# Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients?

A Gonzalez,[1] H Maradit Kremers,[1] C S Crowson,[2] K V Ballman,[2] V L Roger,[3] S J Jacobsen,[4] W M O'Fallon,[2] S E Gabriel[5]

[1] Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA; [2] Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA; [3] Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA; [4] Research and Evaluation, Southern California Permanente Medical Group, Pasadena, California, USA; [5] Division of Rheumatology, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA

Correspondence to: Prof. Sherine E Gabriel, Mayo Foundation, 200 First St. SW, Rochester, Minnesota 55905; gabriel.sherine@mayo.edu

Accepted 7 May 2007
Published Online First 22 May 2007

## ABSTRACT

**Objective:** To compare the frequency of traditional cardiovascular (CV) risk factors in rheumatoid arthritis (RA) compared to non-RA subjects, and examine their impact on the risk of developing selected CV events (myocardial infarction (MI), heart failure (HF) and CV death) in these two groups.

**Methods:** We examined a population-based incidence cohort of subjects with RA (defined according to the 1987 American College of Rheumatology criteria), and an age- and sex-matched non-RA cohort. All subjects were followed longitudinally through their complete community medical records, until death, migration, or 1 January 2001. Clinical CV risk factors and outcomes were defined using validated criteria. The $\chi^2$ test was used to compare the frequency of each CV risk factor at baseline. Person-years methods were used to estimate the rate of occurrence of each CV risk factor during follow-up. Cox models were used to examine the influence of CV risk factors on the development of CV outcomes.

**Results:** A total of 603 RA and 603 non-RA subjects (73% female; mean age 58 years) were followed for a mean of 15 and 17 years (total: 8842 and 10 101 person-years), respectively. At baseline, RA subjects were significantly more likely to be former or current smokers when compared to non-RA subjects ($p<0.001$). Male gender, smoking, and personal cardiac history had weaker associations with CV events among RA subjects, compared to non-RA subjects. There was no significant difference between RA and non-RA subjects in the risk imparted with respect to the other CV risk factors (ie, family cardiac history, hypertension, dyslipidaemia, body mass index, or diabetes mellitus).

**Conclusion:** While some traditional CV risk factors imparted similar risk among RA compared with non-RA subjects, others (ie, male gender, smoking and personal cardiac history) imparted significantly less risk for the development of CV disease. These differences in the overall impact of traditional CV risk factors suggest that strategies to prevent CV disease and mortality focused solely on controlling traditional CV risk factors may be relatively less beneficial in RA subjects than in the general population. Further research is needed to determine optimal approaches to reducing CV morbidity and mortality in persons with RA.

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease associated with persistent inflammatory synovitis, progressive joint destruction, and an excess mortality when compared to the general population.[1 2] Cardiovascular (CV) diseases are the underlying cause of death in a substantial proportion of deceased RA subjects.[1 3–10]

While traditional CV risk factors are strong predictors of CV outcomes that contribute to the CV morbidity and mortality in the general population,[11–13] their impact on CV morbidity and mortality in RA is unclear. The objective of this study was to compare the frequency of traditional CV risk factors in RA and non-RA subjects and to determine whether the impact of these risk factors on the risk of developing selected CV outcomes (myocardial infarction (MI), heart failure (HF) and CV death) differed in RA subjects, when compared to those without RA. Thus, by comparing subjects with RA (a chronic systemic inflammatory disease), and non-RA, our goal was to draw inferences regarding the potential relationship between inflammation and CV risk.

## METHODS

The study was conducted within the population of Rochester, Minnesota, USA. This population is well suited for a longitudinal, population-based cohort study of RA subjects because comprehensive medical records for all residents seeking medical care by any medical care provider for over half a century are available. The medical records linkage system of the Rochester Epidemiology Project (REP) allows ready access to the complete (inpatient and outpatient) records from all health care providers for the local population including the Mayo Clinic and its affiliated hospitals, the Olmsted Medical Center and its affiliated community hospital, local nursing homes, and the few private practitioners. The potential of this data system for population-based research studies has been previously described.[14 15] This system assures virtually complete clinical and vital status information for cases of RA among Rochester, Minnesota residents.

