

ORIGINAL RESEARCH

Influence of body mass index on cardiovascular risk in rheumatoid arthritis varies across anti-citrullinated protein antibody status and biologic use

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ABSTRACT

Objectives The impact of body mass index (BMI) on cardiovascular risk in rheumatoid arthritis (RA) is unclear. RA characteristics may influence the association between BMI and risk. Disease activity, which predicts cardiovascular risk, is associated with obesity only among anticitrullinated antibody (ACPA)-positive patients. Biologics alter body composition and mitigate cardiovascular risk in RA. We explored the association of BMI with cardiovascular risk and whether this varied across ACPA status and biologic use.

Methods We evaluated 3982 patients from an international observational cohort. Outcomes included (a) first major adverse cardiovascular event (MACE) encompassing myocardial infarction, stroke or cardiovascular death; and (b) all events comprising MACE, angina, revascularisation, transient ischaemic attack, peripheral arterial disease and heart failure. Multivariable Cox models stratified by centre risk evaluated the impact of BMI, ACPA, biologics and their two- and three-way interactions on outcomes.

Results We recorded 192 MACE and 319 total events. No main effects of BMI, ACPA or biologics were observed. A three-way interaction between them on MACE (p-interaction<0.001) and all events (p-interaction=0.028) was noted. Among ACPA negative patients, BMI was inversely associated with MACE (HR 0.38 (95% CI 0.25 to 0.57)) and all events (HR 0.67 (0.49 to 0.92)) in biologic users but not non-users (p-for-interaction <0.001 and 0.012). Among ACPA-positive patients, BMI was associated with MACE (HR 1.04 [1.01–1.07]) and all events (HR 1.03 (1.00 to 1.06)) independently of biologic use.

Conclusions BMI is inversely associated with cardiovascular risk only among ACPA-negative biologic users. In contrast, BMI is associated with cardiovascular risk in ACPA-positive patients independently of biologic use.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Disease activity is linked to cardiovascular risk in rheumatoid arthritis (RA).
- ⇒ Obesity—measured as body mass index (BMI)—is associated with higher disease activity among ACPA-positive but not among ACPA-negative patients and may adversely impact response to certain biologic disease-modifying antirheumatic drugs (bDMARDs).
- ⇒ bDMARDs mitigate cardiovascular risk and may alter body composition in RA.
- ⇒ The association of BMI as an index of obesity with cardiovascular risk in RA is unclear.

WHAT THIS STUDY ADDS

- ⇒ BMI is associated with cardiovascular risk in ACPA-positive but not ACPA-negative RA patients.
- ⇒ The influence of bDMARDs on the association of BMI with cardiovascular risk differed in ACPA-positive compared with ACPA-negative patients. Among ACPA-negative patients, BMI was inversely associated with MACE and all-event risk in bDMARD users but not in non-users. Among ACPA-positive patients, BMI was directly associated with cardiovascular risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Our findings highlight the differential effect of BMI on cardiovascular risk in ACPA-positive vs ACPA-negative patients and that this association can be further affected by bDMARD use. This may further inform cardiovascular risk stratification and management.

INTRODUCTION

Body mass index (BMI) is a widely used measure of overweight and obesity on both individual and population levels.¹ However, its influence on cardiovascular risk in rheumatoid arthritis (RA) remains unclear. While some studies report an increased risk,^{2,3} others find no association,⁴ and some reporting on cardiovascular and all-cause mortality even describe a protective effect.^{5–8} These discrepancies may be partly attributable to the inherent limitations of BMI as a construct.⁹ Unlike direct measures of fat content, BMI is not normally distributed and has a non-linear relationship with body fat, especially at higher values and particularly in women¹⁰ and patients with RA.^{11,12} Moreover, BMI does not discriminate between fat and lean muscle mass, nor does it provide information on fat distribution, which is more closely linked to cardiovascular risk.¹ Importantly, individuals with similar BMI can exhibit vastly different body compositions.¹³ Sarcopenic obesity—describing decreased lean muscle mass combined with increased fat mass—is over five times more prevalent in women with RA than non-RA females, especially within the normal BMI range.¹⁴

Obesity at RA onset predicted a 41% lower likelihood of achieving remission and a 51% reduced likelihood of sustained remission.⁴ Obesity is further associated with higher disease activity, swollen joint counts and elevated C-reactive protein (CRP) in anticitrullinated protein antibody (ACPA)-positive but not ACPA-negative patients.¹⁵ Given the strong links between disease activity, RA-related inflammation and cardiovascular risk,¹⁶ obesity may influence cardiovascular risk differently according to ACPA status.

Obesity may further adversely affect response to certain biologic disease-modifying antirheumatic drugs (bDMARDs), potentially contributing to disparities in disease activity between obese and non-obese patients.^{17,18} At the same time, bDMARDs can reduce inflammation, lower cardiovascular risk¹⁹ and improve body composition in RA.²⁰ Therefore, the effect of BMI on cardiovascular risk may vary between bDMARD users and non-users. Additionally, ACPA status may influence the effectiveness of certain bDMARD classes, with lower efficacy reported for rituximab,²¹ abatacept²² and tocilizumab²³ in seronegative compared with seropositive RA.

