Risk of Obstructive Sleep Apnea and Its Association with Cardiovascular and Noncardiac Vascular Risk in Patients with Rheumatoid Arthritis: A Population-based Study

Katelynn M. Wilton, Eric L. Matteson, and Cynthia S. Crowson

ABSTRACT. ***Objective.*** To define the incidence of obstructive sleep apnea (OSA) in patients with rheumatoid arthritis (RA) and determine whether OSA diagnosis predicts future cardiovascular disease (CVD) and noncardiac vascular events.

Methods. Medical information pertaining to RA, OSA, CVD, and vascular diagnoses was extracted from a comprehensive medical record system for a geographically defined population of 813 patients previously diagnosed with RA and 813 age- and sex-matched comparator subjects.

Results. The risk for OSA in persons with RA versus comparators was elevated, although not reaching statistical significance (HR 1.32, 95% CI 0.98–1.77; p = 0.07). Patients with RA were more likely to be diagnosed with OSA if they had traditional risk factors for OSA, including male sex, current smoking status, hypertension, diabetes, dyslipidemia, and increased body mass index. Features of RA disease associated with OSA included large joint swelling and joint surgery. Patients with RA with decreased renal function were also at higher risk of OSA. The increased risk of overall CVD among patients with RA who have OSA was similar to the increased CVD risk associated with OSA in the comparator cohort (interaction p = 0.86). OSA diagnosis was associated with an increased risk of both CVD (HR 1.9, 95% CI 1.08–3.27), and cerebrovascular disease (HR 2.4, 95% CI 1.14–5.26) in patients with RA.

Conclusion. Patients with RA may be at increased risk of OSA secondary to both traditional and RA-related risk factors. Diagnosis with OSA predicts future CVD in RA and may provide an opportunity for CVD intervention. (First Release August 1 2017; J Rheumatol 2018;45:45–52; doi:10.3899/jrheum.170460)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
OBSTRUCTIVE SLEEP APNEA
CARDIOVASCULAR DISEASE
RISK ASSESSMENT

Many extraarticular manifestations of rheumatoid arthritis (RA) are linked to underlying systemic inflammation. RA-associated cardiovascular disease (CVD), likely accentuated by the proinflammatory state, is responsible for significant mortality[1,2]. The excess CVD risk seen in RA is independent of standard cardiovascular (CV) risk factors and correlates with RA disease activity[3,4,5]. Prediction of CVD events and associated risk is crucial for informing preventative measures to help alleviate the increased CVD mortality seen in patients with RA.

Within the general population, obstructive sleep apnea (OSA) is an independent risk factor for numerous CVD events[6,7] and is associated with many CV risk factors including obesity, inactivity, hypertension (HTN), hypercholesterolemia, and diabetes mellitus (DM)[5]. Similar to RA, OSA appears to increase the CVD risk through inflammatory mechanisms and is a predictor of CVD events[6,7]. Treatment of OSA through the use of positive airway pressure, which maintains open airways and prevents injurious hypoxic events, may decrease CV risk in affected populations[6].

The incidence of OSA in patients with RA is inadequately studied. Knowledge of the effect of concomitant diagnosis of OSA and RA on CV risk could help to predict and manage CVD events in this particularly high-risk population. The

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Funded by a grant from the US National Institutes of Health (NIH), National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01 AR046849). This research was made possible by the Rochester Epidemiology Project (R01 AG 034676 from the National Institutes of Health) and the CTSA Grant Number UL1 TR000135 from the National Center for Advancing Translational Sciences, a component of the NIH. KMW was supported by the National Institutes of General Medical Sciences (grant T32-GM-65841) and the Mayo Clinic College of Medicine's Medical Scientist Training Program.

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Accepted for publication June 3, 2017.

overlap of these 2 conditions may identify a population of patients who should be especially targeted for CVD evaluation and intervention or may represent an unchanged CVD risk from baseline RA secondary to an already increased risk.

