Prognostic Importance of Low Body Mass Index in Relation to Cardiovascular Mortality in Rheumatoid Arthritis

Hilal Maradit Kremers, Paulo J. Nicola, Cynthia S. Crowson, Karla V. Ballman, and Sherine E. Gabriel

Objective. Various etiologic mechanisms have been implicated in the observed increase in cardiovascular mortality in rheumatoid arthritis (RA). Body mass index (BMI) is associated with cardiovascular mortality in the general population. This study compared the effect of BMI on cardiovascular mortality in a population-based cohort of subjects with RA with that in a cohort of individuals without RA from the same population.

Methods. The RA cohort comprised all members of an incidence cohort of Rochester, Minnesota residents ages ≥18 years who were first diagnosed with RA (by the American College of Rheumatology 1987 criteria) from 1955 through 1994. An age- and sex-matched comparison cohort of subjects without RA was assembled. Both cohorts were followed up longitudinally through their complete (inpatient, outpatient) medical records beginning at age 18 years and continuing until death, migration, or January 1, 2001, and the details of weight and height changes during this period were recorded. High BMI was defined as a BMI >30 kg/m² and low BMI as <20 kg/m². Cox regression models were used to estimate the effect of BMI on cardiovascular mortality after accounting for traditional cardiac risk factors and malignancies.

Results. RA subjects with low BMI at incidence had a significantly higher risk of cardiovascular death (hazard ratio [HR] 3.34, 95% confidence interval [95% CI] 2.23–4.99) compared with non-RA subjects with normal BMI, after adjusting for age, sex, personal cardiac history, smoking status, and presence of diabetes, hypertension, and malignancies. RA subjects with normal BMI at incidence who experienced low BMI during followup also had a higher risk of cardiovascular death (HR 2.09, 95% CI 1.50–2.92) when compared with non-RA subjects who maintained normal BMI throughout followup.

Conclusion. Among patients with RA, low BMI is associated with a significantly increased risk of cardiovascular death.

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease and is associated with higher overall mortality and cardiovascular mortality as compared with persons without RA (1,2). Although inflammatory mechanisms are alleged to contribute to the increased cardiovascular risk in RA patients, the role of various traditional risk factors remains uncertain.

Body mass index (BMI) is a surrogate measure of total body fat content and is commonly used to define obesity (3). Obesity is an established risk factor for coronary heart disease (CHD) and mortality in the general population, and may potentially contribute to the high cardiovascular burden in RA patients through its adverse effects on blood pressure, lipid metabolism, and insulin resistance (4–8). In contrast, the inflammatory disease activity in RA is frequently accompanied by loss of body cell mass, known as rheumatoid cachexia (9). This condition may manifest itself as low BMI and can also potentially contribute to excess cardiovascular burden. However, studies examining the BMI patterns in RA patients and the role of BMI in relation to survival are limited (10–13). The objective of this study was to compare the BMI patterns and the effect of BMI on cardiovascular mortality in a population-based incidence...
cohort of subjects with RA with those in a cohort of individuals without RA from the same population.

PATIENTS AND METHODS

Study population. This study was designed as a retrospective longitudinal cohort study using the data resources of the Rochester Epidemiology Project (REP). The REP is a diagnostic indexing and medical records linkage system, and the potential of the REP for population-based studies has been described previously (14,15). Population-based epidemiologic research in this community is enhanced because of its relative geographic isolation from other urban centers and the fact that nearly all medical care is delivered to local residents by a small number of providers. Furthermore, each provider uses a comprehensive medical records system, whereby all data about an individual are assembled in one place. Medical diagnoses and other key information are routinely abstracted and entered into computerized indices. The medical records linkage system composed of these indices facilitates identification of all cases of a given condition. Thus, the medical records linkage system ensures virtually complete ascertainment of all clinically diagnosed cases in a geographically defined community.