Given these complexities, we hypothesised that the relationship between BMI and cardiovascular risk in RA may depend on both ACPA status and bDMARD use. To test this, we investigated the association of BMI with cardiovascular risk in a large, multi-ethnic consortium of RA patients with long-term follow-up. Specifically, we examined whether ACPA status and bDMARD therapy influenced the relationship between BMI and cardiovascular risk.

METHODS

Patient recruitment

We evaluated 4537 RA patients originating from 13 centres in 10 countries (Netherlands, Norway, Sweden,

United Kingdom, Spain, Greece, USA, Canada, Mexico and South Africa) and participating in an international Cardiovascular Consortium for Rheumatoid Arthritis (ATACC-RA) between 1985 and 2012. Details on this cohort have been previously reported.^{24,25} On enrollment, patients were 18–85 years old, fulfilled 1987 classification criteria for RA, carried no concurrent diagnosis of additional autoimmune syndromes (except for Sjögren's) and had no suspicion or established diagnosis of cardiovascular disease. This included stable angina, acute coronary syndrome, transient ischaemic attack, stroke, peripheral arterial disease, revascularisation or heart failure. Participants were followed either prospectively through regular study visits or retrospectively through chart review. The study was approved by the local institutional review boards of all individual participating centres and in compliance with the declaration of Helsinki. Of 4537 enrolled participants, 529 had missing data on ACPA status and 26 on bDMARD use and therefore were excluded from the analysis. The final sample was comprised of 3982 patients.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Covariates and outcomes

Cardiac risk factors recorded at baseline included hypertension, systolic and diastolic blood pressure, diabetes, smoking status, family history of coronary artery disease, total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides and BMI (kg/m^2). The use of lipid-lowering and antihypertensive medication at the time of enrolment was recorded. Rheumatoid factor (RF) and ACPA status were obtained from the patients' medical record. Swollen and tender joint counts, CRP and erythrocyte sedimentation rate (ESR) levels, and 28-joint disease activity scores with ESR (DAS28-ESR) at the enrolment visit were collected. Information on the use of non-steroidal anti-inflammatory drugs, corticosteroids, conventional synthetic DMARDs (csDMARDs) and bDMARDs at the time of enrolment was also collected, and management strategies were at the discretion of the treating physician. Data on all predictors and covariates were only available at baseline.

Our study had two prespecified composite clinical outcomes: (a) first major adverse cardiovascular event (MACE) defined as non-fatal myocardial infarction, non-fatal stroke or cardiovascular death; and (b) any first cardiovascular event which beyond MACE included stable or unstable angina, coronary revascularisation, transient ischaemic attack, peripheral arterial disease with or without revascularisation and new onset heart failure. Data were collected using standardised definitions. Events were locally adjudicated at the centre of origin and by the respective specialist. Patients sustaining

both MACE and non-MACE events were included in the MACE analysis if the MACE event occurred first and censored thereafter. If a non-MACE event occurred first, then the same patients were considered in the any-event analysis and censored after the index event.

Biologic DMARD exposure

Patients receiving bDMARDs at baseline were considered prevalent users. No information was available regarding bDMARD use or duration prior to or after baseline. Patients were considered bDMARD users if they received bDMARD monotherapy or in combination with csDMARDs. Patients not receiving bDMARDs at baseline were considered non-users, regardless of potential past exposure. Similar definitions for exposure were considered for all medications used on enrolment.

Statistical analysis

Participant characteristics were summarised stratified by ACPA status and bDMARD use as numbers with percentages for categorical variables and means with SD for continuous variables. Non-normally distributed variables were natural logarithm transformed.

Missing data were imputed using multiple imputation by chained equations with 10 iterations. For the main analyses, multivariable Cox regression models evaluated the effect of BMI, ACPA status, bDMARD use, as well as the two- and three-way interactions of BMI with ACPA positivity and/or bDMARD use on the risk of the two prespecified outcomes. Interaction term significance was assessed with likelihood ratio tests. Cox models were stratified by centre cardiovascular event rate (high and low risk groups), as previously described.^{24 25} Model covariates included age, gender, hypertension, diabetes, family history of cardiovascular disease, smoking, cholesterol/HDL-c ratio, disease duration, DAS28-ESR and corticosteroid use. Adjusted HRs with 95% CIs were reported for the prespecified outcomes.

Sensitivity analyses were carried out to assess the robustness of the main findings. First, the main and interaction effects of bDMARD use were evaluated in multivariable Cox regression models with inverse probability of treatment weighting. Stabilised weights were calculated using propensity score values. The individual propensities were estimated using logistic regression with covariates of age, gender, hypertension, diabetes, total cholesterol/HDL ratio, extra-articular RA manifestations and csDMARD use. After weighting, all covariates had a standardised mean difference value of <0.10, indicating balance between bDMARD non-users and users. Second, since bDMARD use became more prevalent in the cohort after 2000, the models involving bDMARD use were evaluated with unweighted adjusted Cox regression limited to patients enrolled on or after 1/1/2000. Third, inverted BMI (iBMI, cm²/kg) was used as a predictor in the unweighted, imputed Cox models, exploring its main effect and two- or three-way interactions with ACPA and/or bDMARDs on the two prespecified outcomes.

iBMI has a linear relationship with lean body mass and is clinically interpretable as a measure of leanness.⁹ Lastly, competing risk regression was performed for risk of MACE and all cardiovascular events to account for the competing event of non-cardiovascular disease-related death, with adjusted sub-hazard ratios (SHRs) and 95% CIs estimated using Fine–Gray models. Stata 15.0 was used for all analyses, and two-tailed P values <0.05 were considered statistically significant.

