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Roles of Postdiagnosis Accumulation of Morbidities and Lifestyle Changes in Excess Total and Cause-Specific Mortality Risk in Rheumatoid Arthritis

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Objective. To elucidate how postdiagnosis multimorbidity and lifestyle changes contribute to the excess mortality of rheumatoid arthritis (RA).

Methods. We performed a matched cohort study among women in the Nurses' Health Study (1976–2018). We identified women with incident RA and matched each by age and year to 10 non-RA comparators at the RA diagnosis index date. Specific causes of death were ascertained via death certificates and medical record review. Lifestyle and morbidity factors were reported biennially; 61 chronic conditions were combined into the Multimorbidity Weighted Index (MWI). After adjusting for baseline confounders, we used inverse probability weighting analysis to examine the mediating influence of postindex MWI scores and lifestyle factors on total, cardiovascular, and respiratory mortality, comparing women with RA to their matched comparators.

Results. We identified 1,007 patients with incident RA and matched them to 10,070 non-RA comparators. After adjusting for preindex confounders, we found that hazard ratios (HRs) and 95% confidence intervals (95% CIs) were higher for total mortality (HR 1.46 [95% CI 1.32, 1.62]), as well as cardiovascular (HR 1.54 [95% CI 1.22, 1.94]) and respiratory (HR 2.75 [95% CI 2.05, 3.71]) mortality in patients with RA compared to non-RA comparators. Adjusting for postindex lifestyle factors (physical activity, body mass index, diet, smoking) attenuated but did not substantially account for this excess RA mortality. After additional adjustment for postindex MWI scores, patients with RA had HRs of 1.18 (95% CI 1.05, 1.32) for total, 1.19 (95% CI 0.94, 1.51) for cardiovascular, and 1.93 (95% CI 1.42, 2.62) for respiratory mortality.

Conclusion. We found that MWI scores substantially accounted for the excess total and cardiovascular mortality among women with RA. This finding underscores the importance of monitoring for the total disease burden as a whole in monitoring patients with RA.

INTRODUCTION

Rheumatoid arthritis (RA) has been associated with an increased incidence of cardiovascular events (1), cancer (2), serious infections (3), and respiratory diseases (4) compared to the general population. Despite advances in RA treatment, a gap between the mortality of patients with RA and the general population persists, perhaps due to worsening lifestyle, morbidity burden, disease progression, and medication side effects (5–7).

Although RA is one of the most common autoimmune diseases, its annual incidence of 38 per 100,000 is relatively low (8). This fact makes the construction of an inception cohort with appro-

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SIGNIFICANCE & INNOVATIONS

- We examined the roles that postdiagnosis factors played in the excess mortality observed in patients with incident rheumatoid arthritis (RA) compared to matched non-RA comparators.
- The parent study, Nurses' Health Study (NHS), provided a rich set of longitudinal information both before and after the diagnosis of RA.
- Increased hazards persisted after accounting for the postdiagnosis lifestyle factors only.
- Accounting for the postdiagnosis multimorbidity as measured by the Multimorbidity Weighted Index mostly eliminated the increased hazards for total and cardiovascular mortality among patients with RA.
- An increased hazard for respiratory mortality remained, suggesting the roles of factors not captured in the NHS, such as interstitial lung diseases.

priate individual-level comparators and lengthy follow-up difficult. As a result, studies have typically been performed using RA-only cohorts and compared to the expected mortality calculated from age-, sex-, and calendar-year–matched population statistics (standardized mortality ratio [SMR] method) (2,5–7,9). The SMR method does not account for the potential discrepancies between patients with RA and the general population beyond these factors, such as differences in smoking and body mass index (BMI). This absence may result in insufficient control for confounding (10,11) and an inability to study the mediators of excess mortality that are influenced by the RA status and predispose patients with RA to excess mortality.

Multimorbidity, the presence of 2 or more chronic conditions in an individual and representation of an individual's accumulating morbidity burden (12,13), likely plays a role in excess mortality. Various indices have been proposed in efforts to evaluate the multimorbidity burden (14). Quantifying the extent to which the excess mortality is explained by such a measure of multimorbidity is of interest because a comprehensive general measure of multimorbidity should explain some part of the excess mortality among patients with RA, leaving the rest to RA-specific issues, including treatment and lifestyle changes. However, challenges exist in providing sufficiently granular information on chronic morbidities to calculate a multimorbidity index both in patients with RA and non-RA comparators without information bias due to differential ascertainment (15).

The Nurses' Health Study (NHS), an ongoing large prospective cohort (n = 121,700) of US female registered nurses with a rich set of covariate history, provided a unique opportunity to examine this question (16). In this study, we aimed to better understand the extent to which an extensive multimorbidity measure (17) explained the excess mortality among patients with RA. If the excess mortality is explained to a large extent by such a multimorbidity measure, the index may prove to be useful as a monitoring tool. If not, an effort to create a more comprehensive measure of multimorbidity may be warranted.

