RHEUMATOLOGY

Original article

Impact of overweight and obesity on patient-reported health-related quality of life in systemic lupus erythematosus

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Abstract

Objectives. Associations between BMI and health-related quality of life (HRQoL) in SLE have been implied, but data are scarce. We determined the impact of overweight and obesity on HRQoL in a large SLE population.

Methods. We pooled cross-sectional baseline data from the BLISS-52 (NCT00424476) and BLISS-76 (NCT00410384) trials ($N = 1684$). HRQoL was evaluated using the 36-item Short Form Health Survey (SF-36), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale and the European Quality of Life 5-dimension questionnaire (EQ-5D). Comparisons between BMI groups were conducted using the Mann–Whitney U test and adjustments using linear regression. Clinical relevance was determined by minimal clinically important differences (MCIDs).

Results. In total, 43.2% of the patients had BMI above normal and 17.4% were obese. Overweight and obese patients reported worse SF-36 physical component summary (PCS), physical functioning, role physical, bodily pain and FACIT-Fatigue scores than normal weight patients. Divergences were greater than corresponding MCIDs and more prominent with increasing BMI. Despite no clinically important difference in SF-36 mental component summary scores across BMI categories, patients experienced progressively diminished vitality and social functioning with increasing BMI. In linear regression analysis, BMI above normal and obesity were associated with worse PCS (standardized coefficient $\beta = -0.10$, $P < 0.001$ and $\beta = -0.17$, $P < 0.001$, respectively), FACIT-Fatigue ($\beta = -0.11$, $P < 0.001$ and $\beta = -0.16$, $P < 0.001$) and EQ-5D ($\beta = -0.08$, $P = 0.001$ and $\beta = -0.12$, $P < 0.001$) scores, independently of demographic and disease-related factors. The impact of BMI on the PCS and FACIT-Fatigue was more pronounced than that of SLE activity.

Conclusion. Patients with SLE and BMI above normal experienced clinically important HRQoL diminutions in physical aspects, fatigue and social functioning. A survey of potential causality underlying this association is warranted.

Key words: SLE, health-related quality of life, obesity, patient-reported outcomes

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Rheumatology key messages
• Overweight and obese patients with SLE experienced clinically important impairments regarding physical HRQoL and fatigue.
• SLE patients' physical HRQoL, fatigue and social functioning were gradually worse with increasing BMI.
• The impact of BMI on physical HRQoL and fatigue was greater than that of SLE activity.

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CLINICAL SCIENCE

Introduction

SLE is a chronic multisystem autoimmune disease that most commonly affects women of childbearing age. Despite considerable advances on improving life expectancy and preventing organ damage accrual over the past decades [1], patients with SLE still experience a substantially impaired health-related quality of life (HRQoL) compared with the general population, and constitutional symptoms such as fatigue remain frequent complaints [2–4].

Factors contributing to HRQoL diminutions in patients with SLE include fatigue, pain, depression and increased BMI [2, 5–7]. Obesity is associated with poor functional capacity, high concentrations of inflammatory markers and high disease activity [8–10]. In juvenile-onset SLE, obesity has detrimental effects on overall HRQoL [6]. In adult SLE patients, higher BMI is associated with an impaired physical HRQoL [5, 6], while the effect regarding mental aspects remains controversial, with inconsistent reports from different cohorts [5, 6, 9]. Overall, data are scarce and conflicting and the clinical significance of the associations between BMI and HRQoL has not been thoroughly investigated.

In the present study, the aim was to determine the impact of overweight and obesity on physical and mental HRQoL aspects in the large SLE populations of the BLISS-52 (NCT00424476) and BLISS-76 (NCT00410384) clinical trials.

Methods

Study design and population

This is a post hoc analysis of prospectively collected data from two phase 3 randomized clinical trials of belimumab in SLE, i.e. the BLISS-52 [11] and BLISS-76 [12] trials. The study design was cross-sectional. We utilized pooled baseline data from the two trials ($n = 1684$), i.e. data collected prior to the intended trial intervention.

The BLISS-52 trial comprised 865 adult seropositive (ANA titre $\geq$1:80 and/or anti-dsDNA antibody $\geq$30 IU/ml) patients with active SLE, defined as a Safety of Estrogen in Lupus National Assessment–SLEDAI (SELENA-SLEDAI) [13] score $\geq$6 at enrolment despite standard of care therapy, the latter comprising fixed doses of corticosteroids, NSAIDs, antimalarial agents or immunosuppressants for at least 30 days before the first study dose. Organ damage was assessed using the SLICC/ACR Damage Index (SDI) [14]. The BLISS-76 trial included 819 patients with SLE and had a similar design to that of the BLISS-52 trial, but a longer follow-up until week 76.

The similarity in the design allowed us to analyse pooled data from the two trials. After exclusion of three patients with no available BMI data, the total number of patients qualifying for analysis was 1681. However, since BLISS-52 was primarily conducted in Latin America, Asia Pacific and Eastern Europe while BLISS-76 was primarily conducted in North America and Europe, we also performed separate analyses of data from the BLISS-52 and BLISS-76 trials. Data were made available by GlaxoSmithKline (Uxbridge, UK) through the Clinical Study Data Request Consortium.

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all study participants prior to enrolment in the BLISS programmes. Ethical permission for the present investigation was obtained by the Swedish ethical review authority (ref. 2019-05498).

Measurements of HRQoL

SLE patients' perception of HRQoL was determined using generic instruments, i.e. the Medical Outcomes Study (MOS) 36-item Short Form Health Survey (SF-36) [15], the three-level European Quality of Life 5-dimension (EQ-5D) health questionnaire [16] and the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale [17]. The SF-36 questionnaire consists of 36 questions, grouped in eight subscales, i.e. physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), social functioning (SF), vitality (VT), role emotional (RE) and mental health (MH). The responses to the SF-36 were scored with the SF-36v2 manual [18], yielding subscale scores from 0 to 100. Next, the SF-36 subscales were computed according to a three-step procedure, including Z-score transformation and weighting based on the general US population, to generate two summary measures, the physical component summary (PCS) and the mental component summary (MCS). Although all subscales are weighted in the derivation of PCS and MCS, PF, RP, BP and GH are referred to as the physical aspects and SF, VT, RE and MH as the mental aspects of the SF-36. In terms of interpretation, higher scores on SF-36 subscales and component summaries represent a better HRQoL.

