass index (BMI) 30 or greater, blood pressure (BP) level 140/90 mm/Hg or greater (or self-report of high BP or taking BP medication), high-density lipoprotein cholesterol (HDL-C) level 1.0 mmol/L or less, triglyceride (TG) level 2.0 mmol/L or more (or self-report of dyslipidemia or on cholesterol-lowering agent), IGT defined as random glucose level at 6.1 mmol/L or greater (or taking diabetes medication). We omitted urine microalbuminuria as a MetS criterion in our definition

Table 1. Baseline characteristics (stratified by sex) of participants by MetS status at cohort entry (total cohort n = 1543)[a]

	MEN			WOMEN		
Participant Characteristics	MetS (N = 188, 42%)	No MetS (N = 255, 58%)	*P* value[b]	MetS (N = 288, 26%)	No MetS (N = 812, 74%)	*P* value[b]
Demographic characteristics						
Age (years)	63 (12)	57 (14)	<0.0001	58 (12)	51 (15)	<0.0001
Caucasian	152 (81)	220 (86)	0.12	236 (82)	617 (76)	0.04
Smoking						
Never	50 (27)	87 (34)	0.01	124 (43)	402 (49)	0.02
Current	31 (16)	60 (24)		42 (15)	143 (18)	
Past	107 (57)	108 (42)		121 (42)	266 (33)	
Postmenopausal (n = 659)	...	...	...	220 (33)	439 (66)	<0.0001
More than high school education	78 (41)	117 (46)	0.36	134 (47)	481 (59)	0.0002
RA symptom duration (months)	5.7 (2.9)	5.8 (2.9)	0.84	5.6 (2.9)	6.1 (3.1)	0.009
Comorbidity groupings						
Cardiovascular disease	61 (32)	41 (16)	<0.0001	39 (14)	69 (9)	0.01
Pulmonary disease	12 (6)	38 (15)	0.01	47 (16)	112 (14)	0.29
Thyroid disease	19 (10)	15 (6)	0.10	57 (20)	143 (18)	0.40
Renal disease	4 (2)	2 (1)	0.23	7 (2)	11 (1)	0.21
Fibromyalgia	2 (1)	1 (0)	0.39	9 (3)	15 (2)	0.20
Osteoarthritis or back pain	35 (19)	47 (18)	0.96	76 (26)	151 (19)	0.005
Osteoporosis	3 (2)	5 (2)	0.78	22 (8)	56 (7)	0.67
Psychiatric disorders	13 (7)	20 (8)	0.71	48 (17)	95 (12)	0.03
Total No. comorbidities	3 (2)	2 (2)	<0.0001	3 (2)	2 (2)	<0.0001
RA measures						
RF or ACPA + (80 missing)	103 (65%)[c]	163 (80)[c]	0.002	201 (79)[c]	572 (81)[c]	0.50
TJC-28	10 (7)	9 (7)	0.81	9 (6)	9 (7)	0.96
SJC-28	9 (7)	9 (6)	0.33	7 (5)	7 (6)	0.98
PTGA (0-10 cm scale)	5.7 (3.0)	5.8 (3.0)	0.90	6.2 (3.0)	5.9 (2.8)	0.20
MDGA (0-10 cm scale)	5.1 (2.5)	5.4 (2.6)	0.21	4.8 (2.5)	4.9 (2.5)	0.57
ESR (mm/hr)	26.1 (22.3)	27.2 (24.6)	0.65	32.3 (23.2)	26.3 (22.7)	0.0002
CRP (mg/dL)	18.1 (22.6)	19.7 (23.3)	0.49	15.8 (18.1)	12.6 (17.6)	0.01
DAS28-CRP category						
Remission	7 (4)[c]	6 (3)[c]	0.82	11 (4)[c]	42 (6)[c]	0.32
Low disease activity	7 (4)[c]	10 (4)[c]		6 (2)[c]	31 (4)[c]	
Moderate disease activity	61 (36)[c]	79 (35)[c]		96 (36)[c]	281 (38)[c]	
High disease activity	96 (56)[c]	130 (58)[c]		154 (58)[c]	388 (52)[c]	
Missing	17 (9)	30 (12)		21 (7)	70 (9)	
HAQ-DI score	1.0 (0.8)	0.9 (0.7)	0.37	1.2 (0.7)	1.1 (0.7)	0.0002
Metabolic parameters						
BMI (kg/m^2)	31.9 (4.7)	26.9 (3.5)	<0.0001	33.8 (6.8)	25.7 (5.2)	<0.0001
Systolic blood pressure (mm Hg)	138 (19)	129 (15)	<0.0001	136 (18)	123 (17)	<0.0001
Diastolic blood pressure (mm Hg)	80 (11)	79 (9)	0.34	80 (9)	75 (10)	<0.0001
Total cholesterol/HDL Ratio	6.2 (10.1)	3.1 (1.4)	0.01	3.9 (1.8)	2.8 (1.2)	<0.0001
LDL cholesterol (mmol/L)	2.4 (0.9)	2.8 (0.9)	0.004	2.8 (1.0)	2.8 (0.9)	0.36
HDL cholesterol (mmol/L)	1.1 (0.7)	1.5 (0.8)	0.001	1.3 (0.8)	1.6 (0.5)	0.005
Triglycerides (mmol/L)	1.9 (1.3)	1.2 (0.5)	<0.0001	2.0 (1.1)	1.1 (0.5)	<0.0001
Random glucose (mmol/L)	7.3 (4.1)	5.4 (1.3)	<0.0001	6.6 (3.4)	5.1 (1.1)	<0.0001
Uric acid (mmol/L)	338.1 (73.0)	327.7 (63.9)	0.32	303.8 (86.9)	252.7 (61.2)	<0.0001
Creatinine (umol/L)	83.1 (21.5)	78.6 (14.7)	0.02	68.7 (17.8)	64.3 (14.8)	0.0004
Alanine aminotransferase (U/L)	27.1 (16.5)	25.3 (14.8)	0.26	24.4 (14.7)	21.6 (16.2)	0.013
RA treatment						
NSAID/COXIB	83 (44)	131 (51)	0.13	145 (50)	487 (60)	0.005
Corticosteroids						
Oral (PO)	80 (43)	81 (32)	0.02	86 (30)	176 (22)	0.005
Oral mean dose (mg)	12.8 (8.2)	14.7 (10.8)	0.21	16.2 (14.4)	14.7 (12.1)	0.38