Our study defined the risk of OSA development in a cohort of patients newly diagnosed with RA in comparison to an age- and sex-matched comparator cohort, and examined the association of OSA diagnosis on the risk of subsequent CVD and noncardiac vascular events among patients with RA.

MATERIALS AND METHODS

Study population. An inception cohort of all cases of RA first diagnosed between January 1, 1980, and December 31, 2007 (n = 813), among Olmsted County (Minnesota, USA) residents ≥ 18 years of age was assembled as previously described[8]. The incidence date was defined as the earliest date at which the patient fulfilled at least 4 of the 7 American College of Rheumatology 1987 classification criteria for RA[9]. A comparison cohort of subjects without RA with similar age, sex, and calendar year was also previously assembled. All patients in both cohorts were followed up longitudinally through their complete medical records until death, migration from Olmsted County, or July 1, 2016. Two subjects in the non-RA cohort denied use of their medical records for research purposes per Minnesota law and were excluded from these analyses. The study protocol was approved by Review Boards from the Mayo Clinic (675-99) and the Olmsted Medical Center (018-OMC-06).

Data relevant to OSA diagnosis were extracted from the medical record. OSA diagnoses were defined by formal diagnosis by a physician paired with an abnormal sleep study (either plethysmography or overnight oximetry) indicating OSA. Additional information collected at the time of OSA diagnosis included relevant data from sleep studies [Apnea/hypoapnea Index (AHI), Respiratory Disturbance Index (RDI), Epworth Sleepiness Scale (ESS)], measures of inflammation [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), blood neutrophils, blood lymphocytes], height, weight, medication information (concerning statin, prednisone, and tumor necrosis factor inhibitor usage), and whether the patient was provided with a prescription for devices to treat OSA. At followup, compliance data, updated AHI, and ESS values were collected where available. Information on longterm oxygen therapy for OSA treatment was also collected.

Previous data collection included CVD and noncardiac vascular events occurring at any time during the patient's history. CVD events included myocardial infarction (MI; hospitalized or silent), revascularization procedures, angina, and heart failure (HF). MI and HF were both defined using objective criteria commonly used in epidemiologic studies, as previously described[10]. Noncardiac vascular diseases, including venous thromboembolism (deep venous thrombosis or pulmonary embolism), cerebrovascular events (hemorrhagic stroke, nonhemorrhagic stroke, transient ischemic attack, or amaurosis fugax), and peripheral arterial events (abdominal aortic aneurysm, renal artery stenosis, peripheral artery disease, or arterial thromboembolism) were previously collected based on fulfillment of previously defined criteria[11].

Smoking status and body mass index (BMI) were obtained at RA incidence/index date. HTN, dyslipidemia, and DM were abstracted from the medical records at RA incidence/index date and throughout followup, and were defined using standardized diagnostic criteria[10]. Reduced kidney function was defined as 2 consecutive estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 at least 90 days apart using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation[12,13]. The date the patient was considered to have reduced kidney function is the second date of eGFR < 60 ml/min/1.73 m^2. Chronic alcoholism was included as previously identified from physician diagnosis in the medical record[10].

The information on RA characteristics included rheumatoid factor (RF) positivity, ESR at RA incidence, date of first large-joint swelling, joint erosions/destructive changes on radiographs, joint surgeries (i.e., arthroplasty and synovectomy), and severe extraarticular manifestations of RA[10]. Severe extraarticular manifestations were defined according to Malmö criteria and included pericarditis, pleuritis, Felty's syndrome, glomerulonephritis, vasculitis, peripheral neuropathy, scleritis, and episcleritis[14]. Data regarding start and stop dates for use of systemic glucocorticoids, disease-modifying antirheumatic drugs [DMARD; methotrexate (MTX), hydroxychloroquine, other conventional DMARD, and biologic response modifiers] were collected for all patients. Data on the use of nonsteroidal antiinflammatory drugs including coxibs were also recorded.