RESULTS

Patients were mostly female (n=2936, 73.7%), seropositive for RF (n=2621, 66.7%) or ACPA (n=2377, 59.7%) and with moderate to severe disease activity (DAS28-ESR=4.1±10.5). At baseline, 504 (12.7%) patients received bDMARDs, 80/504 (15.9%) as monotherapy and 424/504 (84.1%) in combination with csDMARDs. Among 2377 ACPA-positive patients, 315/2377 (13.3%) were bDMARD users, while 189/1605 (11.8%) used bDMARDs among ACPA-negative patients. Patient characteristics stratified by ACPA status and bDMARD use are shown in [table 1](#).

The mean follow-up was 5.8±4.4 years. Overall, 319 patients suffered cardiovascular events; 40 incurred both MACE and non-MACE events; the first event was MACE in six, non-MACE in 23 and concurrent in 11. There were 192 first MACE events (17 cardiovascular deaths, 106 myocardial infarctions and 69 strokes) over 23 065 patient years with a crude incidence rate of 8.32 (95% CI 7.23 to 9.59) per 1000 patient-years. There were 319 first total events (six cardiovascular deaths, 100 myocardial infarctions, 65 strokes, 50 angina pectoris diagnoses, 24 transient ischaemic attacks, 28 peripheral arterial disease diagnoses, 20 revascularisations and 26 heart failure diagnoses) over 22 771 patient-years of follow-up with a crude incidence rate of 14.01 (95% CI 12.55 to 15.63) per 1000 patient-years. Incidence rates for MACE and all events among ACPA-positive patients were 9.17 (95% CI 7.75 to 10.85) and 14.12 (95% CI 12.32 to 16.18) and among ACPA-negative patients 6.8 (95% CI 5.23 to 8.83) and 13.81 (95% CI 11.48 to 16.62), respectively (p=0.056 and p=0.856). Among ACPA-positive bDMARD users, crude incidence rates per 1000 patient-years were 6.86 (95% CI 3.57 to 13.18) for MACE and 12.40 (95% CI 7.6 to 20.24) for all events. The corresponding rates in ACPA-positive bDMARD non-users were 9.40 (95% CI 7.90 to 11.18) and 14.28 (95% CI 12.40 to 16.46), p=0.367 and p=0.605, respectively. Among ACPA-negative bDMARD users, incidence rates were 3.63 (95% CI 0.91 to 14.50) for MACE and 9.31 (95% CI 3.87 to 22.36) for all events. The corresponding rates in ACPA-negative bDMARD non-users were 7.03 (95% CI 5.38 to 9.17) and 14.13 (95% CI 11.69 to 17.08), p=0.371 and p=0.370, respectively.

In multivariable Cox models stratified by centre risk, the main effects of BMI, bDMARD use and ACPA positivity were not significant for either MACE or any cardiovascular events ([figure 1](#)). An interaction

Table 1 Sample characteristics at baseline (n=3982)

	Available N	ACPA(-) no bDMARD (n=1416)	ACPA(+) no bDMARD (n=2062)	ACPA(-) bDMARD user (n=189)	ACPA(+) bDMARD user (n=315)
Age, years	3982	57.0±14.3	53.6±13.9	53.5±13.9	55.6±11.1
Male gender	3982	368 (26.0)	595 (28.9)	36 (19.1)	47 (14.9)
RA duration, years	3962	3.7±6.4	4.1±7.5	10.0±8.8	11.2±8.0
Age at RA diagnosis	3961	53.3±14.5	49.6±13.8	44.2±14.9	44.5±11.9
RF positive	3927	496 (35.8)	1809 (88.0)	58 (33.5)	258 (82.7)
ESR, mm/hour	3923	20.9±18.7	27.9±22.8	18.3±15.7	21.3±18.3
Log CRP, mg/L	3107	2.0±1.2	2.4±1.2	1.5±1.0	1.7±1.0
Swollen joint count	2970	5.7±5.8	6.8±5.9	2.9±3.7	2.7±3.6
Tender joint count	2970	5.6±6.1	6.0±6.0	4.0±4.8	3.3±5.0
DAS28-ESR	2954	4.0±1.5	4.4±1.5	3.5±1.4	3.4±1.3
Hypertension	3981	586 (41.4)	875 (42.5)	54 (28.6)	141 (44.8)
Systolic BP, mmHg	3848	139.6±22.8	138.2±22.8	133.0±19.2	133.8±19.0
Diastolic BP, mmHg	3847	80.7±11.1	80.8±11.5	80.0±9.3	78.5±9.9
Total cholesterol, mg/dL	3619	203.6±43.1	200.5±44.5	200.6±40.9	198.6±42.0
LDL-c, mg/dL	3564	121.3±37.6	120.1±37.6	116.8±34.9	114.5±34.9
HDL-c, mg/dL	3582	57.2±17.3	54.8±16.5	62.3±17.6	60.8±18.6
Triglycerides, mg/dL	3605	126.8±69.5	124.1±67.1	111.8±74.6	125.2±72.9
Current smoker	3878	280 (20.3)	551 (27.7)	45 (23.8)	61 (19.4)
Ever smoker	3878	671 (48.6)	1140 (57.2)	98 (51.9)	161 (51.1)
Diabetes mellitus	3982	118 (8.3)	115 (5.6)	15 (7.9)	35 (11.1)
Family history of CVD	3075	318 (27.9)	342 (23.9)	35 (18.5)	76 (24.2)
Body mass index, kg/m ²	3646	27.5±5.2	26.6±5.0	27.3±5.7	27.9±5.5
Methotrexate	3968	377 (26.8)	590 (28.7)	130 (68.8)	228 (72.4)
Other csDMARDs	3816	326 (23.8)	413 (21.1)	30 (16.2)	120 (40.0)
Corticosteroid	3974	351 (24.9)	463 (22.5)	72 (38.1)	120 (38.2)
Antihypertensive therapy	3980	272 (19.2)	420 (20.4)	42 (22.2)	99 (31.4)
Lipid-lowering therapy	3977	156 (11.0)	182 (8.8)	27 (14.3)	70 (22.2)

