Exercise Partially Explains the Impact of Body Mass Index on Disease Activity in Ankylosing Spondylitis

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Abstract

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Background. Ankylosing spondylitis (AS) patients have elevated cardiovascular (CV) morbidity and mortality compared to general population comparators of the same age and sex. Although obesity is an important and modifiable CV risk factor, there are few prospective studies addressing the impact of higher body mass index (BMI) on clinical outcomes in AS. The aim of this study is to assess the relationship of BMI with disease activity in AS patients, and the extent to which the effect is mediated through exercise.

Methods. Data were available for 283 adults with AS meeting the 1984 modified New York criteria from a prospective cohort, who were followed at a single site at visits every 6 months with a median follow-up of 7 years. BMI (kg/m^2) and disease activity as measured by the Ankylosing Spondylitis Disease Activity Score (ASDAS) represented the exposure and outcome, respectively. In the main analysis, we included 183 subjects who had at least one available BMI and one available ASDAS measure during any study visit; missing values were imputed using multiple imputation with chained equations. To determine the association of BMI and disease activity, we used generalized estimating equations to account for repeated measures per subject. We adjusted for age, sex, race, current smoking, nonsteroidal anti-inflammatory drug (NSAID) use, tumor necrosis factor inhibitor (TNFi) use, and follow-up time, and for interactions between BMI and sex and BMI and time. We then performed a causal mediation analysis to estimate the direct effect of BMI on disease activity, and the indirect effect through exercise.

Results. Among 183 subjects, 77% were male, 70% were white, and the mean±standard deviation age was 40.8±13.3 years. In adjusted analyses, higher BMI was significantly associated with higher disease activity over time; on average, for a 1 kg/m^2 higher BMI, the ASDAS was 0.06 units higher (95% CI 0.02-0.09). This association did not differ by sex (p=0.89) but did differ over time (p=0.03). The direct effect of an overweight/obese BMI accounted for most of the total effect on disease activity, with a much smaller indirect effect mediated by exercise (9%).

Conclusion. Higher BMI was associated with higher disease activity in a prospective AS cohort. We found that being overweight/obese largely influences disease activity directly, rather than indirectly through exercise. This suggests that other mechanisms such as increased inflammation may better explain the obesity-disease activity association. Interventions targeting obesity may improve both disease activity and CV risk in this population.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory arthritis that affects the spine and sacroiliac joints and can be separated into ankylosing spondylitis (AS), which is also known as radiographic axSpA (r-axSpA), and nonradiographic axSpA (nr-axSpA). Epidemiologic studies of axSpA have shown that elevated acute phase reactants, smoking, and baseline radiographic damage are risk factors for more severe disease and structural spinal progression [1,2]. In addition, multiple population-based studies have demonstrated increased cardiovascular (CV) events and CV-related mortality in axSpA [3–7].

Traditional CV risk factors in the general population include diabetes mellitus, hypertension, dyslipidemia, tobacco smoking, and obesity [8]. Although obesity is an important and modifiable CV risk factor, there have been limited studies addressing the impact of higher body mass index (BMI), or of being overweight or obese, on clinical outcomes in axSpA. In a US-based registry of patients with AS and psoriatic arthritis (PsA), obesity was a significant predictor of tumor necrosis factor inhibitor (TNFi) switching or discontinuation [9]. Two systematic reviews and meta-analyses assessing the effect of BMI on TNFi response in multiple inflammatory diseases found that higher BMI was associated with increased odds of an inadequate response to TNFi treatment in individuals with axSpA [10,11]. Other studies have looked into the association of BMI and disease activity in axSpA, but these have all been cross-sectional, which limits the interpretation of their findings [12–19].

The longitudinal association of BMI and disease activity in axSpA has not been investigated outside of cohort studies of TNFi treatment response. The causal pathway that links BMI and disease activity also requires further elucidation. The aim of this study is to assess whether higher BMI is associated with higher disease activity in AS patients, and to what extent this association is mediated through exercise. Results from this study will support a more causal interpretation for whether BMI, a modifiable risk factor, can potentially improve disease activity in this patient population.

