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Original Article: The roles of post-diagnosis accumulation of morbidities and lifestyle changes on excess total and cause-specific mortality risk in rheumatoid arthritis.

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Significance & Innovations:

- We examined the roles post-diagnosis factors played in the excess mortality observed in incident rheumatoid arthritis (RA) patients 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 post-diagnosis lifestyle factors only.
- Accounting for the post-diagnosis multimorbidity as measured by the Multimorbidity Weighted Index mostly eliminated the increased hazards for total and cardiovascular mortality among RA patients.
- An increased hazard for respiratory mortality remained, suggesting the roles of factors not captured in the NHS, such as interstitial lung diseases.

ABSTRACT (Word count = 247; max 250 structured in AC&R)

OBJECTIVE: To elucidate how post-diagnosis 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 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 post-index MWI and lifestyle factors on total, cardiovascular, and respiratory mortality, comparing women with RA to their matched comparators.

RESULTS: We identified 1,007 incident RA patients and matched to 10,070 non-RA comparators. Adjusting for pre-index confounders, RA patients had elevated HRs and 95%CIs for total (1.46 [1.32,1.62]), cardiovascular (1.54 [1.22,1.94]), and respiratory (2.75 [2.05,3.71]) mortality, compared to non-RA comparators. Adjusting for post-index lifestyle factors (physical activity, BMI, diet, smoking) attenuated but did not substantially account for this excess RA mortality. After additional adjustment for post-index MWI, RA patients had HRs and 95%CIs of 1.18 [1.05,1.32] for total, 1.19 [0.94,1.51] for cardiovascular, and 1.93 [1.42,2.62] for respiratory mortality.

CONCLUSION: We found that MWI 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 RA patients.

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 RA patients 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 makes the construction of an inception cohort with appropriate 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-time matched population statistics (standardized mortality ratio (SMR) method) (9,2,5–7). The SMR method does not account for the potential discrepancies between RA patients and the general population beyond these factors, such as differences in smoking, and body mass index (BMI). This may result in insufficient control for confounding (10,11) and an inability to study the mediators of the excess mortality that are influenced by the RA status and predispose RA patients to excess mortality.

Multimorbidity, the presence of two 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 multimorbidity burden (14). Quantifying the extent to which the excess mortality is explained by such a measure of multimorbidity is of interest as a comprehensive general measure of multimorbidity should explain some part of the excess mortality among RA patients 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 RA patients and non-RA comparators without information bias due to differential ascertainment (15).

The Nurses' Health Study (NHS), an ongoing large (n = 121,700) prospective cohort of US female registered nurses with a rich set of covariate history, provided a unique opportunity to examine this (16). In this study, we aimed to better understand the extent to which an extensive multimorbidity measure (17) explained the excess mortality among RA patients. 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, the need for a more comprehensive measure of multimorbidity may be warranted.

METHODS

Participants and eligibility

NHS enrolled 121,700 female registered nurses in 1976 aged 30-55 years. Since then, the prospective follow-up has continued every two 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 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 screened positive, medical records were requested and independently reviewed by two 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 (CCP or 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 incident RA patient, we matched 10 non-RA comparators who had never self-reported RA at or prior to index date by age and calendar year at 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.

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

We selected covariates identified as associated with risk for developing RA and mortality (16,22,24–31). We classified time-varying covariates as pre-index and post-index (**Figure 1**).

Pre-index and post-index covariates. For pre-index covariates, we used the characteristics of the RA cases and matched non-RA comparators one questionnaire cycle prior to the index date. Median

household income was derived from the participant's 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 race/ethnicity as well as menopausal status and postmenopausal hormone use. Body mass index (BMI) was calculated from self-reported weight in kilograms / height in meters squared. 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) (35,36). Smoking status (never, past, and current smoker) and pack-years were derived from self-report in the past two years (26). We used four lifestyle covariates (BMI, physical activity, AHEI, and smoking pack-years) as time-updated *post*-index covariates to examine their roles in mediating the association of RA and total and cause-specific mortality.

Pre-index and post-index multimorbidity. To capture the totality of multiple chronic conditions and diseases before and after index date, we used the validated Multimorbidity Weighted Index (MWI) (17,37). 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 (SF-36) 10-item physical functioning scale (17). MWI better predicted 10-year mortality than the Charlson Comorbidity Index (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 (**sTable 1**) were considered intermittent and included in each survey year reported but not carried forward. The NHS questionnaire included both common chronic conditions with prevalence similar to those seen in the general population but also rare but debilitating conditions such as ALS that are rarely captured in other surveys. Our adaptation of the MWI is explained in **sTable 1** and the accompanying supplementary text.