We designed a retrospective, population-based cohort study. The study population consisted of a previously described[16 17] inception cohort of all subjects who fulfilled the 1987 American College of Rheumatology criteria[18] for RA between 1 January 1955 and 1 January 1995 among Rochester, Minnesota residents ⩾18 years of age, and an age- and sex-matched cohort of subjects without RA. RA incidence date was defined as the first date of fulfilment of four (out of the seven) diagnostic criteria. For each subject with RA, an individual without RA having a similar birth year (+/−3 years), sex and length of medical record was

randomly selected from the same underlying population. These subjects comprised the non-RA cohort. Each non-RA subject was assigned an index date corresponding to the RA incidence date (baseline) of the corresponding RA patient. All subjects were followed longitudinally through their entire medical records, until death, migration, or 1 January 2001 (end of follow-up for the study).

### Ascertainment of CV risk factors

Detailed information was collected regarding each clinically documented occurrence of the CV risk factors during the entire follow-up period. Traditional CV risk factors were defined according to standardised diagnostic criteria.

Personal and family cardiac history were ascertained at baseline and included presence of angina pectoris, coronary artery disease, coronary insufficiency, ischemic heart disease, MI (including silent events), HF, pulmonary oedema and coronary revascularisation procedures (ie, coronary artery bypass graft, percutaneous angioplasty, insertion of stents and atherectomy). Positive family cardiac history was defined as presence of heart disease in first degree relatives.

Cigarette smoking status was determined at baseline by medical record abstraction and categorised as "current", "former", or "never". Use of other tobacco products (eg, pipe, cigar) was not considered.

Hypertension was defined according to the criteria of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure.[19 20] Subjects with two or more ambulatory blood pressure readings ⩾140 mmHg systolic and/or 90 mmHg diastolic were considered to be hypertensive and the first date they fulfilled these criteria was considered the hypertension incidence date. Subjects who did not fulfil these criteria, but who had a physician's diagnosis of hypertension in their medical records and/or were receiving antihypertensive agents were also considered hypertensive and the earliest recorded date of hypertension diagnosis was considered the hypertension incidence date.

Dyslipidaemia was defined according to the cut-off values proposed by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines.[21 22] Dyslipidaemia was considered present if low-density lipoprotein (LDL)-cholesterol level was ⩾0.41 mmol/L, total cholesterol level was ⩾6.20 mmol/L, high-density lipoprotein (HDL)-cholesterol level was <1.03 mmol/L or triglycerides level was ⩾1.69 mmol/L.

Obesity was defined in accordance with the clinical guidelines on the "Identification, Evaluation and Treatment of Overweight and Obesity in Adults".[23] Body mass index (BMI) (defined as weight in kilograms divided by the square of the height in metres (weight/height$^2$ in kg/m$^2$)) was categorised as high BMI (obesity), defined as BMI ⩾30 kg/m$^2$, or low BMI, defined as BMI <20 kg/m$^2$, at baseline and at the date of first entry into either the high BMI or the low BMI category during follow-up.

Diabetes mellitus (DM) was defined according to the diagnostic criteria adopted by the World Health Organization consultation group in 1998 as fasting plasma glucose ⩾7 mmol/L or a 2-h plasma glucose ⩾11.11 mmol/L following a glucose load, a clearly documented history of DM and/or current treatment with hypoglycaemic agents (including insulin).[24] The date subjects first fulfilled these diagnostic criteria was considered the DM incidence date.

### Ascertainment of CV outcomes

The outcomes in this study included: MI, HF, and CV death and were assessed according to the definitions below.

#### Myocardial infarction

Data were collected regarding all non-fatal MIs that occurred in RA and non-RA subjects throughout the follow-up period. Hospitalised MIs were defined according to standard epidemiological[25 26] criteria and classified as definite, probable, suspect, or no MI based on the presence of cardiac pain, biomarker values and the Minnesota coding of the electrocardiogram (ECG).[27 28] Definite and probable MIs were used for analyses.

#### Heart failure

HF was defined using the Framingham Heart Study criteria.[29] These validated criteria[30] require the simultaneous presence of at least two major criteria (paroxysmal nocturnal dyspnoea or orthopnea, neck vein distention, rales, cardiomegaly, acute pulmonary oedema, S3 gallop, increased venous pressure higher or equal to 16 cm of water, circulation time higher or equal to 25 s, hepatojugular reflux), or one major criterion and two minor criteria (ankle oedema, night cough, dyspnoea upon exertion, hepatomegaly, pleural effusion, vital capacity decreased by one third from maximum, tachycardia rate of higher or equal to 120 beats/min, weight loss ⩾4.5 kg in 5 days in response to treatment).

