

Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies

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Objectives. RA is known to be associated with a high cardiovascular (CV) risk. Longitudinal data suggest that RA disease course may have become milder over the past decades. Thus, we set out to estimate the magnitude of the overall increase in CV mortality associated with RA and to determine whether it has decreased over the past 50 years.

Methods. We performed a systematic review and a meta-analysis of literature in MEDLINE and EMBASE databases from January 1960 to November 2008. All cohort studies reporting CV mortality risk were included. We then calculated pooled standardized mortality ratios (SMRs) of CV mortality, and determined their evolution with time using meta-regression analysis.

Results. Seventeen studies were analysed, corresponding to a total of 91 916 patients. The overall pooled SMR was 1.6 (95% CI 1.5, 1.8; $I^2 = 93\%$; $P(\text{het}) < 0.0001$). Mid-cohort year ranged from 1945 to 1995 (<1980, seven studies; 1980–90, five studies; >1990, five studies). Meta-regression analyses revealed neither any trend in SMR over time ($P = 0.784$) nor any relation with disease duration at the time of inclusion ($P = 0.513$).

Conclusions. Our results show that RA is associated with a 60% increase in risk of CV death compared with general population. Despite changes in RA course over the past decades, SMR for CV death has not changed. This suggests that targeting a reduction in CV mortality should still be considered as a major issue in RA.

KEY WORDS: Rheumatoid arthritis, Cardiovascular mortality.

Introduction

RA is a chronic systemic inflammatory disease, of unknown origin, that affects 0.5–1% of the adult population [1, 2]. Among extra-articular features, the existence of a high risk of cardiovascular (CV) disease has emerged as a cause of morbidity and mortality in these recent years [3–7]. With regards to RA mortality, causes of death also include infection, renal, gastrointestinal and pulmonary diseases, but CV disease has been particularly studied in recent years. Some hypotheses have been generated to explain such an increased risk of CV events, including conventional vascular risk factors [8, 9], inflammation itself which could promote atherosclerotic plaques development or increase their vulnerability, accelerated thrombosis [10–12] and the influence of some therapies [13].

It has been recently suggested that the disease course of RA has changed over the past decades. In fact, RA incidence may have decreased but some data also suggest that RA may tend to become milder over time as estimated by measurements of inflammation, disease activity score and functional disability [14–16]. The fact whether this has translated into a decrease in the impact of RA on CV mortality remains unknown. We therefore conducted a systematic review and meta-analysis of cohort studies to investigate whether relative increase in CV mortality has decreased in RA patients over the past five decades.

Methods

Eligible studies were the cohort studies of patients with RA diagnosed according to the recommendations available during the study period [17]. Articles had to report enough data to compute a CV disease-specific standardized mortality ratio (SMR). We searched MEDLINE and EMBASE databases between January 1960 and November 2008, using the terms 'rheumatoid arthritis' AND ('mortality' or 'myocardial infarction' or 'cardiovascular disease' or 'coronary artery disease'). In addition, the references of selected studies were examined, as well as guidelines, any relevant reviews and personal files. In order to identify recent studies that are not yet published as full papers, we also searched books of abstracts from 2007 to 2008 conferences [European League Against Rheumatism (EULAR) and ACR]. There was no language restriction. Eligibility of references retrieved by the search was assessed independently by the two reviewers and disagreements resolved at each step. Data were extracted separately by the two reviewers (Y.A. and C.M.) from the selected studies using a standardized form. Disagreements were resolved by consensus among all authors.

Statistical analysis

We computed individual CV disease-specific SMRs as the ratio between observed and expected numbers of CV deaths, extracted from each study. We then performed meta-analyses of log SMR. The standard error of log SMR was estimated by $1/\sqrt{O}$, with O being the observed number of CV deaths [18]. Statistical heterogeneity was assessed using the I^2 statistic ($I^2 \geq 50\%$ corresponding to substantial heterogeneity and $I^2 \geq 75\%$ to considerable heterogeneity). We used a random effects model to estimate a combined log SMR, which we then back-transformed. Publication bias was assessed using a funnel plot and Begg's test of the correlation between effect sizes and their variances.

To assess change in SMR, we pre-defined three periods based on the mid-time follow-up of patients in the selected studies, i.e. the mid-cohort year, as follows: <1980, 1980–90 and ≥ 1990 . The mid-cohort year was calculated as the median year between the starting year of the inclusion period and the ending year of the

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follow-up period. We performed indirect comparison of the combined SMR across the three periods. In addition, we used meta-regression analyses to assess changes in log SMR with study of mid-cohort year or disease duration. All analyses were performed using STATA software (STATA 9.2, StataCorp L, College Station, TX, USA).

Results

Among a total of 1938 identified references, 1852 were excluded on the basis of their title or abstract, resulting in 86 articles examined for full text. There were finally 17 independent studies (91 916 patients) in which CV disease-specific SMR was available (Fig. 1).