The FACIT-Fatigue scale is a generic 13-item questionnaire that assesses the impact of fatigue over the preceding 7 days. The scores generated have a span from 0 to 52, with higher scores representing greater fatigue.

The three-level EQ-5D health questionnaire consists of two distinct indices, i.e. a visual analogue scale (VAS) measuring patients' health perception from 0 (worst health perception) to 100 (best health perception) and a questionnaire consisting of five questions addressing self-care, mobility, daily activity, pain/discomfort and anxiety/depression. Patients' responses to these five questions are next summarized into a utility index score. In the present study, EQ-5D utility index scores were calculated based on the valuation of EQ-5D health states from a general US population sample [19]. In terms of interpretation, higher utility index scores represent a better HRQoL.

BMI and HRQoL

The patients were stratified into four groups based on their BMI according to cut-off values established by the

World Health Organization (WHO): underweight (BMI <18.5 kg/m^2), normal weight ($18.5 \le$ BMI <25 kg/m^2), overweight ($25 \le$ BMI <30 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) [20]. Further, we divided the obesity group into three subgroups: type I obesity ($30 \le$ BMI <35 kg/m^2), type II obesity ($35 \le$ BMI <40 kg/m^2) and type III obesity (BMI ≥ 40 kg/m^2). In certain analyses, we grouped overweight and obese individuals into a subset herein termed 'BMI above normal' patients.

Next we determined minimal clinically important differences (MCIDs) for scores in the different HRQoL instruments, based on previously reported cut-offs. In cases of varying thresholds in the literature, the most stringent one was used. Thus the MCID for SF-36 PCS and MCS scores was defined as ≥ 2.5, while the corresponding MCID for SF-36 subscale scores was defined as ≥ 5.0 [21]. The MCID for FACIT-Fatigue scores was set to ≥ 4 [22, 23]. For the EQ-5D VAS, the MCID was defined as ≥ 10 [24] and for the EQ-5D utility index score it was set to ≥ 0.082 [25].

Statistical analysis

Data are presented as number (percentage) or mean (s.d.). For comparisons between BMI groups, the non-parametric Mann–Whitney U test was used. The Pearson's χ^2 test was used to investigate contingent associations between binomial variables. Finally, linear regression analysis was used to evaluate associations of demographic and clinical factors with different HRQoL aspects. Multiple linear regression models were created for assessment of independence and confounding potentiality. P-values <0.05 were considered statistically significant. Statistical analyses were performed using the SPSS software version 25 (IBM, Armonk, NY, USA). GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA) was used for the construction of graphs.

Results

Patient characteristics

Table 1 summarizes demographic and SLE disease characteristics across BMI groups. Supplementary Table S1, available at *Rheumatology* online, shows the corresponding data for the BMI above normal group and the different obesity subgroups.

A total of 727 of 1681 patients (43.2%) had a BMI over the normal range, while 293 participants (17.4%) were obese. The prevalence of BMI above normal and obesity were highest among Black/African American patients (63.7% and 30.1%, respectively), with the corresponding proportions among White/Caucasian being 48.9% and 22.5%, among Native American 42.0% and 13.4% and among Asian patients 22.1% and 4.0%, respectively.

There was no difference in SELENA-SLEDAI scores across different BMI groups. However, overweight [0.82 (s.d. 1.30), $P = 0.006$] and obese patients [1.19 (s.d. 1.54), $P < 0.001$] had higher SDI scores compared with SLE patients of normal weight [0.63 (s.d. 1.07)].

The frequency of patients receiving antimalarial agents was lower within the overweight group (61.1%) compared with the normal weight group (67.8%; $P = 0.015$). In contrast, the proportion of patients receiving immunosuppressive agents was higher within the obesity (54.9%) compared with the normal weight group (46.3%; $P = 0.011$). Notably, obese patients were on lower daily prednisone equivalent doses [9.2 mg/day (s.d. 8.0)] than patients with normal BMI [11.3 mg/day (s.d. 8.5), $P < 0.001$; Table 1].

MOS SF-36

Overweight and obese patients reported lower PCS, PF, RP and BP scores compared with normal weight patients; the differences were greater than the corresponding MCIDs and more prominent with increasing BMI (Fig. 1). The obese group had lower GH scores [36.5 (s.d. 18.6)] compared with normal weight patients [42.4 (s.d. 18.9), $P < 0.001$; Supplementary Table S2, available at *Rheumatology* online] and the differences were greater than the MCIDs in the type 2 and 3 but not the type 1 obesity subgroups. All three obesity subgroups reported worse PCS, PF, BP and GH scores compared with the overweight group (Fig. 1). In the BLISS-52 trial, we observed clinically important differences between patients with BMI above normal and normal weight patients in PF and RP and between obese and normal weight patients in PCS, PF, RP and BP (Supplementary Table S3, available at *Rheumatology* online). In the BLISS-76 trial, patients with BMI above normal and obese patients experienced worse PCS, PF, RP and BP than normal weight patients, with the differences being greater than the corresponding MCIDs (Supplementary Table S4, available at *Rheumatology* online).

When mental HRQoL was analysed, overweight patients had lower MCS scores [39.8 (s.d. 11.8)] than normal weight subjects [41.5 (s.d. 11.2), $P = 0.029$], but the difference was not clinically important ($<$MCID), whereas obese patients did not show differences compared with the other groups (Fig. 1). However, we found progressively reduced VT and SF scores with increasing BMI, with all obesity subgroups displaying clinically meaningful differences ($\ge$MCID) compared with the normal weight group. MH scores did not differ across the BMI groups (Fig. 1). In analysis stratified by trial, the difference in MCS and MH scores exceeded the MCID in the BLISS-52 trial (Supplementary Table S3, available at *Rheumatology* online) but not in the BLISS-76 trial (Supplementary Table S4, available at *Rheumatology* online) in the comparison between obese and normal weight patients, while VT and SF scores showed greater differences than the corresponding MCID in both trials.

No differences were seen in SF-36 component summary or subscale scores between underweight and normal weight SLE patients (Supplementary Table S5, available at *Rheumatology* online).