The rates of cardiovascular death in a cohort of subjects with RA (exposed cohort) were compared with those in a cohort of subjects without RA (unexposed cohort). The exposed cohort included individuals belonging to a previously described population-based incidence cohort of subjects with RA (16,17). Briefly, the RA cohort consisted of Rochester, Minnesota residents ages ≥18 years who first fulfilled the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 criteria for RA (18) between January 1, 1955 and January 1, 1995. The incidence date was defined as the first date of fulfillment of 4 of the 7 classification criteria. Each RA subject was individually matched to 1 randomly selected Rochester resident who had no diagnosis of inflammatory arthritis, was of the same age (within 3 years) and sex, and had a similar length of enrollment in the records-linkage system. Non-RA study subjects were assigned an index date corresponding to the incidence date of their matched RA subject.

Data collection. The entire inpatient and outpatient medical records of study subjects were reviewed longitudinally by 4 trained nurse abstractors, within the time period beginning at age 18 years (or date of migration to Olmsted County for those who first became residents after age 18) and continuing until death, migration from Olmsted County, or January 1, 2001. Data were collected according to a prespecified and pretested protocol. Multiple iterative comparisons were performed in which samples of medical records were reviewed by all nurse abstractors. Guided by the results of these studies, the protocol and data entry instruments were revised to reduce ambiguity and ensure agreement. Regular weekly meetings were held throughout the data abstraction period to identify and correct problems in data collection, interpretation of definitions, and application of study criteria. Before commencing data analysis, an extensive series of checks for data consistency, proper sequences of dates, and an evaluation of missing or incomplete data were performed. Where necessary, medical records were reviewed again, and questions were resolved by consensus of the investigative team.

The primary outcome in this study was cardiovascular death. All causes of death (including both underlying and contributory causes) as reported in the medical records and/or death certificates were collected for all deceased subjects. Cardiovascular death was associated with the following underlying causes of death: CHD (i.e., myocardial infarction), arrhythmias, dysrhythmias, hypertension, congestive heart failure (CHF), pulmonary edema, rheumatic heart disease, valvular stenosis or insufficiency, ruptured aortic aneurysm, and sudden cardiac death. All subjects were tracked nationally to ascertain their vital status, and death certificates were obtained from the respective states for subjects who died out of state. At the end of the study (January 1, 2001), followup for vital status was complete for 90% of the study population.

BMI (weight/height in kg/m²) was the primary exposure variable. We recorded the first documentation of the adult (age ≥18 years) person’s height and weight as well as all weight changes of ≥15 pounds (6.8 kg) and all height changes of ≥2 inches (6 cm) over the entire followup period. BMI was calculated for each encounter. Low BMI was defined as a BMI <20 kg/m² and high BMI (obesity) as ≥30 kg/m². The obesity definition was in accordance with the guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults (3).

Cardiac risk factors were ascertained throughout the followup period and were defined as follows. Dyslipidemia, in accordance with the diagnostic criteria of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (19), was defined as a total cholesterol level ≥240 mg/dl, low-density lipoprotein cholesterol level ≥160 mg/dl, high-density lipoprotein cholesterol level ≤40 mg/dl, triglycerides level ≥150 mg/dl, a clearly documented history of dyslipidemia, or treatment with specific lipid-lowering therapy. Diabetes mellitus, in accordance with the World Health Organization 1998 diagnostic criteria (20), was considered present if at least 2 measurements of the plasma glucose level during fasting were ≥126 mg/dl or the 2-hour plasma glucose level was ≥200 mg/dl, a clearly documented history of diabetes was noted, or treatment with hypoglycemic agents had been administered. Hypertension was defined in accordance with the diagnostic criteria of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (21), with subjects considered hypertensive if they had ≥2 ambulatory blood pressure readings that were ≥140 mm Hg systolic and/or 90 mm Hg diastolic, had ever been given a physician’s diagnosis of hypertension, or had received treatment with antihypertensive agents. Other variables included as potential predictors were personal cardiac history, family history of CHD, smoking status, menopausal status, and malignancies. Personal cardiac history was defined as clinical diagnoses of angina pectoris, myocardial infarction, silent myocardial infarction, CHF, or revascularization procedures.