SUBJECTS AND METHODS

Subjects and eligibility. NHS enrolled 121,700 female registered nurses in 1976, ages 30–55 years. Since then, the prospective follow-up has continued every 2 years to date through mailed questionnaires. The questionnaires collect information on sociodemographics, anthropometrics, behaviors, medications, dietary intake, and health conditions. Only 4.4% of person-years have been lost to follow-up (18). The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and the Harvard T. H. Chan School of Public Health.

Identification of incident RA. Participants who self-reported a new physician diagnosis of RA in the biennial NHS questionnaires received a validated follow-up questionnaire for connective tissue disease screening (19). If the screening was positive, medical records were requested and independently reviewed by 2 physicians to confirm RA based on the 1987 American College of Rheumatology (ACR) (20) or 2010 ACR/European League Against Rheumatism (21) classification criteria. We further classified RA cases as seropositive (positivity of rheumatoid factor or anti–cyclic citrullinated peptide antibody [anti–citrullinated protein antibody (ACPA)], if available) and seronegative (both antibodies negative) from the results of clinical testing in the record. We excluded women who had prevalent RA in 1976. The index date was defined as the date of diagnosis, as obtained by medical record review. RA cases were identified up to and including the 2014 questionnaire cycle.

Matched non-RA comparators. For each confirmed patient with incident RA, we matched by age and calendar year 10 non-RA comparators who had never self-reported RA at or prior to the index date. To avoid the issue of misalignment of the start of the follow-up and eligibility assessment, we did not use comparators' future RA development status for baseline exclusion. Instead, they were censored at the time of RA development. This censoring only excluded 0.24% of the person-time.

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Mortality outcomes. Our outcomes of interest were total and cause-specific mortality. For cause-specific mortality, we focused on cardiovascular and respiratory mortality (16). We identified mortality through the National Death Index, state cancer registries, and family reports (22,23). Trained NHS study physicians reviewed death certificates, medical records, and autopsy reports (if available) to assign a single primary underlying cause of death. Mortality data were last collected on December 4, 2018, which serves as the end of follow-up for this study.

Covariates. *Preindex and postindex covariates.* We selected covariates identified as associated with the risk for developing RA and mortality (16,22,24–31). We classified time-varying covariates as preindex and postindex (Figure 1). For preindex covariates, we used the characteristics of the RA cases and matched non-RA comparators at 1 questionnaire cycle prior to the index date. Median household income was derived from the participants' address and US Census tract-level data by zip code. US residence regions were classified as New England, Mid-Atlantic, Midwest, South, and West based on zip code. Participants self-reported their race/ethnicity as well as menopausal status and postmenopausal hormone use. BMI was calculated from self-reported weight in kg/m^2. Weekly hours of moderate-to-vigorous physical activity were calculated from a validated survey (32,33). Using the food-frequency questionnaires (34), we calculated the Alternate Healthy Eating Index (AHEI) score (35,36). Smoking status (never, past, and current smoker) and pack-years were derived from self-report in the past 2 years (26). We used 4 lifestyle covariates (BMI, physical activity, AHEI score, and smoking pack-years) as time-updated postindex covariates to examine their roles in mediating the association of RA and total and cause-specific mortality.

Preindex and postindex multimorbidity. To capture the totality of multiple chronic conditions and diseases before and after the index date, we used the validated Multimorbidity Weighted Index (MWI) (17,37). The MWI was developed to quantify the contributions of 74 common and chronic conditions by their impact on health-related quality of life (HRQoL), measured by the Short Form 36 health survey (SF-36) 10-item physical functioning scale (17). MWI scores better predicted 10-year mortality than the Charlson Comorbidity Index (CCI) (38) and disease count (37). Physician-diagnosed conditions were self-reported through a binary yes/no response. Participants could also voluntarily list other conditions not assessed in the questionnaire. Most conditions were considered irreversible and/or requiring lifelong maintenance/treatment, and once reported as present, carried forward. A few conditions were considered intermittent and included in each survey year reported but not carried forward (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24120/abstract). The NHS questionnaire included both common chronic conditions with a prevalence similar to those seen in the general population and also rare but debilitating conditions, such as amyotrophic lateral sclerosis, that are rarely captured in other surveys. Our adaptation of the MWI is explained in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24120/abstract, and the accompanying supplementary text.

Statistical analyses and modeling strategy. We described the baseline characteristics of the RA cases and their matched comparators at 1 questionnaire cycle prior to the index date (Figure 1). We conducted longitudinal descriptive analyses of mortality and the multimorbidity and lifestyle factors using the postindex follow-up data. The slope difference and