Table 1 Demographic and clinical characteristics of patients

Characteristics	Normal weight (N = 874)	Underweight (N = 80)	P-value	Overweight (N = 434)	P-value	Obese (N = 293)	P-value
Demographics							
Age, years, mean (s.d.)	35.4 (10.9)	30.0 (9.3)	**<0.001**	40.2 (11.5)	**<0.001**	43.4 (10.7)	**<0.001**
Sex (female), n (%)	831 (95.1)	78 (97.5)	0.328	397 (91.5)	**0.010**	276 (94.2)	0.554
Ethnic origin, n (%)							
Asian	240 (27.5)	35 (43.8)	**0.002**	64 (14.7)	**<0.001**	14 (4.8)	**<0.001**
Black/African American	47 (5.4)	6 (7.5)	0.428	49 (11.3)	**<0.001**	44 (15.0)	**<0.001**
Indigenous American[a]	206 (23.6)	11 (13.8)	**0.045**	107 (24.7)	0.665	50 (17.1)	**0.020**
White/Caucasian	378 (43.2)	28 (35.0)	0.153	210 (48.4)	0.079	179 (61.1)	**<0.001**
Clinical characteristics and concomitant treatments							
SELENA-SLEDAI score, mean (s.d.)	9.6 (3.6)	10.4 (4.3)	0.174	9.8 (3.8)	0.529	9.7 (3.4)	0.972
SLE duration, years, mean (s.d.)	6.3 (6.3)	4.9 (5.5)	0.056	6.4 (6.5)	0.957	7.1 (6.6)	0.055
SDI score, mean (s.d.)	0.63 (1.07)	0.61 (1.0)	0.880	0.82 (1.30)	**0.006**	1.19 (1.54)	**<0.001**
Glucocorticoid use, n (%)	784 (89.7)	74 (92.5)	0.426	368 (84.8)	**0.002**	229 (77)	**<0.001**
Prednisone dose, mg/day, mean (s.d.)	11.3 (8.5)	11.2 (8.4)	0.785	10.8 (9.3)	0.101	9.2 (8.0)	**<0.001**
IS use[b], n (%)	405 (46.3)	33 (41.3)	0.382	215 (49.5)	0.275	161 (54.9)	**0.011**
Azathioprine	204 (23.3)	13 (16.3)	0.148	100 (23.0)	0.904	72 (24.6)	0.667
Methotrexate	113 (12.9)	9 (11.3)	0.667	53 (12.2)	0.714	56 (19.1)	**0.009**
Mycophenolic acid	87 (10.0)	10 (12.5)	0.471	58 (13.4)	0.064	32 (10.9)	0.636
AMA use, n (%)	593 (67.8)	57 (71.3)	0.532	265 (61.1)	**0.015**	181 (61.8)	0.057

P-values are derived from Pearson's χ^2 or Mann–Whitney U tests; the normal weight group was the reference comparator.
[a]Alaska Native or American Indian from North, South or Central America. [b]Excluding antimalarial agents. AMA: antimalarial agents; IS: immunosuppressants.

FACIT-Fatigue

All groups of BMI above normal reported significantly worse FACIT-Fatigue scores compared with the normal weight group [32.1 (s.d. 11.5)] and displayed a gradual impairment with increasing BMI (Fig. 1). The differences were greater than the MCID for all obesity subgroups (type 1, 26.8 (s.d. 11.3); type 2, 24.6 (s.d. 13.6); type 3, 23.7 (s.d. 11.3), $P < 0.001$ for all), but not for the overweight group [29.0 (s.d. 12.1), $P < 0.001$]. Moreover, the differences were greater than the MCID for patients with BMI above normal and obese patients in the pooled dataset (Supplementary Table S2, available at *Rheumatology* online) and the BLISS-76 trial (Supplementary Table S4, available at *Rheumatology* online), but not in the BLISS-52 trial (Supplementary Table S3, available at *Rheumatology* online).

We found no difference in FACIT-Fatigue scores between underweight and normal weight individuals (Supplementary Table S5, available at *Rheumatology* online).

EQ-5D

Overweight and obese patients had worse EQ-5D VAS and utility index scores compared with normal weight subjects. The type 3 obesity subgroup reported worse EQ-5D utility index scores [0.65 (s.d. 0.19)] compared with the overweight group [0.72 (s.d. 0.19), $P = 0.006$]. The corresponding differences in the type 1 and 2 obesity subgroups were not

statistically significant. None of the differences in the EQ-5D VAS or utility index scores between BMI groups were greater than the corresponding MCIDs (Fig. 1). Comparisons between patients with a BMI above normal and normal weight patients as well as between obese and normal weight patients are presented in Supplementary Table S2 for the pooled dataset, Supplementary Table S3 for the BLISS-52 trial and Supplementary Table S4 for the BLISS-76 trial, available at *Rheumatology* online.

No difference was noted in the EQ-5D VAS or utility index scores between underweight and normal weight subjects (Supplementary Table S5, available at *Rheumatology* online).

Linear regression analysis

We next assessed independence and confounding potentiality using multiple linear regression analysis. Based on reports from previous literature, selected covariates included age, sex, ethnicity, SELENA-SLEDAI score, SLE disease duration, SDI score, prednisone (or equivalent) dose and use of antimalarial or immunosuppressive agents [2, 5, 6, 26, 27].

First, we investigated associations between BMI and HRQoL using BMI as a continuous variable in the multivariable models (Fig. 2A–5A; Supplementary Fig. S1A, available at *Rheumatology* online; Supplementary Table S6, available at *Rheumatology* online). Higher BMI was independently associated with more severely impaired