#### Cardiovascular death

All causes of death (including both underlying and contributory causes) as reported in medical records and/or death certificates were collected for all deceased subjects. All subjects were tracked nationally to ascertain vital status, and death certificates were obtained from the respective states for subjects who were deceased out of state. CV death included the following causes of death: coronary heart disease deaths (ie, old, previous or acute MI, stable or unstable angina pectoris, other forms of chronic ischemic heart disease), arrhythmias, dysrrhythmias, hypertension, HF, pulmonary oedema, rheumatic heart disease, valvular stenosis or insufficiency and ruptured aortic aneurysm.

### Statistical methods

Descriptive statistics were used to examine the baseline characteristics of the RA and the non-RA subjects. The $\chi^2$ test was used to compare the frequency of each CV risk factor at baseline. Estimates for the rate of development of each CV risk factor during follow-up (among those who did not have the risk factor at baseline) were obtained using person-years methods. Rate ratios (RR) were used to compare the rate of development of CV risk factors among the RA and non-RA cohorts. Confidence intervals (CI) for RR were obtained using an F approximation.[31] Cox models with age as the time scale, and stratified by sex were used to examine the relative effect of the CV risk factors on CV outcomes (both individually and combined, defined as the earliest of the three outcomes: MI, HF, and CV death) in RA compared to non-RA subjects. Subjects who experienced MI or HF prior to baseline were removed from the analysis of the MI or HF outcome and from the analysis of the combined CV outcome. Dichotomous time-dependent covariates were used to account for risk factors that developed after baseline. Specifically, over the follow-up period, a patient's status was changed from unexposed to exposed at the time of first identification of a particular risk factor. p Values <0.05 were considered statistically significant. In

addition, Poisson regression models were used to assess the absolute increment in CV risk associated with each CV risk factor. The absolute risk estimates the average increase in cardiovascular risk on an absolute scale that is attributable to a risk factor within RA and non-RA cohorts and takes into account the higher baseline cardiovascular risk of RA patients. These models were adjusted for age, sex, and calendar year.

## RESULTS

The study population comprised 603 subjects with RA and 603 non-RA subjects. Table 1 provides the baseline characteristics of the study population. Mean age was 58 years and 73% of subjects were women in both groups. RA subjects were significantly more likely to have been former or current smokers when compared to non-RA subjects ($p<0.001$). The baseline prevalence of personal and family cardiac history, and all other CV risk factors: hypertension, dyslipidaemia, high and low BMI, and DM were similar in both groups (table 1).

The RA and non-RA subjects were followed for a mean of 15 and 17 years, corresponding to 8842 and 10 101 person-years, respectively. Incidence rates for each of the CV risk factors are shown in table 2. RA subjects were significantly more likely to develop low BMI (RR: 1.79, 95% CI 1.28–2.54) and less likely to develop dyslipidaemia (RR: 0.75, 95% CI 0.61–0.91) when compared with non-RA subjects. RA subjects were at similar risk for developing hypertension, and were also less likely to be obese and diabetic than non-RA subjects during follow-up, but none of these differences reached statistical significance.

During the follow-up, 40 RA subjects experienced a non-fatal MI, 165 RA subjects developed HF, and 171 died of CV causes. In contrast, 46 non-RA subjects experienced MI (fatal and non-fatal), 115 developed HF, and 132 died of CV causes. Overall, 230 RA subjects and 176 non-RA subjects experienced at least one of these events, which comprised the combined outcome. The impact of the traditional CV risk factors on the combined CV outcome was also assessed (table 3). In RA subjects, male gender (HR: 1.32, 95% CI 0.99–1.75), current smoking (HR: 1.32, 95% CI 0.97–1.81), hypertension (HR: 1.97, 95% CI 1.24–3.11), DM (HR: 1.62, 95% CI 1.17–2.24), and low BMI (HR:1.58, 95% CI 1.19–2.10), were associated with a higher risk of developing a CV outcome. Similarly, among non-RA subjects, a higher risk for developing a CV outcome was associated with male gender (HR: 2.22, 95% CI 1.60–3.06), current smoking (HR: 2.19, 95% CI 1.56–3.09), personal cardiac history (HR: 2.35, 95% CI 1.61–3.43), hypertension (HR: 2.75, 95% CI 1.33–5.69), and DM (HR: 2.05, 95% CI 1.46–2.90) respectively. The remaining CV risk factors did not show significant associations with the development of CV outcomes in either the RA or the non-RA cohort.