Values in table are mean±SD or n (%).

ACPA, anti-citrullinated protein antibody; bDMARD, biologic disease modifying antirheumatic drug; BP, blood pressure; Log CRP, natural logarithm transformed C-reactive protein; csDMARDs, conventional synthetic disease modifying anti-rheumatic drug; CVD, cardiovascular disease; DAS28, 28-joint disease activity score; ESR, erythrocyte sedimentation rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; RA, rheumatoid arthritis; RF, rheumatoid factor.

between BMI and ACPA was found for MACE risk (p-for-interaction=0.034) but not for all cardiovascular events (p-for-interaction=0.308). BMI associated with MACE risk among ACPA-positive patients (HR 1.04, 95% CI 1.01 to 1.08, p=0.018; [figure 2](#)) but not ACPA-negative patients (HR 0.96, 95% CI 0.90 to 1.03, p=0.246). However, there was no interaction between BMI and bDMARD use on the risk of MACE (p-for-interaction=0.370) or all cardiovascular events (p-for-interaction=0.105).

Notably, the three-way interaction between BMI, bDMARD use and ACPA was significant for both MACE (p-for-interaction=0.001) and all events (p-for-interaction=0.029). This indicated that the influence of bDMARDs on the relationship between BMI and

cardiovascular risk varied between ACPA-positive and ACPA-negative patients. In ACPA-positive patients, the bDMARD×BMI interaction was not significant for either MACE (p-for-interaction=0.658) or all cardiovascular events (p-for-interaction=0.318). Among ACPA-negative patients, the bDMARD×BMI interaction was significant for both MACE (p-for-interaction<0.001) and all events (p-for-interaction=0.012); specifically, BMI was inversely associated with the risk of MACE (HR 0.36, 95% CI 0.23 to 0.57) and all cardiovascular events (HR 0.67, 95% CI 0.49 to 0.92) in bDMARD users but not non-users ([figure 3](#)). A cumulative hazard plot of the association of BMI with all cardiovascular event risk among ACPA-negative patients stratified by bDMARD use is shown in [figure 4](#).

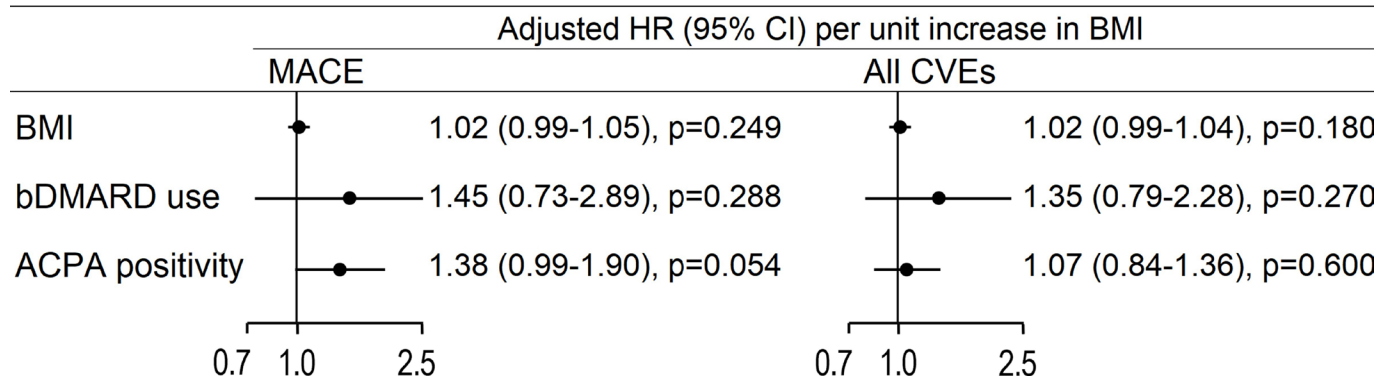


Figure 1 Main effects of BMI, ACPA positivity and bDMARD use on cardiovascular event risk. All models adjust for age, hypertension, diabetes, family history of cardiovascular disease, smoking, total cholesterol/high-density lipoprotein cholesterol ratio, rheumatoid arthritis duration and 28-joint disease activity score with erythrocyte sedimentation rate. BMI, body mass index; bDMARD, biologic disease-modifying anti-rheumatic drug; ACPA, anti-citrullinated protein antibodies; CVEs, cardiovascular events.