(Continues)

Table 1. *(Cont'd)*

Participant Characteristics	MEN			WOMEN		
	MetS (N = 188, 42%)	No MetS (N = 255, 58%)	*P* value[b]	MetS (N = 288, 26%)	No MetS (N = 812, 74%)	*P* value[b]
DMARD therapy						
Biologic DMARD	1 (1)	7 (3)	0.19	10 (3)	17 (2)	0.03
MTX monotherapy	62 (33)	78 (31)		87 (30)	207 (25)	
MTX combination therapy	63 (33)	72 (28)		85 (30)	241 (30)	
MTX triple therapy	21 (11)	30 (12)		40 (14)	86 (11)	
Non-MTX DMARD only	26 (14)	33 (13)		35 (12)	159 (20)	
Other	15 (8)	35 (14)		31 (11)	102 (12)	

Abbreviation: ACPA, anticitrullinated peptide antibody; BMI, body mass index; DAS28, Disease Activity Score 28 joints; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; HDL, high density lipoprotein; LDL, low density lipoprotein; MTX, methotrexate; MDGA, physician global assessment of disease; MetS, metabolic syndrome; NSAID/COXIB, nonsteroidal anti-inflammatory drug, COX-2 inhibitors; PTGA, patient global assessment of disease; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC-28, swollen joint count out of 28 joints; TJC-28, tender joint count out of 28 joints. [a]Variables are reported as mean (standard deviation) or frequency (%). [b]*P* value from *t* test for continuous variables and chi-square for categorical variables. [c]Represents the percentage of nonmissing data.

because the low number of available data and insulin resistance was not an absolute criterion. Menopausal status was by self-report, or by history of hysterectomy and bilateral oophorectomy, current or previous hormonal replacement therapy or age greater than 55 years (12).