METHODS

Study population

The Prospective Study of Outcomes in Ankylosing Spondylitis (PSOAS) cohort has been described in detail elsewhere [20,21]. Briefly, subjects were enrolled if they were at least 18 years old and met the 1984 modified New York criteria for AS [22]. Individuals were recruited from the investigators' clinics, patient support groups, and community rheumatologists. The five participating study sites for the full PSOAS cohort were the following: Cedars-Sinai Medical Center (Los Angeles, CA), University of Texas Health Science Center (Houston, TX), National Institutes of Health (Bethesda, MD), University of California San Francisco [UCSF] (San Francisco, CA), and Princess Alexandra Hospital, Queensland University of Technology (Brisbane, Australia). Enrollment for the PSOAS cohort began in 2002 and continued through 2018. For this study, the subset of patients enrolled and followed at UCSF were utilized because complete longitudinal BMI data were available for this subset only.

Clinical evaluation was performed by a study site investigator using standardized protocols at study entry and at subsequent study visits every six months. At baseline, patient demographics and characteristics of AS disease status, including HLA-B27 status, date of symptom onset, patient-reported outcomes, extra-articular manifestations, comorbidities and medication history were recorded. At study visits every six months, BMI, patient-reported outcomes, and medications were collected. Comorbid conditions, including CV disease and risk factors, were ascertained every two years.

Follow-up evaluations performed every six months utilized questionnaires assessing disease activity, functional impairment, and depression [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [23], Bath Ankylosing Spondylitis Functional Index (BASFI) [24], and the Center for Epidemiologic Studies – Depression (CES-D) scale [25], respectively]. All medications used in the preceding six months were recorded, per patient report and investigator confirmation. The number of missed doses in the past week, month, and six months was also documented, along with whether the patient was still taking the medication. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels were determined at each study visit. Starting in 2013, vital signs, including blood pressure and BMI measures, were also recorded at each study visit.

Variables

Exposure of interest. The exposure of interest was BMI (kg/m^2), which is a continuous variable in the dataset. For the mediation analysis, BMI was dichotomized as overweight/obese versus normal/underweight, using the WHO classification for overweight as ≥23 kg/m^2 for Asians and ≥25 kg/m^2 for all other racial categories.

Outcome of interest. The outcome of interest was disease activity as measured by the validated Ankylosing Spondylitis Disease Activity Score (ASDAS), which was a continuous variable (possible range 0.6 – 6.6). The ASDAS includes some questions from the BASDAI, as well as patient and physician global assessments, and laboratory measures (either the CRP or ESR) [26].

Intermediate variable of interest. Exercise was a continuous variable, measured in minutes per week and based on patient self-report. This was derived from two questions asked of patients at each study visit ("In a typical week, how many times do you exercise?" and "how long does each exercise session typically last?").

Other covariates. Age at each study visit was derived from self-reported age at the baseline visit. Race and smoking status (current smoker, yes/no) were self-reported. Nonsteroidal anti-inflammatory drug (NSAID) usage was quantified by the NSAID index according to Assessment of SpondyloArthritis international Society (ASAS) recommendations [27]. An individual taking the full recommended dosage of an NSAID in the six months preceding the study visit would receive an NSAID index of 100, while an individual reporting no use would receive an index of 0. TNFi use was a binary variable for use versus non-use as reported for the six months prior to each study visit.

Longitudinal analysis

To determine the association of BMI with disease activity, we used generalized estimating equations (GEE) with an exchangeable correlation structure and robust standard error estimates to account for repeated measures per subject. Sex and follow-up time were determined *a priori* as potential effect modifiers. If the interaction of these variables with the exposure of interest was not significant at the alpha level of 0.10 then they were included in the final multivariable model as confounders. Other potential confounders were determined *a priori*: age, race, current smoking, NSAID use, and TNFi use.