Figure 1 (which corresponds to columns 2 and 3 of table 3) shows the influence of traditional CV risk factors (expressed as HR and 95% CI) on the combined CV outcome in RA and non-RA subjects, separately. Gender, smoking status, and personal cardiac history appear to have a different influence on CV outcome in RA compared to non-RA subjects.

To demonstrate the relative influence of the traditional CV risk factors for the combined CV outcome within the RA and non-RA cohorts, the absolute risks were estimated for gender, smoking and personal cardiac history. With respect to the relative influence of gender within the RA cohort, the absolute risk of the combined CV outcome is 1.1 per 100 person-years (py) for a 70-year-old female with RA compared to 1.4 per 100 py for a 70-year-old male with RA (an additional 0.3 per 100 py). Within the non-RA cohort, the absolute risk is 0.5 per 100 py for a 70-year-old female without RA compared to 1.1 per 100 py for a 70-year-old male without RA (an additional 0.6 per 100 py).

With respect to smoking, the absolute risk of the combined CV outcome is 2.5 per 100 py for 70-year-old female non-smokers with RA compared to 3.1 per 100 py for 70-year-old smokers with RA (an additional 0.6 per 100 py). In comparison, within the non-RA cohort, the absolute risk is 1.2 per 100 py for 70-year-old female non-smokers without RA compared to 2.7 per 100 py for 70-year-old female smokers without RA (an additional 1.5 per 100 py).

Finally, with respect to personal cardiac history, the absolute risk of the combined CV outcome is 1.1 per 100 py for a 70-year-old female with RA and no personal cardiac history compared to 1.3 per 100 py for a 70-year-old female with RA and a positive cardiac history (an additional 0.2 per 100 py). Within the non-RA cohort, the absolute risk is 0.5 per 100 py for a 70-year-old female without RA and no personal cardiac history compared 1.3 per 100 py for those with a personal cardiac history (an additional 0.8 per 100 py). None of the other risk factors demonstrated a different influence for RA compared to non-RA subjects, so the remaining absolute risks are not shown.

## DISCUSSION

Rheumatic diseases have historically been considered as inflammatory conditions that primarily affect the musculoskeletal system. Only recently has attention been focused on systemic features and comorbidities. This study is among the first population-based analyses examining the distribution and impact of CV risk factors on CV outcomes.

**Table 1** Prevalence of cardiovascular (CV) risk factors at baseline in 603 rheumatoid arthritis (RA) and 603 non-RA subjects

| CV risk factor | RA cohort n (%) | Non-RA cohort n (%) | p Value |
|---|---|---|---|
| Family cardiac history | 287 (48) | 284 (47) | 0.86 |
| Personal cardiac history | 77 (13) | 72 (12) | 0.66 |
| Cigarette smoking status | | | <0.001 |
| Never | 285 (47) | 341 (57) | |
| Former | 148 (25) | 118 (19) | |
| Current | 170 (28) | 144 (24) | |
| Hypertension | 312 (52) | 298 (49) | 0.42 |
| Dyslipidaemia* | 163 (49) | 169 (52) | 0.45 |
| High BMI (≥30 kg/m$^2$) | 71 (13) | 68 (13) | 0.98 |
| Low BMI (<20 kg/m$^2$) | 73 (13) | 63 (12) | 0.50 |
| Diabetes mellitus | 44 (7) | 41 (7) | 0.74 |

*Lipids were measured in 330 subjects in the RA cohort and 323 in the non-RA cohort. BMI, body mass index.