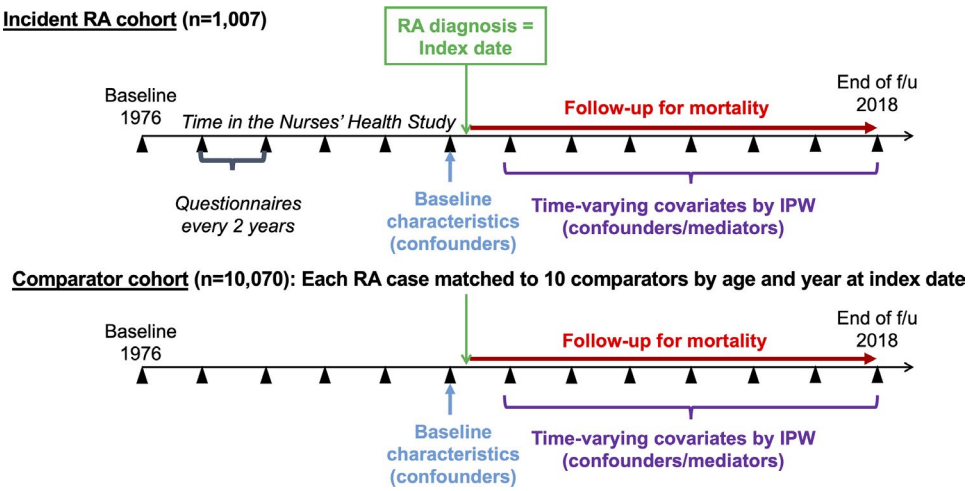

Figure 1. Cohort construction diagram. For each incident rheumatoid arthritis (RA) case, 10 non-RA comparators were matched for age and calendar year. The follow-up (f/u) for this current study started at the time of RA diagnosis or the comparable date for the comparators (index date). IPW = inverse probability weights.

Table 1. Baseline characteristics for women with incident RA (n = 1,007) and matched comparators (n = 10,070) in the Nurses' Health Study*

Characteristics	Patients with RA	Matched non-RA comparators
No.	1,007	10,070
Age, mean ± SD years†	60.3 ± 10.3	60.3 ± 10.3
Household income, median (IQR) $US	59,415 (47,373, 74,985)	59,125 (46,347, 76,453)
US region		
New England	157 (15.6)	1,332 (13.2)
Mid-Atlantic	409 (40.6)	4,351 (43.2)
Midwest	197 (19.6)	1,618 (16.1)
South	80 (7.9)	658 (6.5)
West	159 (15.8)	1,869 (18.6)
White race	981 (97.4)	9,736 (96.7)
Menopausal status and PMH use		
Premenopausal	256 (25.8)	2,968 (30.8)
Postmenopausal and never PMH use	256 (25.8)	2,753 (28.6)
Postmenopausal and any PMH use	240 (24.2)	1,922 (20.0)
Body mass index, mean ± SD kg/m^2	26.0 ± 5.0	25.6 ± 5.1
Physical activity, hours/week, median (IQR)	0.9 (0.0, 3.0)	1.0 (0.0, 3.0)
Alternate Healthy Eating Index, median (IQR)	50.5 (44.3, 57.9)	50.7 (44.0, 58.2)
Smoking status		
Never smoker	361 (36.0)	4,347 (43.2)
Past smoker	436 (43.4)	3,717 (37.0)
Current smoker	207 (20.6)	1,989 (19.8)
Pack-years among ever smokers, median (IQR)	22.0 (10.0, 38.0)	17.0 (5.0, 34.0)
Multimorbidity Weighted Index, mean ± SD	4.2 ± 4.4	3.1 ± 3.9

* Values are the number (%) unless indicated otherwise. Each woman with incident rheumatoid arthritis (RA) occurring during follow-up of the Nurses' Health Study was matched with up to 10 women without RA by age and calendar year at the index date of RA diagnosis. Missing data are not presented. IQR = interquartile range; PMH = postmenopausal hormone use.
† Age is from the index date.

the interaction *P* value were examined using a linear mixed-effects model to account for the intraindividual correlation of repeated measures. We also calculated the organ-system component MWI score (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24120/abstract). Similarly, we conducted longitudinal descriptive analyses of lifestyle factors (BMI, physical activity, cumulative AHEI score, and smoking pack-years).

We performed analyses detailing the association between RA and mortality outcomes compared to the comparator group. First, we used Cox regression, adjusting only for preindex confounders, to estimate the overall increase in the hazards of total and cause-specific mortalities due to RA (model 1). The effect estimate of RA in these models would be interpreted as the total effect of RA on mortality, since postindex mediators postulated to be on the causal pathway are not adjusted. Due to the potentially differential morbidity and mortality implications of seropositive RA versus seronegative RA (16,39), we also conducted stratified analysis by the seropositivity status.