Statistical analysis. Baseline characteristics of the study population were summarized using descriptive statistics. The difference in cardiovascular mortality rates between RA subjects and non-RA study subjects was tested using the log-rank test. The risk of cardiovascular death among subjects with and without RA was compared using Cox regression
models. Age was used as the time scale for these models and the analyses were stratified by sex. Subjects were entered into this analysis at the age when RA incidence was recorded (or the index date for non-RA subjects) with continuation up until the time of death or last followup. The event of interest was cardiovascular death. Subjects who died from other causes and those who were still alive at last followup were censored. The hazard ratio (HR) comparing RA subjects with non-RA study subjects and the 95% confidence interval (95% CI) was then estimated, with adjustment for potential confounders. These potentially confounding variables were included as time-dependent covariates in the analyses, except for family history of CHD, personal cardiac history, menopausal status, and smoking status, which were examined at baseline only. Except for BMI, all time-dependent covariates were dichotomous, in which the status of the subjects changed from unexposed to exposed at the time of diagnosis of a particular risk factor during followup.

In the first set of analyses (Figure 1A), subjects were assigned to respective BMI categories by considering only the height and weight measurements at baseline (i.e., most recently recorded height and weight preceding the incidence/index date or up to 30 days following the incidence/index date). In the second analysis (Figure 1B), all BMI changes throughout the followup period were considered, both prior to and following baseline (incidence/index date). Subjects were cate-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RA cohort (n = 603)</th>
<th>Non-RA cohort (n = 603)</th>
<th>RA cohort</th>
<th>Non-RA cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD years</td>
<td>58.0 ± 15.2</td>
<td>58.2 ± 15.2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>441 (73)</td>
<td>441 (73)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Length of followup, mean ± SD years</td>
<td>NA</td>
<td>NA</td>
<td>14.7 ± 9.7</td>
<td>16.8 ± 10.2</td>
</tr>
<tr>
<td>Cardiac risk factors†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>287 (48)</td>
<td>284 (47)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Personal cardiac history</td>
<td>77 (13)</td>
<td>72 (12)</td>
<td>205 (2.50)</td>
<td>156 (1.67)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>33 (5)</td>
<td>23 (4)</td>
<td>172 (1.99)</td>
<td>127 (1.28)</td>
</tr>
<tr>
<td>Cigarette smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>255 (45)</td>
<td>329 (56)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Former smoker</td>
<td>148 (26)</td>
<td>118 (20)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Current smoker</td>
<td>170 (30)</td>
<td>144 (24)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hypertension</td>
<td>312 (52)</td>
<td>298 (49)</td>
<td>179 (3.67)</td>
<td>214 (3.57)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>163 (49)</td>
<td>169 (52)</td>
<td>158 (2.71)</td>
<td>228 (3.64)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>44 (7)</td>
<td>41 (7)</td>
<td>66 (0.79)</td>
<td>98 (1.02)</td>
</tr>
<tr>
<td>Postmenopausal‡</td>
<td>299 (68)</td>
<td>296 (67)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* The RA cohort was assembled from Rochester, Minnesota residents ≥18 years of age, with the diagnosis ascertained between January 1, 1955 and January 1, 1995 and followed up until January 1, 2001. NA = not applicable; CHD = coronary heart disease.
† Values at baseline are the no. (%) of subjects with the characteristic among subjects in whom the variable was measured. Values after baseline are the no. of subjects with the characteristic (rate/100 person-years).
‡ Among 441 female subjects.