Statistical methods. Descriptive statistics (means, percentages, etc.) were used to summarize the data. Characteristics were compared between cohorts using the chi-square and rank sum tests. The cumulative incidence of OSA adjusted for the competing risk of death was estimated[15]. These methods are similar to the Kaplan-Meier method with censoring of patients who were still alive at last followup. Patients who died before experiencing OSA were appropriately accounted for to avoid overestimation of the rate of occurrence of OSA, which could occur if such subjects were simply censored. Patients who were diagnosed with OSA prior to the diagnosis of RA, or prior to the index date for subjects in the non-RA comparison cohort, were excluded from the analysis of cumulative incidence. Poisson regression models with smoothing splines were used to examine trends in OSA according to calendar year, with direct adjustment for age and sex.

Cox proportional hazards models were used to compare the rate of development of OSA between patients with RA and the non-RA comparison cohort. In addition, Cox models were used to assess the association of risk factors on the development of OSA among patients with RA.

Cox models were also used to assess the effect of OSA on the development of CVD or mortality among patients with RA and non-RA subjects. Traditional CV risk factors were included in these models as adjustors. Time-dependent covariates were used to model risk factors that developed over time. These time-dependent covariates allowed patients to be modeled as unexposed to the risk factor during the followup time prior to development of the risk factor, then change to exposed following development of the risk factor. For the modeling of OSA, patients with OSA prior to index date were considered as exposed from the index date forward, and those who developed OSA during followup were considered as unexposed prior to diagnosis of OSA and exposed after diagnosis of OSA. Interactions between cohort and OSA were examined. Analyses were performed using SAS version 9.4 (SAS Institute) and R 3.2.3 (R Foundation for Statistical Computing).

RESULTS

The study population included 813 patients with RA and 811 subjects without RA. The average age at RA incidence (index date for the non-RA cohort) was 55.9 years (SD 15.7), and 556 (68%) were women (Table 1). There was no difference in the presence of OSA at RA incidence/index date between cohorts (p = 0.99).

The cumulative incidence of OSA was somewhat higher in the patients with RA (97 patients with OSA out of 792 at risk) compared to the subjects without RA (80 patients with OSA out of 790 at risk). This equated to a 10-year cumulative incidence of OSA of 6.6% (95% CI 4.8–8.4) in the RA cohort compared to 5.6% (95% CI 4.0–7.2) in the non-RA cohort (Figure 1). The 20-year cumulative incidence was similarly increased in the RA cohort (12.6%, 95% CI 10.0–15.1) compared to the non-RA cohort (11.4%, 95% CI 8.8–14.0). In other words, patients with RA were somewhat more likely to develop OSA during followup (HR 1.32, 95% CI 0.98–1.77 adjusted for age, sex, and calendar yr of RA

Table 1. Characteristics of 813 patients with RA and 811 subjects without RA at RA incidence/index date. Values are n (%) unless otherwise specified.

Characteristic	RA, n = 813	Non-RA, n = 811	p
Age, yrs, mean ± SD	55.9 ± 15.7	55.9 ± 15.7	0.95
Female	556 (68)	554 (68)	0.97
Length of followup, yrs, mean ± SD	14.8 ± 7.8	15.7 ± 8.2	—
Smoking status			0.002
Never	364 (45)	435 (54)	
Current	177 (22)	142 (18)	
Former	272 (33)	234 (29)	
BMI, kg/m^2, mean ± SD	27.7 ± 5.9	27.7 ± 5.8	0.99
Diabetes mellitus	81 (10)	68 (8)	0.27
Hypertension	314 (39)	278 (34)	0.07
Any prior CVD or noncardiac vascular events	121 (15)	112 (14)	0.54
Presence of OSA	21 (3)	21 (3)	0.99

RA: rheumatoid arthritis; BMI: body mass index; CVD: cardiovascular disease; OSA: obstructive sleep apnea.