Next, we additionally accounted for postindex time-updated lifestyle factors (model 2), followed by postindex time-updated MWI score (model 3), and then both (model 4) using inverse probability weighting (IPW) (40). We employed the IPW framework to balance the distribution of time-varying covariates at each postindex time point between patients with RA and comparators. Due to the 10-times larger size of the non-RA comparator group, IPWs would make the distribution of postbaseline covariates in the RA group similar to those of the comparator group, while keeping the comparator group less modified. Thus, this weighting scheme makes the average trajectory of postindex covariates in the patients with RA similar to that of the non-RA comparators. Intuitively, this result is achieved through down-weighting patients with RA who have accumulated more morbidities than typical in the comparator group and up-weighting those patients with RA who developed fewer morbidities than typical for RA (i.e., at a level comparable to the non-RA comparator group). No interaction terms among the time-varying covariates were included in the weighting models because we did not have definitive hypotheses concerning interactions. We assessed the validity of the weighting models via examination of the stabilized IPW over time (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24120/abstract). The mortality outcome analysis after IPW was conducted via weighted pooled logistic regression (41). We interpreted the association of RA status and mortality that persisted in these IPW analyses as the direct effects of RA not mediated by the factors that were accounted for in the IPW (lifestyle factors, multimorbidity, or both, depending on the model). The decrement in the RA hazard ratio (HR) after accounting for these postindex covariates represented the quantification of the amount of mediation explained by the difference in their trajectories developing between patients with RA and their matched comparators after the index date. A sensitivity analysis with the CCI (38) was also conducted. The descriptive analyses were conducted in R

software, version 3.5, and the IPW analyses were conducted in SAS software, version 9.4 (41). We used an alpha level of 0.05 for confidence intervals (95% CIs) and reported *P* values where applicable.

RESULTS

Participants and baseline characteristics. We identified 1,007 incident RA cases during follow-up since 1976 in the NHS. We chose 10,070 comparators in total. The average calendar year of the index date was 1995. The age as of the index date was balanced, with a mean ± SD of 60 ± 10 years in both groups. Seropositive RA accounted for 623 RA cases (62%), whereas seronegative RA accounted for 384 RA cases. Subjects' preindex characteristics at 1 questionnaire cycle (up to 2 years) before the index date are shown in Table 1. Past and current smoking were more common among individuals with RA (43% versus 21%) than in comparators (37% versus 20%). There were fewer premenopausal women among the RA cases (26% versus 31%). The descriptive statistics of the conditions included in the MWI are shown in Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24120/abstract.

Total and cause-specific mortality. As shown in Supplementary Table 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24120/abstract, the median follow-up duration after the index date was 20 (interquartile range [IQR] 12, 26) years among RA cases and 20 (IQR 12, 28) years among the matched comparators. During follow-up, 431 deaths occurred among patients with RA (43%) and 3,156 deaths occurred among matched comparators (31%). Among all deaths, cardiovascular deaths occurred in 20% of RA cases and 19% of comparators. Respiratory mortality was more common for RA cases (12%) than for matched comparators (7%).

Description of multimorbidity and lifestyle factors before and after the index date. The mean ± SD preindex MWI score was higher for incident RA cases (4.2 ± 4.4) than for matched comparators (3.1 ± 3.9) (Figure 2). The accumulation of morbidities as measured by the MWI was more rapid after incident RA diagnosis than for the matched comparators (mean slope difference 1.43 per decade [95% CI 1.23, 1.63]; interaction $P < 0.001$). When partitioned into major organ systems (Figure 3), the musculoskeletal system was the largest contributor to the MWI score in both groups and had an initial difference as well as a steeper slope for the RA cases. Additionally, cardiovascular and pulmonary components of the MWI had a greater accumulation for RA cases than for matched comparators. The unweighted multimorbidity counts demonstrated similar trends (see Supplementary Figures 2 and 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24120/abstract).

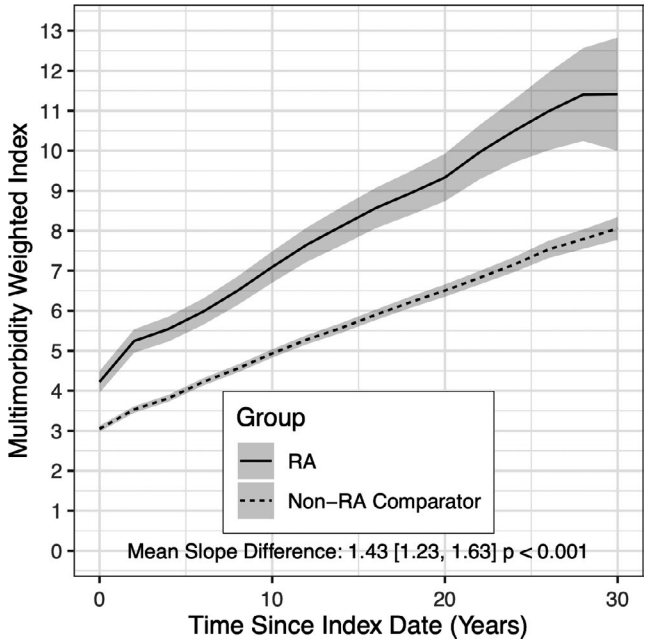

Figure 2. Accumulation of multimorbidity after the index date of rheumatoid arthritis (RA) diagnosis (n = 1,007) or matched date for comparators (n = 10,070) for women in the Nurses' Health Study, as quantified by the Multimorbidity Weighted Index (MWI). The mean slope difference represents the additional accumulation of the MWI score per 10 years (95% confidence interval in shading) among women with RA compared to their matched non-RA comparators, as well as the *P* value for interaction.

