

# Rheumatoid Factor, Smoking, and Disease Severity: Associations with Mortality in Rheumatoid Arthritis

The majority of mortality studies published over the last 15 years have identified excess mortality in rheumatoid arthritis (RA) cohorts compared to that in the general population (Table 1<sup>1-17</sup>), and many have highlighted excess mortality from cardiovascular causes. Methodology and study design seem to affect the magnitude of the mortality rates, with community-based and inception-cohort followup studies being associated with smaller increases in standardized mortality ratios (SMR) than studies of established prevalent RA cohorts. In this issue of *The Journal*, Gonzalez, *et al* explore mortality rates in a population-based cohort of RA patients from Rochester, Minnesota, USA, stratified by rheumatoid factor (RF) status<sup>17</sup>. They report modest increases in SMR for RA patients who were RF-positive, but found that patients with persistently RF-negative RA had mortality rates similar to those in the general population. Other studies have reported similar findings, with excess mortality being observed only in the RF-positive patients in both hospital-based<sup>2</sup> and community-based cohorts<sup>5,18,19</sup>.

Within RA cohorts, RF positivity early in the disease course appears to be a strong predictor of mortality. Van Schaardenburg, *et al* demonstrated, in an inception cohort of 130 RA patients followed for a mean of 5.6 years, that baseline RF-positive RA was associated with a 6-fold increased risk of mortality compared to those patients who were RF-negative at baseline<sup>2</sup>. Conversely, RF-positive disease was not associated with early mortality in a Norwegian cohort of patients with RA<sup>20</sup>. However, many more studies have identified RF as a predictor of mortality within RA cohorts<sup>1,3,14,15,21</sup>.

Gonzalez, *et al* found that much of the excess mortality in their RF-positive patients was due to respiratory and cardiovascular causes<sup>17</sup>. Chronic obstructive pulmonary disease (COPD) was the most commonly identified respiratory cause of death in the RF-positive patients. A 3-fold increased mortality rate was observed in the RF-positive subgroup compared to the general population [SMR 3.36

(95% CI 2.02, 5.24)]. SMR for ischemic heart disease (IHD) including myocardial infarction were elevated [SMR 1.41 (95% CI 1.04, 1.88)] for RF-positive patients, but not in those who were persistently RF-negative. This raises questions about potential mechanisms that may promote cardiovascular and respiratory mortality in RF-positive patients. Is RF itself implicated in premature ageing? Is RF a marker for another biological mediator of early death such as the shared epitope or anti-cyclic citrullinated peptide (anti-CCP) antibodies? Is RF simply a marker for more severe RA, and it is the cumulative burden of inflammation that shortens life? Or is RF a path variable for an environmental risk factor such as smoking?

Smoking is known to be a risk factor for RF-positive RA<sup>22,23</sup>. RA patients who smoke are more likely to be RF-positive and to have higher titers of RF than nonsmokers with RA<sup>24-26</sup>. Indeed, cigarette smoking is also associated with the production of RF in people without RA<sup>5</sup>. Heliovaara, *et al* used population data from the mini-Finland questionnaire to examine whether RF positivity was associated with mortality. They found that people who were RF-positive and had arthritis had increased mortality from all causes. This increased mortality risk persisted after adjusting for age, gender, and smoking status. Interestingly, members of the population who were RF-positive in the absence of arthritis, "false-positive for RF," had increased cardiovascular mortality, which remained significant after adjustment for age, gender, and smoking status.

It seems that the amount and duration of cigarette smoking, but not other tobacco use, is important for the development of RF-positive RA<sup>22</sup> as well as for the development of cardiovascular disease (CVD)<sup>27</sup> and COPD<sup>28</sup>. So could the excess mortality in RF-positive RA simply reflect increased mortality from smoking-related diseases? Gonzalez, *et al* found that RF-positive RA patients recruited after 1985 were less likely to report current smoking than patients with onset of RA in earlier years, but remained more likely to be

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Table 1. Mortality studies in RA cohorts published since 1993.