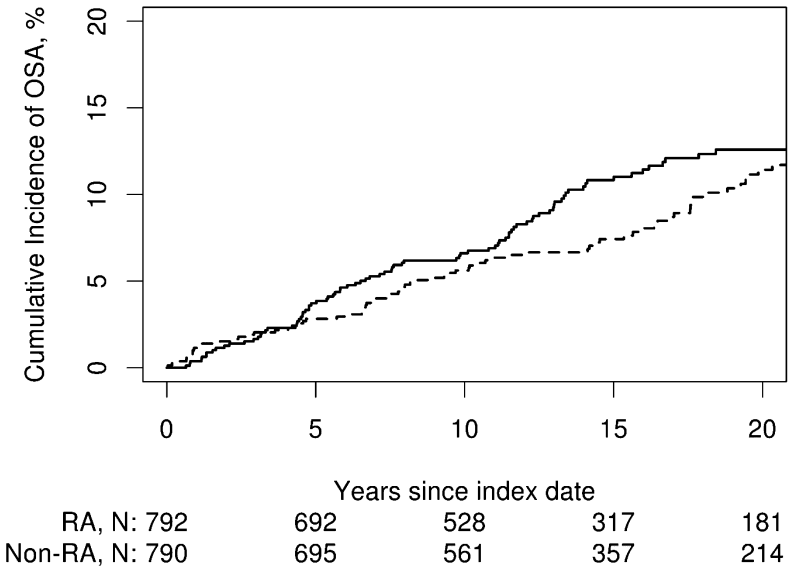

Figure 1. Cumulative incidence of OSA in patients with RA (solid line) versus non-RA comparators (dashed line). The cumulative incidence of OSA was 6.6% (95% CI 4.8–8.4) in RA compared with 5.6% (95% CI 4.0–7.2) in non-RA at 10 years, and 12.6% (95% CI 10.0–15.1) in RA compared with 11.4% (95% CI 8.8–14.0) in non-RA at 20 years after RA incidence/index date. This difference corresponds to a 32% increase in RA compared with non-RA (HR 1.32, 95% CI 0.98–1.77, adjusted for age, sex, and calendar year), but this association did not reach statistical significance (p = 0.07). OSA: obstructive sleep apnea; RA: rheumatoid arthritis.

incidence/index date), but this difference did not reach statistical significance (p = 0.07). The rate of OSA development increased over time in both cohorts.

Among those who were diagnosed with OSA, there were few differences between RA and non-RA regarding characteristics at the time of OSA diagnosis (Table 2). In particular, several measures of OSA activity (ESS, AHI, RDI) were similar between the groups. Additionally, inflammatory markers measured at OSA diagnosis, including ESR and CRP, were similar, although raw blood neutrophil levels were increased in the RA cohort compared to the non-RA cohort. Followup values were also similar, including prescriptions for OSA machines and use compliance, as well as ESS and AHI.

Because of the known association between CV risk factors and OSA in the general population, examination was undertaken of the potential association of RA disease characteristics and CV risk factors with the development of OSA in patients with RA (Table 3). These included measures of RA disease activity and severity. In particular, various CV risk

Table 2. Characteristics of patients with RA and non-RA comparator subjects diagnosed with OSA after RA incidence/index date. Values are mean ± SD (n) unless otherwise specified.