The characteristics of the studies included in the analysis are given in Table 1 [3, 13, 19–33]. Individual CV disease-specific SMRs ranged from 0.91 to 2.20, with 12 studies demonstrating a significant increase in risk of CV mortality in RA patients and five studies finding no association (Fig. 2). The combined CV disease-specific SMR was 1.61 (95% CI 1.48, 1.75; $P < 0.0001$;

$I^2 = 93\%$; $P(\text{het}) < 0.0001$) (Fig. 2). Begg's test did not reveal funnel plot asymmetry, making publication bias unlikely (data not shown).

The mid-cohort year ranged from 1945 to 1995, being < 1980 in seven studies (6769 patients), from 1980 to 1990 in five (81 031 patients) and ≥ 1990 in five studies (3846 patients). The combined CV mortality SMR was 1.45 (95% CI 1.10, 1.90), 1.86 (95% CI 1.75, 1.99) and 1.57 (95% CI 1.31, 1.90), respectively, for the three distinct periods. Meta-regression analysis confirmed that CV disease-specific SMR did not change with mid-cohort year (1.5% increase in SMR per mid-cohort year; $P = 0.78$) (Fig. 3). In order to assess the influence of individual studies, we re-estimated the meta-regression analysis effect omitting each study in turn and did not find any outlier bias (data not shown).

Disease duration was available in nine studies, being < 5 years in four studies [24–26, 33]. There was a significant increase in observed *vs* expected deaths in three studies [24, 25, 33]. Meta-regression analysis did not display any significant influence of disease duration on SMR ($P = 0.51$) (Fig. 4).

TABLE 1. Main characteristics of the 17 included studies

Study	Localization	Study period	Mid-cohort	No. of patients	Age, years	Female, %	Disease duration, years	Follow-up	Completeness of follow-up	Setting	Cause of death assessment	Consecutive sample
Monson [19]	USA	1930–60	1946	1035	NA	74	NA	Up to 1972	27% lost to follow-up	Hospital	DC	Yes
Lewis <i>et al.</i> [20]	UK	1966–76	1971	311	NA	NA	NA	11 years	Completed	Hospital	DC (autopsy 41%)	Yes
Allebeck [21]	Sweden	1971	1974	1165	NA	46	NA	Up to 1978	Completed	Hospital	Autopsy (67%) Medical records	Yes
Vanderbrouke <i>et al.</i> [22]	The Netherlands	1954–57	1969	209	53.5	66	8.1	25 years	Completed	Hospital	Physician interview	Yes
Erhardt <i>et al.</i> [23]	UK	1979	1981	308	59	71	7.4	Up to 1985	Completed	Hospital	DC	Yes
Reilly <i>et al.</i> [24]	England	1957–63	1970	100	51	64	0.31	25 years	Completed	Hospital	Autopsy (19%) Medical records	< 1 year duration
Wolfe <i>et al.</i> [3] ^a	USA and Canada	USA: 1965–90 Canada: 1966–74	1972	3501	53	74	NA	Canada: 15.8 US: 8.5	Among four cohorts, 2.5, 4.5, 33.6 and 10.5%, respectively, were lost to follow-up	Hospital and community based	DC	Yes
Wallberg-Jonsson <i>et al.</i> [13]	Sweden	1979	1987	606	55	68	12.5	15 years	Completed	Hospital	Medical records and DC	No, seropositive
Symmons <i>et al.</i> [25]	England	1964–78	1977	448	47.5	65	NA	21.5 years (6739 person-year)	Completed	Hospital	DC	Yes, subgroup of patients with < 5 year duration
Lindqvist and Eberhardt [26]	Sweden	1985–89	1990	183	51.4	63	0.93	9.8 years	Completed	Hospital	DC	< 2 years disease duration
Sanchez Martinez <i>et al.</i> [27]	Spain	1989	1994	182	63.2	77	NA	9 years	Completed	Hospital	Medical records and DC	Yes
Bjornadal <i>et al.</i> [28]	Sweden	1964–94	1980	46 917	NA	71	NA	489 048 person-years	Completed	Hospital	DC	Yes
Thomas <i>et al.</i> [29]	Scotland	1981–2000	1986	33 318	61.8	73	NA	6.9 years	Completed	Hospital	DC	Yes
Sihvonen <i>et al.</i> [30]	Finland	1988	1993	1042	NA	NA	16	11 years	Completed	Hospital and community based	Medical records and DC	No (retrospective, community based)
Book <i>et al.</i> [31]	Sweden	1978	1988	152	61	78	14	Until March 1998	Completed	Hospital	DC (autopsy 68%)	Yes
Goodson <i>et al.</i> [32]	England	1981–96	1991	1010	60.4	72	0 ^b	11.4 years	3% lost to follow-up	Hospital	DC	Yes
Young <i>et al.</i> [33]	England	1986–97	1995	1429	55	66	0.5	9.1 years	Completed	Hospital	DC	No, > 25 years old < 2 years duration

^aThis study included RA patients from four centres and at different periods. ^bNewly diagnosed RA patients only. DC: death certificates.