**Table 2** Incidence rates (events/100 person-years), rate ratios (rheumatoid arthritis (RA)/non-RA), and 95% confidence intervals of the cardiovascular (CV) risk factors that developed during follow-up in RA and non-RA subjects*

| | Rate per 100 person-years (no. of cases) | | |
|---|---|---|---|
| **Cardiovascular risk factors** | **RA** | **Non-RA** | **Rate ratio (95% CI)** |
| Hypertension | 3.67 (179) | 3.59 (215) | 1.02 (0.84–1.25) |
| Dyslipidaemia | 2.71 (158) | 3.64 (228) | 0.75 (0.61–0.91)† |
| High BMI (≥30 kg/m$^2$) | 0.47 (35) | 0.63 (54) | 0.75 (0.48–1.13) |
| Low BMI (<20 kg/m$^2$) | 1.17 (83) | 0.65 (53) | 1.79 (1.28–2.54)† |
| Diabetes mellitus | 0.79 (66) | 1.02 (98) | 0.78 (0.57–1.06) |

*Subjects with the risk factor at baseline were removed from the analysis of that specific risk factor.
† Significant ($p<0.05$) values.
BMI, body mass index.

With the exception of smoking, which was more common in RA subjects, the distribution of many of the traditional CV risk factors at baseline was similar among RA and non-RA subjects. This finding is similar to other reports in the literature.[32] However, our analysis demonstrates that these risk factors behave differently in RA subjects compared to non-RA subjects. In fact, most of the traditional CV risk factors appear to have a weaker association with CV events (ie, impart a lower risk for CV events) among RA compared to non-RA subjects. In contrast, a non-traditional risk factor (ie, low BMI) appears to increase CV risk among RA subjects but not among non-RA subjects. Thus, the impact of CV risk factors differs in RA compared to non-RA subjects. These observations provide new insights regarding the underlying mechanisms of CV events in RA subjects.

One plausible explanation for the observation that traditional CV risk factors appear to have a weaker association in RA subjects when compared to non-RA subjects is illustrated in table 4. This hypothetical example demonstrates the impact of a traditional CV risk factor (in this case smoking status) on a CV outcome (in this case HF) in hypothetical cohorts of 1000 non-RA and 1000 RA subjects. Assuming that there are 150 HF cases among the non-RA subjects, and that 100 of these HF cases are smokers and 50 are non-smokers; the hazard ratio for HF associated with smoking is 2.0 (100/50). In other words, non-RA smokers in this example are twice as likely to develop HF as non-RA subjects who do not smoke. If smoking imparts the same risk for HF among RA subjects as in non-RA subjects, we would expect 150 HF cases among the RA subjects, 100 smokers and 50 non-smokers (column 3, table 4). However, as previously reported, there is an increased incidence of HF in RA compared to non-RA subjects.[8 33] So, in fact, we expect more HF cases among RA than non-RA subjects. In this example, we assume that there are 100 additional HF cases in RA compared to non-RA subjects, for a total of 250 HF cases among RA subjects (table 4, Column 4). Assuming that the 100 additional HF cases in RA subjects occur as a result of a novel CV risk factor that is unique to RA subjects and is independent of smoking (factor X in table 4), as this factor is independent of smoking, these 100 additional HF cases are distributed equally among smokers and non-smokers (ie, 50 cases in each). Considering this new risk factor, the resulting hazard ratio for HF associated with smoking among RA subjects is (150/100 = 1.5), lower than that for non-RA subjects (100/50 = 2.0).

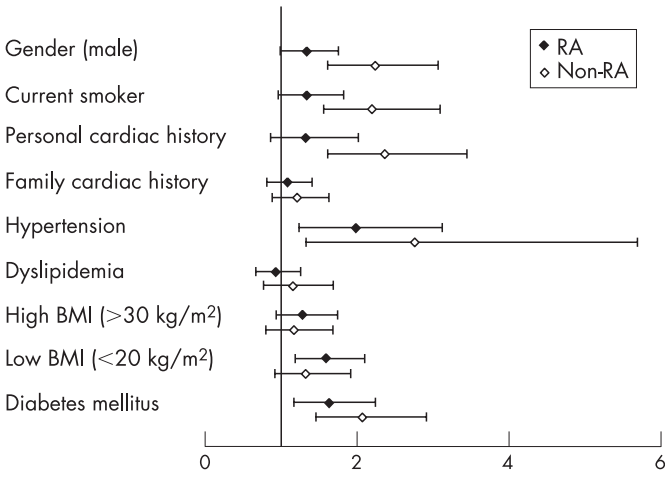
Thus, as illustrated by this hypothetical example, the presence of a novel CV risk factor that promotes HF in RA, but not in non-RA subjects, may result in an apparent dilution effect, making the relative contribution of traditional CV risk factors appear smaller among RA subjects. This hypothesis is indeed consistent with our absolute risk estimates for smoking where the absolute CV risk associated with smoking is actually larger among RA compared with non-RA subjects, despite a weaker hazard ratio estimate.