Statistical analyses and modeling strategy

We described the baseline characteristics of the RA cases and their matched comparators one questionnaire cycle prior to the index date (**Figure 1**).

We conducted longitudinal descriptive analyses of mortality and the multimorbidity and lifestyle factors using the post-index follow-up data. The slope difference and the interaction p-value were examined using a linear mixed-effects model to account for the intra-individual correlation of repeated measures. We also calculated the organ-system component MWI (**sTable 1**). Similarly, we conducted longitudinal descriptive analyses of lifestyle factors (BMI, physical activity, cumulative AHEI, 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 pre-index 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 post-index mediators postulated to be on the causal pathway are not adjusted. Due to the potentially differential morbidity and mortality implications of seropositive RA vs. seronegative RA (16,39), we also conducted stratified analysis by the seropositivity status.

Next, we additionally accounted for post-index time-updated lifestyle factors (Model 2), followed by post-index time-updated MWI (Model 3), and then both (Model 4) using inverse probability weighting (IPW) (40). We employed the IPW framework to balance the distribution time-varying covariates at each post-index time point between RA patients and comparators. Due to the 10-time larger size of the non-RA comparator group, IPWs would make the distribution of post-baseline covariates in the RA group similar to that of the comparator group, while keeping the comparator group less modified. Thus, this weighting scheme makes the average trajectory of post-index covariates in the RA patients similar to that of the non-RA comparators. Intuitively, this is achieved through down-weighting RA patients who have accumulated more morbidities than typical in the comparator group and up-weighting those RA patients 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 as we did not have definitive hypotheses concerning interactions. We assessed the validity of the weighting models via examination of the stabilized IPW over time (**sFigure 1**). 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 after accounting for these post-index covariates represented the quantification of the amount of mediation explained by the difference in their trajectories developing between RA patients and their matched comparators after the index date. A sensitivity analysis with the Charlson Comorbidity Index (CCI) (38) was also conducted.

The descriptive analyses were conducted in R version 3.5, and the IPW analyses were conducted in SAS 9.4 (41). We used an alpha level of 0.05 for confidence intervals 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 of 60 years and a standard deviation (SD) of 10 years in both groups. Seropositive RA accounted for 623 (62%) RA cases, whereas seronegative RA accounted for 384 RA cases. Their pre-index characteristics one questionnaire cycle (up to two years) before the index date are

shown in **Table 1**. Past and current smoking were more common among RA individuals (43%; 21%) than in comparators (37%; 20%). There were fewer premenopausal women among the RA cases (26% vs 31%). The descriptive statistics of the conditions included in the MWI is shown in **sTable 2**.

Total and cause-specific mortality

As shown in **sTable 3**, 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 RA patients (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 matched comparators (7%).

Description of multimorbidity and lifestyle factors before and after index date

The mean pre-index MWI was higher for incident RA cases (4.2, SD 4.4) than matched comparators (3.1, SD 3.9, **Figure 2**). The accumulation of morbidities as measured by the MWI was more rapid after incident RA diagnosis than the matched comparators (mean slope difference 1.43 per decade [95% confidence interval (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 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 greater accumulation for RA cases than matched comparators. The unweighted multimorbidity counts demonstrated similar trends (**sFigures 2** and **3**).

The description of lifestyle factors after the index date is shown in **Figure 4**. BMI trajectories were visually similar across the RA patients and the matched comparators, although a minor slope difference was detectable. The decline in physical activity was more prominent in the RA group than 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 index date (3.3 pack-years more among 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 pre-index confounders using Cox regression

In the initial analyses adjusting for the pre-index confounders, women with RA had hazard ratios (HR) of 1.46 [95% confidence interval (CI): 1.32, 1.62] for total; 1.54 [1.22, 1.94] for cardiovascular; and 2.75 [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 [1.37, 1.77]) and respiratory mortality (3.52

[2.50, 4.96]) compared to their matched comparators. The HRs for seronegative RA were increased for cardiovascular mortality (1.60 [1.13,2.28]) compared to their matched comparators.