Characteristic	RA, n = 97	Non-RA, n = 80	p
Age at OSA diagnosis, yrs	64.4 ± 11.4	64.9 ± 10.8	0.79
Female, n (%)	59 (61)	45 (56)	0.54
AHI	27.0 ± 23.0 (92)	26.4 ± 25.9 (77)	0.56
RDI	39.7 ± 29.7 (86)	40.4 ± 25.4 (77)	0.52
ESS	9.3 ± 5.2 (81)	8.0 ± 4.8 (66)	0.14
CRP, mg/l	7.3 ± 17.3 (51)	2.4 ± 2.4 (11)	0.47
ESR, mm/h	20.4 ± 18.3 (69)	15.3 ± 15.7 (26)	0.12
Blood neutrophils	5.3 ± 2.6 (82)	4.5 ± 1.9 (62)	0.035
Blood lymphocytes	1.6 ± 0.6 (84)	1.7 ± 0.7 (63)	0.14
Neutrophil/lymphocyte ratio	4.3 ± 3.4 (82)	3.3 ± 3.3 (62)	0.011
BMI at OSA diagnosis, kg/m^2	34.2 ± 8.4 (97)	33.6 ± 7.0 (80)	0.74
BMI ≥ 30 kg/m^2 at OSA diagnosis, n (%)	69 (71)	53 (66)	0.48
Statin use, n (%)	23 (24)	27 (34)	0.14
Glucocorticoid use, n (%)	35 (36)	3 (4)	
Biologic use, n (%)	12 (12)	0 (0)	
OSA machine prescription, n (%)	78 (80)	67 (84)	0.50
CPAP	57	56	
BiPAP	8	2	
APAP	0	2	
ASV	4	0	
Oral appliance	0	1	
Followup machine compliance, %	80 ± 30 (62)	80 ± 20 (53)	0.51
Followup AHI	4.2 ± 5.2 (25)	7.9 ± 9.8 (25)	0.34
Followup ESS	6.2 ± 3.6 (51)	6.7 ± 4.6 (47)	0.84
Oxygen use, n (%)	9 (9)	4 (5)	0.28

RA: rheumatoid arthritis; OSA: obstructive sleep apnea; AHI: Apnea/hypoapnea Index; RDI: Respiratory Disturbance Index; ESS: Epworth Sleepiness Scale; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BMI: body mass index; CPAP: continuous positive airway pressure; BiPAP: bilevel positive airway pressure; APAP: automatic titrating positive airway pressure; ASV: adaptive servo-ventilation.

factors including smoking, increased BMI, HTN, hyperlipidemia, and DM were found to be associated with the development of OSA among the patients with RA (Table 3). In addition, some features of RA disease, including decreased kidney function (p = 0.001), presence of large joint swelling (p = 0.007), joint surgery (p < 0.001), and the use of DMARD (including MTX, other DMARD, and biologics) and glucocorticoids were associated with increased risks for developing OSA in patients with RA.

The diagnosis of OSA in both the RA and the non-RA cohorts was significantly associated with an increased risk of CVD events (Table 4). The associations between OSA and the outcomes of interest were similar in patients without RA and those with RA (Table 4). However, OSA appeared to be more strongly associated with peripheral arterial events among the non-RA (HR 3.09, 95% CI 1.15–8.28) than among the patients with RA (HR 1.17, 95% CI 0.34–3.98), though this difference did not reach statistical significance (interaction p = 0.057). Results were similar, but slightly attenuated after additional adjustment for CV risk factors, including smoking, HTN, obesity (BMI ≥ 30 kg/m^2), DM, and dyslipidemia (Table 4). For example, the HR for any CVD or noncardiac vascular event declined from 1.76 to 1.68 among the RA and from 1.62 to 1.57 among the non-RA. Within the RA cohort, there was some evidence that OSA was more strongly associated with development of CVD among patients who were RF-negative (HR 2.90) than those who were RF-positive (HR 1.17; interaction p = 0.046).

DISCUSSION

In our population-based study of patients with RA, there was a trend toward an increased risk of OSA. Diagnosis of OSA in RA was associated with several features of RA, including decreased kidney function, large joint swelling, and joint surgery, as well as DMARD and glucocorticoid medication use. An OSA diagnosis in patients with RA was associated with an increased risk of future CVD events, similar to that seen in the general population.

A few previous studies have reported a borderline increase in the incidence of OSA in patients with RA compared to the general population. One study within the same geographic area as our study showed an increased risk, as determined by the Berlin Sleep Score, of OSA in RA, but only a borderline increase (p = 0.13) in diagnosis of OSA in the setting of RA, suggesting underdiagnosis of OSA in this population[16]. This mirrors the finding of our current study: subjects with RA

Table 3. Association between RA disease characteristics and the development of obstructive sleep apnea in 813 patients with RA. HR are adjusted for age, sex, and calendar year.