First Author, Country	Year	Size of Series	Category	Overall SMR (95% CI)	SMR (95% CI) by RF Status	
					RF-Positive	RF-Negative
Jacobsson, Pima Indians, USA <sup>1</sup>	1993	2979	Community	1.28 (1.01–1.62)	1.61 (1.02–2.55)	
Van Schaardenburg, Netherlands <sup>2</sup>	1993	130	Clinic	1.69	2.78 (1.70, 4.14)	0.45 (0.08, 1.13)
Wolfe, USA/Canada <sup>3</sup>	1994	3501	Clinic	2.26 (SEM 0.05)	RR of 4 separate areas not combined	
Myllykangas, Finland <sup>4</sup>	1995	1666	Clinic	1.37	NA	
Heliovaara, Finland <sup>5</sup>	1995	7217	Community		ERA 1.61 (1.03, 2.51)	ERA 1.88 (0.89, 3.96) Non-ERA 1.03 (0.72, 1.49)
Wallberg-Jonsson, Sweden <sup>6</sup>	1997	606	Clinic	1.57	1.57	
Symmons, UK <sup>7</sup>	1998	448	Clinic	2.70 (2.40–3.10)		NA
Kroot, Netherlands <sup>8</sup>	2000	622	Clinic		2.51 (conditional risk ratio; p = 0.06)	
Chenhata, UK <sup>9</sup>	2001	309	Clinic	1.65 (1.34–1.98)		NA
Bjornadal, Sweden <sup>10</sup>	2002	46,917	Clinic	2.03 (2.00–2.05)		NA
Thomas, UK <sup>11</sup>	2003	9003	Clinic	2.07 (2.01–2.13) M 1.97 (1.93–2.01) F		NA
Pincus, USA <sup>12</sup>	2004	1378	Clinic	1.60		NA
Sihvonen, Finland <sup>13</sup>	2004	604	Community	2.64 (2.63–2.68)		NA
Goodson, UK <sup>14</sup>	2005	1010	Clinic	1.45 (1.22–1.71) M 1.84 (1.64–2.05) F	1.71 (1.41, 2.05) 2.03 (1.79, 2.29)	0.83 (0.53, 1.24) 1.41 (1.11, 1.75)
Young, UK <sup>15</sup>	2007	1429	Clinic	1.27 (1.04–1.46)	OR 1.26 (1.1, 1.6)	
Gonzalez, USA <sup>16</sup>	2007	822	Clinic	1.35 (1.23–1.49)		NA

NA: no analysis by RF status; SMR: standardized mortality ratio; RR: relative risk; OR: odds ratio; ERA: erosive RA.

current smokers than population controls. However, a history of prior cigarette smoking remains an important risk factor for the development of RA<sup>29</sup>, in addition to being associated with increased rates of smoking-related disease for many years after smoking cessation.

Investigators often adjust for (rather than exploring) baseline smoking when examining predictors of mortality and CVD events in RA cohorts<sup>30</sup>. However, baseline smoking was not identified as a predictor of CVD mortality in a cohort of RF-positive RA patients<sup>6</sup>, and the association between RF and mortality persisted after adjusting for baseline smoking status in the population study of Heliovaara, *et al*<sup>5</sup>. Previous investigation of the Rochester cohort of RA patients revealed that, while baseline smoking history was associated with subsequent CVD events in the RA patients, the strength of the association was much lower than that observed in population controls<sup>31</sup>. It would be interesting to explore this same analysis stratified by RF status.

Smoking was associated with atherosclerotic plaque observed on carotid Doppler imaging in a small cohort of patients with seropositive RA<sup>32</sup>. Roman, *et al* observed that there was a 9-fold increased prevalence of current smoking in those RA patients with carotid plaque compared to those without. However, RA patients with plaque were older and

subsequent analyses, adjusting for age, did not reveal any significant association between smoking and carotid plaque in RA patients<sup>33</sup>. Therefore smoking may be associated with atherosclerosis in RA cohorts, although it does not seem to confer the same relative risk of CVD events as that seen in the general population. As cumulative dose of smoking and duration of smoking cessation appear to be important in predicting CVD events and mortality<sup>27</sup>, it may be that pack-years of smoking and duration since cessation should be treated as time-varying covariates in analyses exploring mortality and cardiovascular outcomes in RA. However, in epidemiological studies it is difficult to accurately measure these smoking exposures over time. It is therefore difficult to determine how much of the mortality association with RF-positive RA is due to the atherosclerotic effects of smoking.

Severity of rheumatoid disease appears to be associated with mortality. There is evidence of increased mortality rates in those patients with higher joint counts<sup>34</sup> and higher inflammatory markers<sup>35,36</sup>. Cigarette smoking appears to be associated with more severe rheumatoid disease as well as with RF positivity<sup>37</sup>. Therefore one explanation for the excess mortality in RF-positive patients is that they have more severe RA than those who are RF-negative.

The impact of severe RA on mortality may be mediated

via reduced physical activity that will compromise cardiorespiratory fitness. This might contribute to higher CVD mortality in RF-positive RA patients. Disability has been shown to be a predictor of all-cause and CVD mortality in early inflammatory polyarthritis<sup>38</sup> and established RA<sup>39</sup>.

