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Rheumatoid Arthritis, Anti–Cyclic Citrullinated Peptide Positivity, and Cardiovascular Disease Risk in the Women's Health Initiative

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Objective. **To evaluate the incidence of cardiovascular disease (CVD) morbidity and mortality over the course of 10 years among the more than 160,000 postmenopausal women in the Women's Health Initiative (WHI) in relation to self-reported rheumatoid arthritis (RA), taking disease-modifying antirheumatic drugs (DMARDs), anti–cyclic citrullinated peptide (anti-CCP) positivity, rheumatoid factor (RF) positivity, CVD risk factors, joint pain, and inflammation (white blood cell count and interleukin-6 levels).**

Methods. **Anti-CCP and RF were measured in a sample of WHI participants with self-reported RA (n = 9,988). RA was classified as self-reported RA plus anti-CCP positivity and/or taking DMARDs. Anti-CCP–negative women with self-reported RA and not taking DMARDs were classified as having "unverified RA."**

Results. **Age-adjusted rates of coronary heart disease (CHD), stroke, CVD, fatal CVD, and total mortality were higher in women with RA than in women with no reported RA, with multivariable-adjusted hazard ratios of 1.46 (95% confidence interval [95% CI] 1.17–1.83) for CHD and 2.55 (95% CI 1.86–3.51) for fatal CVD. Among women with RA, anti-CCP positivity and RF positivity were not significantly associated with higher risk of any outcomes, despite slightly higher risk of death for those who were anti-CCP positive than for those who were anti-CCP negative. Joint pain severity and CVD risk factors were strongly associated with CVD risk, even in women with no reported RA. CVD incidence was increased in women with RA versus women with no reported RA at almost all risk factor levels, except for low levels of joint pain or inflammation. Among women with RA, inflammation was more strongly associated with fatal CVD and total mortality than with CHD or CVD.**

Conclusion. **Among postmenopausal women, RA was associated with 1.5–2.5-fold higher CVD risk. CVD risk was strongly associated with CVD risk factors, joint pain severity, and inflammation, but not with anti-CCP positivity or RF positivity.**

Rheumatoid arthritis (RA) is associated with a >1.5-fold increased incidence of coronary heart disease (CHD), stroke, total cardiovascular disease (CVD), fatal CVD, and total mortality (1–3). Despite improved treatment, there is little evidence of reduction in CHD or CVD morbidity or mortality (4). Risk factors for incident

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CHD in RA include traditional CVD risk factors (e.g., cigarette smoking, hypertension, diabetes mellitus, and elevated low-density lipoprotein cholesterol [3,5–7]) and markers of RA severity, including inflammation (8,9), joint pain, and disability (9–11). The presence of anti–cyclic citrullinated peptide antibodies (anti-CCP positivity) is highly sensitive and specific for RA diagnosis among patients in whom RA is suspected (12), but there is increasing evidence of differences between anti-CCP–positive and anti-CCP–negative RA. In our studies, anti-CCP positivity has been found to be associated with the HLA–DR shared epitope (SE) and substantially higher cytokine levels (particularly in patients who are also positive for rheumatoid factor [RF] [13]), as well as with greater mortality (14). Furthermore, current guidance for management of CVD risk recommends that anti-CCP positivity or RF positivity be considered an indicator of higher CVD risk in RA (15). However, it remains unclear how anti-CCP positivity and RF positivity are related to a range of CHD and CVD morbidity and mortality outcomes.

Among the more than 160,000 postmenopausal women in the Women's Health Initiative (WHI), we have conducted the WHI RA Study to evaluate the relationship of self-reported RA, anti-CCP positivity, RF positivity, taking disease-modifying antirheumatic drugs (DMARDs), and other risk factors with CVD and mortality outcomes. We have previously reported that RA patients had >2-fold excess mortality compared with those who never reported RA (14), and RA patients who were anti-CCP positive had a higher proportion of the HLA–DR SE, higher inflammation as measured by white blood cell (WBC) count and cytokine levels (13), and slightly higher total mortality rates than RA patients who were anti-CCP negative (14). Furthermore, in multivariable-adjusted models, a higher WBC count was associated with mortality in anti-CCP–positive and anti-CCP–negative women, but joint pain severity was associated with mortality primarily among women with anti-CCP–positive RA (14).

The objective of the current study was to evaluate the incidence of CHD and CVD outcomes among postmenopausal women (without baseline CVD) in the WHI in relation to RA, anti-CCP positivity, RF positivity, markers of RA severity including joint pain and inflammation (WBC count and interleukin-6 [IL-6] levels), and traditional CVD risk factors. We sought to answer 3 questions. First, do women classified as having RA have an increased incidence of CHD, stroke, and total and fatal CVD compared with women without reported RA or women with unverified RA (likely arthritis)? Second, does the RA-related increased incidence of CVD morbidity and mortality differ by anti-CCP positivity or RF positivity? Finally, is higher CHD and CVD risk modified by levels of traditional CVD risk factors, joint pain, or inflammation?