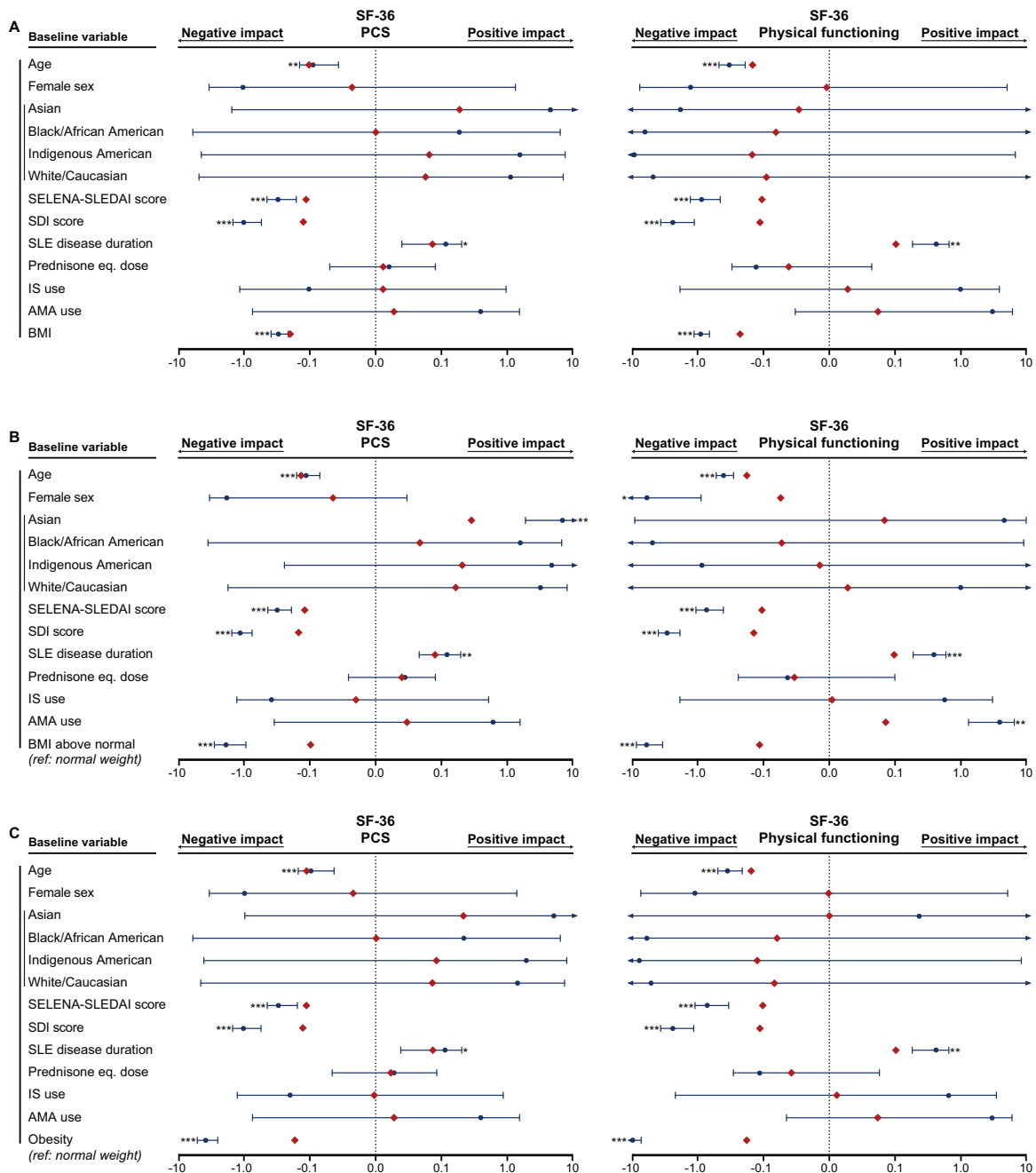FIG. 1 HRQoL indices across different BMI groups of SLE patients
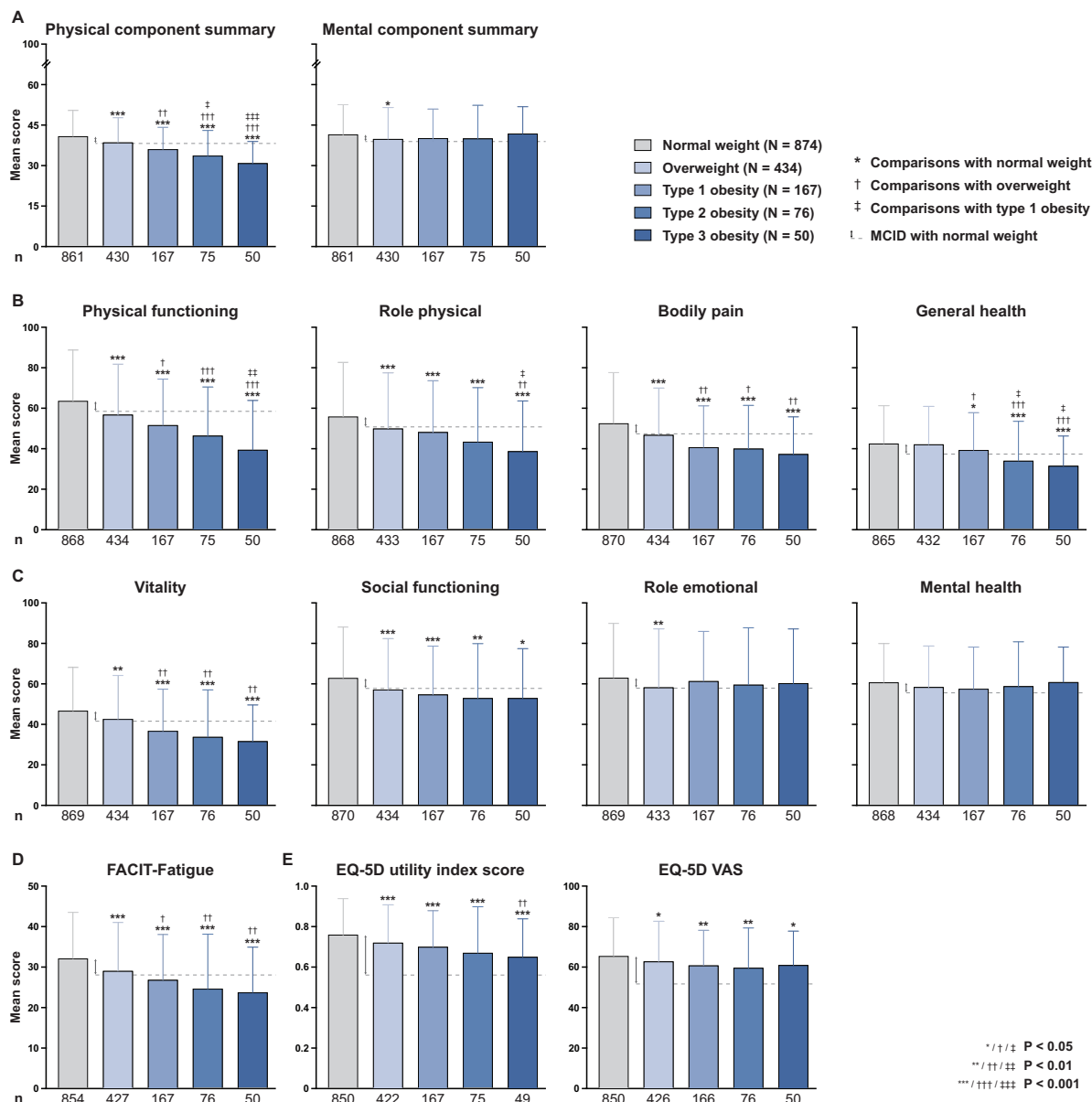
Groups are based on BMI measures, according to cut-off values established by the World Health Organization. The heights of the boxes represent mean scores and the whiskers indicate S.D. Upper bounds of bars below the dashed lines represent means that differ from the mean scores in the corresponding normal weight group by more than the MCID, the latter denoted by double-sided arrows. Symbols above the whiskers indicate statistically significant differences. Since the number of observations in the subgroups may differ from the total number of patients due to missing data, the number of available observations (*n*) is provided.