Sensitivity analyses of bDMARD use in models using inverse probability weighted multivariable Cox models yielded similar results. There was again a three-way BMI×bDMARD × ACPA interaction for MACE and all events (p-for-interaction<0.001 and 0.015, respectively). Specifically, the BMI×bDMARD interaction was significant in ACPA-negative patients for both MACE (p-for-interaction<0.001) and all cardiovascular events (p-for-interaction=0.001; [figure 3](#)), but not in ACPA positive (p-for-interaction=0.756 and 0.289, respectively).

In unweighted multivariable models limited to patients enrolled from 2000 forward, again the BMI × bDMARD × ACPA interaction was significant for MACE (p-for-interaction=0.001) and all cardiovascular events (p-for-interaction=0.024). The BMI × bDMARD interaction was similarly significant for MACE and all events in ACPA-negative patients (p-for-interaction <0.001 and 0.008, respectively; [figure 3](#)) but not in ACPA-positive patients (p-for-interaction=0.657 and 0.504, respectively).

Results were also generally similar in sensitivity analyses with iBMI as a predictor in the unweighted, multivariable Cox models. The iBMI × ACPA interaction was significant for MACE (p-for-interaction=0.025) such that iBMI associated with MACE among ACPA-positive patients (HR 0.97, 95% CI 0.94 to 0.99, p=0.017) but not ACPA-negative patients (HR 1.03, 95% CI 0.98 to 1.08, p=0.228). The three-way iBMI × bDMARD × ACPA interaction was significant for MACE (p-for-interaction<0.001) and all cardiovascular events (p-for-interaction=0.018). Similarly to the main analysis, in ACPA-negative patients, the iBMI × bDMARD interaction was significant for MACE and all events (p-for-interaction <0.001 and 0.002, respectively) such that iBMI associated with risk only in bDMARD users ([figure 5A](#)).

Lastly, in multivariable Fine-Gray models where non-cardiovascular disease-related death (n=75) was considered as a competing risk, results were concordant with those of the primary analyses. Likewise, there was a three-way BMI × bDMARD × ACPA interaction for both outcomes (p-for-interaction=0.001 for MACE and 0.029 for all events), with a significant BMI × bDMARD interaction for MACE and all events in ACPA-negative (p-for-interaction<0.001 and 0.018, respectively) but not ACPA-positive (p-for-interaction=0.769 and 0.478, respectively) patients ([figure 5B](#)).

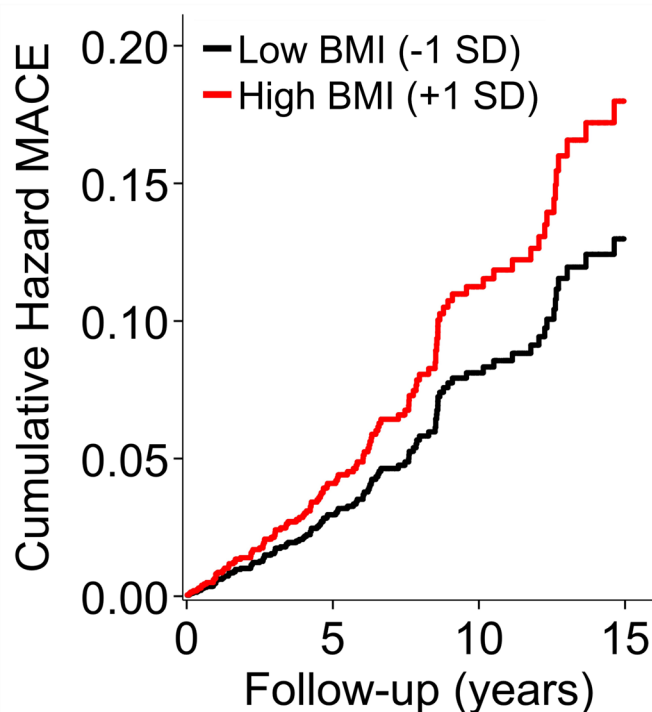


Figure 2 Cumulative hazard of MACE in ACPA-positive patients at low BMI (one SD below the mean) and high BMI (one SD above the mean). ACPA, anti-citrullinated protein antibodies; BMI, body mass index; MACE, major adverse cardiovascular event.