PATIENTS AND METHODS

Participants and data collected in the WHI. Detailed descriptions of the WHI (16) and the WHI RA Study (13,14) have been reported previously. Briefly, between 1993 and 1997, 40 clinical centers enrolled 161,808 women ages 50–79 years into one of the clinical trials (n = 68,132) or the observational study (n = 93,676) (16). At baseline and followup, WHI participants were asked if they had arthritis and, if yes, whether it was RA; 16,469 women reported RA at baseline or followup. Histories of drugs taken, including DMARDs, were also obtained both at baseline and at followup, in the case of the latter every 3 years in the clinical trial and at year 3 in the observational study. Taking DMARDs was defined as currently taking of hydroxychloroquine, sulfasalazine, minocycline, methotrexate, leflunomide, azathioprine, cyclosporine, gold, cyclophosphamide, or antirheumatic biologic agents (13,14). At the baseline WHI examination, women were asked to report joint pain severity (none, mild, moderate, severe) and swelling of joints during the past 4 weeks, but not the specific joint or number of joints affected. Women reported their current health status, disability, physical functioning, and employment status (17). Lipids were not routinely measured in WHI participants, so "high cholesterol" was defined as self-reported high levels of cholesterol or taking lipid-lowering medications, as in other WHI reports. WHI participants also reported history of cigarette smoking, hypertension, diabetes mellitus, history of CHD at baseline, physical activity, waist circumference, general health, age, education, and ethnicity (18). The WBC count was also measured at baseline in all WHI participants, as described (19).

Definitions of events. Cardiovascular outcomes and deaths were identified by semiannual or annual followup with family, friends, and medical care providers as well as use of the National Death Index and obituaries. Only ~1–2% of WHI participants have been lost to followup. Cardiovascular- and cancer-related morbidities in the WHI were centrally adjudicated using standardized methods as previously described (20). Incident CHD was defined as fatal and nonfatal myocardial infarction (MI), angina, coronary revascularization (angioplasty or bypass surgery), or death due to definite or possible CHD. Incident CVD was defined as CHD, stroke, transient ischemic attack, carotid artery surgery, heart failure (HF), or death due to CVD. Fatal CVD included only deaths due to CVD.

Biomarker testing in the WHI RA Study. Anti-CCP2, RF, and antinuclear antibodies were measured in the phase 1 sample, which consisted of 9,988 of the 15,188 WHI participants who reported RA at baseline or followup; these 15,188 participants were white, black, and Hispanic women for whom blood samples were available (13,14,18). Based on the anti-CCP results from the phase 1 sample, a phase 2 sample (n = 2,993) was selected for measurement of cytokines and HLA–DR typing for the SE (13). Detailed descriptions of the sampling and laboratory methodologies have been reported previously (13,14). The current study evaluating incident CVD during followup was restricted to women who reported RA at baseline (or baseline and followup) and without prevalent CVD at baseline.

The following RA-related assays were performed on the entire phase 1 sample of 9,988 women who reported RA in

the WHI, as previously described (13,14). Anti-CCP2 and RF were assayed in the Rheumatology Clinical Research Laboratory at the University of Colorado, using baseline serum samples stored at −70°C and not previously thawed. On the phase 2 sample, HLA–DR typing was done at the University of Pittsburgh (21), and IL-6 was measured using multiplex cytokine profiling in baseline plasma samples stored at −70°C (13,22).

Classification of self-reported RA by anti-CCP status and taking of DMARDs. A previously reported chart review validation study (19) demonstrated that among WHI participants, the positive predictive value of self-reported RA was 14.8% (similar to that in other large cohort studies), but was 62.2% when combined with self-reported taking of DMARDs, 80% when combined with anti-CCP positivity, and 100% when combined with both self-reported taking of DMARDs and anti-CCP positivity. The negative predictive value was ~90% for any of the improved definitions (23,24). Therefore, as in our previous studies, clinical RA was defined as self-reported RA and anti-CCP positivity and/or taking DMARDs at baseline (not including taking oral steroids) (13,14). Women who reported RA but who were anti-CCP negative and did not report taking DMARDs were unlikely to have clinical RA (94% did not have clinical RA on chart review) (23) and were therefore classified as having "unverified RA." WHI participants who never reported RA were classified as having "no reported RA."

Statistical analysis. Due to the complex sampling design of our study, sampling weights, defined as 1/sampling fraction, were determined for each woman and incorporated in the analyses as previously described in detail (13,14). Analyses were performed with SAS software, version 9.3 (SAS Institute). All models were 2-sided with an alpha level of 0.05. Age-adjusted rates and their 95% confidence intervals (95% CIs) were calculated using the direct method with the entire WHI population as the standard population. Cox proportional hazards models were used to assess the association between RA and time to events, which was calculated from baseline to the date of the event or to the end of followup for subjects without events. The proportional hazards assumption was tested using interaction terms of group and exposures with time. For multivariable models assessing RA-related CVD risk, potential effect modification of risk factor associations by RA was assessed by including multiplicative interaction terms for each covariate with RA (yes versus no), as described in the Results.