The description of lifestyle factors after the index date is shown in Figure 4. BMI trajectories were visually similar across the patients with RA and the matched comparators, although a minor slope difference was detectable. The decline in physical activity was more prominent in the RA group than in comparators. Both groups exhibited similar minor improvements over time in dietary quality, as measured by the AHEI. RA cases had higher smoking pack-years at the index date (3.3 pack-years more among patients with RA) and throughout follow-up. Accounting for censoring by death through mixed-effects modeling, accumulation of further smoking exposure was similar (additional –0.02 pack-years of smoking exposure per decade for RA [95% CI –0.21, 0.16]; $P = 0.801$).

RA and mortality risk adjusting for only preindex confounders using Cox regression. In the initial analyses adjusting for the preindex confounders, women with RA had HRs of 1.46 (95% CI 1.32, 1.62) for total, 1.54 (95% CI 1.22, 1.94) for cardiovascular, and 2.75 (95% CI 2.05, 3.71) for respiratory mortality compared to the matched comparators. As shown in Table 2, seropositive RA cases had even higher HRs for the total (1.56 [95% CI 1.37, 1.77]) and respiratory mortality (3.52 [95% CI 2.50, 4.96]) compared to their matched comparators. The HRs for seronegative RA were increased for cardiovascular mortality (1.60 [95% CI 1.13, 2.28]) compared to their matched comparators.

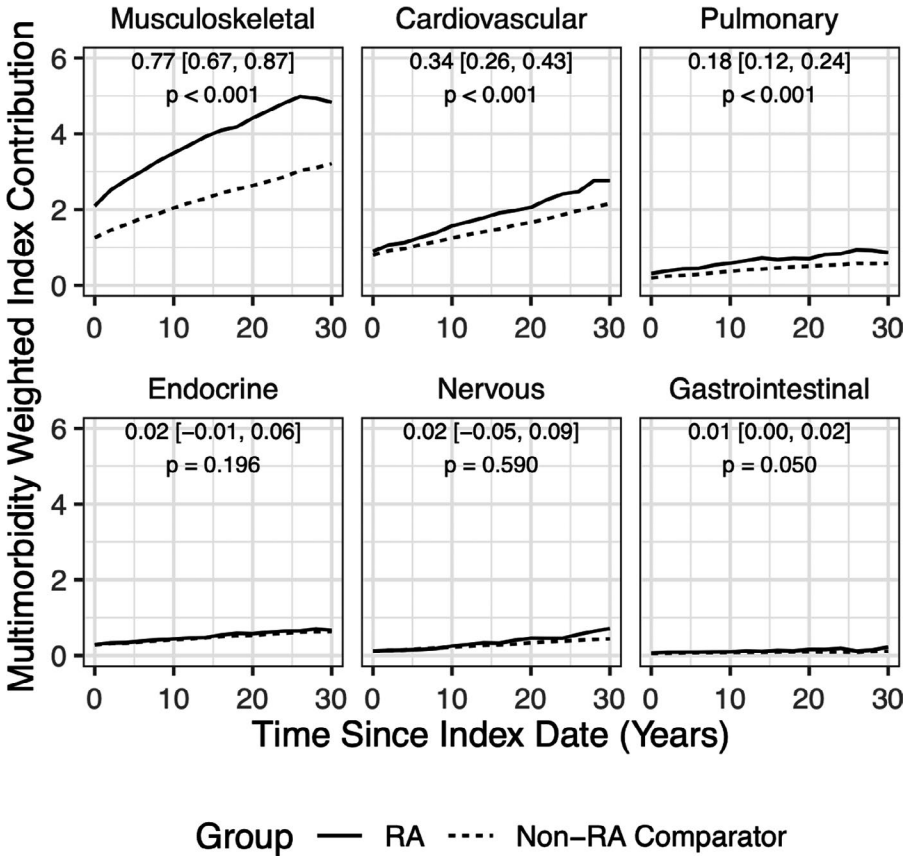

Figure 3. Accumulation of the major components (musculoskeletal, cardiovascular, pulmonary, endocrine, gastrointestinal, and nervous) of the Multimorbidity Weighted Index (MWI) after the index date of rheumatoid arthritis (RA) diagnosis (n = 1,007) or matched date for comparators (n = 10,070) for women in the Nurses' Health Study. The in-figure numbers are the mean slope differences that represent additional increase of each component of the MWI per 10 years (95% confidence interval) among women with RA compared to their matched non-RA comparators, as well as the *P* value for interaction. See Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24120/abstract, for further information on the components.