More severe RA is also associated with a higher cumulative inflammatory disease burden. Atherosclerosis is now accepted to be an inflammatory condition, and elevation of inflammatory markers including high-sensitivity C-reactive protein (CRP) has been associated with the subsequent development of CVD events in the general population<sup>40,41</sup>, and histological study has identified the presence of inflammatory cells in atherosclerotic plaque in the general population. If atherosclerosis is promoted by chronic low-grade inflammation, as suggested by Ridker<sup>41</sup>, it is plausible that atherosclerosis may be accelerated in chronic systemic inflammatory conditions like RA<sup>42</sup>. A previous study of the Rochester RA cohort demonstrated that cumulative inflammation measured using the erythrocyte sedimentation rate (ESR) was associated with subsequent CVD events<sup>35</sup>. In addition, modest elevations in baseline CRP were associated with subsequent CVD mortality in patients with early inflammatory polyarthritis who were registered with the Norfolk Arthritis Register (NOAR)<sup>36</sup>. However, in the NOAR cohort, a raised CRP was not associated with mortality in the RF-negative subgroup. Effective drug therapy, which reduces inflammation in RA, has been shown to reduce all-cause and CVD mortality<sup>43,44</sup>, and responders to anti-tumor necrosis factor- $\alpha$  therapies were found to have a lower incidence of myocardial infarction than nonresponders<sup>45</sup>. Therefore RF-positive patients may have increased ischemic heart disease mortality because they have increased levels of chronic inflammation, and suppression of this inflammation may lead to improved survival.

Other factors associated with RF status and severity of RA include anti-CCP status and presence of the HLA-DRB1 shared epitope. High titers of anti-CCP predicted mortality in a study of RA patients in Finland<sup>21</sup>. A recent study<sup>46</sup> reported that, while RF status and anti-CCP status were each associated with mortality in inflammatory polyarthritis, possession of both markers did not confer a higher mortality risk. However, the subgroup of patients who were current smokers, were anti-CCP-positive, and possessed 2 copies of the shared epitope had increased risk of all-cause mortality [hazard ratio, HR 3.57 (95% CI 1.34, 9.50)] and in particular CVD mortality [HR 7.81 (95% CI 2.63, 23.22)]. In addition there was a significant interaction between these 3 variables in the models predicting mortality. Therefore mortality outcome in inflammatory arthritis appears to be associated with variables that promote more severe disease.

It has been hypothesized that circulating immune complexes and RF might have a direct effect on endothelial cells to promote atherosclerosis<sup>47</sup>. Dessein, *et al* reported that RF and interleukin 6 were associated with biomarkers of

endothelial dysfunction in RA patients, even after adjusting for traditional CVD risk factors<sup>48</sup>. Impaired nitrate-mediated vascular dilation was found to be associated with circulating levels of immune complexes in RA<sup>49</sup>, and this has been suggested to be one of the mechanisms by which atherosclerosis is promoted in RA<sup>50</sup>. It is interesting to note that B lymphocytes have been identified in atherosclerotic plaques of RA patients<sup>51</sup>, while in atherosclerotic plaques of non-rheumatoid patients T lymphocyte infiltration is observed. Therefore there is some modest evidence that RF may be involved in the pathogenesis of atherosclerosis in RA.

Excess mortality in RA is largely confined to those who are RF-positive. It is still unclear whether RF itself contributes to the reduced life expectancy of patients with RA, or whether it is simply a marker for more severe disease and higher cigarette smoking exposure. Early use of disease modifying antirheumatic drugs and use of biologic agents to suppress inflammatory disease is likely to influence the life expectancy of these patients, and it will be interesting to explore whether CVD outcomes in patients treated with B cell suppression are improved. However, it is likely that a combined approach is required, with modification of lifestyle factors, as well as suppression of the inflammatory disease process, to improve the mortality outcome in RF-positive subjects.

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## REFERENCES

1. Jacobsson LTH, Knowler WC, Pillemer S, et al. Rheumatoid arthritis and mortality — a longitudinal study in Pima Indians. *Arthritis Rheum* 1993;36:1045-53.
2. van Schaardenburg D, Hazes JMW, de Boer A, Zwilerman AH, Meijers KAE, Breedveld FC. Outcome of rheumatoid arthritis in relation to age and rheumatoid factor at diagnosis. *J Rheumatol* 1993;20:45-52.
3. Wolfe F, Mitchell DM, Sibley JT, Fries JF. The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994;37:481-94.
4. Myllykangas-Luosujarvi R, Aho K, Kautiainen H, Isomäki H. Shortening of lifespan and causes of excess mortality in a population-based series of subjects with rheumatoid arthritis. *Clin Exp Rheumatol* 1995;13:149-53.
5. Heliovaara M, Aho K, Knekt P, Aromaa A, Maatela J, Reunanen A. Rheumatoid factor, chronic arthritis and mortality. *Ann Rheum Dis* 1995;45:811-4.
6. 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.