RESULTS

Participant characteristics. As previously reported (13,14), CVD risk factors were slightly worse for women in the WHI with RA than women with no reported RA (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39198/abstract). Also as previously reported, women with unverified RA (anti-CCP negative and not reporting taking DMARDs) had a higher mean body mass index (BMI), a greater waist circumference, and higher prevalences of hypertension, diabetes mellitus, and high cholesterol than women with RA or women with no reported RA. Women with RA had higher RF titers and IL-6 levels than women with unverified RA (RF and IL-6 were not measured in women who did not report RA). Compared with women with RA who were anti-CCP negative and reported taking DMARDs, anti-CCP–positive women with RA tended to have a lower BMI, a smaller waist circumference, and lower prevalences of diabetes mellitus and high cholesterol, but more of them were current smokers and they had strikingly higher IL-6 levels, RF titers, and WBC counts and a slightly higher prevalence of fair/poor health. Fair/poor health and severe joint pain were slightly more common in anti-CCP–positive women with RA who were taking DMARDs than in those not taking DMARDs.

Comparison of age-adjusted cardiovascular event rates by RA group. The age-adjusted incidence rate (per 1,000 person-years) for CVD outcomes and total mortality was calculated for all women with RA (anti-CCP positive and/or reporting taking DMARDs), women with unverified RA (anti-CCP negative and not reporting taking DMARDs), and women with no reported RA, as well as for the 3 subsets of women with RA classified by anti-CCP status and taking of DMARDs (Table 1). Compared with women with no reported RA, women with RA had approximately ≥1.5-fold higher incidence rates of CHD, stroke, and total CVD and >2-fold higher incidence rates of fatal CVD and total mortality ($P < 0.05$ for all). Women with RA also had higher rates of total CVD, fatal CVD, and total mortality ($P < 0.05$) compared with women with unverified RA. Age-adjusted CHD and total CVD rates were lower for anti-CCP–positive women with RA reporting or not reporting taking DMARDs than for anti-CCP–negative women with RA reporting taking DMARDs, but fatal CVD and total mortality rates were similar or higher, although differences were generally not statistically significant (Table 1). Results were similar when taking DMARDs was redefined as including oral steroids or as taking DMARDs reported at any time during followup rather than at baseline only (not shown).

Age-adjusted incidence rates of CVD by risk factor combinations. At each level of CVD risk factors, the age-adjusted CVD incidence rate (per 1,000 person-years) was ~1.5–2-fold higher for women with RA than for women with no reported RA, and the rates were intermediate for women with unverified RA (Table 2). Within each group, CVD incidence rates were increased >4-fold for those with diabetes mellitus and hypertension compared with those with no risk factors. However, despite these similar relative risks, the difference in absolute risk of CVD (incidence rate [per 1,000 person-years]) was magnified by RA and risk factors. For exam-

Table 1. Weighted age-adjusted incidence rate (per 1,000 person-years) among the WHI participants by groups of women with RA, with unverified RA, or not reporting RA*

	Women with no reported RA	Women with unverified RA (anti-CCP negative and not taking DMARDs)	All women with RA (anti-CCP positive and/or taking DMARDs)	Subsets of all women with RA		
				Anti-CCP negative and taking DMARDs	Anti-CCP positive and taking DMARDs	Anti-CCP positive and not taking DMARDs
CHD						
Incidence (95% CI)	5.78 (5.57–6.00)	7.09 (6.00–8.38)†	8.56 (5.88–12.50)†	11.01 (5.64–21.56)	9.17 (4.92–17.19)	6.65 (3.45–13.08)
No./total no. of events	7,909/123,474	416/5,162	80/894	25/365	29/309	26/220
Stroke						
Incidence (95% CI)	2.57 (2.42–2.72)	3.32 (2.60–4.27)†	4.53 (2.67–7.77)†	4.78 (1.74–13.72)	3.70 (1.41–10.63)	5.18 (2.36–11.55)
No./total no. of events	3,245/123,481	183/5,162	39/894	11/220	10/309	18/365
Total CVD						
Incidence (95% CI)	10.03 (9.74–10.32)	13.18 (11.66–14.92)†	17.31 (13.27–22.65)†‡	23.41 (15.24–36.16)§¶	16.02 (10.02–25.71)	15.79 (11.40–21.91)
No./total no. of events	13,415/123,476	751/5,162	156/894	49/220	49/309	58/365
Fatal CVD						
Incidence (95% CI)	1.71 (1.60–1.82)	2.50 (1.78–3.19)†	4.06 (2.41–7.48)†‡	3.54 (1.25–11.49)	5.53 (2.71–12.46)	3.46 (1.42–8.75)
No./total no. of events	123/481	156/5,162	39/894	9/220	16/309	13/365
Total mortality						
Incidence (95% CI)	7.54 (7.30–7.79)	9.91 (8.66–11.36)†	17.44 (13.52–22.58)†‡	14.69 (8.65–25.65)	20.19 (13.41–30.64)	17.39 (11.60–26.21)
No./total no. of events	10,487/123,481	611/5,162	167/894	38/220	62/309	67/365

* Excluding those with cardiovascular disease (CVD) at baseline or rheumatoid arthritis (RA) only at followup. WHI = Women's Health Initiative; CHD = coronary heart disease; 95% CI = 95% confidence interval.
† $P < 0.05$ versus women with no reported RA.
‡ $P < 0.05$ versus women with unverified RA.
§ $P = 0.06$ versus women with anti–cyclic citrullinated peptide (anti-CCP)–negative RA who were taking disease-modifying antirheumatic drugs (DMARDs).
¶ $P < 0.05$ versus women with anti-CCP–negative RA (those taking DMARDs and those not taking DMARDs combined).