Since BMI measures were not included in the PSOAS dataset prior to 2013, but were available in the electronic medical record within 36 months of corresponding study visits, these data were extracted for the individuals within PSOAS who were followed at UCSF (n=283). In our main analyses, individuals from this UCSF subset who did not have any measures of the exposure (BMI) or outcome (ASDAS) of interest in any of their study visits were excluded, leaving 183 subjects. Most exclusions were due to missing BMI information. For the remainder of the pre-specified variables, multiple imputation with chained equations (MICE) was performed with five iterations [28–30].

In addition, the following sensitivity analyses were performed (1) a complete case analysis (n=176); (2) MICE on the complete UCSF dataset (n=283), including those without any BMI or ASDAS measures; and (3) single imputation with the last observation carried forward (LOCF) on the main analysis dataset (n=183).

Mediation analysis

We performed a mediation analysis to estimate the direct effect of overweight/obese status on disease activity, and the indirect effect through exercise (causal diagram shown in **Figure 1**). The goal of mediation analysis is to understand if and to what extent the effect of the exposure on the outcome is mediated through the intermediate variable. Traditional mediation methods such as the Baron and Kenny “causal steps” approach, while less complex, are limited due the assumption of no interaction between the exposure and the mediator [31]. Causal mediation analysis is based on counterfactuals and the potential outcomes framework [32]. It is based on assumptions of no unmeasured confounding between the exposure and mediator, and the mediator and outcome, and allows for exposure-mediator interaction. In addition, the sequential ignorability assumption states that the exposure is statistically independent of potential outcomes and potential mediators; and given the actual exposure level and baseline confounders, the observed mediator is ignorable [33].

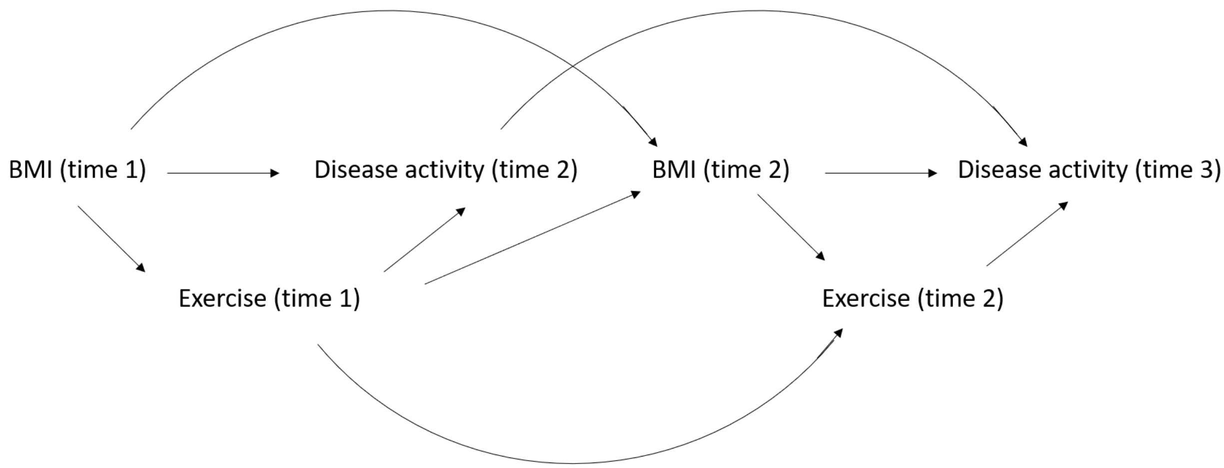

Figure 1: Directed acyclic graph demonstrating relationships between the exposure, outcome, and mediator of interest

The *total effect* can be decomposed into natural direct and indirect effects. The *natural direct effect* is the effect of the exposure on the outcome independent of the mediator. It contrasts the potential outcomes for disease activity between those with overweight/obese BMI versus those with normal BMI, while the level of the mediator (exercise) is held constant. The *natural indirect effect* is the effect of the exposure on the outcome through the mediator. It contrasts potential outcomes for disease activity for the mediator (exercise) at the value it would have in the setting of an overweight/obese BMI, versus the mediator at the value it would have in the setting of a normal BMI. We also determined the proportion of the effect of an overweight/obese BMI that is mediated through exercise (*proportion mediated*).