Discussion

The main results of our meta-analysis are (i) the confirmation of the increased CV mortality associated with RA and its magnitude of 60% in comparison with age- and sex-matched general population and (ii) the constancy of SMR over the past five decades.

There are several lines of evidence showing that RA is associated with an increased CV risk [5]. In 2008, two meta-analyses were published [6, 7]. The former study is by far non-exhaustive and mixed the SMR and the incidence rate ratios, due to which no conclusion could be derived from its analysis [6]. The largest one, although recently published, did not include the studies over 2005 and thus missed data [7]. Despite the limitations of those previous analyses, our results are consistent with their overall findings that RA patients have a 50–60% increase in CV mortality compared with the general population [6, 7].

It has been suggested that the disease course of RA may have become milder with time [14–16]. Indeed, Welsing *et al.* [14] demonstrated that RA patients who were recently included in their cohort had lower disease activity at baseline, as well as

over the first 5 years of their disease, and a more favourable course when compared with patients included less recently. Several reasons may be considered to explain such a possible improvement in the course of RA. Changes in natural history cannot be excluded, but a better knowledge of RA by practitioners should be considered as it may result in an earlier diagnosis and a prompter management of RA. Therefore, the new strategy of treatment [34, 35] probably highly accounts for improvements, and the introduction of new drugs must also be emphasized [36]. Importantly, some studies suggested that MTX and biologics are associated with reduced CV disease in RA patients [37–39].

Our results could be regarded as in conflict with these studies as we document that SMR remains constant over the past five decades. In order to allow adequate interpretation, one should keep in mind that SMR is the ratio of the observed and expected CV death. On one hand, as CV mortality has declined in the general population over the past 50 years, our results may suggest that CV in the specific context of RA has also decreased. On the other hand, our results may be interpreted as the lack of progress in the management of RA as a risk factor for CV disease.

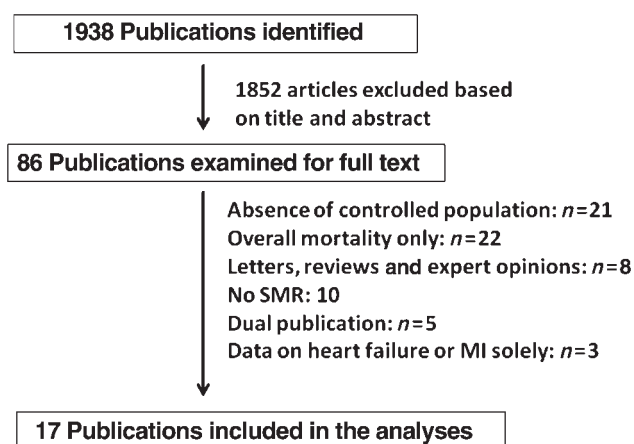


FIG. 1. Study flow chart.

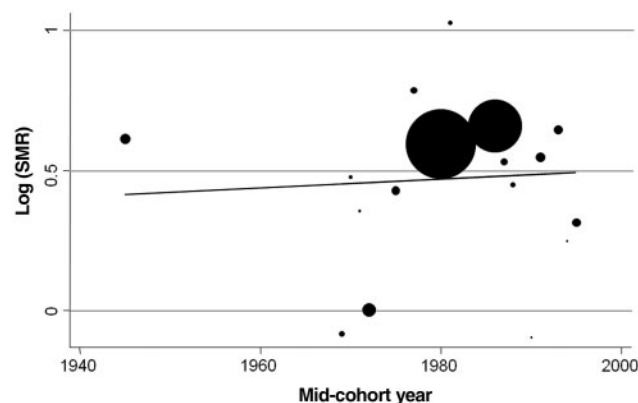


FIG. 3. Meta-regression of change in SMR (log scale) with mid-cohort year. Each circle represents an individual study, the size of the circle indicating the weight given to the study, which is inversely proportional to the study variance.