Some potential limitations should be considered when interpreting our results. As the study is a retrospective cohort study, it is not possible to ascertain traditional CV risk factors at pre-specified regular intervals for both groups. However, because our data resources provide complete ascertainment of all health care provided for local residents (including, inpatient and outpatient care from all providers), we were able to obtain information on CV risk factors in all instances where such information was documented in subjects' medical records. Because both RA subjects and CV events were defined according to information contained in the medical records, RA subjects

**Table 3** Influence of traditional cardiovascular (CV) risk factors on combined CV outcomes (myocardial infarction (MI), heart failure (HF), or CV death) in rheumatoid arthritis (RA) subjects compared to non-RA subjects

| **Characteristic** | **RA: HR (95% CI)** | **Non-RA: HR (95% CI)** | **p Value** |
|---|---|---|---|
| Gender (male)* | 1.32 (0.99–1.75) | 2.22 (1.60–3.06) | 0.018 |
| Current smoker* | 1.32 (0.97–1.81) | 2.19 (1.56–3.09) | 0.008 |
| Personal cardiac history* | 1.31 (0.86–2.01) | 2.35 (1.61–3.43) | 0.012 |
| Family cardiac history* | 1.07 (0.82–1.39) | 1.20 (0.89–1.62) | 0.486 |
| Hypertension† | 1.97 (1.24–3.11) | 2.75 (1.33–5.69) | 0.299 |
| Dyslipidaemia† | 0.92 (0.67–1.26) | 1.14 (0.77–1.68) | 0.437 |
| High BMI (≥30 kg/m$^2$)† | 1.27 (0.93–1.74) | 1.16 (0.80–1.67) | 0.720 |
| Low BMI (<20 kg/m$^2$)† | 1.58 (1.19–2.10) | 1.31 (0.91–1.91) | 0.114 |
| Diabetes mellitus† | 1.62 (1.17–2.24) | 2.05 (1.46–2.90) | 0.157 |

*Characteristics measured only at baseline.
†Characteristics measured at baseline and during follow-up and analysed as time dependent covariates.
BMI, body mass index.




◇ = Hazard ratios. Lines: 95% confidence intervals.
- Combined endpoint: MI, HF, or CV death

**Figure 1** Influence of traditional cardiovascular (CV) risk factors on combined endpoints in rheumatoid arthritis (RA) and non-RA subjects.

and/or events that did not come to medical attention would have been missed. However, it is unlikely that individuals with either RA or CV events would not come to medical attention. We did not include more recent subjects with RA, who were treated with newer medications such as the biologics, and thus were unable to compare the results in recent RA subjects who have had newer, earlier, or more aggressive treatments in the past 5 years. Future research should address the association between the extent of disease activity, treatment with biologics and the relative role of CV risk factors within the RA cohort. Finally, the Rochester, Minnesota population during the calendar years under investigation was predominantly white. Therefore our findings may not be generalisable to non-white individuals. With the exception of a higher proportion of the population with higher education levels, the sociodemographic characteristics of Olmsted County residents closely resemble those of the US white population.

Our study has several strengths. These include a population-based design, standardised and reproducible approach for case ascertainment, the long and complete follow-up of all the subjects studied, and the use of standardised and reproducible validated criteria to identify RA subjects, CV risk factors, and CV outcomes.

In conclusion, while the prevalence and incidence of many of the traditional CV risk factors were similar among RA and non-RA subjects, there were notable differences in the impact of some traditional CV risk factors on CV outcome among RA when compared to non-RA subjects. These results indicate that CV disease prevention strategies focused solely on controlling traditional CV risk factors may not have the same impact in persons with RA as would be expected based on estimates from the general population. The apparent weaker effect of some CV risk factors in RA subjects suggests that competing mechanisms may play a role in the development of CV disease in RA. Further research, including prospective studies, is needed in order to uncover the underlying determinants of RA associated CV morbidity and mortality in order to identify therapeutic strategies that could, perhaps, ameliorate this phenomenon.