RA and mortality risk further accounting for postindex factors using IPW. Accounting for postindex lifestyle factors via IPW attenuated but did not eliminate the increased HRs for mortality for women with RA (Table 2, model 2): total mortality 1.38 (95% CI 1.23, 1.54), cardiovascular mortality 1.39 (95% CI 1.09, 1.78), and respiratory mortality 2.40 (95% CI 1.76, 3.28). However, accounting for postindex multimorbidity factors (Table 2, model 3) more strongly attenuated mortality, in particular, the total mortality (HR 1.25 [95% CI 1.13, 1.40]) and cardiovascular mortality (HR 1.23 [0.97, 1.55]), but also respiratory mortality (HR 2.03 [95% CI 1.50, 2.76]). Accounting for both postindex lifestyle and multimorbidity factors in the same model (Table 2, model 4) resulted in the most attenuation of HRs for total mortality (1.18 [95% CI 1.05, 1.32]) and cardiovascular mortality (1.19 [95% CI 0.94, 1.51]) for RA. The HR for respiratory mortality was attenuated but remained statistically significant at 1.93 (95% CI 1.42, 2.62). Even higher HRs remained for the seropositive RA subset: 1.31 (95% CI 1.14, 1.51) for total mortality and 2.68 (95% CI 1.88, 3.82) for respiratory mortality, although cardiovascular mortality difference was nearly eliminated (1.13 [95% CI 0.82, 1.57]). Among the seronegative RA subset, this total mortality difference was attenuated and no longer statistically significant 1.01 (95% CI 0.84, 1.21). These results represent the potential pathways that account for excess RA mortality according to the measured postindex factors in each model. A sensitivity analysis with the CCI (38) generally gave similar results, although attenuation was not as prominent (see Supplementary Table 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24120/abstract).

DISCUSSION

To elucidate the evolution and influence of postindex multimorbidity as measured with the MWI (17) on the excess mortality among patients with incident RA, we used the NHS, a large prospective cohort of female nurses who were free of RA at cohort inception in 1976. As in previous reports (16), we found that patients with RA had increased total, cardiovascular, and respiratory mortality, adjusting for preindex confounders, including smoking, physical activity, BMI, dietary intake, and multimorbidity. The

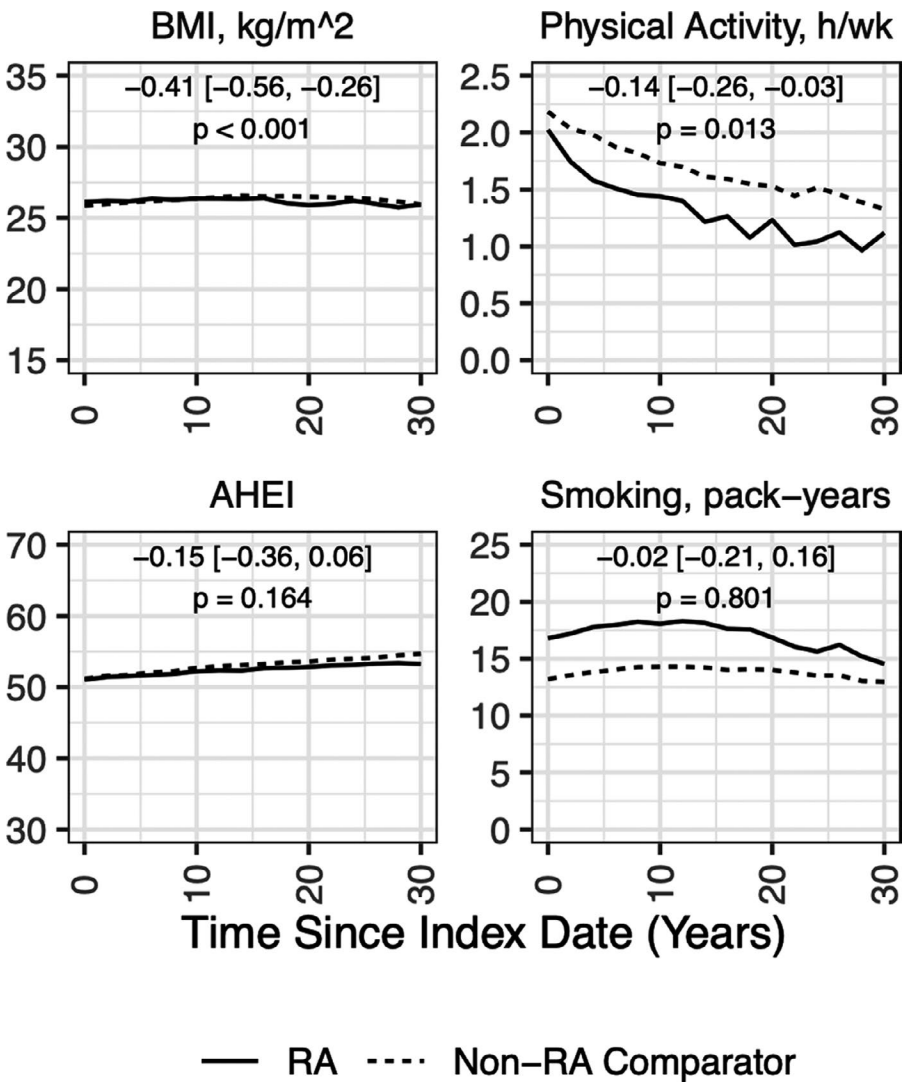

Figure 4. Changes in continuous measures of lifestyle factors (body mass index, moderate-to-vigorous physical activity, dietary intake, and smoking) over time after the index date of rheumatoid arthritis (RA) diagnosis (n = 1,007) or matched date for comparators (n = 10,070) for women in the Nurses' Health Study. The numbers represent the mean slope difference per 10 years (95% confidence interval) comparing women with RA to their matched non-RA comparators, as well as the *P* value for interaction. AHEI = Alternate Healthy Eating Index; BMI = body mass index; h/wk = hours/week.

results accounting for postindex lifestyle changes and MWI score extend previous studies by allowing us to examine which of these elements may explain excess RA mortality with more substantiality. Accounting for postindex lifestyle changes did not explain the excess risk for total, cardiovascular, or respiratory mortality. However, additionally accounting for postindex MWI score attenuated estimates of excess cardiovascular mortality in RA. The excess risk for patients with RA persisted even after accounting for multimorbidity factors for total mortality and respiratory mortality.