Characteristics	HR (95% CI)	p
RA characteristics		
Age, per 10-yr increase	1.12 (0.97–1.29)	0.12
Male sex	1.64 (1.09–2.47)	0.017
Calendar year of incidence/index date	1.10 (1.06–1.14)	< 0.001
ESR at index, per 10 mm/h	1.05 (0.95–1.16)	0.297
RF-positive	1.28 (0.84–1.95)	0.243
Current smoker	0.51 (0.28–0.94)	0.031
Former smoker	1.13 (0.74–1.71)	0.565
Time-dependent characteristics		
Hypertension	2.32 (1.40–3.85)	0.001
Diabetes mellitus	1.85 (1.17–2.92)	0.008
Dyslipidemia	2.40 (1.31–4.37)	0.004
Prior CVD	1.73 (1.05–2.87)	0.032
BMI ≥ 30 kg/m^2	4.99 (2.98–8.36)	< 0.001
BMI < 20 kg/m^2	0.28 (0.12–0.65)	0.003
Alcoholism	0.53 (0.21–1.31)	0.170
Reduced kidney function*	2.06 (1.32–3.20)	0.001
Rheumatoid nodules	1.21 (0.80–1.85)	0.369
Erosions/destructive changes	1.46 (0.97–2.19)	0.070
Severe extraarticular manifestations*	1.41 (0.75–2.65)	0.286
Large joint swelling	2.25 (1.25–4.05)	0.007
Joint surgery	2.30 (1.47–3.61)	< 0.001
Methotrexate	1.86 (1.18–2.92)	0.007
Hydroxychloroquine	1.14 (0.75–1.73)	0.545
Other DMARD	1.69 (1.10–2.60)	0.016
Biologic	2.44 (1.55–3.84)	< 0.001
Glucocorticoids	2.18 (1.22–3.88)	0.008
COX-2	2.35 (1.53–3.64)	< 0.001
NSAID	1.24 (0.60–2.58)	0.561

* For study definition, see Materials and Methods: Study Population section. RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; CVD: cardiovascular disease; BMI: body mass index; DMARD: disease-modifying antirheumatic drug; COX-2: cyclooxygenase 2 inhibitors; NSAID: nonsteroidal antiinflammatory drug.

were slightly more likely to be diagnosed with OSA, although this finding did not reach statistical significance (p = 0.07).

Additional studies of OSA have focused on subsets of populations diagnosed with RA. In patients with RA involvement in anatomical areas relevant for OSA, specifically the occipitocervical area[17] or temporomandibular joint[18], about 80% had evidence of OSA. In addition, hospitalized patients with RA also had an increased risk of severe apnea syndrome[19]. These findings may relate to severe cases of RA or to patients with RA with specific anatomic involvement. Unlike our current study, which accounted for RA beginning at diagnosis, previous studies on this topic focused on prevalent RA cases without accounting for time since diagnosis, thus representing more established and potentially more severe RA.

The link between OSA and CV risk is well established within the general population. Although OSA predisposes individuals to CVD events, the diligent use of corrective sleep apparati, including continuous positive airway pressure (CPAP) and bilevel positive airway pressure, attenuates this risk[6,7]. In our study, many of the same risk factors that predispose to OSA in the general population, including male sex, obesity, smoking, HTN, and diabetes[7], are also predisposed to OSA in RA, reflecting common risk factors in both populations. In addition, some RA-related disease features, including joint swelling, joint surgery, and medications used to treat RA, as well as decreased renal function in the RA cohort, also correlated with OSA diagnosis in this population.

It is unclear whether these 2 general areas of OSA disease risk seen in RA are at all related: lifestyle/metabolic syndrome (as in the general population) and the RA disease burden. The vast majority of patients with both RA and OSA are reportedly overweight, with many of the traditional CV risk factors[16,19]. However, a small minority of patients with RA, generally with high disease activity, were significantly underweight[19]. A relationship between RA disease severity and OSA has been previously documented in retrospective studies, case reports, and case series[17,18,20,21,22,23,24,25], which describe individuals with RA in whom critical structures around the upper airway are eroded, including the temporomandibular joint and occipitocervical area. In these patients, who presumably have a high RA disease burden, mechanical change in the bone structure could compromise the airway independent of visceral adiposity. It was not possible to adequately assess this issue in our current retrospective study.