**Funding:** This work was supported in part by a grant from the National Institutes of Health, NIAMS (R01 AR46849) and the National Institutes of Health (AR-30582) US Public Health Service.
**Competing interests:** None declared

## REFERENCES

1. **Gabriel SE,** Crowson CS, Maradit Kremers H, Doran MF, Turesson C, O'Fallon WM, *et al*. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. *Arthritis Rheum* 2003;**48**:54–8.
2. **Ward MM.** Recent improvements in survival in patients with rheumatoid arthritis: better outcomes or different study designs? *Arthritis Rheum* 2001;**44**:1467–9.
3. **Maradit Kremers H,** Gabriel SE. Epidemiology of the rheumatic diseases. In: Harris ED, Ruddy S, Sledge CB, eds. *Kelley's textbook of rheumatology*. Vol. 1, 7th edn. Philadelphia, Pennsylvania: W B Saunders Company, 2004.
4. **Gonzalez A,** Maradit-Kremers H, Crowson CS, Gabriel SE. Survival trends and risk factors for mortality in rheumatoid arthritis. *Int J Adv Rheumatol* 2005;**3**:38–46.
5. **Solomon DH,** Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, *et al*. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis [comment]. *Circulation* 2003;**107**:1303–7.
6. **Del Rincon I,** Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001;**44**:2737–45.
7. **Maradit Kremers H,** Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 2005;**52**:722–32.
8. **Nicola PJ,** Crowson CS, Maradit Kremers H, Ballman KV, Roger VL, Jacobsen SJ. Contribution of congestive heart failure and ischemic heart disease to excess mortality in rheumatoid arthritis. *Arthritis Rheum* 2006;**54**:60–7.
9. **Goodson N,** Marks J, Lunt M, Symmons D: Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. *Ann Rheum Dis* 2005;**64**:1595–1601.
10. **Wallberg-Jonsson S,** Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. *J Rheumatol* 1997;**24**:445–51.
11. **Kannel WB,** Schtzkin A. Sudden death: lessons from subsets in population studies. *J Am Coll Cardiol* 1985;**5**:141B–9B.
12. **Schatzkin A,** Cupples L, Heeren T, Morelock S, Kannel WB. Sudden death in the Framingham Heart Study: differences in incidence and risk factors by sex and coronary disease status. *Am J epidemiol* 1984;**120**:888–99.
13. **Dessein PH,** Joffe BI, Veller MG, Stevens BA, Tobias M, Reddi K, *et al*. Traditional and nontraditional cardiovascular risk factors are associated with atherosclerosis in rheumatoid arthritis. *J Rheumatol* 2005;**32**:435–42.
14. **Kurland L,** Molgaard C. The patient record in epidemiology. *Sci Am* 1981;**245**:54–63.
15. **Melton L.** History of the Rochester Epidemiology Project. *Mayo Clinic Proc* 1996;**71**:266–74.
16. **Gabriel SE,** Crowson CS, O'Fallon WM. The epidemiology of rheumatoid arthritis in Rochester, Minnesota, 1955–1985. *Arthritis Rheum* 1999;**42**:415–20.
17. **Doran MF,** Pond GR, Crowson CS, O'Fallon WM, Gabriel SE. Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. *Arthritis Rheum* 2002;**46**:625–31.
18. **Arnett FC,** Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24.

**Table 4** Hypothetical example demonstrating the relative impact of smoking status on the risk of heart failure (HF) in 1000 rheumatoid arthritis (RA) and 1000 non-RA subjects

| | Non-RA subjects with heart failure, n = 150 | | RA subjects with heart failure, n = 250 | |
|---|---|---|---|---|
| Factor X† | No | Yes | No | Yes |
| Current smoking | 100 | 0 | 100 | 50 |
| No smoking | 50 | 0 | 50 | 50 |
| Hazard ratio (HR) smoking/no smoking | 100/50 = 2.0 | | 150/100 = 1.5 | |

*All data are hypothetical
†Factor X = other mechanism of disease?