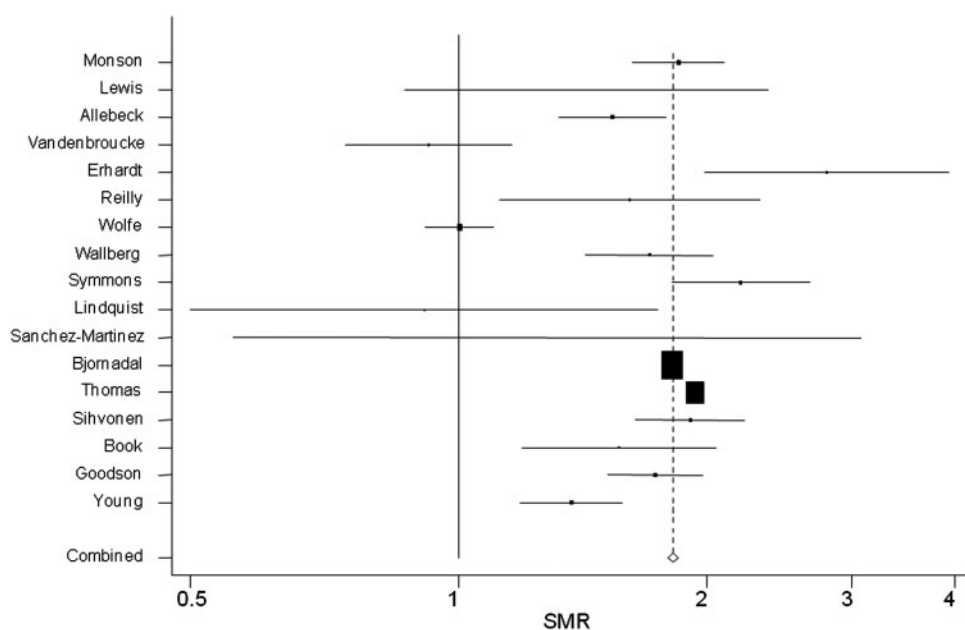


FIG. 2. Forest plot of CV disease-specific SMR for patients with RA. Each square represents an individual SMR estimate, the size of the square being proportional to the weight given to the study. The lines represent the 95% CI for the point estimate in each study. The diamond represents the combined SMR.

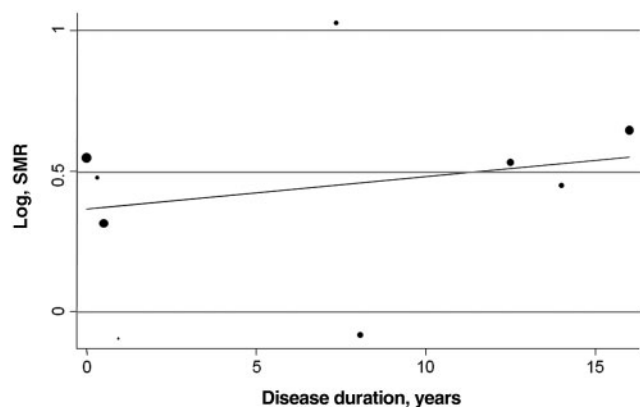


FIG. 4. Meta-regression of change in SMR (log scale) with disease duration.

Some studies have suggested that CV risk begins to increase only after 5–7 years of evolution of RA [40–42]. In our analysis, we included four studies that focused on patients with ‘short disease duration’ (<5 years) [24–26, 33]. Only one of these studies, that included 183 patients, failed at demonstrating an excess in CV risk in RA patients [26]. In addition, we did not demonstrate a significant influence of disease duration on CV SMR among included studies. Another explanation to our results may be that the exposure to the most recent treatments may have not been long enough and/or the proportion of patients who have received such DMARDs may be too small in the most recent cohorts to demonstrate any trends over time [43]. This will remain a great challenge in a near future but one must admit that our data do not even provide a positive signal towards improvement. CV mortality in RA patients is influenced not only by RA severity or therapeutics but also by many parameters. Traditional risk factors for atherosclerosis may be important to consider [44]. In this issue, several studies have demonstrated that the prevalence of traditional CV risk factors and their modifications after CV events in the general population has not been dramatically altered in recent years [45]. Lastly, some data have suggested that RA patients may not receive optimal primary or secondary preventive care [46]. Our results should therefore not be interpreted as a failure of new treatment strategies to reduce CV mortality. They rather suggested that the awareness may still not be enough and that physicians must be encouraged to concomitantly treat RA early and aggressively, but also pay special attention to CV risk factor modification and education [38, 47, 48].

Our study has some limitations. First, there was a significant heterogeneity across studies. However, heterogeneity was mainly due to important variations in effect sizes rather than inconsistent effect across studies, and we used a random effects model to account for the between-studies variability. We must also acknowledge that SMRs are sometimes not fully comparable across studies because each SMR uses a different standard. SMR is comparable across studies only when the age and sex distribution and the age- and sex-specific death rates are similar. Most of the included studies were conducted in northern Europe, a region at high risk of CV events. However, the north–south gradient in CV risk applies for both the control population and RA patients and is unlikely to influence SMR.

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Rheumatology key messages

- The combined CV disease-specific SMR is 1.61 (95% CI 1.48, 1.75; $P < 0.0001$).
- No improvement in CV mortality over time could be observed.
- A research strategy aiming at the reduction of CV mortality in RA patients is needed.

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