RA and mortality risk further accounting for post-index factors using IPW

Accounting for post-index 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 [1.23, 1.54]; cardiovascular mortality 1.39 [1.09, 1.78]; and respiratory mortality 2.40 [1.76, 3.28]. However, accounting for post-index multimorbidity factors (**Table 2** Model 3) more strongly attenuated mortality, in particular, the total mortality (1.25 [1.13, 1.40]) and cardiovascular mortality (1.23 [0.97, 1.55]), but also respiratory mortality (2.03 [1.50, 2.76]). Accounting for both post-index lifestyle and multimorbidity factors in the same model (**Table 2** Model 4) resulted in the most attenuation of HRs for total mortality (HR 1.18 [1.05, 1.32]) and cardiovascular mortality (HR 1.19 [0.94, 1.51]) for RA. The HR for respiratory mortality was attenuated but remained statistically significant at 1.93 [1.42, 2.62]. Even higher hazards remained for the seropositive RA subset: 1.31 [1.14, 1.51] for total mortality and 2.68 [1.88, 3.82] for respiratory mortality, although cardiovascular mortality difference was nearly eliminated (1.13 [0.82, 1.57]). Among the seronegative RA subset, this total mortality difference was attenuated and no longer statistically significant 1.01 [0.84, 1.21]. These results represent the potential pathways that account for excess RA mortality according to the measured post-index factors in each model. A sensitivity analysis with the CCI (38) generally gave similar results (**sTable 4**), although attenuation was not as prominent.

DISCUSSION

To elucidate the evolution and influence of post-index multimorbidity as measured with the MWI (17) on the excess mortality among incident RA patients, we utilized 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 RA patients had increased total, cardiovascular, and respiratory mortality adjusting for pre-index confounders, including smoking, physical activity, BMI, dietary intake, and multimorbidity. The results accounting for post-index lifestyle changes and MWI extend previous studies by allowing us to examine which of these elements may explain excess RA mortality with more substantially. Accounting for post-index lifestyle changes did not explain the excess risk for total, cardiovascular, or respiratory mortality. However, additionally accounting for post-index MWI attenuated estimates of excess cardiovascular mortality in RA. The excess risk for RA patients 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 post-index

MWI suggests major contributions from accumulating multimorbidity burden as measured by 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 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 drugs use.

Multimorbidity, defined as the presence of multiple, concurrent chronic conditions within one 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 towards multimorbidity and how the measurement should be made are topics of continued debate. Among many scales available, we utilized the MWI (17) for several reasons. 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, MWI is easy to implement, but additionally accounts for the differential impact of each condition. Weighting conditions, as in 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 morbidities beyond the musculoskeletal system (44). We observed more rapid accumulation of the morbidity burden as measured by MWI for RA patients 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 under-recognition and sub-optimal treatment for many coexisting conditions, for example accumulating cardiovascular conditions (45). An international study found that RA patients 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 that show the important contribution of the faster accumulation of the morbidity burden as measured by 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 RA patients than their matched comparators at the 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 RA patients may represent barriers to exertion such as dyspnea (49). As such, delineating the feedback relationship between multimorbidity and lifestyle factors may be important.

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

The major trade-off for a study based on the NHS is the non-diverse nature of the cohort. The NHS is composed only of US female nurses who were aged 30-55 years old, mostly white, and were required to be healthy and working at the initiation of the cohort in 1976. Therefore, generalizability to the population of RA patients 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.

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. 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; however, the average calendar year of the index date was 1995, indicating 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 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 RA patients are prone to developing.

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TABLES

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

	RA Patients	Matched Non-RA Comparators
n	1,007	10,070
Age (mean (SD))**	60.3 (10.3)	60.3 (10.3)
Household income, $US dollars (median, [IQR])	59,415 [47,373, 74,985]	59,125 [46,347, 76,453]
US Region (n, %)		
New England	157 (15.6)	1332 (13.2)
Mid-Atlantic	409 (40.6)	4351 (43.2)
Midwest	197 (19.6)	1618 (16.1)
South	80 (7.9)	658 (6.5)
West	159 (15.8)	1869 (18.6)
White race (n, %)	981 (97.4)	9736 (96.7)
Menopausal status and PMH use (n, %)		
Premenopausal	256 (25.8)	2968 (30.8)
Postmenopausal and never PMH use	256 (25.8)	2753 (28.6)
Postmenopausal and any PMH use	240 (24.2)	1922 (20.0)
Body mass index, kg/m^2 (mean (SD))	26.0 (5.0)	25.6 (5.1)
Physical activity, h/wk (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 (n, %)		
Never smoker	361 (36.0)	4347 (43.2)
Past smoker	436 (43.4)	3717 (37.0)
Current smoker	207 (20.6)	1989 (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)

Missing data are not presented.

*Each woman with incident rheumatoid arthritis occurring during follow-up of the Nurses' Health Study was matched to up to 10 women without rheumatoid arthritis by age and calendar year at the index date of RA diagnosis.

**Age is as of index date

Abbreviations: RA: rheumatoid arthritis; SD: standard deviation; IQR: interquartile range; PMH: postmenopausal hormone use.

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. 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 index date.