19. **Anonymous.** The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997;**157**:2413–46.
20. **Chobanian AV,** Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, *et al*. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. *JAMA* 2003;**289**:2560–71.
21. **NCEP**. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;**285**:2486–97.
22. **NCEP**. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993;**269**:3015–23.
23. **Expert panel on the identification, evaluation, and treatment of overweight and obesity in adults**. Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. *Arch Intern Med* 1998;**158**:1855–67.
24. **Alberti KG,** Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic Medicine* 1998;**15**:539–53.
25. **Roger VL,** Killian J, Henkel M, Weston SA, Goraya TY, Yawn BP, *et al*. Coronary disease surveillance in Olmsted County objectives and methodology. *J Clin Epidemiol* 2002;**55**:593–601.
26. **White AD,** Folsom AR, Chambless LE, Sharret AR, Yang K, Conwill D, *et al*. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. *J Clin Epidemiol* 1996;**49**:223–33.
27. **Edlavitch SA,** Crow R, Burke GL, Huber J, Prineas R, Blackburn H. The effect of the number of electrocardiograms analyzed on cardiovascular disease surveillance: the Minnesota Heart Survey (MHS). *J Clin Epidemiol* 1990;**43**:93–99.
28. **Mascioli SR,** Jacobs DR Jr, Kottke TE. Diagnostic criteria for hospitalized acute myocardial infarction: the Minnesota experience. *Int J Epidemiol* 1989;**18**:76–83.
29. **Ho KK,** Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993;**22**(4 Suppl A):6A–13A.
30. **Mosterd A,** Deckers JW, Hoes AW, Nederpel A, Smeets A, Linker DT, *et al*. Classification of heart failure in population based research: an assessment of six heart failure scores. *Eur J Epidemiol* 1997;**13**:491–502.
31. **Cox DR.** Some simple approximate tests for Poisson variates. *Biometrika* 1953;**40**:354–60.
32. **Solomon DH,** Curhan GC, Rimm EB, Cannuscio CC, Karlson EW. Cardiovascular risk factors in women with and without rhaumatoid arthritis. *Arthritis Rheum* 2004;**50**:3444–9.
33. **Nicola P,** Maradit Kremers H, Roger V, Jacobsen S, Crowson C, Ballman K, *et al*. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. *Arthritis Rheum* 2005;**52**:412–20.


## FUNDING AVAILABLE FOR RESEARCH PROJECTS

The Committee on Publication Ethics (COPE) has established a Grant Scheme to fund research in the field of publication ethics. The Scheme is designed to provide financial support to any member of COPE for a defined research project that is in the broad area of the organisation's interests, and specifically in the area of ethical standards and practice in biomedical publishing. The project should have a specific goal and be intended to form the kernel of a future publication.

A maximum sum of £5000 will be allocated to any one project, but applications for smaller sums are welcomed.

**The terms and conditions of the Grant are as follows:**

- At least one of the applicants must be a member of COPE.
- Calls for applications will be made twice a year with closing dates of 1 December and 1 June. An electronic version of the application form must be sent to the Administrator no later than 12 pm (noon GMT) on the closing date for consideration by COPE Council.
- The application must contain a lay summary of the project, a definition of the question to be posed, sufficient methodological detail to allow assessment of the viability of the project, a clear timeline and a definition of the likely deliverables. A full justification for the sum requested must accompany the application.
- A report on the progress of the research should be presented within one year of the award and at the end of the project. The grant must be used within two years from the date of award, and balance sheets must be forwarded annually. These should be sent to the Administrator. Any remaining funds after two years must be returned.
- It is anticipated that the work stemming from the project will be presented at one of COPE's annual seminar meetings within 2–3 years of the award. Such data may also be published in peer-reviewed journals. Any publications or related presentations at meetings by the recipient emanating in part or whole from COPE's support should be duly acknowledged and copies sent to the Administrator.

Applications are reviewed by a COPE sub-committee. Applicants will be advised of a decision as soon as practicable after the deadline date.

An application form can be obtained by contacting Linda Gough, COPE administrator, at LGough@bmj.com or 020 7383 6602. For more information on COPE, see http://www.publicationethics.org.uk/

The closing date for receipt of applications is 1 December 2007 or 1 June 2008.

# Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients?

A Gonzalez, H Maradit Kremers, C S Crowson, K V Ballman, V L Roger, S J Jacobsen, W M O'Fallon and S E Gabriel

*Ann Rheum Dis* 2008 67: 64-69 originally published online May 21, 2007
doi: 10.1136/ard.2006.059980