Table 2. Baseline BMI categories and BMI changes among 603 rheumatoid arthritis (RA) subjects and 603 non-RA subjects, ascertained between January 1, 1955 and January 1, 1995 and followed up until January 1, 2001*

<table>
<thead>
<tr>
<th>Cohort, baseline BMI category</th>
<th>Low BMI</th>
<th>Stable or no switch</th>
<th>High BMI</th>
<th>Both low and high BMI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-RA cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low BMI</td>
<td>NA</td>
<td>63 (97)</td>
<td>2 (3)</td>
<td>–</td>
<td>65</td>
</tr>
<tr>
<td>Normal BMI</td>
<td>88 (22)</td>
<td>253 (62)</td>
<td>62 (15)</td>
<td>5 (1)</td>
<td>408</td>
</tr>
<tr>
<td>High BMI</td>
<td>2 (3)</td>
<td>66 (97)</td>
<td>NA</td>
<td>–</td>
<td>68</td>
</tr>
<tr>
<td>Missing†</td>
<td>8 (16)</td>
<td>35 (70)</td>
<td>7 (14)</td>
<td>–</td>
<td>50</td>
</tr>
<tr>
<td>RA cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low BMI</td>
<td>NA</td>
<td>71 (97)</td>
<td>2 (3)</td>
<td>–</td>
<td>73</td>
</tr>
<tr>
<td>Normal BMI</td>
<td>114 (27)</td>
<td>243 (58)</td>
<td>48 (12)</td>
<td>14 (3)</td>
<td>419</td>
</tr>
<tr>
<td>High BMI</td>
<td>3 (4)</td>
<td>68 (96)</td>
<td>NA</td>
<td>–</td>
<td>71</td>
</tr>
<tr>
<td>Missing†</td>
<td>1 (9)</td>
<td>9 (82)</td>
<td>1 (9)</td>
<td>–</td>
<td>11</td>
</tr>
</tbody>
</table>

* Body mass index (BMI) categories are as follows: low <20 kg/m², normal 20–30 kg/m², and high >30 kg/m². NA = not applicable.
† A total of 29 subjects in the RA cohort and 12 subjects in the non-RA cohort were missing both baseline and subsequent BMI data and therefore are not included in the results.
Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated from a Cox regression model adjusted for personal cardiac history, smoking status, and presence of diabetes mellitus, hypertension, and malignancies.

Figure 1. Effect of body mass index (BMI) on cardiovascular mortality among rheumatoid arthritis (RA) and non-RA subjects, by categories of low (<20 kg/m²), normal (20–30 kg/m²), and high (>30 kg/m²) BMI at baseline (A) and ever (B). Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated from a Cox regression model adjusted for personal cardiac history, smoking status, and presence of diabetes mellitus, hypertension, and malignancies.

The RA incidence cohort consisted of 603 patients, each of whom was age- and sex-matched to 1 non-RA subject (Table 1). The majority of the subjects (73%) in both cohorts were female, and the mean age at baseline (incidence/index date) was 58 years. By January 1, 2001, 356 subjects (59%) in the RA cohort and 306 subjects (51%) in the non-RA cohort were deceased. The underlying and/or the contributory cause of death was classified as cardiovascular in 214 RA subjects and in 167 non-RA subjects.

Of the 603 RA subjects, 73 (12%) had low BMI (<20 kg/m²) at or around the RA incidence date (Table 2). In addition, 132 RA subjects (22%) experienced low BMI at some time during the followup period. Among the 603 non-RA subjects, 65 (11%) had low BMI at the index date. In addition, 103 non-RA subjects (17%) experienced low BMI at some time during followup. Very few subjects in both cohorts moved from the low to the high BMI category or from the high to the low BMI category (Table 2).

RA subjects with a low BMI at baseline had a significantly increased risk of cardiovascular death (HR 3.34, 95% CI 2.23–4.99) compared with non-RA subjects with normal BMI, after adjusting for personal cardiac history, smoking status, and the presence of diabetes, hypertension, and malignancies (Figure 1A). In contrast, among non-RA subjects, low BMI at baseline was not associated with the risk of cardiovascular death (HR 0.73, 95% CI 0.41–1.31) compared with non-RA subjects with a normal BMI (Figure 1A). This corresponded to a 4-fold increase in the risk of cardiovascular death associated with low BMI among RA subjects as compared with non-RA subjects (ratio of the HRs 4.56, 95% CI 2.36–8.80, P < 0.001).