Models and covariates	Total mortality HR [95% CI]	Cardiovascular mortality HR [95% CI]	Respiratory mortality HR [95% CI]
All RA (vs. matched comparators)			
(1) Baseline confounders model	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 model	1.38 [1.23,1.54]	1.39 [1.09,1.78]	2.40 [1.76,3.28]
(3) Baseline confounders + Time-updated multimorbidity model	1.25 [1.13,1.40]	1.23 [0.97,1.55]	2.03 [1.50,2.76]
(4) Baseline confounders + Time-updated lifestyle and multimorbidity factors model	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 model	1.56 [1.37,1.77]	1.49 [1.09,2.02]	3.52 [2.50,4.96]
(2) Baseline confounders + Time-updated lifestyle model	1.47 [1.28,1.70]	1.24 [0.88,1.73]	3.30 [2.32,4.69]
(3) Baseline confounders + Time-updated multimorbidity model	1.39 [1.21,1.59]	1.23 [0.90,1.68]	2.69 [1.89,3.83]
(4) Baseline confounders + Time-updated lifestyle and multimorbidity model	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 model	1.30 [1.10,1.54]	1.60 [1.13,2.28]	1.45 [0.76,2.77]
(2) Baseline confounders + Time-updated lifestyle model	1.24 [1.03,1.49]	1.55 [1.08,2.24]	1.10 [0.54,2.22]
(3) Baseline confounders + Time-updated multimorbidity model	1.04 [0.87,1.25]	1.20 [0.84,1.71]	1.07 [0.55,2.10]
(4) Baseline confounders + Time-updated lifestyle and multimorbidity model	1.01 [0.84,1.21]	1.18 [0.83,1.69]	1.07 [0.57,2.04]

The all RA analyses included 1,007 women with all 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.

(1) Baseline confounders model: Adjusted for matching factors (age and calendar year) at index date of rheumatoid arthritis diagnosis as well as *baseline* factors assessed prior to index date: annual family income, body mass index, physical activity, Alternate Healthy Eating Index, smoking, and Multimorbidity Weighted Index.

(2) Baseline confounders + Time-updated lifestyle model: Adjusted for variables in (1) as well as *time-updated* lifestyle factors (body mass index, physical activity, Alternate Healthy Eating Index, smoking) assessed after index date. Adjustment used inverse probability weighting.

(3) Baseline confounders + Time-updated multimorbidity model: Adjusted for variables in (1) as well as *time-updated* Multimorbidity Weighted Index after index date. Adjustment used inverse probability weighting.

(4) Baseline confounders + Time-updated lifestyle and multimorbidity model: Adjusted for variables in (2) as well as *time-updated* Multimorbidity Weighted Index after index date. Adjustment used inverse probability weighting.