We used a two-stage approach in which the outcome was regressed on the exposure, mediator, exposure-mediator interaction term, and confounders; and the mediator was regressed on the exposure and the confounders [32,34]. In this approach, the natural direct and indirect effects are estimated using

Monte Carlo simulations. The mediation analysis was performed on the imputed data using MICE on 183 subjects (as per the main analysis). A sensitivity analysis was conducted to determine the robustness of the mediation analysis against violations of the sequential ignorability assumption. That is, if the sequential ignorability assumption is true, then the correlation between the two error terms of the regression models would equal zero ($\rho=0$). A larger value of ρ would indicate that a very strong correlation between error terms would be needed for the indirect effect to be fully explained by unmeasured confounders. Mediation analysis was performed using the Stata mediation package using the medeff and medsens commands [34]. All analyses were performed in Stata version 15 (StataCorp, College Station, Texas).

RESULTS

Baseline characteristics of subjects included in the main analysis (n=183) and stratified by BMI are shown in **Table 1.** Among the 183 subjects overall , 77% were male, 70% were white, and the mean±standard deviation (SD) age was 40.8±13.3 years. The mean first-available BMI was 25.7±4.8 kg/m^2. Those with higher BMI were older, had longer symptom duration and a higher proportion of abnormally elevated CRP, and fewer minutes of exercise per week, compared to those with lower BMI. Characteristics of patients with missing exposure and/or outcome values (n=103) are shown in **Supplemental Table 1**. These patients had fewer study visits and were older with a longer AS symptom duration, compared to those who were included in the main analysis.

Longitudinal analysis

In the main analysis, higher BMI was significantly associated with a higher ASDAS over time (β 0.06 per 1 kg/m^2, 95% CI 0.02-0.09). There was a statistically significant interaction between BMI and follow-up time in the study (p=0.03), indicating that there was a greater rate of change of mean ASDAS per year of study follow-up for those with lower BMI. There was no statistically significant interaction between BMI and sex (p=0.89).

Table1: Baseline characteristics of the main AS study population, stratified by overweight/obese BMI

Variables	Whole study population N=183	Normal/ underweight BMI N=84	Overweight/ obese BMI N=99
Demographics			
Age, years	40.8 ± 13.3	35.2 ±10.2	45.5 ± 13.8
Male gender	77%	77%	84%
Race			
White	70%	64%	74%
Black	1%	1%	0%
Asian	16%	21%	11%
Other	13%	14%	15%
Number of study visits	7.8 ± 4.5	7.6 ± 4.1	8.0 ± 4.8
Disease characteristics			
Symptom duration, years	17.9 ± 12.5	14.8 ± 9.7	20.4 ± 13.8
Abnormal CRP[a]	36%	27%	44%
BASDAI (0-10)	3.6 ± 2.4	3.1 ± 2.3	3.9 ± 2.4
ASDAS (0-10)	1.6 ± 1.0	1.4 ± 0.9	1.7 ± 1.0
NSAID use	72%	73%	71%
Glucocorticoid use	6%	5%	7%
TNFi use	46%	49%	44%
Cardiovascular disease and risk factors			
BMI, units	25.7 ± 4.8	20.1± 2.2	28.9 ± 4.0
Cardiovascular disease[a]	2%	3%	1%
Diabetes	2%	1%	3%
Current smoker	4%	4%	5%
Exercise, minutes/week	173.3 ± 179.8	200.8 ± 209.9	149.7 ± 146.3

[§] First available
Abbreviations: BMI, body mass index; CRP, C-reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; NSAID, nonsteroidal anti-inflammatory drug; TNFi, tumor necrosis factor inhibitor.
Data were missing for: abnormal CRP (n=1), BASDAI (n=2), ASDAS (n=3), diabetes (n=3), CVD (n=3), exercise (n=1).
[a]CRP was abnormal if above the upper limit of the reference range associated with the value.
[b]Cardiovascular disease was the composite of patient-reported coronary artery disease, coronary bypass surgery, coronary angioplasty, heart attack, heart valve problems, and angina.