The observed association with low BMI remained significant in a subsequent analysis when subjects were assigned to the low BMI category if they ever experienced low BMI at any time during followup (Figure 1B). Compared with non-RA subjects who remained in the

when cholesterol screening became more prevalent. The reciprocal of the predicted probabilities from these models was then used as a case weight in the Cox models that assessed the importance of dyslipidemia as a predictor of cardiovascular death (22). Dyslipidemia was not a significant predictor of cardiovascular death after propensity scoring analysis and, therefore, was excluded from the multivariable model in order to avoid removal of subjects with missing values. All significant cardiac risk factors were entered into a multivariable model. All 2-way interactions among significant main effects were examined. P values of less than 0.05 were considered significant.

RESULTS

The RA incidence cohort consisted of 603 patients, each of whom was age- and sex-matched to 1 non-RA subject (Table 1). The majority of the subjects (73%) in both cohorts were female, and the mean age at baseline (incidence/index date) was 58 years. By January 1, 2001, 356 subjects (59%) in the RA cohort and 306 subjects (51%) in the non-RA cohort were deceased. The underlying and/or the contributory cause of death was classified as cardiovascular in 214 RA subjects and in 167 non-RA subjects.

Of the 603 RA subjects, 73 (12%) had low BMI (<20 kg/m²) at or around the RA incidence date (Table 2). In addition, 132 RA subjects (22%) experienced low BMI at some time during the followup period. Among the 603 non-RA subjects, 65 (11%) had low BMI at the index date. In addition, 103 non-RA subjects (17%) experienced low BMI at some time during followup. Very few subjects in both cohorts moved from the low to the high BMI category or from the high to the low BMI category (Table 2).

RA subjects with a low BMI at baseline had a significantly increased risk of cardiovascular death (HR 3.34, 95% CI 2.23–4.99) compared with non-RA subjects with normal BMI, after adjusting for personal cardiac history, smoking status, and the presence of diabetes, hypertension, and malignancies (Figure 1A). In contrast, among non-RA subjects, low BMI at baseline was not associated with the risk of cardiovascular death (HR 0.73, 95% CI 0.41–1.31) compared with non-RA subjects with a normal BMI (Figure 1A). This corresponded to a 4-fold increase in the risk of cardiovascular death associated with low BMI among RA subjects as compared with non-RA subjects (ratio of the HRs 4.56, 95% CI 2.36–8.80, P < 0.001).

The observed association with low BMI remained significant in a subsequent analysis when subjects were assigned to the low BMI category if they ever experienced low BMI at any time during followup (Figure 1B). Compared with non-RA subjects who remained in the
Table 3. Hazard ratios (95% confidence intervals) for cardiovascular mortality among rheumatoid arthritis (RA) subjects as compared with non-RA subjects, according to baseline and subsequent body mass index (BMI) categories*

<table>
<thead>
<tr>
<th>Baseline BMI, subsequent BMI</th>
<th>Non-RA</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low BMI (&lt;20 kg/m²)</td>
<td>0.83 (0.46–1.51)</td>
<td>3.06 (1.99–4.69)</td>
</tr>
<tr>
<td>Low or normal BMI</td>
<td>ND†</td>
<td>ND†</td>
</tr>
<tr>
<td>High BMI (20–30 kg/m²)</td>
<td>1.41 (0.92–2.15)</td>
<td>2.09 (1.50–2.92)</td>
</tr>
<tr>
<td>Normal BMI (20–30 kg/m²)</td>
<td>1 (reference group)</td>
<td>1 (reference group)</td>
</tr>
<tr>
<td>Low BMI</td>
<td>1.99 (1.16–3.42)</td>
<td>1.33 (0.87–2.02)</td>
</tr>
<tr>
<td>Normal BMI</td>
<td>1.16–3.42</td>
<td>1.33 (0.87–2.02)</td>
</tr>
<tr>
<td>High BMI</td>
<td>0.80 (0.44–1.40)</td>
<td>0.95 (0.57–1.61)</td>
</tr>
<tr>
<td>High or normal BMI</td>
<td>ND†</td>
<td>ND†</td>
</tr>
</tbody>
</table>