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

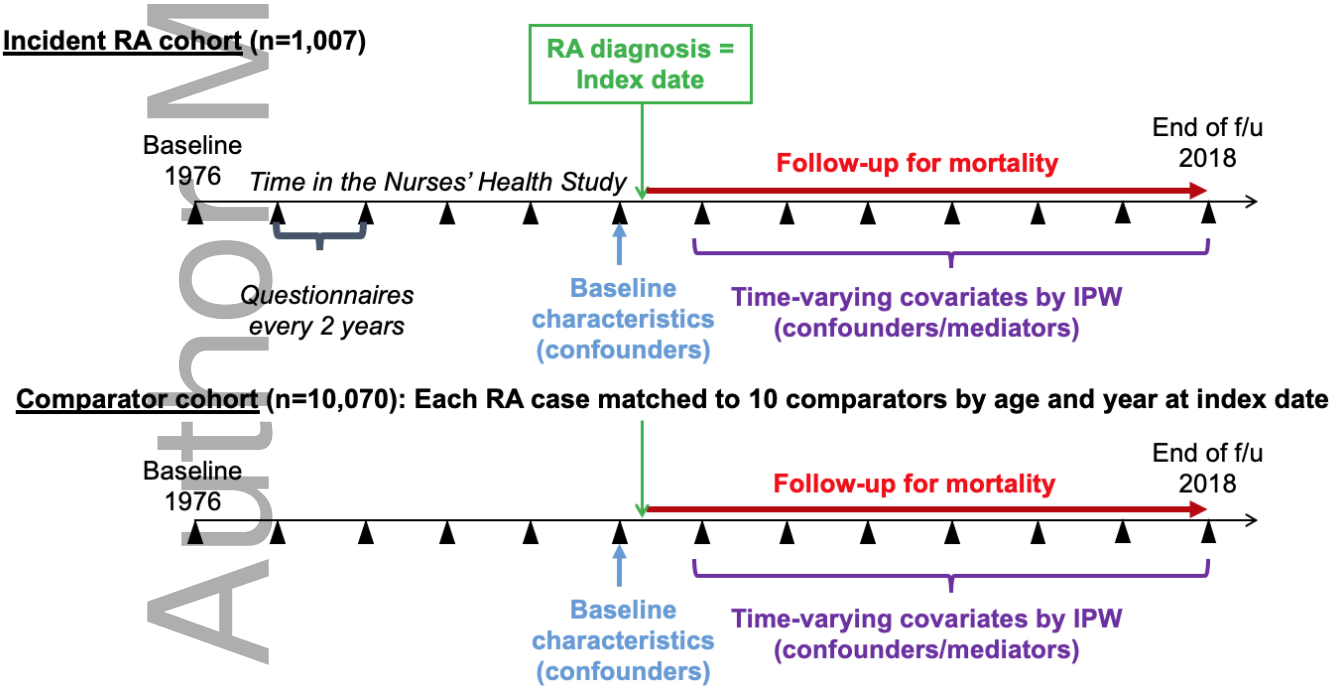


Figure 2. Accumulation of multimorbidity after the index date of RA diagnosis (n=1,007) or matched date for comparators (n=10,070) for women in the Nurses' Health Study, as quantified by the Multimorbidity Weighted Index. The mean slope difference represents the additional accumulation of the Multimorbidity

Weighted Index per 10 years [95% confidence interval] among women with RA compared to their matched non-RA comparators, as well as the p for interaction. RA: rheumatoid arthritis.

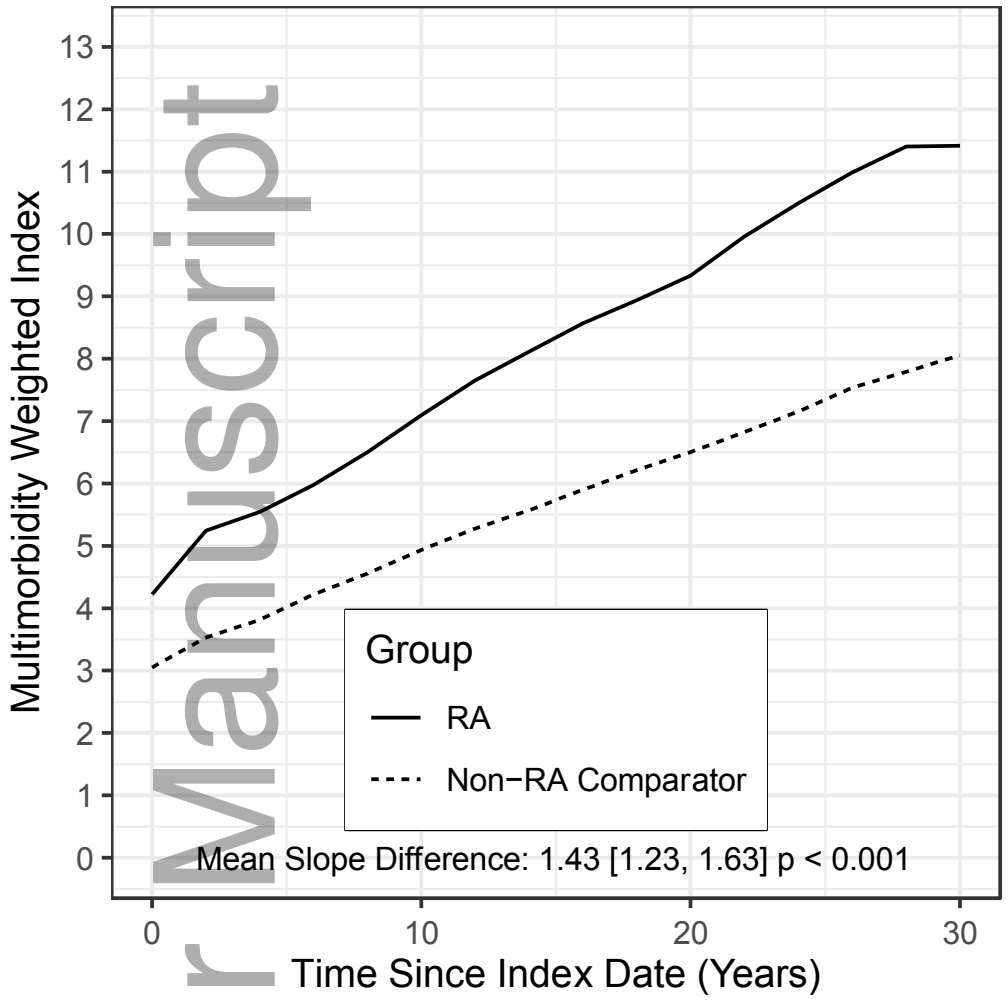


Figure 3. Accumulation of the major components (musculoskeletal, cardiovascular, pulmonary, endocrine, gastrointestinal, and nervous) of the Multimorbidity Weighted Index after the index date of RA diagnosis (n=1,007) or matched date for comparators (n=10,070) for women in the Nurses' Health Study. The in-figure numbers are the mean slope differences that represent additional increase of each component Multimorbidity Weighted Index per 10 years [95% confidence interval] among women with RA compared their matched non-RA comparators, as well as the p for interaction. See Supplemental Table for further information on the components. RA: rheumatoid arthritis.