DISCUSSION

This study evaluated the relationship between BMI, as a measure of obesity, and cardiovascular risk in a large,

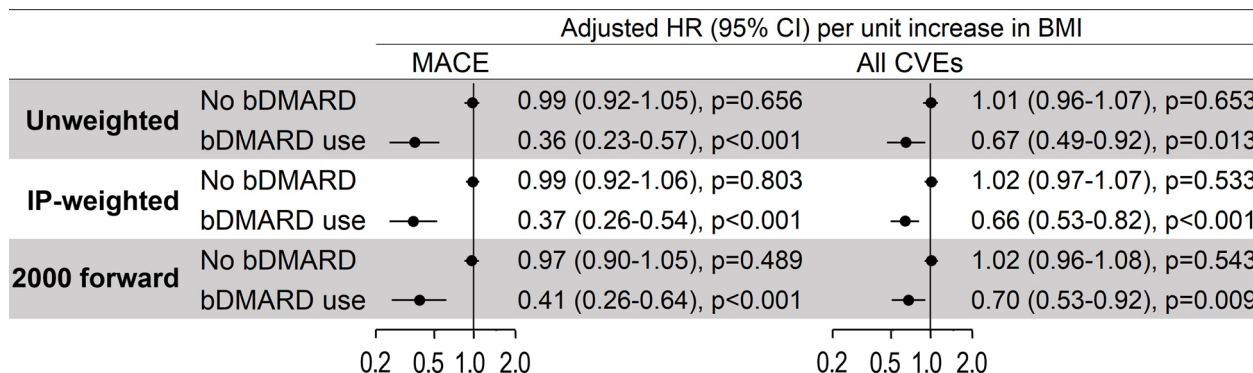


Figure 3 Effect of BMI on cardiovascular risk in ACPA-negative patients stratified by bDMARD use in unweighted models, models with inverse probability weighting and unweighted models limited to sample enrolment from 2000 forward. All models adjust for age, hypertension, diabetes, family history of cardiovascular disease, smoking, total cholesterol/high-density lipoprotein cholesterol ratio, rheumatoid arthritis duration and 28-joint disease activity score with erythrocyte sedimentation rate. ACPA, anti-citrullinated protein antibodies; bDMARD, biologic disease modifying anti-rheumatic drug; BMI, body mass index; CVEs: cardiovascular events; IP-weighted, inverse probability weighted analyses.

multinational, ethnically diverse, observational cohort of RA patients without cardiovascular disease at enrolment and with long-term follow-up. The use of BMI for the definition and classification of overweight, obesity and recommendations thereof at a patient level is supported by 12 separate guidelines published in WHO 'stratum A' nations.²⁶ It is an easily and standardly collected metric in routine clinical practice and will therefore continue to be relevant in clinical decision-making.

In our multivariable Cox models, BMI was not significantly associated with either MACE or any cardiovascular events overall. This finding aligns with some prior studies but not others.²⁻⁸ One potential explanation is that certain comorbidities treated as confounders in our multivariable models—such as diabetes, hypertension, and disease activity—might instead act as mediators of the effect of obesity on cardiovascular risk, thus attenuating the observed association.² Indeed, adjustments for disease activity, severity, disability and comorbidities

neutralised the impact of obesity on RA mortality in prior reports.^{2,6} However, in our study, BMI showed no association with cardiovascular risk in unadjusted models, therefore obviating this possibility. Alternatively, weight changes after enrolment may have confounded the relationship between baseline BMI and cardiovascular outcomes.² Weight loss has been linked to increased cardiovascular⁸ and overall mortality² independently of baseline BMI, while weight gain might be protective.² Furthermore, increases in body fat, sarcopenia and sarcopenic obesity are all more pronounced within the non-obese BMI range in RA.^{13,27} Since 78% of our patients displayed non-obese BMI, increasing BMI may not necessarily correspond to proportional gain in fat or cardiometabolic risk.

Since obesity is associated with higher disease activity in ACPA-positive but not ACPA-negative patients¹⁵ and recognising that RA-related inflammation is linked to cardiovascular risk,¹⁶ we hypothesised that the effect of BMI on cardiovascular risk may differ based on ACPA status. Indeed, BMI is associated with risk in ACPA-positive but not ACPA-negative patients. ACPA presence vs absence characterises disease endotypes with similar clinical manifestations yet fundamentally different pathophysiology.²⁸ Indeed, ACPA positivity is associated with significant differences in synovial and peripheral T-cell-derived proinflammatory cytokines,²⁸ higher macrophage infiltration and proinflammatory M1 polarisation within both synovial tissues and atherosclerotic plaques.²⁸⁻³³ Accordingly, our ACPA-positive patients displayed higher disease activity, ESR and CRP compared with ACPA negative ones. On the other hand, obesity influences both cytokines and disease activity in RA³⁴: progressively increasing BMI may affect inflammatory cytokine output through rising production of adipokines that act as immunometabolic regulators.³⁴ Notably, ACPA positivity was inversely associated with BMI in our cohort, and this relationship was not mediated by systemic inflammation (CRP). This suggests that the ACPA positive endotype

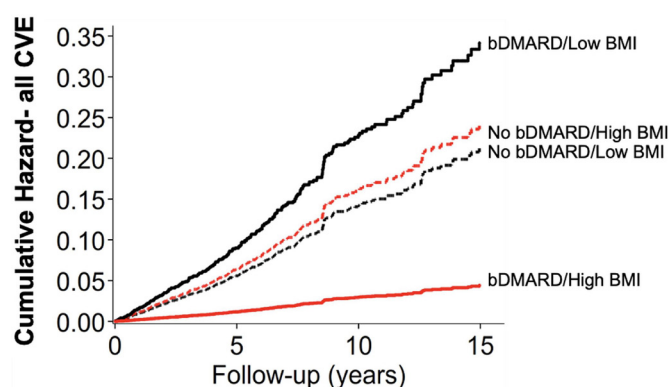


Figure 4 Cumulative hazard plots of all cardiovascular events in ACPA-negative bDMARD users and non-users at low BMI (one SD below the mean) and high BMI (one SD above the mean). ACPA, anti-citrullinated protein antibodies; bDMARD, biologic disease modifying antirheumatic drug; BMI, body mass index, Cum, cumulative, CVEs, cardiovascular events.