* Hazard ratios and 95% confidence intervals were calculated from a time-dependent Cox regression model adjusted for personal cardiac history, smoking, and presence of diabetes mellitus, hypertension, and malignancies.
† Not done (ND); too few subjects (<3) in these categories.

Changes in the BMI during followup were also examined in relation to the risk of cardiovascular death (Table 3). RA subjects with normal-range or high BMI at baseline also experienced a higher risk of cardiovascular death if they had a BMI of <20 kg/m² during followup (HR 2.09, 95% CI 1.50–2.92). Among non-RA subjects, although high BMI at baseline was not associated with an increased risk of cardiovascular death, any subsequent change to BMI >30 kg/m² was associated with a significantly increased risk (HR 1.99, 95% CI 1.16–3.42). This analysis suggests that the excess risk of cardiovascular death associated with low BMI in RA subjects persisted even if these subjects maintained low BMI or later achieved a normal BMI. There was minimal possibility of a bias associated with recent (closest to death) weight loss, because only 18 cardiovascular deaths (6 non-RA subjects and 12 RA subjects) occurred within 1 year of the recorded low BMI. These analyses were repeated considering normal BMI (20–25 kg/m²) and overweight BMI (>25–30 kg/m²), and the results were essentially identical. Inclusion of any glucocorticoid use in the multivariable model had no impact on the HR estimates.

Finally, we considered BMI changes as a time-dependent exposure variable in which subjects were considered exposed to low BMI only during the time periods when their BMI was <20 kg/m², and likewise were considered as exposed to high BMI during the time periods when their BMI was >30 kg/m². Low BMI among RA subjects (compared with normal BMI among non-RA subjects) was still associated with a 3-fold increase (HR 3.45, 95% CI 2.46–4.83) in the risk of cardiovascular death, after adjusting for personal cardiac history, smoking status, diabetes, hypertension, and malignancies.

**DISCUSSION**

In this retrospective cohort study, we compared BMI patterns and the effect of BMI on cardiovascular mortality in a population-based incidence cohort of subjects with RA with that in an age- and sex-matched non-RA cohort. Our findings demonstrate that low BMI (<20 kg/m²) is an important predictor of increased cardiovascular mortality in RA subjects. Low BMI at RA diagnosis is associated with a 3-fold increased risk of cardiovascular death compared with that in non-RA subjects with normal BMI. The risk associated with low BMI persists irrespective of whether the subjects maintain low BMI or achieve a normal BMI during the disease course. Furthermore, despite normal BMI at the time of RA diagnosis, experiencing low BMI during the disease course is also associated with a significantly increased risk of cardiovascular death.

In the general population, BMI is strongly associated with overall mortality and cardiovascular mortality (4–7). Increased mortality associated with high BMI is biologically plausible, due, at least partially, to the adverse effects of obesity on blood pressure, lipoprotein metabolism, and insulin resistance (8). However, several studies also reported a J- or U-shaped relationship, especially among elderly women, and the interpretation of the increased mortality at the low end of the BMI continuum remains controversial (23–30). This finding is attributed, at least partially, to the confounding effects of cigarette smoking and comorbidities, which were more prevalent among people with a low BMI (24,25). The findings of recent studies also suggest a role for the detrimental effects of lower muscle mass, rather than low body weight per se (31), the contributory role of low levels of adipose tissue–derived estrogen in older women with a low BMI (29), and the subclinical inflammation associated with aging (32). RA is a chronic systemic inflammatory disease most commonly found in the elderly population and may represent a model of hyperinflammation or accelerated aging (33). Therefore, our findings have implications not only for patients with RA but also for the etiology of the association between low BMI and cardiovascular mortality in the general popu-
lation. Physicians who care for patients with RA should pay close attention to the management of cardiovascular risk factors, especially among those RA patients who have a low BMI or who are losing weight.