Table 2. Weighted age-adjusted CVD incidence rate (per 1,000 person-years) among the WHI participants by risk factor combinations and groups of women with RA, with unverified RA, or not reporting RA*

	All women with RA (anti-CCP positive and/or taking DMARDs)	Women with unverified RA (anti-CCP negative and not taking DMARDs)	Women with no reported RA
No smoking, hypertension, diabetes mellitus, or high cholesterol			
Incidence (95% CI)	10.75 (5.75–20.89)†‡	8.28 (6.14–11.20)	6.35 (5.94–6.78)
No./total no. of events	25/217	125/1,320	2,480/36,299
Smoking only			
Incidence (95% CI)	16.99 (10.83–26.78)†‡	10.50 (8.09–13.65)	8.18 (7.72–8.66)
No./total no. of events	56/327	163/1,445	3,446/41,205
Hypertension only			
Incidence (95% CI)	16.99 (8.13–37.74)	15.36 (11.77–20.20)	12.53 (11.72–13.41)
No./total no. of events	19/106	161/907	2,540/17,297
Hypertension and smoking only			
Incidence (95% CI)	27.35 (16.80–45.21)†‡	18.50 (14.39–23.84)	16.59 (15.63–17.61)
No./total no. of events	45/179	186/941	3,253/18,041
Diabetes mellitus and hypertension only			
Incidence (95% CI)	45.72 (10.98–216.51)	37.77 (22.09–65.29)	27.03 (23.14–31.60)
No./total no. of events	5/16	43/124	477/1,746

* Excluding those with cardiovascular disease (CVD) at baseline or rheumatoid arthritis (RA) only at followup. WHI = Women's Health Initiative; anti-CCP = anti–cyclic citrullinated peptide; DMARD = disease-modifying antirheumatic drug; 95% CI = 95% confidence interval.
† $P < 0.05$ versus women with unverified RA.
‡ $P < 0.05$ versus women with no reported RA.

Table 3. Weighted age-adjusted CHD incidence rate (per 1,000 person-years) among the WHI participants by joint pain severity and groups of women with RA, with unverified RA, or not reporting RA*

	Joint pain severity				
	None	Mild	Moderate	Severe	*P* for trend
All women with RA (anti-CCP positive and/or taking DMARDs)					
Incidence (95% CI)	4.33 (0.61–30.71)	6.50 (3.10–13.80)	10.67 (6.25–18.29)	9.27 (4.24–20.47)	0.23
No./total no. of events	2/38	21/295	39/356	18/198	
Women with unverified RA (anti-CCP negative and not taking DMARDs)					
Incidence (95% CI)	5.75 (3.23–10.49)	5.55 (4.19–7.37)	8.12 (6.15–10.75)	10.62 (7.34–15.42)	<0.0001
No./total no. of events	32/493	146/2,208	150/1,653	83/754	
Women with no reported RA					
Incidence (95% CI)	4.60 (4.26–4.97)	5.67 (5.36–5.99)	7.27 (6.71–7.87)	9.10 (7.87–10.53)	<0.0001
No./total no. of events	1,849/37,480	3,681/57,816	1,800/21,982	533/5,458	
Women with no reported RA but reporting arthritis at baseline					
Incidence (95% CI)	5.62 (4.76–6.65)	6.13 (5.67–6.64)	7.58 (6.92–8.31)	9.33 (7.97–10.93)	<0.0001
No./total no. of events	411/6,020	1,869/25,138	1,384/15,600	461/4,497	
Women with no reported RA and not reporting arthritis at baseline					
Incidence (95% CI)	4.36 (3.99–4.77)	5.25 (4.85–5.69)	6.65 (5.64–7.86)	7.81 (5.15–11.88)	<0.0001
No./total no. of events	1,438/31,460	1,812/32,678	416/6,382	72/961	

* Excluding those with cardiovascular disease at baseline or rheumatoid arthritis (RA) only at followup. CHD = coronary heart disease; WHI = Women's Health Initiative; anti-CCP = anti–cyclic citrullinated peptide; DMARD = disease-modifying antirheumatic drug; 95% CI = 95% confidence interval.

Table 4. Weighted age-adjusted risk of events among the WHI participants by RA-related variables and groups of women with RA or with unverified RA*

Risk factor	All women with RA (anti-CCP positive and/or taking DMARDs)	Anti-CCP–positive women with RA	Anti-CCP–negative women with RA and taking DMARDs	Women with unverified RA (anti-CCP negative and not taking DMARDs)
RF (positive vs. negative)				
CHD	1.06 (0.83–6.39)	2.31 (0.83–6.39)	1.00 (0.40–2.49)	1.04 (0.78–1.39)
CVD	1.11 (0.79–1.57)	1.37 (0.76–2.47)	1.80 (0.99–3.27)	1.11 (0.90–1.37)
Fatal CVD	1.18 (0.46–4.18)	1.39 (0.46–4.18)	0.73 (0.14–4.00)	1.39 (0.92–2.10)
Death	1.17 (0.65–1.70)	1.05 (0.65–1.70)	1.12 (0.54–2.34)	1.23 (0.99–1.53)
Log WBC count (per SD)				
CHD	2.05 (1.03–4.06)†	2.39 (1.06–5.40)†	1.93 (0.54–6.87)	2.74 (1.99–3.78)†
CVD	1.23 (1.08–1.41)†	1.16 (0.99–1.37)	1.55 (1.19–2.03)†	1.33 (1.24–1.43)†
Fatal CVD	2.51 (0.96–6.52)†	1.52 (0.50–4.57)	24.24 (2.64–222.70)†	2.23 (1.29–3.84)†
Death	3.93 (2.48–6.22)†	3.59 (2.15–5.99)†	5.48 (1.81–16.54)†	1.97 (1.49–2.62)†
Log IL-6 level (per SD)‡				
CHD	1.12 (0.92–1.37)	1.22 (0.96–1.54)	1.19 (0.70–2.01)	0.92 (0.78–1.09)
CVD	1.14 (0.99–1.31)	1.17 (0.99–1.38)	1.50 (1.06–2.12)†	0.92 (0.81–1.03)
Fatal CVD	1.39 (1.03–1.87)†	1.42 (1.01–1.99)†	1.54 (0.69–3.47)	1.21 (0.99–1.49)
Death	1.31 (1.15–1.49)†	1.34 (1.16–1.54)†	1.10 (0.72–1.69)	0.95 (0.83–1.08)