7. Symmons DPM, Jones MA, Scott DL, Prior P. Longterm mortality outcomes in patients with rheumatoid arthritis: Early presenters continue to do well. *J Rheumatol* 1998;25:1072-7.
8. Kroot EJA, van Leeuwen MA, van Rijswijk MH, et al. No increased mortality in patients with rheumatoid arthritis: Up to 10 years of follow up from disease onset. *Ann Rheum Dis* 2000;59:954-8.
9. Chehata JC, Hassell AB, Clarke SA, et al. Mortality in rheumatoid arthritis: relationship to single and composite measures of disease activity. *Rheumatology Oxford* 2001;40:447-52.
10. Bjornadal L, Baecklund E, Yin L, Granath F, Klareskog L, Ekblom A. Decreasing mortality in patients with rheumatoid arthritis: Results from a large population based cohort in Sweden, 1964-95. *J Rheumatol* 2002;29:906-12.
11. Thomas E, Symmons DPM, Brewster DH, Black RJ, Macfarlane GJ. National study of cause-specific mortality in rheumatoid arthritis, juvenile chronic arthritis, and other rheumatic conditions: A 20 year followup study. *J Rheumatol* 2003;30:958-65.
12. Pincus T, Keysor J, Sokka T, Krishnan E, Callahan LF. Patient questionnaires and formal education level as prospective predictors of mortality over 10 years in 97% of 1416 patients with rheumatoid arthritis from 15 United States private practices. *J Rheumatol* 2004;31:229-34.
13. Sihvonen S, Korpela M, Laipala P, Mustonen J, Pasternack A. Death rates and causes of death in patients with rheumatoid arthritis: A population-based study. *Scand J Rheumatol* 2004;33:221-7.
14. Goodson NJ, Marks J, Lunt M, Symmons DPM. Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with an onset in the 1980's and 1990's. *Ann Rheum Dis* 2005;64:1595-601.
15. Young A, Koduri G, Bailey M, et al. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. *Rheumatology Oxford* 2007;46:350-7.
16. Gonzalez A, Maradit Kremers H, Crowson CS, et al. The widening mortality gap between rheumatoid arthritis patients and the general population. *Arthritis Rheum* 2007;56:3583-7.
17. Gonzalez A, Icen M, Maradit-Kremers H, et al. Mortality trends in rheumatoid arthritis: the role of rheumatoid factor. *J Rheumatol* 2008;35:1009-14.
18. Mikuls TR, Saag KG, Criswell LA, et al. Mortality risk associated with rheumatoid arthritis in a prospective cohort of older women: results from the Iowa Women's Health Study. *Ann Rheum Dis* 2002;61:994-9.
19. Goodson NJ, Wiles NJ, Lunt M, Barrett E, Silman AJ, Symmons DPM. Mortality in early inflammatory polyarthritis: cardiovascular mortality is increased in seropositive patients. *Arthritis Rheum* 2002;46:2010-9.
20. Nikolaisen C, Rekvig OP, Nossent HC. Rheumatoid factor by laser nephelometry and Waaler-Rose assay: prognostic value in patients with recent-onset rheumatoid arthritis. *Scand J Rheumatol* 2005;34:269-76.
21. Sihvonen S, Korpela M, Mustila A, Mustonen J. The predictive value of rheumatoid factor isotypes, anti-cyclic citrullinated peptide antibodies, and antineutrophil cytoplasmic antibodies for mortality in patients with rheumatoid arthritis. *J Rheumatol* 2005;32:2089-94.
22. Stolt P, Bengtsson C, Nordmark B, et al. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. *Ann Rheum Dis* 2003;62:835-41.
23. Nyhall-Wahlin BM, Jacobsson LT, Petersson IF, Turesson C, BARFOT study group. Smoking is a strong risk factor for rheumatoid nodules in early rheumatoid arthritis. *Ann Rheum Dis* 2006;65:601-6.
24. Matthey DL, Dawes PT, Clarke S, et al. Relationship among the HLA-DRB1 shared epitope, smoking, and rheumatoid factor production in rheumatoid arthritis. *Arthritis Rheum* 2002;47:403-7.
25. Masdottir B, Jonsson T, Manfredsdottir V, Vikingsson A, Brekkan A, Valdimarsson H. Smoking, rheumatoid factor isotypes and severity of rheumatoid arthritis. *Rheumatology Oxford* 2000;39:1202-5.
26. Wolfe F. The effect of smoking on clinical, laboratory, and radiographic status in rheumatoid arthritis. *J Rheumatol* 2000;27:630-7.
27. Bazzano LA, He J, Muntner P, Vupputuri S, Whelton PK. Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Ann Intern Med* 2003;138:891-7.
28. Sethi JM, Rochester CL. Smoking and chronic obstructive pulmonary disease. *Clin Chest Med* 2000;21:67-86.
29. Costenbader KH, Feskanich D, Mandl LA, Karlson EW. Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women. *Am J Med* 2006;119:503-11.
30. Turesson C, McClelland RL, Christianson TJ, Matteson EL. Severe extra-articular disease manifestations are associated with an increased risk of first ever cardiovascular events in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007;66:70-5.
31. Gonzalez A, Maradit Kremers H, Crowson CS, et al. Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients? *Ann Rheum Dis* 2008;67:64-9.
32. Wallberg-Jonsson S, Ohman M, Rantapaa-Dahlqvist S. Which factors are related to the presence of atherosclerosis in rheumatoid arthritis? *Scand J Rheumatol* 2004;33:373-9.
33. Roman MJ, Moeller E, Davis A, et al. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. *Ann Intern Med* 2006;144:249-56.
34. Jacobsson LT, Turesson C, Hanson RL, et al. Joint swelling as a predictor of death from cardiovascular disease in a population study of Pima Indians. *Arthritis Rheum* 2001;44:1170-6.
35. 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.
36. Goodson NJ, Symmons DPM, Scott DGI, Bunn D, Lunt M, Silman AJ. Baseline C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis. *Arthritis Rheum* 2005;52:2293-9.
37. Saag KG, Cerhan JR, Kolluri S, Ohashi K, Hunninghake GW, Schwartz DA. Cigarette smoking and rheumatoid disease severity. *Ann Rheum Dis* 1997;56:463-70.
38. Farragher TM, Lunt M, Bunn DK, Silman AJ, Symmons DP. Early functional disability predicts both all-cause and cardiovascular mortality in people with inflammatory polyarthritis: results from the Norfolk Arthritis Register. *Ann Rheum Dis* 2007;66:486-92.
39. Wolfe F, Michaud K, Gefeller O, Choi HK. Predicting mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2003; 48:1530-42.
40. Tracy RP. Inflammation markers and coronary heart disease. *Curr Opin Lipidol* 1999;10:435-41.
41. Ridker PM. Connecting the role of C-reactive protein and statins in cardiovascular disease. *Clin Cardiol* 2003;26:1139-44.
42. van Leuven SI, Franssen R, Kastelein JJ, Levi M, Stoes ES, Tak PP. Systemic inflammation as a risk factor for atherothrombosis. *Rheumatology Oxford* 2008;47:3-7.
43. Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002;359:1173-7.
44. Jacobsson LT, Turesson C, Nilsson JA, et al. Treatment with TNF blockers and mortality risk in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007;66:670-5.