High BMI or obesity was implicated as a risk factor for RA, but the findings are not conclusive (10,11,34,35). Furthermore, weight and BMI changes during the disease course have been reported in small series of patients with established disease (12,13). In those studies, RA subjects had a higher prevalence of low BMI, and the reduction in body mass was greatest for muscle mass, whereas adipose mass was well-maintained (13). Otherwise, BMI has rarely been examined as a risk factor in studies of cardiovascular disease in RA. In 2 previous studies (36,37), BMI data were based on self reports and were cross-sectional, and BMI values were included as a linear covariate in multivariable analyses. However, given our findings, the assumption that there is a linear relation between unit increases in BMI and cardiovascular mortality may be an oversimplification of the true association, and is unlikely to capture the increased risk associated with low BMI in RA patients.

There are a number of possible explanations for the increased risk of cardiovascular death associated with low BMI in RA subjects. Patients with RA experience rheumatoid cachexia, which is a loss of body cell mass, predominantly in skeletal muscle (9). Low BMI in RA patients may indicate rheumatoid cachexia and can also partially explain the strong association between functional capacity and the mortality risk that has been reported previously in RA patients. Studies by Roubenoff and colleagues provide supporting evidence of the role of inflammation in the etiology of rheumatoid cachexia and suggest how it may relate to cardiovascular morbidity and mortality (9,38,39). Rheumatoid cachexia appears to be mediated by excess production of proinflammatory cytokines, reduced peripheral insulin action, and low physical activity. Low physical activity may further predispose RA patients to fat gain and cachectic obesity, which result in reduced muscle mass in the presence of excess fat mass. Our findings demonstrate that the increased cardiovascular risk associated with low BMI is confined to RA subjects, a group with a high burden of inflammation. Therefore, low BMI in our RA cohort is possibly an indicator of rheumatoid cachexia, and the mechanisms described by Roubenoff and colleagues may contribute to the increased cardiovascular risk in RA subjects. Despite problems associated with the interpretation of BMI as a measure of body composition, especially in the elderly (40–42), there is evidence to suggest that low lean body mass can be accurately reflected by low BMI, although increased fatness cannot be captured accurately by high BMI (41).

If low BMI were due to the inflammatory disease process in RA, one would expect to observe an increase in frequency of low BMI, and consequently, an increase in mortality rates over time in RA subjects. However, our previous findings (2) indicate that there is no association between RA disease duration and cardiovascular mortality; i.e., the risk of cardiovascular death for a 50-year-old woman who had RA for more than 8 years is similar to that for another 50-year-old woman who had RA for less than 1 year. In addition, we recently demonstrated that the risk of CHD (hospitalized and silent myocardial infarctions) precedes the ACR criteria–based diagnosis of RA (43). Therefore, given the lack of association of cardiovascular mortality with disease duration, and the higher risk of myocardial infarction prior to RA diagnosis, as well as recent studies demonstrating the presence of systemic inflammatory activity and serologic abnormalities several years prior to the onset of RA symptoms (44), it is not surprising that low BMI, even at RA incidence, is associated with cardiovascular mortality.

The strengths of this study are several-fold. The study included population-based cohorts with extensive followup data on BMI changes and potential confounders for the association between BMI and cardiovascular mortality. The RA subjects included in this study are from a large community-based RA cohort assembled over almost half a century, since 1955. We were able to review the medical records retrospectively, both prior to and following the incidence/index date, and used consistent diagnostic criteria to ascertain cardiac risk factors and cardiovascular events.