* Excluding those with cardiovascular disease (CVD) at baseline or rheumatoid arthritis (RA) only at followup. Values are the hazard ratio (95% confidence interval). WHI = Women's Health Initiative; anti-CCP = anti–cyclic citrullinated peptide; DMARD = disease-modifying antirheumatic drug; RF = rheumatoid factor; CHD = coronary heart disease; WBC = white blood cell; IL-6 = interleukin-6.
† $P < 0.05$.
‡ Only measured in a subset of women.

ple, for women with RA versus women with no reported RA, the excess risk of CVD was $10.75 - 6.35 = 4.4$ events per 1,000 person-years among those with no CV risk factors, but the excess risk of CVD was $45.72 - 27.03 = \sim 18.7$ events per 1,000 person-years among those with diabetes mellitus and hypertension. Most risk factors showed a similar pattern in relation to CHD incidence, except that among women with RA, CHD rates were not lower among those with a BMI of <25 kg/m^2 compared with those with a BMI of 25–30 kg/m^2, and were highest among past smokers rather than current smokers (see Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39198/abstract).

The age-adjusted CHD incidence rate (per 1,000 person-years) was 1.5–2-fold higher for those with severe joint pain than for those with no joint pain in women with RA, women with unverified RA, and women with no reported RA with or without arthritis reported at baseline (Table 3). Higher CHD incidence rates for women with RA than for women not reporting RA were observed primarily among those with moderate or severe joint pain, with little difference at the categories of no or mild joint pain. Results were similar for CVD incidence rates (not shown).

Age-adjusted relative risks (expressed as hazard ratios [HRs] with 95% CIs) for CHD, CVD, fatal CVD, and death in relation to inflammation-related factors (RF positivity, WBC count, and IL-6 level) were evaluated separately for all women with RA (anti-CCP positive and/or reporting taking DMARDs), anti-CCP–positive women with RA, anti-CCP–negative women with RA reporting taking DMARDs, and women with unverified RA (anti-CCP negative and not reporting taking DMARDs) (Table 4). (Women who never reported RA were not sampled for our biomarker cohort, and IL-6 was measured in only a subset [$\sim$30%] of the biomarker cohort [13].) For RF positivity, HRs did not reach statistical significance for any outcomes in women with RA, women in the RA subsets, or women with unverified RA, although among anti-CCP–positive women with RA, the HR for CHD was >2 (Table 4). In contrast, a higher WBC count was associated with higher risks of CHD, CVD, fatal CVD, and death for all women with RA and women with unverified RA. For all women with RA, anti-CCP–positive women with RA, and anti-CCP–negative women with RA reporting taking DMARDs, HRs per log WBC count were stronger for death than for CHD. Similarly, among all women with RA or anti-CCP–positive women with RA, log IL-6 level was significantly associated with fatal CVD and death but not with CHD or CVD. Further, log IL-6 level was not significantly associated with any outcomes among women with unverified RA.

Table 5. Weighted multivariable-adjusted risk of CHD or fatal CVD among the WHI participants, comparing women with RA with those not reporting RA*

	Incident CHD		Fatal CVD	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Model 1: RA vs. no reported RA	1.49 (1.20–1.86)	0.000	2.56 (1.86–3.51)	<0.0001
Age, per year	1.07 (1.07–1.08)	<0.0001	1.15 (1.14–1.16)	<0.0001
Smoking (ever vs. never)	1.25 (1.19–1.30)	<0.0001	1.44 (1.32–1.56)	<0.0001
Hypertension (yes vs. no)	1.69 (1.61–1.77)	<0.0001	1.91 (1.75–2.09)	<0.0001
Diabetes mellitus (yes vs. no)	2.42 (2.25–2.60)	<0.0001	2.49 (2.19–2.83)	<0.0001
BMI, per 1 unit	1.02 (1.02–1.02)	<0.0001	1.02 (1.01–1.03)	<0.0001
High cholesterol (yes vs. no)	1.35 (1.28–1.44)	<0.0001	0.96 (0.86–1.08)	0.541
Model 2 (adjusts for model 1 covariates plus joint pain)				
RA vs. no reported RA	1.35 (1.08–1.68)	0.009	2.41 (1.75–3.32)	<0.0001
Joint pain		<0.0001		<0.0001
Mild vs. none	1.15 (1.09–1.22)		0.87 (0.78–0.96)	
Moderate vs. none	1.36 (1.27–1.45)		1.00 (0.88–1.13)	
Severe vs. none	1.51 (1.37–1.67)		1.38 (1.16–1.64)	
Model 3 (adjusts for model 1 covariates plus health status)				
RA vs. no reported RA	1.39 (1.11–1.73)	0.004	2.24 (1.63–3.08)	<0.0001
Fair/poor health vs. other	1.58 (1.46–1.70)	<0.0001	2.22 (1.97–2.51)	<0.0001
Model 4 (adjusts for model 1 covariates plus WBC count)				
RA vs. no reported RA	1.46 (1.17–1.83)	0.001	2.55 (1.86–3.51)	<0.0001
Log WBC count (per SD)	1.52 (1.43–1.62)	<0.0001	1.59 (1.42–1.78)	<0.0001