This current report extends our previous study in the NHS that examined the total and cause-specific mortalities in RA (16). In this study, we have more closely examined potential causes of the excess mortalities in RA. In particular, we used the MWI, a novel index to quantify multimorbidity, accounting for importance to physical HRQoL (17,37). Our finding in the models accounting for postindex MWI scores suggests major contributions from accumulating multimorbidity burden as measured by the MWI after RA diagnosis, resulting in increased total and cardiovascular mortality. This extensive 61-condition index accounted for excess mortality more than the 19-condition CCI, as seen in the greater magnitude of attenuation of excess RA mortality for the MWI compared to CCI. The residual elevation in the respiratory mortality even after accounting for MWI score may indicate the importance of other factors that were not captured in the NHS. These missing factors could include interstitial lung disease, infections, and disease-modifying antirheumatic drug use.

Multimorbidity, defined as the presence of multiple, concurrent chronic conditions within 1 person, occurs more commonly than the presence of a single chronic disease in the adult population (42). How we should define the set of conditions that count

Table 2. Hazard ratios for total and cause-specific mortality for women with RA (reference: matched comparators) in the Nurses' Health Study, balancing time-varying covariates before and after the index date of RA diagnosis using inverse probability weighting*

Models and covariates†	Total mortality	Cardiovascular mortality	Respiratory mortality
All RA (vs. matched comparators)			
1. Baseline confounders	1.46 (1.32, 1.62)	1.54 (1.22, 1.94)	2.75 (2.05, 3.71)
2. Baseline confounders + time-updated lifestyle factors	1.38 (1.23, 1.54)	1.39 (1.09, 1.78)	2.40 (1.76, 3.28)
3. Baseline confounders + time-updated multimorbidity	1.25 (1.13, 1.40)	1.23 (0.97, 1.55)	2.03 (1.50, 2.76)
4. Baseline confounders + time-updated lifestyle/multimorbidity	1.18 (1.05, 1.32)	1.19 (0.94, 1.51)	1.93 (1.42, 2.62)
Seropositive RA (vs. matched comparators)			
1. Baseline confounders	1.56 (1.37, 1.77)	1.49 (1.09, 2.02)	3.52 (2.50, 4.96)
2. Baseline confounders + time-updated lifestyle factors	1.47 (1.28, 1.70)	1.24 (0.88, 1.73)	3.30 (2.32, 4.69)
3. Baseline confounders + time-updated multimorbidity	1.39 (1.21, 1.59)	1.23 (0.90, 1.68)	2.69 (1.89, 3.83)
4. Baseline confounders + time-updated lifestyle/multimorbidity	1.31 (1.14, 1.51)	1.13 (0.82, 1.57)	2.68 (1.88, 3.82)
Seronegative RA (vs. matched comparators)			
1. Baseline confounders	1.30 (1.10, 1.54)	1.60 (1.13, 2.28)	1.45 (0.76, 2.77)
2. Baseline confounders + time-updated lifestyle factors	1.24 (1.03, 1.49)	1.55 (1.08, 2.24)	1.10 (0.54, 2.22)
3. Baseline confounders + time-updated multimorbidity	1.04 (0.87, 1.25)	1.20 (0.84, 1.71)	1.07 (0.55, 2.10)
4. Baseline confounders + time-updated lifestyle/multimorbidity	1.01 (0.84, 1.21)	1.18 (0.83, 1.69)	1.07 (0.57, 2.04)

* Values are the hazard ratio (95% confidence interval). The all-RA analyses included 1,007 women with all rheumatoid arthritis (RA) and 10,070 matched comparators. The seropositive RA analyses included 623 women with seropositive RA and 6,230 matched comparators. The seronegative RA analyses included 384 women with seronegative RA and 3,840 matched comparators. Model 1 shows the effect of RA on mortality outcomes adjusted for confounding factors. Models 2–4 shows the residual effects of RA on mortality not accounted for by the listed mediating factors occurring after the index date.