The average followup time in this study was 27.4 years prior to and 15 years following the incidence/index date. During such a long followup period, subjects may have gained or lost weight several times. Repeated weight and height measurements both prior to and following the incidence/index date allowed us to extensively account for the BMI changes. This is important because one-time measurements are not an accurate indicator of risk over a long followup period, and because weight changes can be another important risk factor for mortality (45). We accounted for major confounders (i.e., smoking, comorbidity) as well as cardiac risk factors (e.g., presence of CHD, CHF, hypertension, diabetes) both at baseline and during followup. Finally, we relied on measured weight and height, rather than self-reported values, to calculate BMI. This is important because the reliability of self-reported weight and height
may vary substantially with age and BMI categories (46,47) (e.g., underreporting of actual weight by obese people).

The results of this study have some potential limitations. Selection bias is a potential problem due to losses to followup. At the end of the study, the vital status of 10% of the study population was not known. In fact, these subjects remained under observation for a mean of 13.1 years. There were no differences with respect to vital status followup between the RA and the non-RA cohorts. Comparison of the baseline characteristics revealed that the 10% of subjects on whom vital status was not available had a similar BMI to those who remained under observation until the end of the study ($P = 0.67$). Therefore, the fact that vital status data were missing for 10% of our study population is unlikely to affect the comparison of the risk differences associated with low BMI in the RA and non-RA cohorts.

Our findings may not be generalizable to non-white individuals because the Rochester population during the calendar years under investigation was >95% white. With the exception of a higher proportion of the working population employed in the health care industry, and correspondingly higher education levels, the local population is socioeconomically similar to American whites (15).

Our long followup time may limit the external validity of our findings, since the standard of care and the natural history of RA has changed considerably over the last 2 decades. Our findings need to be re-addressed in future studies to assess whether the same trends persist in more aggressively treated patients.

The present study was a retrospective observational study that relied on the clinical information recorded in the patients’ medical records. Diseases or characteristics not recorded in the medical records would have been missed. For example, subjects with RA typically have reduced physical activity. Physical activity is associated with both BMI and cardiovascular mortality (48). Therefore, the extent of physical activity may be an important unmeasured confounder or an effect modifier for the association between BMI and cardiovascular mortality in this study.

It is possible that BMI was measured more frequently around the time of significant weight loss or weight gain than at other times. In our analysis, we minimized the influence of this potential limitation by using BMI categories, instead of actual values. Furthermore, we were more likely to include the extreme BMI categories (our primary exposure of interest) and assign an accurate date for the BMI change.

We were not able to distinguish whether low BMI was associated with loss of muscle mass or adipose tissue redistribution, because we did not obtain additional measures of body composition other than weight and height. Although it is possible that more precise anthropometric measures of adiposity and muscle mass may be better predictors of cardiovascular mortality in RA subjects (e.g., waist:hip ratio may be a better marker of abdominal adiposity in older women [26]), BMI is a clinically relevant measure, and among the elderly, it has been shown to be a good indicator of low muscle mass (41). In addition, the purpose of our study was to compare RA subjects with non-RA subjects in an attempt to demonstrate whether BMI confers equal risk for cardiovascular death in RA versus non-RA subjects.

In conclusion, our findings demonstrate that among subjects with RA, low BMI is an important predictor of cardiovascular death. RA represents a model of hyperinflammation. If low BMI in RA is a consequence of inflammation, then our findings lend support to the hypothesis that inflammation may play a role in the pathogenesis of cardiovascular disease.

**ACKNOWLEDGMENTS**

We are grateful to Dianne Stiebner, Denise Herman, Glenda Kendall, and Vicky Roeder for performing data collection and editing from the medical records, and Drs. Veronique L. Roger and Steven J. Jacobsen for their valuable comments on the manuscript.

**REFERENCES**

10. Voigt LF, Koepsell TD, Nelson JL, Dugowson CE, Daling JR.