The results of the sensitivity analyses are presented in **Table 2**. In the complete case analysis, main effects estimates were similar to the main analysis. With use of the full study population (n=283) with imputed missing values using MICE, the association of BMI with disease activity was in the same direction as the main analysis but did not reach statistical significance. Imputation using LOCF also produced similar results for the main effects, compared to the main and complete case analyses.

Table 2: Association of BMI with disease activity as measured by ASDAS in multivariable longitudinal analyses

Analysis	β	95% CI
Main analysis with imputation of covariates using MICE (n=183)	0.06	0.02-0.09
Complete case analysis (n=176)	0.05	0.004-0.09
Entire cohort with imputation of exposure, outcome, and covariates using MICE (n=283)	0.03	-0.01-0.07
Imputation using LOCF (n=183)	0.05	0.01-0.08

Abbreviations: MICE, multiple imputation with chained equations; LOCF, last observation carried forward; CI, confidence interval.

β represents the difference in mean ASDAS per one kg/m^2 difference in BMI, after adjustment for other variables in the model. Analyses controlled for age, sex, race, current smoking, NSAID use, and TNFi use. Sex was not a statistically significant effect modifier in any of the analysis; follow-up time was a significant effect modifier in the main analysis only.

Mediation analysis

In the causal mediation analysis, which examined exercise as a mediator between BMI and disease activity, there was no statistically significant interaction between the exposure and the mediator (p=0.22). Direct and indirect effects for an overweight/obese BMI compared to a normal BMI were 0.66 (95% CI 0.43, 0.87) and 0.06 (95% CI 0.01, 0.13) unit differences in ASDAS, respectively. The total effect of overweight/obese BMI, on average, was of a 0.72 point increase in the ASDAS. Exercise mediated 9% of the effect of an overweight or obese BMI on disease activity. In the mediation sensitivity analysis, a negative correlation of 0.16 between the error terms of the two regression models would be required for the indirect effect to be fully explained by unmeasured confounders.

DISCUSSION

To our knowledge, this was the first study to assess the association of BMI and disease activity among individuals with axSpA. We found that on average, higher BMI was significantly associated with higher disease activity in this prospective AS cohort. We found that being overweight/obese largely influences disease activity directly, rather than indirectly through exercise. This suggests that mechanisms other than exercise, such as increased inflammation, may better explain this association. Interventions targeting obesity may improve both disease activity and CV risk in this population.

These results are in concordance with a systematic review and meta-analysis assessing the association between BMI and disease activity as reported by BASDAI and ASDAS in axSpA [35].We systematically searched for studies evaluating BMI and disease activity as the exposure and outcome of interest, respectively, in axSpA. Twelve studies were included in the meta-analysis. Among all studies reporting the BASDAI at baseline, the pooled standardized mean difference (SMD) of the BASDAI for those with an obese or overweight/obese BMI compared to a normal BMI was 0.38 (95% CI 0.21-0.55; I^2 75.2%), indicating a significant association of higher BMI with higher BASDAI score. The pooled SMD of the ASDAS for those with an obese or overweight/obese BMI compared to a normal BMI was 0.40 (95% CI 0.27-0.54; I^2 0%).

