Current and early life weight and associations with mortality in rheumatoid arthritis

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Abstract

Objective

Obesity is paradoxically associated with a lower risk of mortality in chronic illnesses including rheumatoid arthritis (RA). Weight loss in patients with poor health, however, may in part explain this observation. This study evaluated the impact of weight early in life and weight loss on mortality in patients with RA.

Methods

Patients with RA (age >40 years) were active participants in a prospective clinical registry with up to 17 years of follow-up. Current and age-30 body mass index (BMI) were determined from self-report of height and weight from semi-annual questionnaires. Mortality was assessed from National Death Index. Risks of obesity reported from both early in life and at enrolment in the registry were evaluated using Cox proportional hazards models.

Results

Among 12,679 participants (80% female), there were 1,520 deaths in 80,502 person-years. Obesity at enrolment (BMI >30 kg/m^2) was modestly associated with greater mortality [HR: 1.34 (1.18,1.53) p=0.001]. Adjusting for disability and comorbidities hypothesised to be mediators in the causal pathway between obesity and mortality further attenuated this association [HR: 0.92 (0.80,1.06) p=0.24]. In contrast, obesity at age 30 was strongly associated with mortality [HR: 2.00 (1.65,2.42) p<0.001]. Additionally, weight loss since age-30 was a strong, dose-dependent predictor of mortality independent of enrolment BMI.

Conclusion

The risk of obesity is substantially underestimated when epidemiologic methods do not account for long-term weight changes. Both obesity and weight loss are strongly associated with mortality risk in patients with RA.

Key words

obesity, mortality, rheumatoid arthritis

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Introduction

Among patients with chronic illness or older age, overweight and obesity have often been associated with a lower risk of mortality, despite the known deleterious health effects of excess weight (1-4). This observation, often termed the obesity paradox, is observed in rheumatoid arthritis (RA) (5).

Explaining the underlying basis for the obesity paradox has important implications for patient care and epidemiologic research. Taken at face value, the obesity paradox suggests that excess weight has a biologically protective effect in patients with chronic disease and implies that clinicians should encourage weight gain and discourage weight loss in certain circumstances. Yet these epidemiologic paradoxes may simply be the product of biases and methodologic errors.

Previous studies have suggested that unintentional weight loss may help explain the obesity paradox, with more severe chronic disease leading to both lower body weight and greater mortality risk (6-10). As a result, patients with low body weight may then appear to be at higher risk of death. In other words, weight loss is a potential confounder in the relationship between obesity and mortality since it is associated with being thin and associated with poor long-term outcomes such as mortality. In support of this hypothesis, studies in the general population and in RA have suggested that weight histories can add valuable information to epidemiologic analyses (9, 11, 12).

Epidemiologic studies also commonly adjust for comorbid conditions when assessing relationships between obesity and mortality (1-3). This common practice seems intuitive but may, in fact, contribute to an exacerbation of the obesity paradox. For example, if obesity leads to diabetes and diabetes increases the risk of dying from a heart attack, then diabetes is called a "mediator" – it lies on the causal pathway between obesity and mortality. In other words, obesity increases the risk of death by causing diabetes. Adjusting for diabetes, or any mediator, may lead to obesity appearing "safer" than it actually is, contributing to the observation of an obesity paradox.

In this study, we evaluated a large sample of patients with RA who were enrolled in a clinical registry that included measures of both current weight and weight early in life (age 30). We hypothesised that greater weight early in life (before the occurrence of unintentional weight loss due to chronic illness) would not demonstrate paradoxical associations with mortality. Similarly, analyses accounting for weight loss since early life would recognise stronger associations between obesity and mortality among patients with RA. In addition, we explored the impact of adjusting for comorbidities that might be mediators (in the causal pathway) of the effect of obesity on mortality.

Methods

Study setting

This prospective cohort study evaluated patients who were active participants in the National Data Bank for Rheumatic Diseases (*Forward*) between 1999 to 2016 and >40 years of age at enrolment. Forward is a patient-based multi-disease, multi-purpose rheumatic disease registry with patients enrolled from the community-based rheumatology practices across the U.S. and followed-up with regular questionnaires. All patients with RA have received a diagnosis from a rheumatologist. Key patient data is validated regularly using medical records. The registry has been described in detail elsewhere [13, 14]. The study was approved by Via Christi Hospitals Whichta, Inc. Institutional Review Board (IRB00001674). All patients sign informed consent prior to participating.