physical aspects of HRQoL, i.e. lower PCS (standardized coefficient $\beta = -0.20$, $P < 0.001$), PF ($\beta = -0.23$, $P < 0.001$), RP ($\beta = -0.12$, $P < 0.001$), BP ($\beta = -0.12$, $P < 0.001$) and GH ($\beta = -0.13$, $P < 0.001$) scores (Supplementary Table S6, available at *Rheumatology* online). In contrast, no association was found between BMI and SF-36 MCS scores ($\beta = -0.04$, $P = 0.264$; Fig. 4A), but we found a negative impact of BMI on VT

($\beta = -0.16$, $P < 0.001$; Fig. 5A) and SF ($\beta = -0.11$, $P = 0.001$; Fig. 4A).

Next we created separate models for the BMI above normal group and the obesity group, with the normal weight group as the reference comparator in both cases (Fig. 2B and C–Fig. 5B and C; Supplementary Fig. S1B–C, available at *Rheumatology* online; Supplementary Table S7, available at *Rheumatology* online; Supplementary
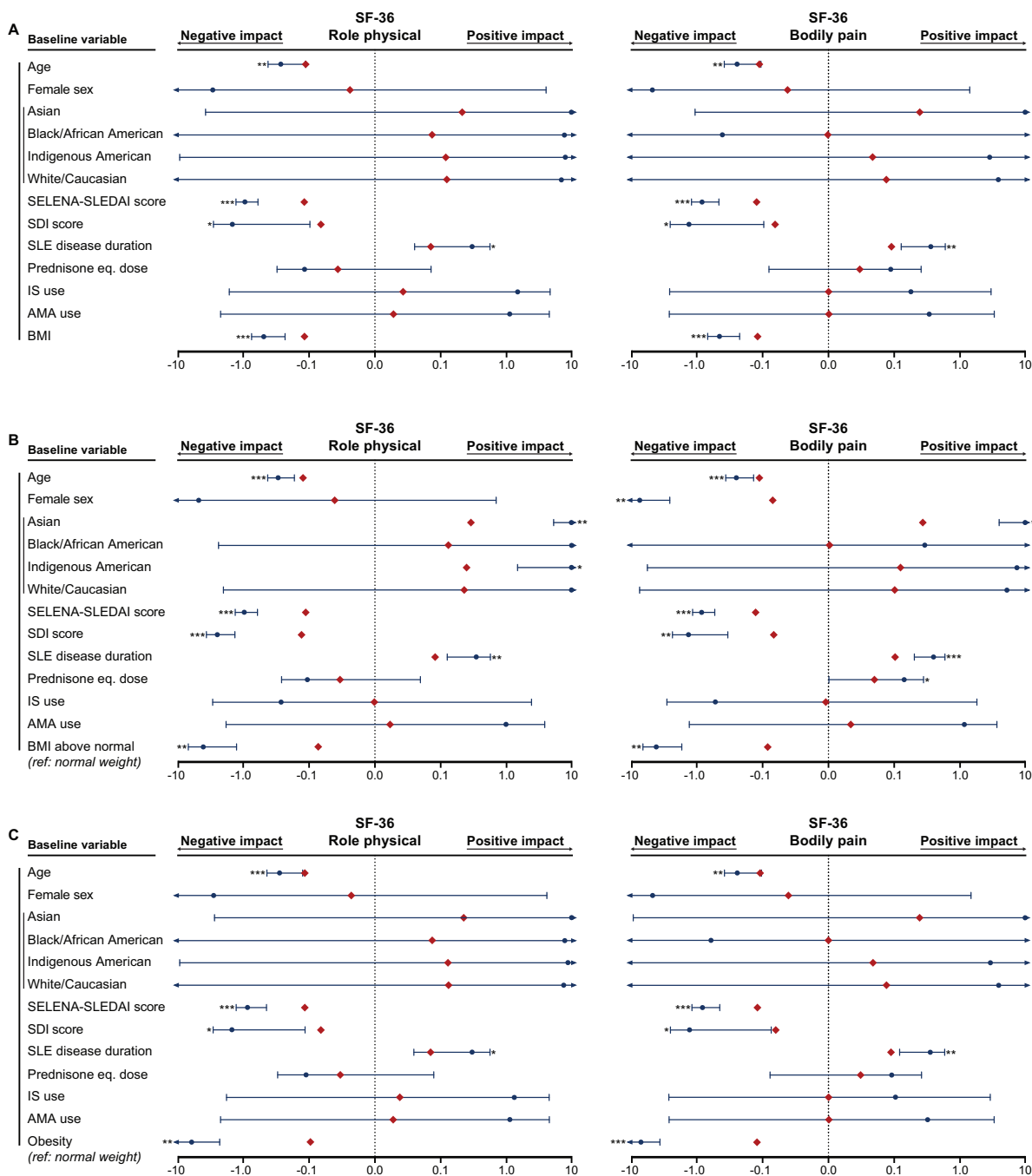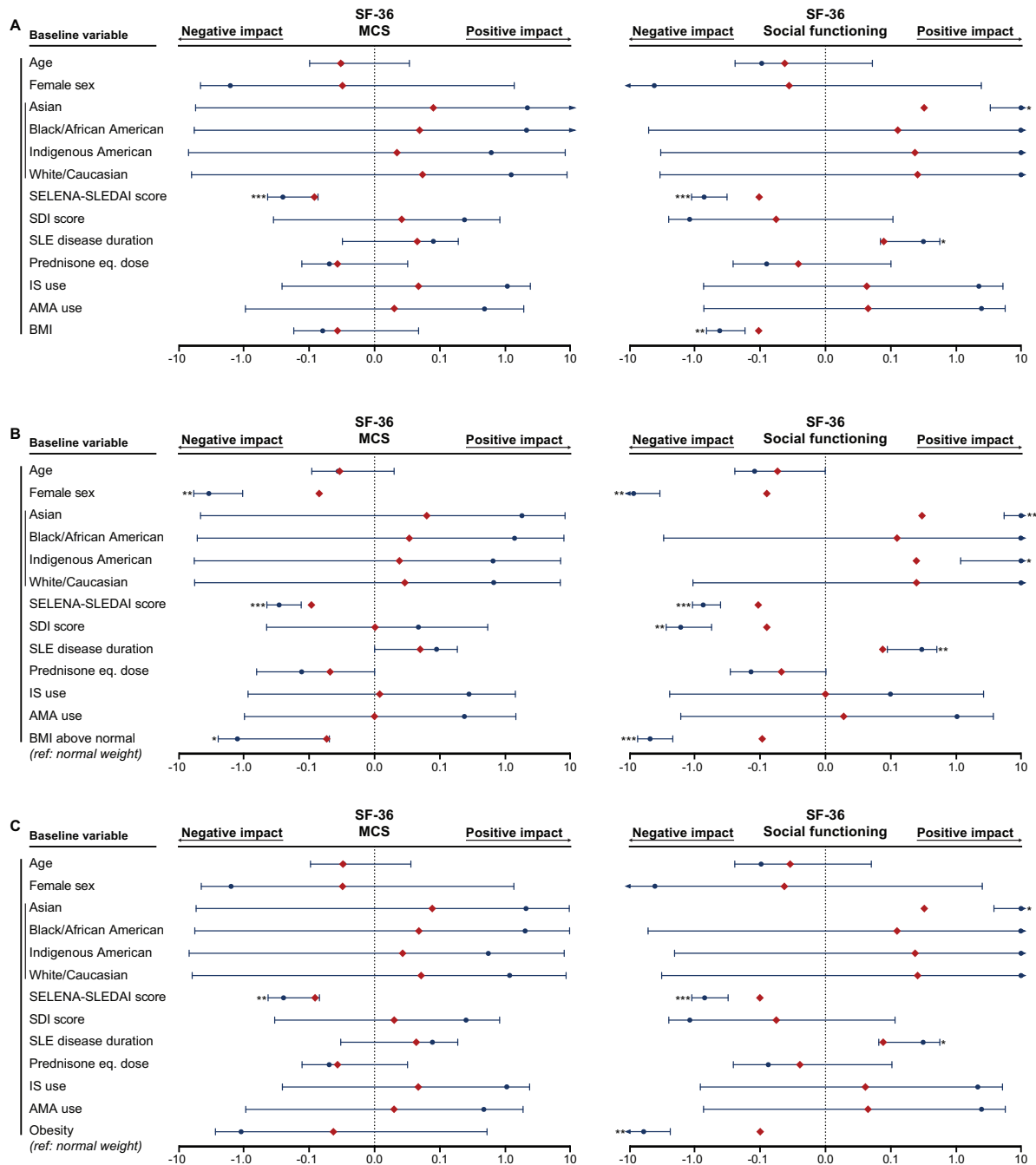
The forest plots illustrate results from multiple linear regression models. (**A**) BMI was analysed as a continuous variable. Separate models for the (**B**) BMI above normal and (**C**) obesity groups were created, with the normal weight group as the reference comparator in both cases. The dark blue circles represent the unstandardized coefficients and the whiskers represent the 95% CIs. The red diamonds represent the standardized coefficients. Asterisks indicate statistically significant associations. Level of significance: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. AMA: antimalarial agents.