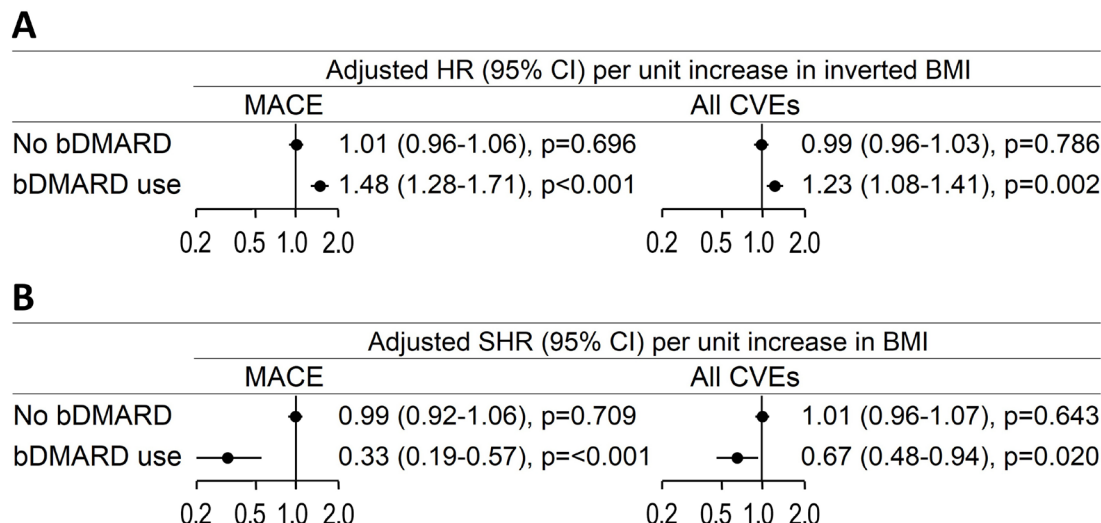


Figure 5 (A) Effect of inverted BMI on cardiovascular risk in ACPA-negative patients stratified by bDMARD use. All models adjust for age, hypertension, diabetes, family history of cardiovascular disease, smoking, total cholesterol/high-density lipoprotein cholesterol ratio, rheumatoid arthritis duration and 28-joint disease activity score with erythrocyte sedimentation rate. (B) Competing risk regression analysis for MACE and all cardiovascular events accounting for the competing risk of non-cardiovascular disease-related death. BMI, body mass index; ACPA, anti-citrullinated protein antibodies; bDMARD, biologic disease modifying anti-rheumatic drug; SHR, sub-hazard ratio; CVEs, cardiovascular events; MACE, major adverse cardiovascular events.

and BMI (adiposity) may share at least some inflammatory cytokine pathways, active within the adipose tissue itself.³⁴ Yet, both ACPA and BMI also use unique pro-inflammatory cytokine pathways.³⁴ Recognising that inflammation is strongly linked to cardiovascular risk, the altered cytokine balance promoted by a rising BMI may amplify or synergise with ACPA-specific cytokine pathways and promote risk.

Importantly, previous studies have linked seropositivity, disease activity and inflammation with sarcopenia and sarcopenic obesity.^{13 27 35} Additionally, complex associations between seropositivity and inflammation with metabolic syndrome in RA have been reported.^{36–38} Accordingly, we observed that disease activity was significantly associated with metabolic syndrome in ACPA-positive but not ACPA-negative patients. This data in aggregate suggests that increasing BMI in ACPA-positive patients may represent a higher prevalence of sarcopenic obesity and metabolic syndrome, both of which are linked to cardiovascular risk.^{14 35 39}

bDMARDs, which effectively control inflammation and reduce cardiovascular risk,^{19 40–42} may also improve body composition in RA.²⁰ Since obesity reportedly attenuated responses to certain bDMARDs,^{17 18} we posited that the effect of BMI on cardiovascular risk might differ between bDMARD users and non-users. Yet, no interaction between BMI and bDMARD use on cardiovascular risk was observed. This analysis was, however, limited by the lack of data on weight changes and bDMARD duration pre- and post-baseline, both of which are independently associated with cardiovascular outcomes in RA.^{2 19}