Assessment of Body Mass Index

All patients reported their weight and height on each bi-annual questionnaire. Approximately one half of all registry patients (13,357/23,347; 57%) reported their weight at age 30. The survey question was introduced in 2005 and active participants were allowed to respond at any time during their follow-up. Body mass index (BMI) was determined at age 30 and at enrolment (weight [kg]/modal height [m]^2) and categorised according to published World Health Organisation categories (15). Patients with a BMI <14 kg/m^2 were excluded

Table I. Patient characteristics at enrolment by BMI category at age 30.

	BMI category at age 30				
	Underweight <18.5 kg/m^2	Normal weight 18.5-25 kg/m^2	Overweight 25-30 kg/m^2	Obese >30 kg/m^2	*p*-value
n.	413	8,448	2,837	1,619	
Age (yrs)	57.3 (12.4)	59.5 (12.0)	56.7 (12.0)	51.4 (11.4)	<0.001
Female, n (%)	385 (93%)	7,241 (85%)	1,856 (65%)	1,353 (84%)	<0.001
White, n (%)	386 (93%)	8,015 (94%)	2,662 (94%)	1,475 (91%)	<0.001
Enrolment BMI	22.5 (4.9)	26.3 (5.0)	31.5 (5.6)	37.8 (8.3)	<0.001
Diabetes, n (%)	24 (6%)	625 (7%)	388 (14%)	347 (21%)	<0.001
Hypertension, n (%)	126 (31%)	3,447 (41%)	1,438 (51%)	928 (57%)	<0.001
Any heart disorder, n (%)	65 (16%)	1,253 (15%)	458 (16%)	263 (16%)	0.20
Thyroid disease	49 (12%)	1,328 (16%)	389 (14%)	282 (17%)	0.002
RDCI (0-9)	2.0 (1.9)	2.0 (1.8)	2.3 (1.8)	2.7 (1.9)	<0.001
HAQ Score (0-3)	1.13 (0.74)	1.02 (0.71)	1.03 (0.73)	1.22 (0.72)	<0.001
Disease duration (yrs)	15.8 (14.6)	14.1 (12.6)	12.6 (11.6)	11.6 (10.8)	<0.001
Currently smoking, n (%)	32 (8%)	453 (5%)	153 (5%)	103 (6%)	0.08
Work disability, n (%)	75 (18%)	1,045 (12%)	428 (15%)	396 (24%)	<0.001
Global health (SF-36)	47 (23)	50 (23)	47 (23)	40 (22)	<0.001

BMI: Body Mass Index; RDCI: Rheumatic Disease Comorbidity Index; HAQ: Health Assessment Questionnaire.

(n=3). Percent weight change from age 30 to enrolment was determined and categorised as previously defined based on percent change (16).

Mortality, demographics, comorbidity and patient-reported disability

Vital status was determined from linkage to the National Death Index and alternative family member contact. We included factors that were pre-hypothesised to contribute to mortality in patients with RA. Physical functioning was assessed with the Health Assessment Questionnaire (HAQ), a validated patient-reported outcome measure (17). Comorbidity was calculated using the Rheumatic Disease Comorbidity Index (RDCI), a validated quantitative measure of comorbid illness (18). Patient global assessment of overall health was derived from the SF-36 (19). Demographics, smoking, work disability, specific comorbidities, and duration of disease were each assessed at enrolment.

Statistical analysis

Characteristics of the study population at enrolment were described across BMI categories at age 30 in order to assess relationships between BMI early in life and characteristics of the study population at enrolment in the registry. The analysis also evaluated relationships between age-30 BMI and enrolment characteristics of the population *(e.g.* diabetes, hypertension, disability, and comorbidity) using multivariable linear and logistic regression and adjusting for current age, sex, and race.

The overarching aim of this study was to compare different epidemiologic approaches to estimating the risk of obesity in this setting. In the primary analysis, sequential multivariable Cox proportional hazard models evaluated associations between BMI categories and mortality, adjusting for demographics, disease duration, and smoking status at enrolment. Theses analyses aimed to compare the estimated risks for BMI category at age 30 to the estimated risks for BMI category at enrolment.

We also aimed to assess the risks associated with enrolment BMI category after adjusting multivariable models for additional factors that were associated with age 30 BMI and for which obesity was a likely contributing etiologic factor. The goal of these analyses was to illustrate differences in the resulting estimates of risk for obesity when regression models are adjusted for factors that are both the result of obesity and can lead to early mortality (*i.e.* mediators in the causal pathway). In these analyses, we adjusted Cox models for comorbidity scores, diabetes, hypertension, physical functioning, work disability, and global health assessments.