Statistical analysis. Baseline sample characteristics were summarized as means ±SD or number (percentage) as appropriate. The Student's *t*-test was used to compare means for continuous variables, and the chi square test was used to compare proportions for binary variables. Univariate and multivariable logistic regression analyses were performed to estimate crude and adjusted associations between baseline variables and prevalent MetS in men and women, respectively. Predictor variables were initially selected for relevance a priori on clinical grounds (Disease Activity Score 28 [DAS28]–C-reactive protein [CRP] categorical disease activity, with remission/low disease activity as the referent) and retained in multivariable analyses if associated with MetS at a significance level of $P < 0.10$ in univariate analyses in either men or women, respectively.

The following sensitivity analyses were performed: 1) multivariable logistic regression of entire MetS sample testing for a priori select interaction effects of sex by smoking, education level, seropositivity, Health Assessment Questionnaire-Disability Index (HAQ-DI) score, DAS28-CRP score, history of pulmonary disease, psychiatric disease, or osteoarthritis based on observed sex differences in univariate analyses; 2) excluding subjects with a history of CVD at or before baseline from logistic regression analyses; and 3) stratified logistic regression results in women by menopausal status. All analyses were performed using SAS (version 9.4).

RESULTS

The sample included 1543 participants with ERA that met study eligibility criteria. A participant flow diagram is presented (Supplementary Figure 1). Participants who were excluded

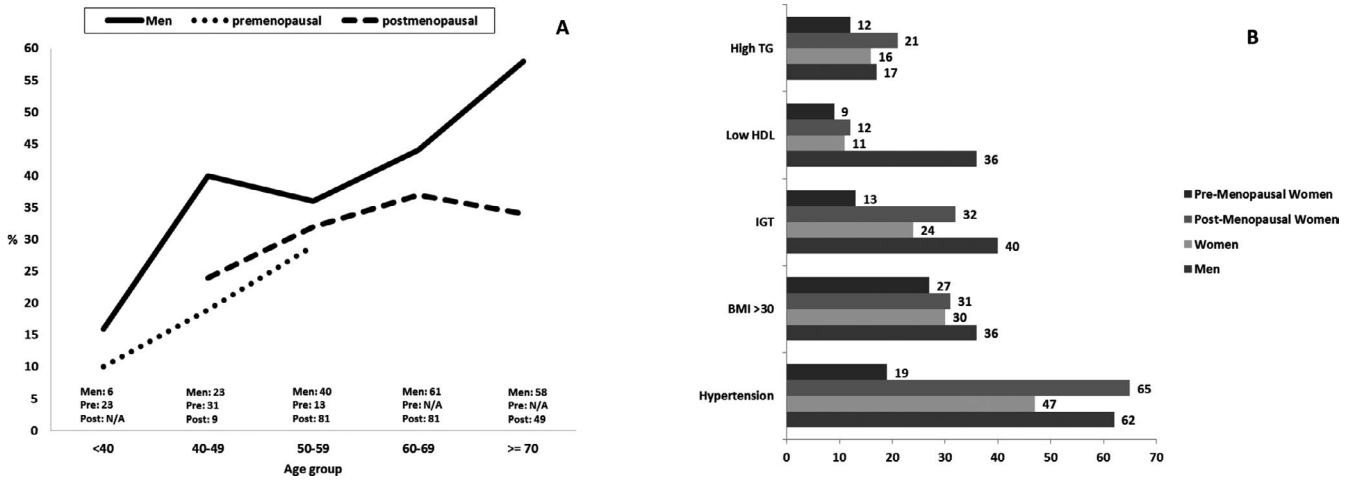

Figure 1. Prevalence and components of MetS in the CATCH cohort. Panel A. Age and sex-stratified prevalence of MetS. Panel B. Prevalence of MetS components by sex and menopausal status. Pre, pre-menopausal; post, post-menopausal, BMI, body mass index; HDL, high density lipoprotein; IGT, impaired glucose tolerance; TG, triglycerides.