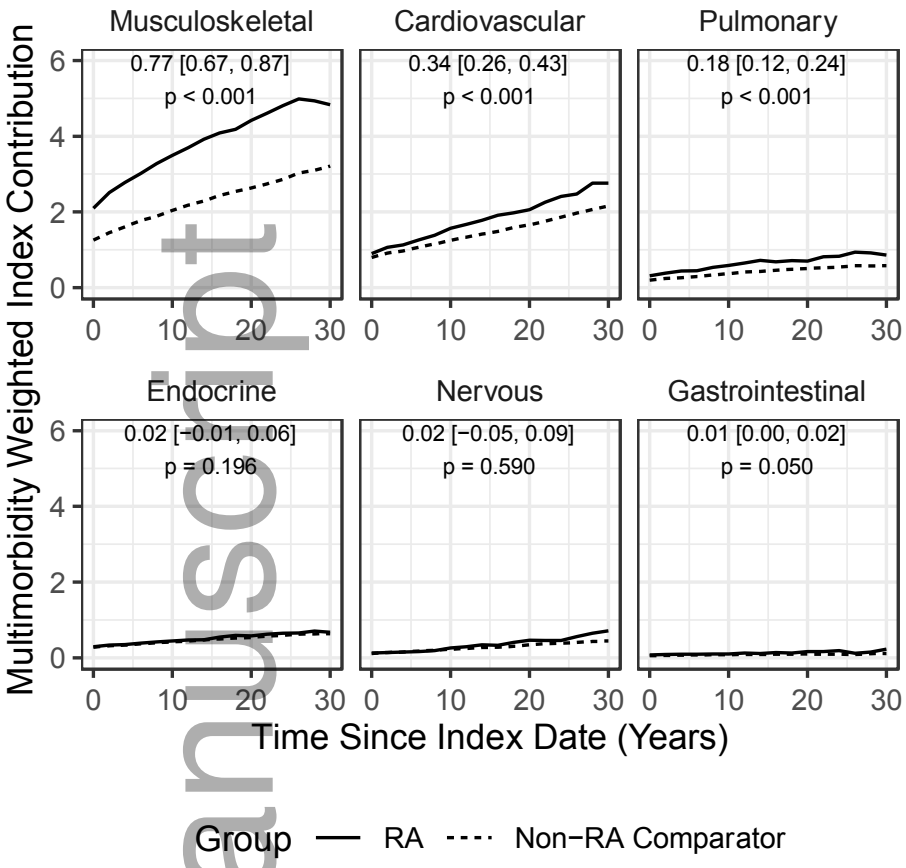
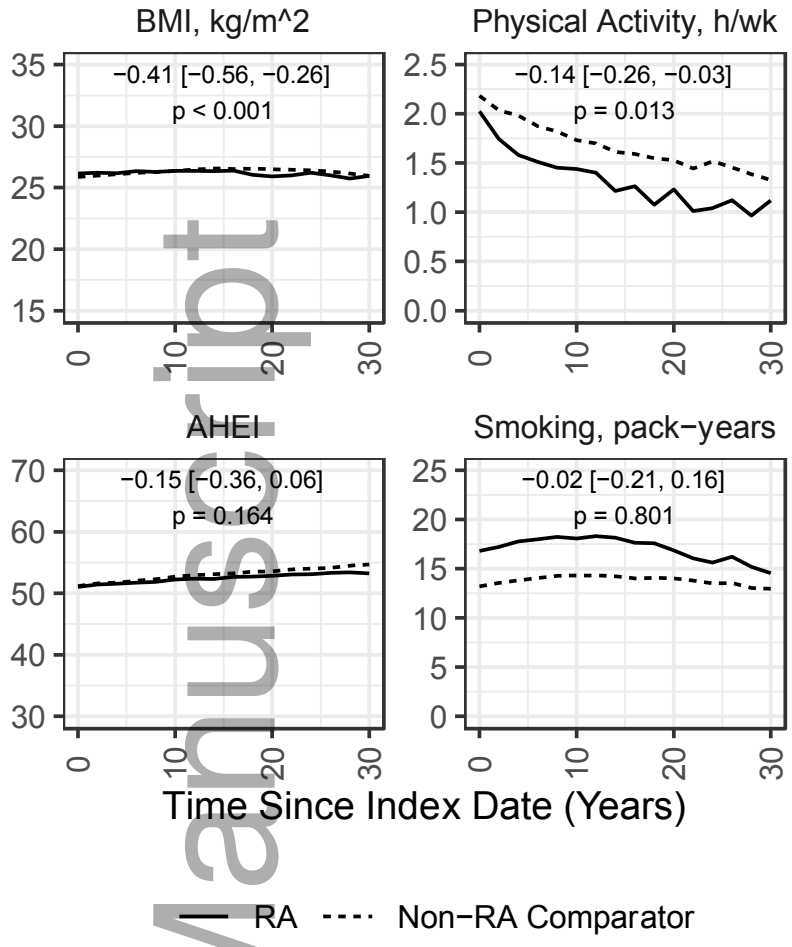