We performed several sensitivity analyses. These included the exclusion of follow-up time occurring prior to 2005 (the year patients were initially asked to report their BMI at age 30) to reduce any impact of immortal time bias. We also assessed the effect of studying only patients who were diagnosed with RA after age 30. Analyses were performed using Stata 14.0 software (StataCorp, LP, College Station, TX).

Results

Characteristics of the study population stratified by BMI category at age 30 are shown in Table I. Among 12,268 eligible participants (80% women), the mean (SD) age and disease duration were 59.9 (10.5) and 13.9 (12.4) years, respectively. BMI was greater at enrolment than at age 30 [Mean (SD): 28.7 (7.0) v. 24.6 (5.5) $p<0.0001$]. A greater proportion of participants were obese at enrolment [n=4,357 (35.5%) v. n=1,337 (10.9%)] and a smaller proportion of participants had low BMI at enrolment [n=186 (1.5%) v. n=369 (3.0%)]. The majority of patients with low BMI at enrolment (122, 66%) did not have low BMI at age 30, indicating that they had lost weight to reach a low BMI category at enrolment.

Compared to normal BMI at age 30, an obese age-30 BMI was associated with greater disability scores [β: 0.20 (0.17, 0.24) $p<0.001$], comorbidity scores [β: 0.83 (0.73, 0.93) $p<0.001$], and worse global health scores [β: -8.1 (-9.4, -6.8) $p<0.001$] at enrolment after adjusting for sex, race, and age at enrolment (full models not shown). An obese age-30 BMI was also associated with greater odds of diabetes [OR 4.33 (3.72, 5.05)

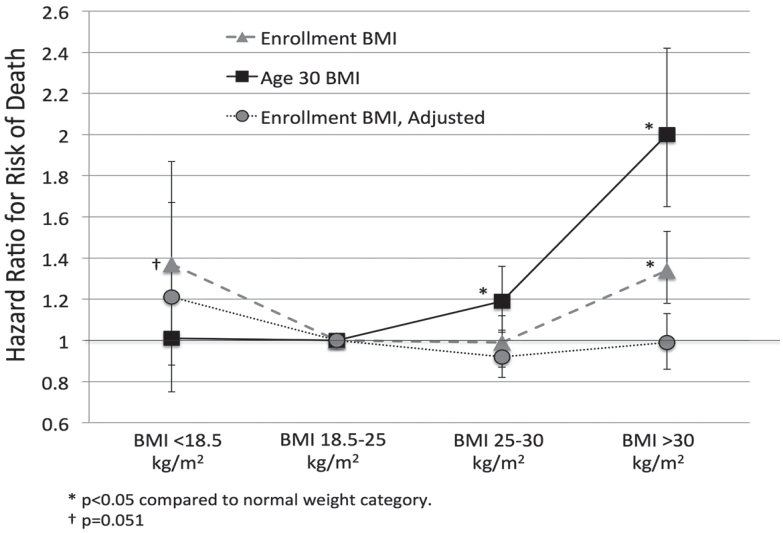

Fig. 1. Associations between BMI category (at enrolment or at age 30) and risk of death in Cox proportional hazards models.
All models are adjusted for age, sex, race, smoking, and disease duration among patients with age >40 years. The third model, labelled "adjusted" is further adjusted for disability (HAQ), comorbidity (RDCI), diabetes, hypertension, global health scores (SF-36), and work disability.
HAQ: Health Assessment Questionnaire; RDCI: Rheumatic Disease Comorbidity Index; BMI: Body Mass Index.

Table II. Associations between BMI category at age 30 (Model 1) or enrolment (Model 2 and 3) and risk of death after enrolment before and after adjustment for factors hypothesised to be mediators in the causal pathway between obesity and mortality.

	Model 1: Age 30 BMI n=12,268; PY=78,152	Model 2: Enrolment BMI n=12,268; PY=78,132	Model 3: Enrolment BMI + Mediators n=11,845; PY=76,925
	HR (95% CI)	HR (95% CI)	HR (95% CI)
BMI category			
Underweight	1.01 (0.75, 1.35)	1.37 (1.00, 1.88)	1.21 (0.88, 1.67)
Normal weight	1 (reference)	1 (reference)	1 (reference)
Overweight	1.19 (1.04, 1.36)**	0.99 (0.87, 1.12)	0.92 (0.82, 1.05)
Obese	2.00 (1.65, 2.42)***	1.34 (1.18, 1.53)***	0.99 (0.86, 1.13)
Diabetes	--	--	1.39 (1.18, 1.62)***
Hypertension	--	--	1.15 (1.03, 1.29)*
RDCI (0-9)	--	--	1.14 (1.10, 1.18)***
HAQ Score (0-3)	--	--	1.09 (0.99, 1.19)*
Work Disability	--	--	1.64 (1.39, 1.94)***
Global Health (SF-36)	--	--	0.99 (0.99, 0.99)***