In the setting of RA, OSA diagnosis predicts future CVD. CVD risk is increased by both the burden of RA disease and OSA diagnosis, suggesting that patients with both conditions are at an increased risk of CVD events and should be closely monitored. In this cohort, there was a clear additional effect of co-occurrence of OSA and RA on CVD risk. This observation underscores OSA as an important risk factor for CVD in this population, and suggests that the contribution of each of these conditions to CVD risk might be through independent mechanisms. In RA, the increased CVD risk is linked to RA-related disease activity and burden[26], including lymphocyte-driven inflammation, which may be secondary to the increased quantity of circulating, activated, and more differentiated T cells[27]. In contrast, OSA results in intermittent hypoxia and hypercapnia, causing chronic microarousals and sleep fragmentation. This leads to sympathetic activation, oxidative stress, and systemic inflammation[7], which contribute to endothelial cell damage[28].

Interestingly, in our study, peripheral arterial event risk was unaffected by the diagnosis of OSA in RA. As with many other CV-related conditions, RA diagnosis is associated with an increased risk of peripheral arterial events[29,30,31]. The observation that OSA diagnosis in patients with RA correlates with increased risk of central but not peripheral atherosclerotic disease may relate to the anatomy of the artery (i.e., the femoral artery is muscular; the carotid artery is elastic), location of the artery, or on the pathological process leading

Table 4. Associations between OSA and CVD/noncardiac vascular disease/any cardio- or cerebrovascular disease–related mortality in 813 patients with RA and 811 subjects without RA.

Outcomes	RA			Non-RA			p**
	Events, n	HR† (95% CI)	HR* (95% CI)	Events, n	HR† (95% CI)	HR* (95% CI)	
CVD	168	1.88 (1.08–3.27)	1.77 (1.01–3.10)	124	1.87 (1.02–3.42)	1.64 (0.89–3.03)	0.84
Myocardial infarction	50	0.94 (0.32–2.74)	0.92 (0.31–2.72)	45	2.09 (0.84–5.21)	2.02 (0.78–5.21)	0.31
Heart failure	10	1.07 (0.47–2.41)	0.98 (0.43–2.23)	83	1.37 (0.61–3.10)	1.29 (0.56–2.96)	0.71
Noncardiac vascular event	91	1.93 (0.95–3.92)	1.71 (0.84–3.50)	51	2.10 (0.97–4.51)	2.04 (0.92–4.51)	0.24
Cerebrovascular disease	65	2.44 (1.14–5.26)	2.01 (0.92–4.39)	31	2.18 (0.86–5.55)	2.46 (0.91–6.66)	0.49
Peripheral vascular disease	43	1.17 (0.34–3.98)	1.28 (0.37–4.46)	25	3.09 (1.15–8.28)	2.58 (0.92–7.26)	0.057
Any CVD or noncardiac vascular event	211	1.76 (1.04–2.98)	1.68 (0.98–2.85)	157	1.62 (0.93–2.83)	1.57 (0.89–2.76)	0.86
Overall mortality	323	1.20 (0.81–1.78)	1.24 (0.82–1.86)	248	0.69 (0.38–1.26)	0.76 (0.42–1.40)	0.12

†Adjusted for age, sex, and calendar year of RA incidence/index date. *Adjusted for age, sex, calendar year of RA incidence/index date, smoking, hypertension, obesity (BMI, obesity, calendar year of RA incidence). **p value for interaction between RA/non-RA status and OSA. OSA: obstructive sleep apnea; CVD: cardiovascular disease; RA: rheumatoid arthritis; BMI: body mass index.

to formation of atherosclerotic plaque. Similarly, the effect of OSA on the development of peripheral arterial events might not be directly related to conventional pathologic-anatomic mechanisms. RA-related immunopathogenesis may contribute to initiation of peripheral artery plaques, but not to the advancing state of the lesions[29]. If OSA also interacted at the same early step in this process, the combined effect might be redundant, resulting in no increased risk over that seen from RA alone.