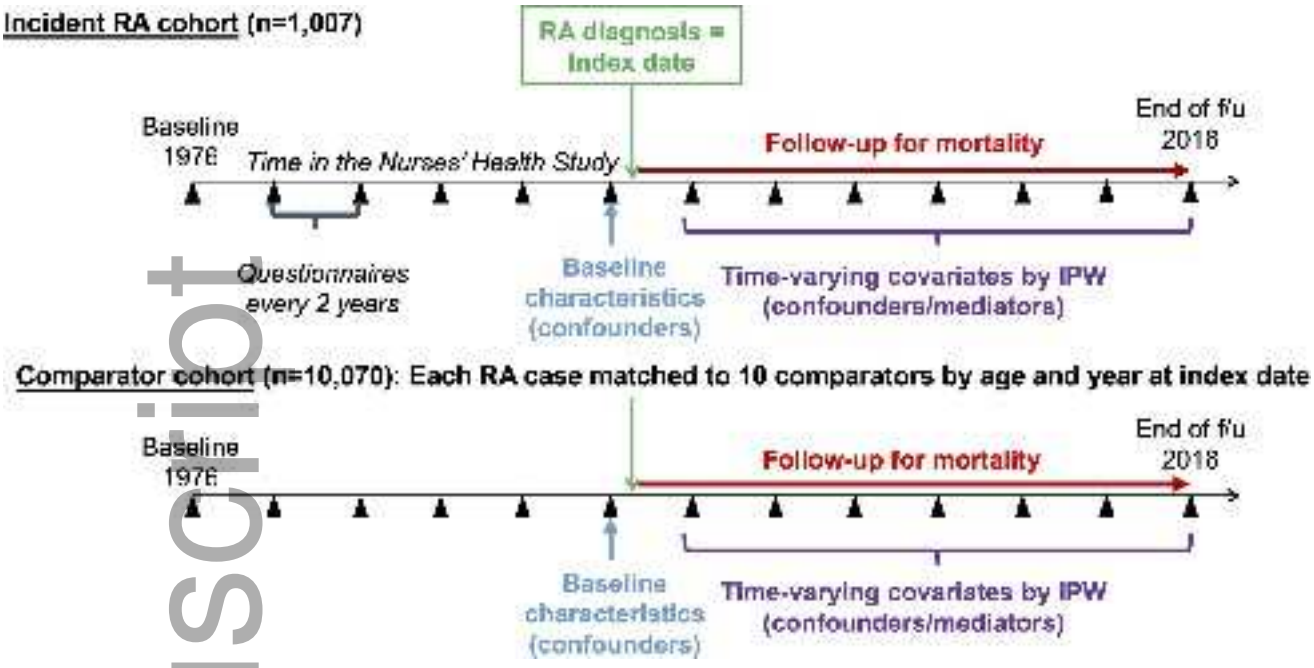