All models also adjusted for age, sex, race, disease duration, current smoking.
PY: person-years; BMI: Body Mass Index; RDCI: Rheumatic Disease Comorbidity Index; HAQ: Health Assessment Questionnaire. *p<0.05, **p<0.01, ***p<0.001.

p<0.001], hypertension [OR 3.00 (2.67, 3.37) p<0.001], and work disability [OR 1.96 (1.68, 2.26) p<0.001] at enrolment. There were 1,520 deaths in 80,502 person-years of follow-up. Similar to the general population, most common causes of death included diseases of the heart (28%), malignant neoplasms (22%), and respiratory illnesses (17%). Obesity at age 30 was strongly associated with mortality [HR 2.00 (1.65, 2.42) p<0.001]. In contrast, obesity at enrolment was only modestly associated with mortality [HR 1.34 (1.18, 1.53) p<0.001] (Fig. 1, Table II). Adjustment for factors that might be potential mediators between obesity and mortality in multivariable models further reduced the observed strength of associations between obesity and mortality, such that obesity was no longer associated with higher mortality [HR 0.99 (0.89, 1.13), p=0.85] (Fig. 1, Table II). Weight loss from age 30 to enrolment was associated with greater mortality independent of enrolment BMI in a dose-dependent manner, with a loss of weight of 10% or greater associated with nearly twice the risk of death [HR 1.88 (1.51, 2.25) p<0.001] (Table III). Risks of obesity at enrolment were observed to be greater in models that included weight change since age 30 (Table III). Similarly, restricting these models to only patients with stable weight since age 30 showed substantially higher risks for obesity [n=2,110; HR: 2.29 (1.56, 3.37) p<0.001] (full models not shown).

In sensitivity analyses, similar results were observed when excluding exposed time before 2005 (not shown). In addition, sensitivity analyses found no significant differences in associations among those who were diagnosed before or after age 30. There were also no significant interactions between enrolment BMI and weight loss from age 30.

Discussion

This study illustrates dramatic differences in the estimation of the risks of obesity on mortality in patients with RA when considering BMI at enrolment *versus* an estimate of BMI from early in life. These results suggest that changes in weight that occur prior to enrolment in clinical studies can substantially confound relationships between obesity and mortality. Adjusting for comorbidities that may be important mediators can further bias results. Importantly, these data confirm that excess weight is unlikely to provide a biologically protective benefit against early mortality in RA. Patients with a history of obesity and patients with weight loss are both at greater risk of early death.

The importance of assessing weight earlier in life in order to understand the obesity paradox has been recently appreciated and studied in the general population (11, 12, 20). In prior studies in the general population, greater maximum lifetime weight was also more strongly associated with greater mortality than current weight (11). The observation of paradoxical associations with weight in RA are even more pronounced than those observed in the general population and are likely applicable to chronic diseases associated with weight loss and cachexia such as congestive heart fail-

Table III. Cox proportional hazard models evaluating the independent associations between BMI at enrolment and weight loss since age 30.

	Model 1 n=12,268; PY=78,152		Model 2 n=12,268; PY=78,131	
	HR (95% CI)		HR (95% CI)	
BMI category at enrolment				
Underweight (<18.5 kg/m^2)	1.37 (1.00, 1.88)	0.051	0.92 (0.66, 1.29)	0.64
Normal weight (20-25 kg/m^2)	1 (reference)	--	1 (reference)	--
Overweight (25-30 kg/m^2)	0.99 (0.87, 1.12)	0.70	1.10 (0.96, 1.26)	0.16
Obese (≥30 kg/m^2)	1.34 (1.18, 1.53)	<0.001	1.52 (1.30, 1.76)	<0.001
% Weight change since age 30				
Increase 10% (n=7,656)	--	--	0.85 (0.74, 0.99)	0.04
Increase 5% (n=1,408)	--	--	0.83 (0.69, 1.00)	0.05
Stable (n=2,110)	--	--	1 (reference)	--
Decrease 5% (n=496)	--	--	1.31 (1.04, 1.72)	0.02
Decrease 10% (n=598)	--	--	1.88 (1.51, 2.35)	<0.001

All models adjusted for age, sex, white race, disease duration, and current smoking at enrolment. Model 2 also included percent weight change since age 30.

ure, diabetes, and chronic lung disease, among other rheumatic diseases (1, 21, 22). This study generally demonstrates the need for close and careful consideration of epidemiologic models and causal pathways when changes in exposures over time are linked to changes in health status. In this context, it is important to also point out that similar biases in epidemiologic studies may be experienced when exposures and behaviours are observed to change in relationship to severe or deteriorating health status. For example, changes in alcohol use over the life-span are tied to health status and may confound the commonly observed relationship of a protective effect of moderate alcohol use on mortality (23, 24). For the reasons above, some authors have suggested avoiding the term "obesity paradox" as it implies a paradoxical biologic effect that likely does not exist (8, 20).