Table S8, available at *Rheumatology* online). Obesity was independently associated with lower scores in all components related to physical HRQoL, whereas BMI above normal was negatively associated with PCS as well as all physical SF-36 aspects except GH (Figs 2 and 3). Notably, obesity was the covariate showing the most

Fɪɢ. 3 Associations of BMI with SF-36 RP and BP

The forest plots illustrate results from multiple linear regression models. (**A**) BMI was analysed as a continuous variable. Separate models for the (**B**) BMI above normal and (**C**) obesity groups were created, with the normal weight group as the reference comparator in both cases. The dark blue circles represent the unstandardized coefficients and the whiskers represent the 95% CIs. The red diamonds represent the standardized coefficients. Asterisks indicate statistically significant associations. Level of significance: *P < 0.05, **P < 0.01, ***P < 0.001. IS: immunosuppressants; AMA: antimalarial agents.

pronounced associations with HRQoL diminutions in physical aspects, yielding greater absolute values of β coefficients compared with age, SELENA-SLEDAI score, SDI score and disease duration. We found no association between obesity and MCS scores (β = −0.04, P = 0.182; Fig. 4; Supplementary Table S8, available at

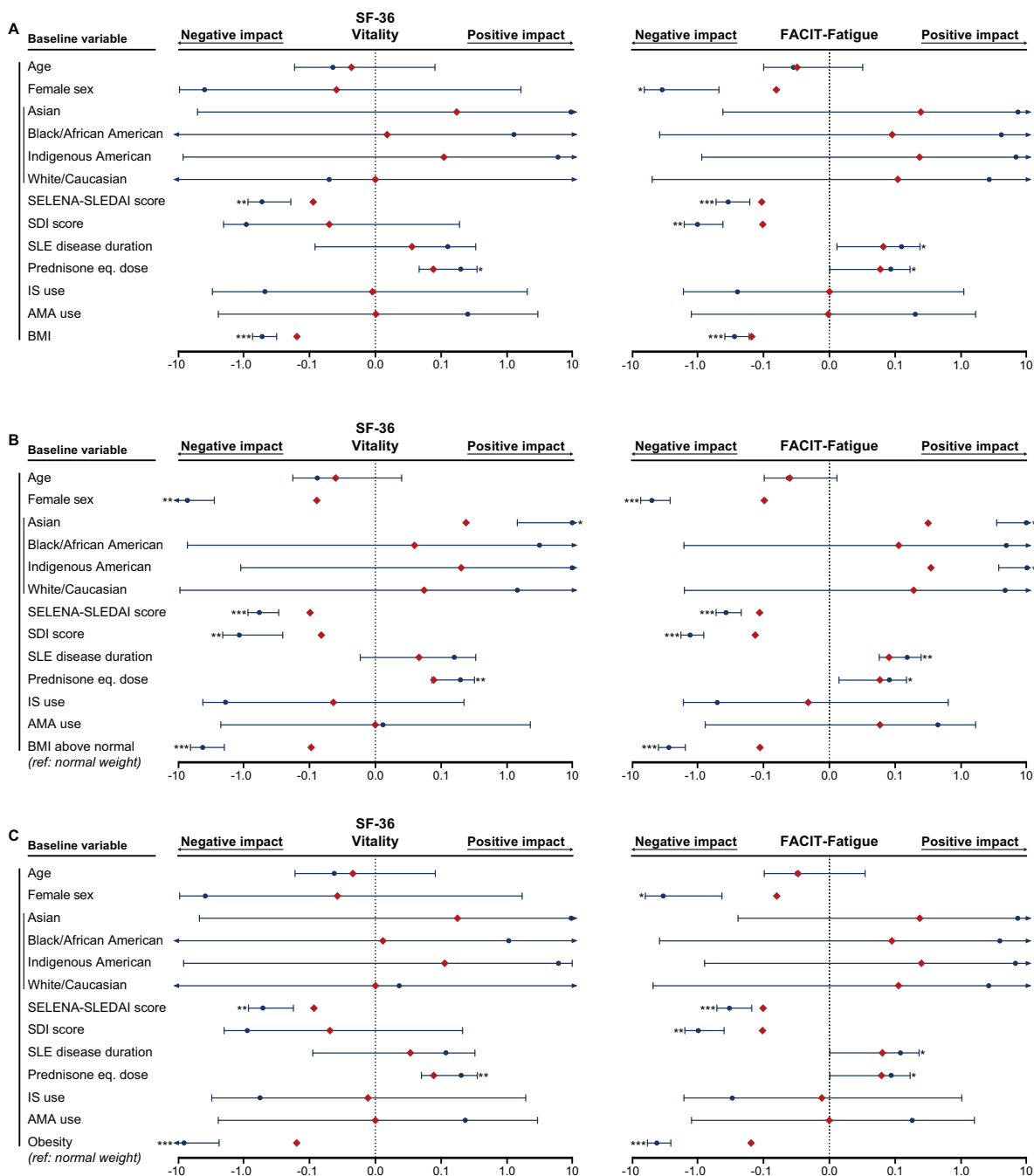Fig. 4 Associations of BMI with SF-36 MCS and SF

The forest plots illustrate results from multiple linear regression models. (**A**) BMI was analysed as a continuous variable. Separate models for the (**B**) BMI above normal and (**C**) obesity groups were created, with the normal weight group as the reference comparator in both cases. The dark blue circles represent the unstandardized coefficients and the whiskers represent the 95% CIs. The red diamonds represent the standardized coefficients. Asterisks indicate statistically significant associations. Level of significance: *P < 0.05, **P < 0.01, ***P < 0.001. IS: immunosuppressants; AMA: antimalarial agents.

Rheumatology online), but BMI above normal ($\beta = -0.05$, $P = 0.041$) was associated with lower MCS scores (Supplementary Table S7, available at *Rheumatology* online). Furthermore, we observed a negative impact of BMI above normal and obesity on VT ($\beta = -0.09$, $P < 0.001$ and $\beta = -0.16$, $P < 0.001$, respectively; Fig. 5) and SF ($\beta = -0.09$, $P < 0.001$ and $\beta = -0.10$, $P = 0.001$, respectively; Fig. 4).

FIG. 5 Associations of BMI with SF-36 VT and FACIT-Fatigue

The forest plots illustrate results from multiple linear regression models. (**A**) BMI was analysed as a continuous variable. Separate models for the (**B**) BMI above normal and (**C**) obesity groups were created, with the normal weight group as the reference comparator in both cases. The dark blue circles represent the unstandardized coefficients and the whiskers represent the 95% CIs. The red diamonds represent the standardized coefficients. Asterisks indicate statistically significant associations. Level of significance: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. IS: immunosuppressants; AMA: antimalarial agents.

Likewise, there was an association between diminished FACIT-Fatigue scores and high BMI, independent of SLE disease duration and prednisone equivalent dose positively impacting on FACIT-Fatigue scores and female sex, SELENA-SLEDAI score and SDI score negatively impacting on FACIT-Fatigue scores (Fig. 5). Furthermore, higher BMI was consistently associated with lower EQ-5D utility index scores in all models

([Supplementary Fig. S1](#), available at *Rheumatology* online). High BMI was associated with low EQ-5D VAS scores when BMI was treated as a continuous variable ($\beta = -0.07$, $P = 0.045$), but statistical significance was not reached when BMI was treated as a dichotomous variable assessing the impact of BMI above normal ($\beta = -0.05$, $P = 0.063$) and obesity ($\beta = -0.06$, $P = 0.061$).

Higher SELENA-SLEDAI scores were associated with lower SF-36 PCS and MCS scores as well as lower FACIT-Fatigue scores in all models. We also found that SDI scores were negatively associated with SF-36 PCS scores and FACIT-Fatigue scores, but no association was seen with SF-36 MCS scores. Finally, older age was associated with impairments in physical aspects of SF-36, i.e. PCS, PF, RP and BP ([Figs 2](#) and [3](#)), but no association was found with regard to mental aspects of SF-36, with the exception of RE ($\beta = -0.10$, $P = 0.005$).

Discussion

In the present post hoc analysis of the BLISS-52 and BLISS-76 trials, we demonstrated that overweight and obese patients with SLE experience clinically important impairments of HRQoL, especially with regard to physical aspects and fatigue. The observed associations were independent of age, sex, ethnic origin, disease duration, disease activity, organ damage accrual and current immunosuppressive treatment. Interestingly, we found that HRQoL diminutions were more prominent with increasing BMI with regard to physical domains, social functioning and fatigue.

The physical aspects of HRQoL showed the most prominent diminutions in patients with BMI above normal. These diminutions were clinically important regarding all outcomes in the obesity subgroups and all except SF-36 GH in overweight patients. Moreover, study participants with a gradually higher BMI experienced a gradually worse HRQoL in all physical SF-36 items. Importantly, these associations were independent of demographic and disease-related factors in linear regression analysis. Our findings are in conformity with previous studies of adult [5, 6] and juvenile [28] SLE populations, which, irrespective of the tool used for the HRQoL evaluation, reported poor physical performance in obese patients.