* Excluding those with cardiovascular disease (CVD) at baseline or rheumatoid arthritis (RA) only at followup. CHD = coronary heart disease; WHI = Women's Health Initiative; HR = hazard ratio; 95% CI = 95% confidence interval; BMI = body mass index; WBC = white blood cell.

Multivariable models of cardiovascular risk. Associations of RA and risk factors with incident CHD and fatal CVD were evaluated further in multivariable-adjusted Cox proportional hazards regression models (Table 5). After adjustment for age, smoking, hypertension, diabetes mellitus, BMI, and high cholesterol, women with RA had a 1.5-fold increased risk of incident CHD and a 2.5-fold increased risk of fatal CVD compared with women with no reported RA (model 1). These increased relative risks were only modestly attenuated with further adjustment for joint pain, health status, or log WBC count (models 2–4), each of which was also significantly associated with CHD and with fatal CVD. HRs in models 2 and 3 were similar with further adjustment for log WBC count, which also remained significantly associated with CHD and with fatal CVD (not shown). For incident CHD, only health status had a statistically significant interaction with RA ($P = 0.015$).

Stratified analyses showed that the risk of CHD conferred by fair/poor health was stronger for women with RA, as shown in Supplementary Table 2 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39198/abstract). For risk of fatal CVD, hypertension ($P = 0.02$) and joint pain ($P = 0.01$) had interactions with RA. In stratified analyses, the increased risk of fatal CVD with RA (versus no reported RA) was attenuated among women with hypertension (HR 1.58 [95% CI 0.91–2.75], $P = 0.11$), similar to CVD results in Table 2. Stratified analyses showed that the risk of fatal CVD with RA (versus no reported RA) was increased with moderate joint pain (HR 2.85 [95% CI 1.77–4.58]) and severe joint pain (HR 3.56 [95% CI 2.08–6.08]), but was not increased with no joint pain (HR 0) or mild joint pain (HR 1.26 [95% CI 0.56–2.81]).

Finally, whether risk factors explained different patterns of CVD morbidity and mortality across RA groups was assessed in Cox models adjusted for age, smoking, hypertension, diabetes mellitus, BMI, and (log) WBC count, with women with no reported RA as the reference group (Figure 1). Overall, multivariable-adjusted HRs for CHD, stroke, CVD, fatal CVD, and death were higher for women in all RA categories (anti-CCP positive and not reporting taking DMARDs, anti-CCP positive and reporting taking DMARDs, and anti-CCP