This study also demonstrates that adjustment for factors that might be hypothesised to be in the causal pathway between obesity and increased mortality exacerbate the observation of an obesity paradox (25). Age-30 BMI was associated with comorbidity, disability, and global health at later enrolment in this clinical registry. It is likely that some of this relationship is observed because obesity *mediates* the development of these outcomes. Because adjustment for comorbidity at enrolment assumes that comorbidity is a confounder of the association between BMI and mortality, as opposed to a mediator, the adjustment incorrectly reduces the estimate of the causal risks of greater BMI. It is worth also pointing out that RA may itself be a mediator of the effect of obesity on mortality, and thus a study that includes only patients who have developed RA may also generally underestimate the risk of obesity in the general population. We are aware of no studies that highlight these issues in epidemiologic studies among patients with chronic inflammatory diseases like RA.

It is not surprising that weight loss was strongly associated with early mortality in this study since unintentional weight loss is commonly observed in the context of chronic illness, greater morbidity, and a higher risk of death (26). Interestingly, we also found that weight gain since the age of 30 appeared protective in this study. This finding may seem counterintuitive. However, weight gain is expected in mid-life. Therefore, a lack of expected weight gain in this population may also be a marker of poor health. Prior studies have not demonstrated consistent relationships between weight gain and mortality in other populations, perhaps due to differences in the populations studied (27-29). For example, weight gain in early adulthood among healthy individuals is associated with adverse health outcomes (29) while gain later in life and among those with diabetes is not associated with greater mortality. Thus relationships with weight gain and mortality also appear to be altered with aging and chronic illness (27, 30). It seems likely that weight gain is not biologically protective but rather that it often occurs during times of relative good health, even as it leads to poor health in the long-term. Furthermore, our regression models condition on current weight, and therefore the protective effect of weight gain may stem from the identification of individuals with less cumulative exposure to obesity (*i.e.* lifelong obesity *versus* more recent development of obesity).

While clinicians and investigators should acknowledge the advantage of assessing weight earlier in life, these methods are imperfect. For example, weight histories do not distinguish between intentional and unintentional weight loss. Most weight loss observed in similar observational studies is unintentional (31). Presumably, healthy and purposeful weight loss would have different implications that cannot be distinguished with these data. In addition, the self-report of BMI may suffer from recall bias. Prior research leads us to expect an underestimation of BMI, particularly among the more obese individuals when the exposure is self-reported (32). The impact of this bias might be hypothesised to result in a further underestimation of the risks of obesity for all approaches. Selection bias due to depletion of susceptible patients is also a consideration. If obese patients at age 30 are more likely to die prior to enrolment, the registry will include only healthier survivors, potentially leading to further underestimation of risk for obesity. While the purpose of this study was not to provide the true unbiased risk of obesity in this population, we anticipate that, given these limitations, the actual risk of obesity may remain underestimated, even using the methods described here. We did not explore other long-term outcomes including cause-specific mortality. Causes of death in this population mirrored other published studies that evaluated associations between weight loss and mortality in RA and demonstrated similar associations for all causes of death (33, 34).

Strengths of this study include the large sample with patient-report of weight early in life as well as validated outcomes and co-variable assessments. The study design allowed for a comprehensive as-

sessment of the individual contribution of weight and weight loss to mortality in a population at risk of weight loss and cachexia. Moving forward, epidemiologic studies attempting to characterise causal relationships between BMI and outcomes in RA and other chronic inflammatory conditions should consider the clear potential for bias when reporting seemingly paradoxical relationships. Methods that consider complex interactions between illness, weight, and long-term outcomes are important to accurately estimate the causal risks of obesity. The accurate quantification of the causal effects of obesity on both short-term and long-term outcomes is important and challenging in practice given that obesity is highly prevalent and consistently associated with disease activity, biomarkers, and outcomes in RA (35-38).

In conclusion, this study suggests that both obesity and unintentional weight loss are important contributors to the risk of death in patients with RA. Because weight varies over time in relationship to health status, a fully understanding of the risks of excess weight requires considering not only the current weight, but also changes in weight that have occurred over the life-span.

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