The association between OSA and CVD in patients with RA is most pronounced in RF-negative subjects. One previous study showed a greatly increased risk of CVD events in patients with RF-positive RA, but CVD event frequency comparable to that seen in the general population for patients with RF-negative RA[32]. The increased CVD risk seen in RF-positive RA may be secondary to more inflammation, while the CVD risk in RF-negative RA may be primarily based on traditional CV risk factors, as seen in the general population. Thus, OSA confers increased risk similar to that seen in the general population in those patients with RF-negative RA, but has less of an effect on increasing the CVD risk in RF-positive RA, likely because in this population the majority of the risk is driven by inflammation.

To our knowledge, our study is the first to examine whether OSA diagnosis in patients with RA predicts future CVD, and one of few to document the incidence of OSA within the setting of RA. Our study benefitted from a geographical medical record linkage system allowing for the selection of sex- and age-matched comparators from the same underlying population. The use of complete inpatient and outpatient medical records provided comprehensive ascertainment of all study outcomes that came to medical attention for these residents of Olmsted County. Potential limitations are those inherent in a retrospective study, and that both the RA and the comparator cohort populations are predominantly white and generally overweight. These specific demographics may limit applicability to other patient populations, particularly in patients from other races and those with different risk factor profiles. However, results from studies in Olmsted County have generally been consistent with national data, where available[33].

Our study relied on the physician diagnosis of OSA paired with an abnormal sleep study, predominantly polysomnography, although some patients were included who had abnormal overnight oximetry highly predictive of OSA. This strict definition leads to the exclusion of many cases of clinically unrecognized OSA or patients who were not interested in a complete OSA evaluation and treatment. As a result, the full extent of undiagnosed OSA could not be ascertained as completely as might be possible in a prospective study; confounding cannot be excluded. This could have affected some results and led to underestimation of the total incidence of OSA; however, this underestimation would likely affect both the RA and non-RA cohorts. This is an obstacle in most research concerning OSA because it is likely that a significant proportion of patients who satisfy diagnostic criteria are untested due to a lack of symptom recognition.

In our study, the possible underdiagnosis of OSA, secondary to general fatigue being mistakenly attributed to RA, may result in an underestimate of the incidence of OSA in the cohort of patients with RA, leading to a false-negative result concerning the incidence of OSA in patients with RA. This is especially relevant considering the statistically nonsignificant increase in OSA diagnosis in this RA cohort ($p = 0.07$). In the ascertainment of cardiac risk, the inclusion of some patients with RA and OSA in the RA-only group would likely result in an increased CV risk in this group, thereby biasing the study against showing an increased risk of CVD given a patient with OSA and RA. Given these limitations, which bias against positive findings, the incidence of OSA in RA and the association of OSA with increased CV risk in patients with RA may be underestimated.

In addition, it is important to note that many of the symptoms of OSA could be mistaken for RA disease activity,

particularly fatigue, trouble sleeping, and inability to focus. In patients with RA presenting with new instances of these symptoms or with what appears to be increased RA disease activity, evaluation of sleeping habits may be warranted, and in some cases, testing for OSA may prove beneficial both in terms of quality of life and CVD risk. Especially considering the effectiveness of CPAP intervention in alleviating symptoms and reducing CVD risk in the general population[6,7], diagnostic testing for OSA in patients with RA could be warranted.

Our study indicates that an increased risk of OSA is likely in RA, and that diagnosis of both RA and OSA in an individual patient signals additional CVD risk that should be accounted for in clinical practice. Diagnosis of OSA in RA is associated with many of the same risk factors as in the general population and should be considered in the assessment of CVD risk. It is possible that symptoms of OSA such as fatigue may be attributed to RA disease activity and affect disease management decisions.

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