Since ACPA status may influence the efficacy of certain bDMARD classes,^{21–23} we hypothesised that the relationships between BMI, bDMARD use and cardiovascular risk

may additionally vary by ACPA status. Indeed, a significant three-way interaction between BMI, bDMARD use and ACPA status was observed for both MACE and all cardiovascular events: BMI inversely associated with cardiovascular risk in ACPA-negative bDMARD users but not in non-users. It is possible that higher BMI in ACPA-negative bDMARD users may indicate greater lean mass. Supporting this idea, studies using dual X-Ray absorptiometry (DXA) reported that BMI increases in bDMARD users correlated with gains in lean mass rather than fat mass.²⁰ Accordingly, our ACPA-negative patients displayed higher BMI, body weight and lower disease activity and inflammation compared with ACPA-positive patients; more importantly, ACPA-negative bDMARD users showed lower disease activity and systemic inflammation than ACPA-negative non-users. Alternatively, and not mutually exclusively, higher BMI in ACPA-negative bDMARD users may reflect metabolically healthy obesity, a phenotype characterised by normal glucose and lipid metabolism, absence of hypertension, lower visceral and liver fat and reduced cardiovascular risk.⁴³ Indeed, ancillary analyses revealed higher rates of metabolically healthy obesity in our ACPA-negative compared with ACPA-positive patients (10.6% vs 6.1%, $p=0.018$). Notably, ACPA-negative bDMARD users exhibited an even higher rate of metabolically healthy obesity (10.9%) compared with ACPA-positive bDMARD users (3.2%). This may signify lower visceral fat inflammation in ACPA-negative patients, associated with lower cardiometabolic risk.

There are several lessons learnt from this data. First, there is no uniform or wide-ranging association between BMI and cardiovascular risk in RA. Therefore, BMI may not be informative in cardiovascular risk stratification at an individual patient level when used in isolation. Rather,

its relationship with cardiovascular risk is nuanced and influenced by RA-specific characteristics, particularly ACPA status and bDMARD use. Among ACPA-positive patients, BMI was associated with greater cardiovascular risk, and this was independent of bDMARD use. Among ACPA-positive patients, increasing BMI may reflect progressively lower lean mass and excessive fat accumulation along with significant fat inflammation, characteristic of sarcopenic obesity and metabolic syndrome, both of which are linked to cardiovascular risk. In contrast, among ACPA-negative patients, BMI was inversely associated with cardiovascular risk exclusively in bDMARD users but not in non-users. A rising BMI among ACPA-negative bDMARD users may indicate higher lean mass and/or higher fat mass, yet without visceral adipose inflammation, consistent with metabolically healthy obesity, which is associated with lower cardiovascular risk.

Our findings may have clinical implications on individual patient care. A high BMI in an ACPA-positive patient may compel a more diligent control of both systemic and visceral adipose tissue inflammation—perhaps preferentially with anti-cytokine therapies,^{44 45} support and optimisation of nutritional status, mitigation of high energy expenditure and aggressive targeting of metabolic syndrome and insulin resistance.⁴⁶ Further implementation of high-intensity progressive resistance training programmes and/or nitrogen supplementation can increase muscle mass and reduce fat mass.⁴⁶ However, in the case of a high BMI in an ACPA-negative patient on bDMARD therapy, more standard lifestyle modifications aiming at body weight and fat reduction might be sufficient and effective. Implementation of imaging modalities that accurately characterise body composition may help characterise the individual contributions of lean and fat mass in the aforementioned scenarios and illuminate the nuanced relationship of adipose tissue volume, distribution and inflammation with cardiovascular risk.

Study strengths include the use of a large, ethnically diverse, multinational, unselected cohort of patients reflective of real-life clinical practice and enhancing the external validity and generalisability of our findings. However, several limitations warrant consideration. Recruitment through academic and referral centres with an interest in RA-associated cardiovascular disease may have prompted more aggressive risk factor management and therefore introduced referral bias. Differences in patient surveillance and event adjudication across centres are also potential sources of bias. Data on RA characteristics, cardiovascular risk factors and medication use were only collected at baseline, precluding analysis of time-varying effects. Concerns about the performance of BMI as a proxy for obesity in RA remain relevant.⁹ Unlike the U- or J-shaped relationship seen in general patients,⁴⁷ the association between BMI and cardiovascular risk does not appear nonlinear in our cohort (not shown), consistent with a prior report.⁶ Notably, sensitivity analyses using inverted BMI as a measure of leanness yielded consistent results. There is additional risk of prevalent

user bias; however, this is more relevant when the risk of an outcome is highest during early treatment,^{48 49} which is not the case for cardiovascular disease in RA.⁵⁰ Lastly, as with many observational studies, residual confounding from unmeasured variables as well as differences in follow-up time and other selection biases may affect our findings, despite rigorous statistical adjustments and sensitivity analyses.

CONCLUSION

BMI had no main effect on cardiovascular risk in RA patients. However, ACPA status significantly modified this relationship. In ACPA-positive patients, BMI is associated with higher event risk, likely reflecting sarcopenic obesity and metabolic syndrome. In contrast, in ACPA-negative patients, BMI was inversely associated with cardiovascular risk specifically in bDMARD users, potentially reflecting increased lean mass or metabolically healthy obesity. Future studies should prioritise the use of tools such as DXA scans to better characterise body composition in RA and develop strategies to address sarcopenic obesity, particularly in ACPA-positive patients.

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