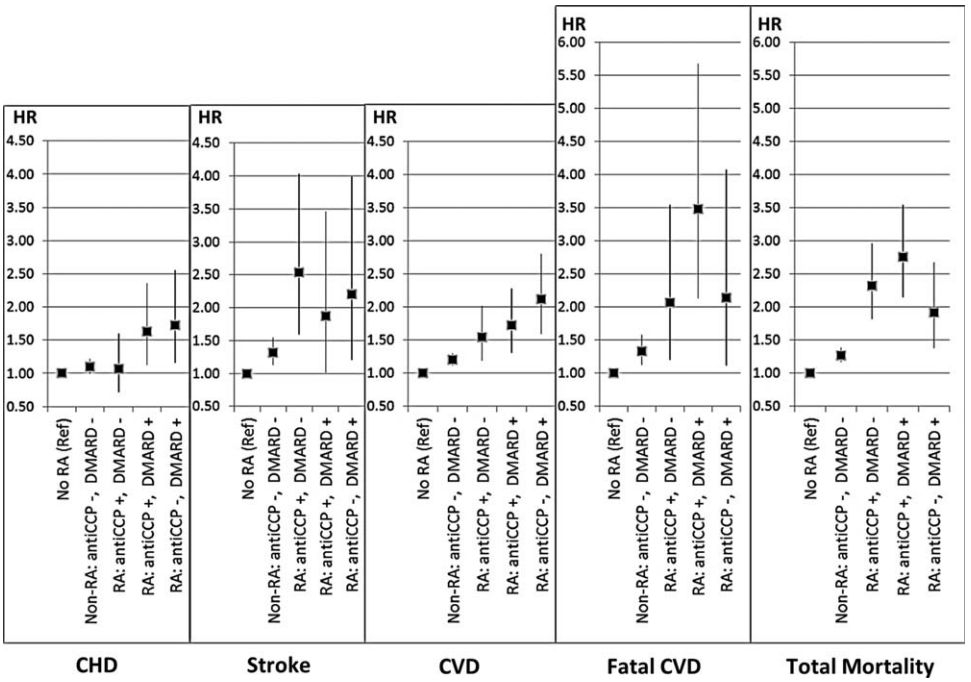

Figure 1. Multivariable-adjusted risk of cardiovascular events by groups of women with rheumatoid arthritis (RA), with unverified RA, or not reporting RA. Values are hazard ratios (HRs) and 95% confidence intervals, calculated from Cox proportional hazards models with no reported RA as the reference (ref.), adjusted for age, smoking, hypertension, diabetes mellitus, body mass index, and (log) white blood cell count. Non-RA represents unverified RA (anti–cyclic citrullinated peptide–negative [anti-CCP−] women not reporting taking disease-modifying antirheumatic drugs [DMARD−]); anti-CCP+ represents anti-CCP–positive women; and DMARD+ represents women reporting taking DMARDs. CHD = coronary heart disease; CVD = cardiovascular disease.

negative and reporting taking DMARDs) compared with women with no reported RA. The only exception was that for anti-CCP–positive women with RA not reporting taking DMARDs, CHD risk was similar to that for women with no reported RA. As with age-adjusted rates, HRs for CHD, stroke, and CVD in anti-CCP–positive women with RA reporting taking DMARDs were similar to or smaller than those in anti-CCP–negative women with RA reporting taking DMARDs, although HRs for fatal CVD and total mortality risk were similar to or higher in anti-CCP–positive women with RA (reporting or not reporting taking DMARDs) than in anti-CCP–negative women with RA reporting taking DMARDs.

DISCUSSION

Few studies have evaluated anti-CCP positivity and RF positivity in relation to both cardiovascular morbidity and mortality. In our study of postmenopausal women with self-reported RA, the first major finding was that neither anti-CCP positivity nor RF positivity was significantly associated with similar or higher incidence rates of CVD morbidity or mortality, despite being associated with higher levels of inflammation (13). However, anti-CCP–positive women with RA (reporting or not reporting taking DMARDs) had similar or higher rates of fatal CVD and total mortality and lower or similar rates of CHD and CVD compared with anti-CCP–negative women with RA reporting taking DMARDs. Traditional CVD risk factors as well as inflammation (i.e., WBC count), fair/poor health, and joint pain were strongly associated with CHD and fatal CVD, but adjusting for these factors only modestly attenuated the RA-related risk and did not explain differences in CVD morbidity or mortality. Furthermore, as in other studies, anti-CCP positivity was associated with a higher prevalence of current and former smoking, but results persisted when adjusted for smoking.

A study of 937 patients with RA showed that anti-CCP positivity was associated with increased risk of ischemic heart disease (odds ratio 2.58 [95% CI 1.17–5.65]), but not with increased risk of HF or stroke (25). That study included men, in whom half of the ischemic heart disease events occurred. Other studies have shown that anti-CCP positivity was significantly associated with total mortality (26,27) or fatal CVD (27), but not with CVD (26,28). In a study of outcomes following MI,

seropositivity for RF and/or anti-CCP was associated with a marginally increased risk of death, but not with HF or recurrent ischemia (29). Although citrullination is found within the atherosclerotic plaque (30), 2 studies showed no association of higher coronary atherosclerosis with anti-CCP positivity (30,31). Overall, our study results suggest that associations of anti-CCP positivity or RF positivity with CVD morbidity and mortality may be related to increased inflammation, joint pain, and disease activity associated with anti-CCP positivity or RF positivity, rather than to anti-CCP positivity or RF positivity per se. However, given the limitations of the current investigation, as described below, additional studies will be needed to test this hypothesis.

A second finding was that RA was associated with larger relative risks of fatal CVD and total mortality than of CVD or CHD, and among women with RA, inflammation markers (i.e., WBC count and IL-6 levels) had stronger associations with fatal CVD and total mortality than with CVD or CHD. We previously reported that the >2-fold excess mortality for RA versus no reported RA was associated with a higher baseline WBC count among subgroups in the WHI RA Study, independent of CVD risk factors (14). In the WHI, WBC count was associated with nonfatal MI, stroke, and total mortality, but particularly with fatal CVD, over a mean 6.1 years of followup, independent of CVD risk factors (19). Similar results have been reported from studies of human immunodeficiency virus (i.e., stronger associations of IL-6 with mortality [32] than with CVD [33]). There are several possible explanations. The occurrence of sudden cardiac death as the initial manifestation of CVD may be increased among RA patients (34). Poor renal function may contribute to fatal CVD in RA patients (35). Finally, RA patients may have a higher prevalence of unrecognized MI (36) or other silent myocardial damage or lung disease (37–39) related to systemic inflammation and disease activity (40) that increase mortality independent of CHD and that may also differ by patients' anti-CCP status (37,41).