Table 2. Sex-stratified univariable and multivariable adjusted logistic regression analyses of baseline associations with MetS

	Men		Women	
Participant Characteristics	Univariate OR (95% CI)	Multivariable Adjusted OR (95%CI)	Univariate OR (95% CI)	Multivariable Adjusted OR (95%CI)
Demographic characteristics				
Age (years)	1.03 (1.02-1.05)	1.02 (1.00-1.04)	1.04 (1.03-1.05)	1.03 (1.01-1.04)
Caucasian	0.67 (0.40-1.12)	...	1.43 (1.02-2.02)	1.20 (0.82-1.77)
Smoking				
Current	0.89 (0.52-1.57)	0.89 (0.46-1.73)	0.95 (0.64-1.42)	0.92 (0.59-1.44)
Past	1.72 (1.11-2.67)	1.40 (0.82-2.37)	1.48 (1.09-1.98)	1.18 (0.85-1.65)
More than high school education	0.84 (0.57-1.22)	...	0.60 (0.46-0.79)	0.79 (0.58-1.07)
RA symptom duration (months)	0.99 (0.93-1.06)	...	0.94 (0.90-0.99)	0.96 (0.91-1.00)
Comorbidity groupings				
Pulmonary disease	0.39 (0.19-0.77)	0.42 (0.19-0.93)	1.22 (0.84-1.77)	...
Thyroid disease	0.56 (0.28-1.13)	...	0.86 (0.61-1.22)	...
Renal disease	0.36 (0.07-2.01)	...	0.55 (0.21-1.43)	...
Osteoarthritis or back pain	1.01 (0.62-1.64)	...	1.56 (1.15-2.16)	1.24 (0.86-1.79)
Psychiatric disorders	0.87 (0.42-1.80)	...	1.51 (1.04-2.21)	1.51 (0.99-2.31)
RA measures				
RF or ACPA+	0.48 (0.30-0.77)	0.54 (0.33-0.89)	0.86 (0.62-1.26)	...
TJC-28	1.00 (0.98-1.03)	...	1.0 (0.98-1.02)	...
SJC-28	1.02 (0.99-1.04)	...	1.0 (0.98-1.02)	...
PTGA (0-10 cm scale)	0.99 (0.94-1.06)	...	1.03 (0.98-1.08)	...
MDGA (0-10 cm scale)	0.95 (0.86-1.03)	...	0.98 (0.93-1.04)	...
ESR (mm/hr)	0.99 (0.99-1.00)	...	1.01 (1.01-1.02)	...
CRP (mg/dL)	0.99 (0.99-1.00)	...	1.01 (1.00-1.02)	...
DAS28-CRP				
Moderate disease activity	1.63 (0.81-3.28)	1.69 (0.76-3.77)	1.14 (0.66-1.96)	0.94 (0.52-1.71)
High disease activity	1.34 (0.67-2.66)	1.32 (0.60-2.91)	1.59 (0.94-2.69)	0.97 (0.52-1.81)
HAQ-DI score	1.12 (0.87-1.44)	...	1.44 (1.19-1.75)	1.27 (1.00-1.62)
Metabolic parameters				
Uric acid (mmol/L)	1.00 (0.99-1.01)	...	1.01 (1.01-1.01)	...
Creatinine (umol/L)	1.01 (1.01-1.03)	1.01 (0.99-1.03)	1.02 (1.01-1.02)	1.01 (0.99-1.02)
Alanine aminotransferase (U/L)	1.01 (0.96-1.02)	...	1.01 (1.00-1.09)	1.01 (1.00-1.02)
RA treatment at baseline				
Corticosteroids				
Oral (PO)	1.59 (1.08-2.35)	1.35 (0.84-2.17)	1.54 (1.14-2.08)	1.30 (0.95-1.87)
Parenteral	1.02 (0.67-1.57)	...	0.80 (0.59-1.09)	...
Oral mean dose (mg)	0.98 (0.95-1.01)	...	1.01 (0.99-1.03)	...

Abbreviation: ACPA, anti-citrullinated peptide antibody; BMI, body mass index; CI, confidence interval; DAS28, Disease Activity Score 28 joints; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; HDL, high density lipoprotein; LDL, low density lipoprotein; MTX, methotrexate; MDGA, physician global assessment of disease; MetS, metabolic syndrome; NSAID/COXIB, nonsteroidal anti-inflammatory drug, COX-2 inhibitors; OR, odds ratio; PTGA, patient global assessment of disease; RA, rheumatoid arthritis; REM, remission; RF, rheumatoid factor; SJC-28, swollen joint count out of 28 joints; TJC-28, tender joint count out of 28 joints

because of missing data had significantly shorter disease duration, higher blood pressure, and lower prevalence of CVD (9%) than those included in the study (14%) (Supplementary Table 1).