† Model 1, baseline confounders: adjusted for matching factors (age and calendar year) at the index date of RA diagnosis as well as for baseline factors assessed prior to the index date: annual family income, body mass index, physical activity, Alternate Healthy Eating Index (AHEI) score, smoking, and Multimorbidity Weighted Index (MWI) score. Model 2, baseline confounders + time-updated lifestyle: adjusted for variables in model 1 as well as time-updated lifestyle factors (body mass index, physical activity, AHEI score, smoking) assessed after the index date; adjustment used inverse probability weighting. Model 3, baseline confounders + time-updated multimorbidity: adjusted for variables in model 1 as well as time-updated MWI score after the index date; adjustment used inverse probability weighting. Model 4, baseline confounders + time-updated lifestyle/multimorbidity: adjusted for variables in model 2 as well as time-updated MWI score after the index date; adjustment used inverse probability weighting.

toward multimorbidity and how the measurement should be made are topics of continued debate. Among many scales available, we used the MWI (17) for several reasons. The MWI is a comprehensive, continuous measure that includes more conditions and more precisely captures the broad distribution of multimorbidity in the population. Similar to disease count, the MWI is easy to implement but additionally accounts for the differential impact of each condition. Weighting conditions, as in the MWI, provides a better model fit than disease count for predicting future physical functioning, cognitive functioning, and mortality (37,43). Since the notion of multimorbidity is to focus on the patient as an individual rather than on a specific disease (13), the weights should ideally represent each condition's impact on a patient-centered measure, such as HRQoL. The MWI was initially developed with these points in mind, using the SF-36 physical functioning to weight disease severity (17). Important for our study, the MWI has been demonstrated to be a useful measure to predict future mortality, with higher accuracy than the CCI (37).

Our study emphasizes the importance of consideration of multimorbidity in rheumatologic care. Although the hallmark of RA may be its characteristic joint involvement, the chronic inflammatory nature of RA and its treatment result in the development of morbidities beyond the musculoskeletal system (44). We observed more rapid accumulation of the morbidity burden as measured by MWI scores for patients with RA in several organ systems in the descriptive analyses in comparison to their matched comparators drawn from the same population. Multimorbidity has an impact on multiple aspects of RA care. Patients with RA may have underrecognition and suboptimal treatment for many coexisting conditions, for example accumulating cardiovascular conditions (45). An international study found that patients with RA with multimorbidity were less likely to be on biologic disease-modifying antirheumatic drugs (46), which may indicate the hesitance of physicians for initiating more aggressive therapy for RA or the reliance on corticosteroids, which could worsen multimorbidity. Our results showing the important contribution of the faster

accumulation of the morbidity burden, as measured by the MWI, to the excess mortality of RA further emphasize the need to carefully consider how multimorbidity should be detected and treated.

Although their roles may be less prominent than multimorbidity in the current study, lifestyle factors should not be disregarded. For example, smoking is an important risk factor for the development of RA (26,10,47,48), and smoking exposure was considerably higher among patients with RA than among their matched comparators at baseline and throughout the follow-up, although their slopes were similar after accounting for survivor bias (preferential censoring by mortality among heavy smokers). The decrease in physical activity with aging among patients with RA may represent barriers to exertion such as dyspnea (49). Therefore, delineating the feedback relationship between multimorbidity and lifestyle factors may be important.

Deriving our study cohort from the NHS allowed us to identify patients with incident RA with systematically collected questionnaires extending from the prediagnosis period until decades after diagnosis. Having individual-level matched comparators enabled us to adjust for various preindex factors and to assess the influence of postindex factors.

The major trade-off for a study based on the NHS is the nondiverse nature of the cohort. The NHS is composed only of US female nurses who were ages 30–55 years, mostly white, who were required to be healthy and working at the initiation of the cohort in 1976. Therefore, generalizability to the population of patients with RA beyond this type of demographic remains to be confirmed. Even with the rich data on repeated measures of potential confounders and mediators, there may be inherent inaccuracy of self-reported data. Therefore, residual confounding and unmeasured mediation are possible. While the MWI offered advantages for this analysis of overall morbidity burden, it is true that an overall index does not allow examination of influence on mortality at the individual condition level. We attempted to provide additional insights by demonstrating the organ system–level major contributors of MWI scores.

The NHS is a study among female nurses in general and is not a rheumatology-specific disease or drug registry. As a result, the routine data collection in the NHS has been geared toward lifestyle factors and typical lifestyle-associated diseases such as cancer, cardiovascular disease, and diabetes mellitus. Variables that are relevant to rheumatology practice, but infrequent among the general population, such as interstitial lung diseases and antirheumatic medication use, were not captured. However, since the study participants are health professionals, the positive predictive values are known to be high for many of the self-reported conditions that were included (50). The inception of the NHS occurred in 1976, but the average calendar year of the index date was 1995, indicating that the diagnosis and follow-up of RA cases in our study extended into the biologic era. Serologic status at RA diagnosis relied on clinical testing, so some older RA cases did not have ACPA testing done.

In summary, accumulating multimorbidity as measured by the MWI after RA diagnosis accounted for much of the excess total and cardiovascular mortality for RA. Patients with seropositive RA had very elevated respiratory mortality, even after accounting for lifestyle factors and common chronic morbidities. Our findings emphasize the need for rheumatologists and primary care providers to actively take part in monitoring for multimorbidity that patients with RA are prone to developing.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Sparks had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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