Figure 4. Changes in continuous measures of lifestyle factors (body mass index, moderate to vigorous physical activity, dietary intake, and smoking) over time after the index date of RA diagnosis (n=1,007) or matched date for comparators (n=10,070) for women in the Nurses' Health Study. The numbers represent 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 for interaction. AHEI: Alternate Healthy Eating Index; BMI: body mass index; RA: rheumatoid arthritis.





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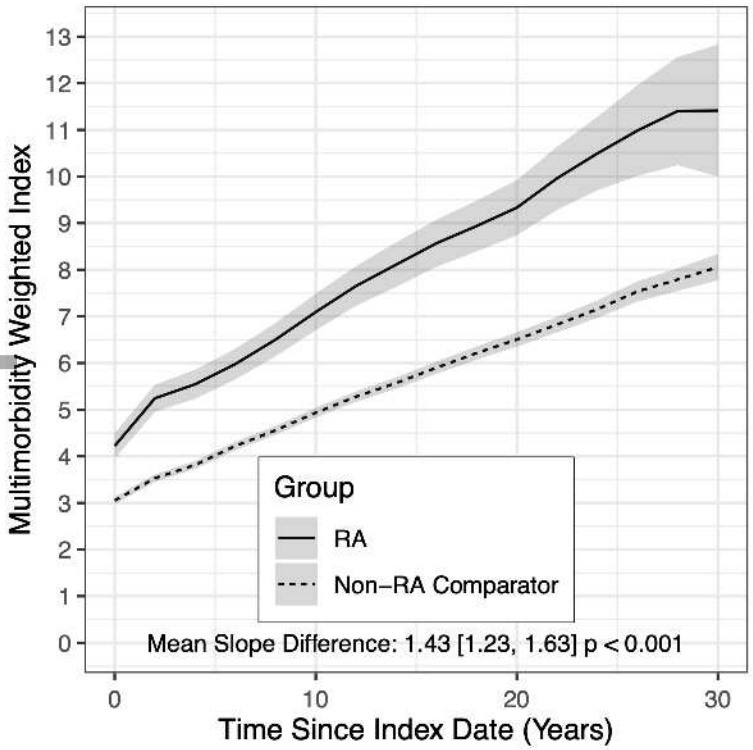

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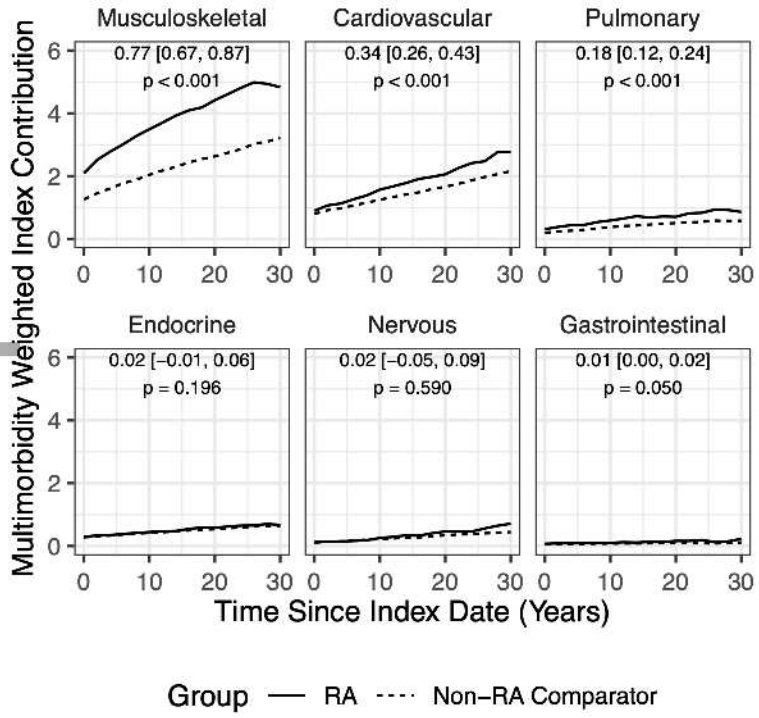

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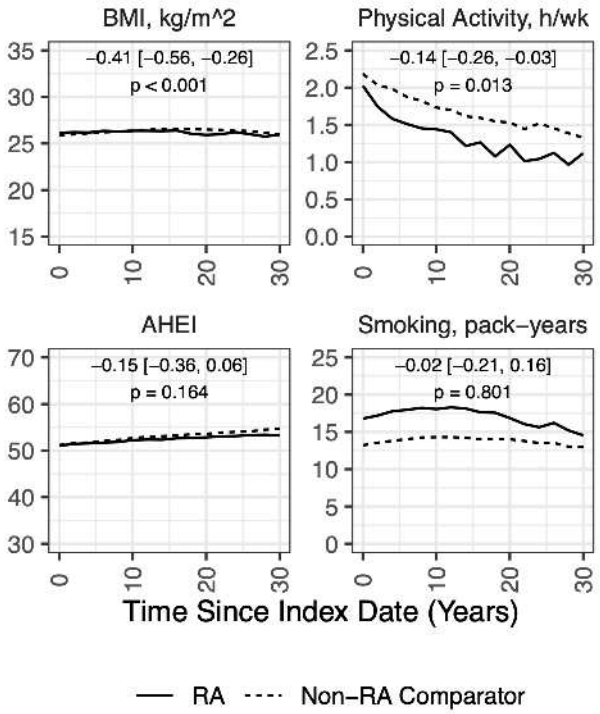

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