The study sample was 71% female, and 65% were postmenopausal. The mean age was 54 years (SD 15 years), whereas the mean age for menopausal women and for premenopausal women was 62 years (SD 9) and 38 years (SD 9), respectively. DAS28 at cohort entry was moderate or high in more than 90%, and treatment with conventional synthetic disease-modifying antirheumatic drugs (DMARD) just prior to or at the baseline visit was common (Table 1).

At baseline, 476 (31%) of the total sample met criteria for MetS. Participants with MetS were older, more frequently past smokers, and had a greater number of total comorbidities, including CVD (Table 1). Metabolic parameters, such as uric acid, creatinine, and alanine transferase levels, were higher in participants with MetS. Oral corticosteroid use at baseline was higher in men and women with MetS (Table 1). Disease activity was moderate or high in the majority and did not differ by MetS status (Table 1).

The prevalence of MetS was significantly higher in men 188 (42%) than women 288 (26%, $P < 0.001$) across all age groups (Figure 1A). MetS prevalence was higher in postmenopausal (33%) than premenopausal (15%) women. Individual MetS components were more frequent in men compared with women, with the exception of elevated triglyceride level (Figure 1B) and were higher for hypertension, IGT, and triglyceride levels in postmenopausal women compared with premenopausal women (Figure 1B).

The results of univariable analyses, stratified by sex, are shown in Table 2. Men with MetS were more likely to be seronegative, past smokers, and less likely to have pulmonary dis-

ease. There were positive associations between self-reported osteoarthritis and psychiatric disorders, increasing HAQ-DI scores and lower education as well as a negative association with disease duration and MetS in women but not men (Table 2). There were no significant associations between MetS status and disease activity state or DAS28 components in men or women. However, there was a significant positive association in univariate models between oral corticosteroid use and MetS in both sexes (Table 2). All observed univariable associations were attenuated after adjustment in multivariable logistic regression, except for the negative association with seropositivity (odds ratio [OR] 0.54, 95% confidence interval [CI] 0.33-0.89) and pulmonary disease (0.43, 95% 0.20-0.94) and MetS in men, and a positive association with increasing age (OR 1.03, 95% 1.01-1.04) in women (Table 2).

In a sensitivity analysis of the entire MetS sample (men and women combined), there were significant interactions for sex by ethnicity, pulmonary disease, and seropositivity on MetS status. When patients with pre-existing CVD were excluded (n = 108 women and 102 men), thyroid disease (hypo- or hyperthyroidism) was negatively associated with MetS (OR 0.37, 95%CI 0.14-0.98) in men. Shorter symptom duration (OR 0.94, 95%CI 0.89-0.99), HAQ-DI score (OR 1.45, 95%CI 1.12-1.89) and self-reported psychiatric comorbidity (OR 1.77, 95%CI 1.12-2.80) were associated with MetS in women by multivariable analyses (data not shown).

The analyses stratified by menopausal status are found in Supplementary Table 2. In postmenopausal women, the only variable independently associated with MetS was corticosteroid use at baseline (OR 1.60, 95% CI 1.09-2.36). Higher age (OR 1.07, 95% CI 1.03-1.10) and psychiatric comorbidity (OR 2.11, 95% CI 1.02-4.38) was positively associated with MetS in premenopausal women only.

DISCUSSION

In this study, a high proportion of ERA subjects had coexisting MetS at baseline. Our key findings were significant variations in MetS prevalence as well as the frequency of the individual MetS components: higher in men compared with women and in postmenopausal versus premenopausal women. These findings suggest that between- and within-sex differences may be important when considering comorbidity management in ERA.

The MetS definition used in this study was a composite of core manifestations of the syndrome, and not based on a single definition. It is reassuring that our MetS prevalence estimate of 31% is in keeping with other published reports. A meta-analysis showed pooled prevalence of 30.6% across 70 studies, although it was not restricted to ERA subjects (3). In this same paper, the MetS prevalence varied between men (32%, 95% CI: 24.37-39.51) and women (33%, 95% CI: 28.09-37.97) but was not statistically significant, whereas our findings revealed a significantly higher prevalence in men (42%) compared with women (26%) (3). As cited, this variability stems from the different MetS definitions available, cohort characteristics, and geographic differences. Therefore, the findings from this North American population may not be generalizable to other early RA cohorts (2,3,13).