Our findings are also similar to prior systematic reviews and meta-analyses in axSpA evaluating the impact of obesity or higher BMI on various clinical outcome measures. Lee et al performed a systematic review of obesity and disease activity outcomes across multiple rheumatic diseases[36]. In axSpA, they found one study reporting a neutral association and six with a positive association. Singh et al performed a meta-analysis of the impact of BMI on TNFi response in observational cohort studies and RCTs and found that in axSpA, higher BMI was associated with increased odds of an inadequate response to TNFi treatment (six studies; pooled OR 3.36, 95% CI (1.33-8.51), $I^2 = 81\%$) [10]. The impact of obesity on imaging measures has also been explored. Bakirci et al performed a systematic review on the association of BMI and imaging-defined inflammation and damage in SpA including PsA [37]. In four studies, higher BMI was associated with new syndesmophyte formation. In one study, higher BMI was also associated with a higher structural damage score by the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS).

The association of high BMI with disease activity has been studied in PsA, with similar findings as in axSpA. In prospective cohorts of PsA patients on TNFi therapy, Di Minno et al have shown that obesity was associated with a lower probability of achieving or maintaining minimal disease activity, and that a weight loss of ≥5% in overweight or obese individuals predicts treatment response [38,39]. Obesity was also associated with worse response to TNFi in large Scandinavian PsA registries [40].

The biologic mechanisms that are believed to underlie obesity as a chronic inflammatory state involve the production of pro-inflammatory cytokines by adipose tissue[41]. Higher BMI and higher fat mass have been associated with chronic pain in multiple populations[42–44]. Obesity may be related to disease activity independent of inflammation, such as through mechanical loading and stress[45].

Strengths

As prior studies were cross-sectional in nature, our study had the strength of using a long-standing prospective cohort of AS patients with multiple study visits (median total follow-up of around seven years). We also applied a causal mediation analysis to assess the extent to which the BMI impacts disease activity through exercise. This approach allows us to start disentangling the causal pathway between increased adiposity and high disease activity in AS. This has benefits over a more conventional mediation analysis, since the latter requires the underlying assumption that the mediator does not interact with the exposure of interest. In our scientific question of interest, this assumption is likely violated [32]. Causal mediation analysis also allows for the decomposition of the total effect into direct and indirect effects, and the quantification of these effect estimates.

Limitations

We used GEE to evaluate the association of BMI with disease activity over time. However, GEE does not account for time-varying covariates, such as exercise, that may as both confounders and mediators in different time intervals within the hypothesized causal pathway of interest.

In this study, there were missing data from study visits. Under the assumption of missing at random we performed MICE for the main analysis. Results were concordant in the sensitivity analyses using LOCF and a complete case approach. However, we are unable to exclude bias induced from the multiple imputation procedure, particularly if the imputation model was misspecified. In studies with repeated data, MICE has a major limitation in that imputation models may fail to converge due to issues of overfitting or collinearity when multiple variables with repeated measures are involved. On the other hand, bias may be induced if measurements excluded from the imputation models have independent effects [30].

Although we performed a causal mediation analysis, our models still rest upon a strong sequential ignorability assumption [33]. This assumption would be violated in the presence of unmeasured confounders, measurement error of the mediator (leading to overestimation of the direct effect and underestimation of the indirect effect, if there is nondifferential misclassification), confounders of the mediator-outcome association (leading to collider stratification bias), and the presence of post-exposure confounding. In the presence of mediator-outcome confounding by a variable that is also caused by the exposure, marginal structural models (MSM) with inverse probability weighting (IPW) can be used to estimate the controlled direct effect of an exposure on an outcome of interest [32]. However, use of MSM with IPW would require the same strong assumptions as the causal mediation analysis performed in this study in order to obtain unbiased estimates of the natural direct and indirect effects.

CONCLUSION

In this longitudinal observational study, higher BMI was associated with higher disease activity among individuals with AS. We found that being overweight/obese had a primarily direct effect on disease activity, that does not operate through exercise, which suggests other mechanisms such as increased inflammation may explain this association. Future work should focus on the components of BMI and disease activity that are important in this relationship, particularly those factors that are modifiable and can be targeted by specific interventions.

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