45. Dixon WG, Watson KD, Lunt M, Hyrich KL, British Society for Rheumatology Biologics Register Control Centre Consortium, Silman AJ, et al. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2007;56:2905-12.
46. Farragher TM, Goodson NJ, Nasseem H, et al. Association of the HLA-DRB1 gene with premature death, particularly from cardiovascular disease, in patients with rheumatoid arthritis and inflammatory polyarthritis. *Arthritis Rheum* 2008;58:359-69.
47. Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? *Arthritis Rheum* 2002;46:862-73.
48. Desseign PH, Joffe BI, Singh S. Biomarkers of endothelial dysfunction, cardiovascular risk factors and atherosclerosis in rheumatoid arthritis. *Arthritis Res Ther* 2005;7:634-43.
49. Szekanecz Z, Kerekes G, Der H, et al. Accelerated atherosclerosis in rheumatoid arthritis. *Ann NY Acad Sci* 2007;1108:349-58.
50. Wallberg-Jonsson S, Cvetkovic JT, Sundqvist KG, Lefvert AK, Rantapaa-Dahlqvist S. Activation of the immune system and inflammatory activity in relation to markers of atherothrombotic disease and atherosclerosis in rheumatoid arthritis. *J Rheumatol* 2002;29:875-82.
51. Aubry MC, Riehle DL, Edwards WD, et al. B-Lymphocytes in plaque and adventitia of coronary arteries in two patients with rheumatoid arthritis and coronary atherosclerosis: preliminary observations. *Cardiovasc Pathol* 2004;13:233-6.