Epidemiologically, MetS prevalence increases in the general population with age, so it is not surprising that postmenopausal women had a greater frequency of MetS. The prevalence of MetS in our postmenopausal subgroup (33%) falls within the range reported by a global meta-analysis of postmenopausal women with estimated MetS prevalence between 13% and 46% (5). Our high postmenopausal prevalence of MetS may relate to a previous finding that early menopause (onset younger than 45 years) is more common in ERA and may be hastened by the chronic inflammatory milieu (12). The estrogen-depleted state, in turn, has direct biological effects: redistribution of adipose tissue, weight gain, insulin resistance, and lipid alterations (5). Thus, a susceptible hormonal state coupled with a younger age of menopause onset may increase the accrual time to develop MetS for women with ERA. It is for this reason that many regard menopause as a strong predictor of MetS, independent of woman's age (14).

Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids can induce the same metabolic derangements—namely, hypertension, obesity, and diabetes—that mimic estrogen deficiency. NSAIDs and corticosteroids were more frequently used in men and women (particularly postmenopausal women) with MetS compared with those without MetS, despite similar disease activity levels. Corticosteroid use was also independently associated with MetS in postmenopausal, but not premenopausal, women or men. This suggests that postmenopausal women have a cumulative profile that should be considered as high risk for CVD development. At the bedside, this would translate to judicious use of NSAIDs and corticosteroids, and frequent surveillance of glucose levels, blood pressure, and weight/BMI among postmenopausal women, regardless of age.

Another novel finding was the association between psychiatric illness, which comprised a self-report of depression or anxiety, and MetS in premenopausal women. One speculation is that the coexistence of psychiatric comorbidity and MetS may be mediated by common pathways of diet and physical activity, which was shown to account for 23% of the association between depression and MetS in a recent study (15). Another possibility is that increased appetite and weight gain are common side effects of antidepressants (16). We did not observe a significant difference in BMI among pre- and postmenopausal women, but data were not collected on body fat composition or visceral adiposity, which has been linked to depression (16). This underscores the need to consider psychological factors in addition to the assessment of physical status in ERA and will require further validation in other ERA cohorts.

In men, we found that seropositivity and pulmonary disease were negatively associated with MetS. This appears counterintuitive to the notion that autoantibodies and extra-

articular disease—long regarded as poor prognostic markers of RA—typically lead to greater, not less, comorbidity burden (6). Whether these relationships may be mediated by the effects of past cigarette smoking, which was more common in men with MetS, or a surveillance bias in MetS detection is not clear and will require additional investigation.

The limitations of our study must be recognized. The cross-sectional study design limits any inference on the causal relationship between sex, patient characteristics and development of MetS. We did not have longitudinal data to infer whether RA treatments or changes in disease activity differ by sex and MetS status. With any observational study, we had to contend with missing data and the possibility of selection bias and residual confounding. In particular, we did not have information on important confounders such as physical activity, diet, stress, or other lifestyle/behavioral factors. One key difference between the included and excluded analytic samples was the higher prevalence of CVD, which reflects the "real-world" nature of this study in which physicians likely collected information on MetS more frequently in patients with CVD. Finally, we used an adapted definition of MetS, and results may have differed based on other accepted criteria. However, it is reassuring that our estimates fall within the range reported by others, especially for women with ERA (7).

In conclusion, the characteristics of MetS are different in men and women with ERA. Although men have an overall higher prevalence and frequency of individual MetS components compared with women, postmenopausal women may be a particularly vulnerable subgroup that warrants careful surveillance and screening for MetS. Future research to identify gaps and barriers to MetS screening, by sex, is needed. Whether DMARD and biologic therapies differentially lower the incidence of MetS in men and women over time is additionally required. This will help inform if tailored management of MetS, by sex, will be an effective early strategy to reduce the risk of adverse RA and CVD outcomes.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual contact and all authors approved the final version to be published. Dr. Kuriya had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design. Kuriya, Schieir, Valois, Bykerk, Barra.

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