A third important finding of this study is the association of self-reported joint pain severity with higher CHD incidence not only among women with RA, but also among women with unverified RA, women with other arthritis, and women with neither RA nor arthritis. In multivariable-adjusted models, the risk of CHD conferred by moderate and severe joint pain was similar to or larger than that conferred by RA versus no reported RA. In contrast, only severe joint pain was significantly associated with risk of fatal CVD in multivariable models including women with RA and women with no reported RA. In addition, the ≥1.5-fold increased risk of CHD and CVD in women with RA compared with women with no reported RA was seen at most CVD risk factor levels and even in the absence of CVD risk factors, but was not observed among women with low levels of joint pain or inflammation (WBC count or IL-6 levels). Furthermore, joint pain and WBC count remained significantly associated with CHD and fatal CVD when both were included in the multivariable models (not shown). These results suggest that joint pain and inflammation are key risk markers and possible therapeutic targets for the reduction of CHD and CVD, among women without RA as well as among women with RA.

Our results are consistent with those of several recent RA studies, showing strong associations of cumulative exposure to disease flares, joint pain, and the Disease Activity Score in 28 joints (DAS28) (42) with increased CVD risk (43,44). Furthermore, with anti–IL-6 treatment, greater reductions in the DAS28 and in swollen and tender joint counts were independently related to lower risk of major adverse CV events during followup (44). Higher levels of joint symptomatology may adversely affect adherence to risk factor modification (i.e., increasing physical activity, weight loss, and smoking cessation, or pharmacologic treatment of hypertension and dyslipidemia) (45). Further studies are needed to elucidate the mechanisms underlying the association of joint pain with CVD risk among women with unverified RA, women not reporting RA, and women with RA. Given that antiinflammatory medications such as methotrexate reduce symptomatology (46), our results suggest that clinical trials of antiinflammatory therapies to reduce CVD among non-RA populations should evaluate joint pain as a possible mediator.

The current study has several strengths. It was conducted within the very large, longitudinal WHI study of postmenopausal women from the community (not from the clinic) with standardized data collection, followup, and central adjudication of CVD events. The large sample size allowed stratification by anti-CCP status and taking of DMARDs, and it included the relatively rare comparison group of women with "unverified RA" who reported RA (and arthritis) and had higher levels of joint pain than women who never reported RA. In addition, the study baseline and followup visits took place prior to the widespread use of powerful new biologic RA treatments, which reduces potential confounding from those medications.

However, our results, particularly comparisons of anti-CCP–positive RA with anti-CCP–negative RA, must be interpreted cautiously in light of the study's limitations, described below, and should be considered hypothesis-generating rather than definitive. The fore-

most of these limitations is that in this very large study of women from the community, RA was not diagnosed by clinical examination, and we have no information on duration of disease. Furthermore, our definition of anti-CCP–negative RA requires reported taking of DMARDs, which does not allow us to evaluate anti-CCP–negative RA without taking of DMARDs. However, anti-CCP positivity is fairly sensitive and highly specific for RA, and our key comparisons of anti-CCP positivity with anti-CCP negativity were based on groups who took DMARDs. In addition, taking DMARDs is associated with a more severe disease course, as also seen in our study, since anti-CCP–positive women taking DMARDs had higher levels of joint pain, worse general health, and similar or higher risks of CHD, fatal CVD, and total mortality compared with anti-CCP–positive women not taking DMARDs. However, compared with anti-CCP–negative women taking DMARDs, rates of CHD and CVD morbidity were lower or similar in both anti-CCP–positive groups, while rates of fatal CVD and total mortality were similar or higher in both anti-CCP–positive groups. A small proportion of the women we classified as having "unverified RA" (anti-CCP negative and not reporting taking DMARDs) may have had RA, and they likely had osteoarthritis or other disease, but this potential misclassification also does not explain our key results.

There is also high potential for confounding by medication use in this study. In sensitivity analyses, oral steroids were included in the definition of DMARDs, and this did not materially change our results. The results may have been affected by survival bias (i.e., anti-CCP–positive women may have had nonfatal or fatal CHD or events prior to entering the study that removed them from our cohort). We cannot evaluate survival bias prior to entry into the WHI, but within the WHI, the proportion of women excluded from the current analysis due to preexisting CVD was similar across anti-CCP–positive and anti-CCP–negative groups reporting or not reporting taking DMARDs. Furthermore, results were similar when women with baseline CVD were included in the analyses (not shown). Another limitation is that since lipids were not routinely measured in WHI participants, the standard definition of high cholesterol was self-reported high cholesterol or taking lipid-lowering medications. Therefore, high cholesterol was not a focus of our study, and our results add little clarity to the important question of how lipids and lipoproteins and changes in them are related to CVD outcomes in RA.

In conclusion, among postmenopausal women in the WHI, RA was associated with a higher risk of CHD, stroke, and total CVD (HR ~1.5) and an even higher risk of fatal CVD (HR ~2.5) or total mortality, particularly for those who were anti-CCP positive. CVD morbidity and mortality were not significantly related to anti-CCP positivity or RF positivity, but CHD and CVD risks were related to CVD risk factors and joint pain, and among women with RA, inflammation was associated with fatal CVD and mortality. Interestingly, joint pain severity was associated with higher CHD risk among women with no reported RA and no arthritis as well as among women with RA and women with unverified RA. These results suggest that the treatment of traditional CHD risk factors among RA patients likely remains an important priority for reducing CHD risk (8,15,47–49). In addition, the relationship between joint symptoms and CHD/CVD supports continued focus on whether reduction of joint symptomatology, even in patients without RA, may partially mediate improved CVD-related outcomes, especially in relation to antiinflammatory therapies.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Mackey 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.

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