With regard to mental aspects of HRQoL, vitality and social functioning were substantially impaired in patients with BMI above normal. This association was more prominent with increasing BMI, including increasing degree of obesity. Again, it is worth noting that the observed associations were independent of the impact of disease activity, organ damage and current immunosuppressive treatment. Overweight patients reported poorer SF-36 MCS and RE compared with normal weight individuals, but these differences did not reach the cut-off of clinical importance and were absent in the comparison between obese and normal weight individuals. The lower numbers of patients in the groups of

obesity-level BMI may constitute a possible explanation. Nonetheless, the divergent findings within mental aspects of HRQoL are in line with previous observations both in the general [29–31] and SLE [5, 6, 9] populations. de Zwaan *et al.* [29] found no association between BMI and SF-36 MCS scores and Busutil *et al.* [30] reported no association between BMI and 12-item General Health Questionnaire scores, a self-reported measure for mental well-being [32], both in the general population. Zhu *et al.* [5] showed that overweight and obese patients with SLE had lower SF-36 MCS, VT, SF, RE and MH scores compared with the normal weight group, whereas Tamayo *et al.* [6] found no association between BMI and SF-36 MCS scores in a German cohort of SLE patients.

Associations between BMI and the mental compartment of HRQoL have to be interpreted in the context of the interplay of psychosocial factors influencing HRQoL in opposing directions; such factors may include stress, depressive symptoms, chronic pain and psychological adjustment processes in patients with long-standing disease [33]. Nonetheless, as previously proposed by Busutil *et al.* [30], the potential lack of sensitivity to detect impairment in mental aspects of HRQoL with a generic measure such as the SF-36 as a possible explanation underlying our observations warrants investigation.

Overweight and obese patients reported poor FACIT-Fatigue scores, experiencing a gradual impairment with increasing BMI. As expected, these observations were consistent with the results derived from the analysis of the SF-36 VT subscale. The differences in the overweight and obese groups *vs* normal weight individuals were clinically important; it is worth noting that the MCID in this study was set to 4 points on the FACIT-Fatigue scale [22], albeit lower MCIDs have also been estimated in certain SLE populations [23]. In all models, the impact of high BMI on fatigue was independent of the effect of disease activity, organ damage and concomitant drug use, and even more prominent. These findings have to be interpreted with caution since the degree of SLE activity in this study was limited by the inclusion and exclusion criteria of the BLISS trials, in particular SELENA-SLEDAI scores ≥ 6 and no severe active renal or neuropsychiatric SLE. Nonetheless, the consistency of this association is of particular importance in light of fatigue being the most frequent complaint in patients with SLE, reported by up to 92% of patients in different cohorts [3, 34] and up to 23% of patients in remission [35], pointing to the need for exploration of the underlying reasons at a biological level.

One could argue that disease activity may constitute a link between BMI and fatigue, with overweight maintaining an inflammatory state [10], subsequently resulting in fatigue. In the present study, however, we found no difference in the degree of SLE disease activity across the different BMI categories. Moreover, the literature has been conflicting regarding the relationship between disease activity and fatigue, with some studies reporting

detrimental effects [5, 8, 29] and others showing no association [2, 36], even when the same tools for measuring disease activity were used. Herein the impact of high BMI, in particular obesity, was more pronounced than the impact of disease activity on SF-36 VT and FACIT-Fatigue scores in multivariable regression models. Although the potential bias imposed by the selected SLE population of the BLISS trials has to be reckoned with during interpretation, our findings highlight the importance of including factors such as suboptimal weight in the clinical evaluation for the management of fatigued SLE patients. Indeed, fatigue is acknowledged as one of the most important components of the global SLE burden, which has important implications with regard to socio-economic facets [4]. Results from our study advocate for multidimensional strategies including non-pharmacological approaches, such as weight control, along with pharmacological interventions that have proven efficacy in reducing fatigue [22, 26, 37], towards optimization of patient care and use of societal resources.

Our results were interpreted in the context of previously determined thresholds for clinically important differences, validated for SLE populations [38–40]. The use of validated MCIDs allows clinicians, patients, researchers and policymakers to perform meaningful evaluations of the data, especially when interpretation of the numerical scales of different tools is not intuitive. Furthermore, defining MCIDs is particularly important when large patient samples are analysed, such as the one in the present post hoc analysis, since small and clinically futile numerical differences may reach the level of statistical significance [41, 42]. MCIDs utilized in the present study have been used to assess change over time in previous literature, i.e. improvement or worsening, whereas the comparisons herein were cross-sectional. For this reason, we chose to set the MCIDs to the highest thresholds previously reported. This stringent approach may underestimate some differences, such as the ones observed in the SF-36 MCS, EQ-5D utility index and EQ-5D VAS scores, but ensures the clinical relevance of our findings.

The post hoc nature of the present study was a limitation. The BLISS trials were not designed to evaluate patients' HRQoL and can be underpowered for detecting differences in certain indices. Moreover, our cross-sectional study was not designed to address the potential causal relationship between body weight and HRQoL. It is important to note that data collected within the frame of the BLISS-52 and BLISS-76 trials may differ from what is encountered in daily clinical practice, even if our investigation was based on baseline data only, i.e. prior to the trial intervention. This selection bias introduced by trial design may limit the generalizability of our findings. For instance, patients were strictly selected to have active SLE, defined as a SELENA-SLEDAI score ≥6, and a stable treatment regimen with a prednisone equivalent dose between 0 and 40 mg/day, antimalarial agents, NSAIDs or conventional immunosuppressants for a period of at least 30 days prior to baseline. Finally, patients with severe active lupus nephritis and central nervous system manifestations were excluded from the BLISS programmes. The potential impact of body weight remains to be addressed in these subsets of SLE patients, especially since the mental compartment of HRQoL is expected to be particularly affected in the latter group.

Nonetheless, the large study population and the homogeneous data collection in the BLISS-52 and BLISS-76 trials allowed us to adjust for multiple factors known to impact SLE patients' HRQoL and factors with confounding potentiality. To our knowledge, this is one of the largest analyses to date of SLE patients' BMI in relation to HRQoL.

Conclusion

In the present analysis of 1681 patients with SLE, overweight and obesity were highly associated with clinically important HRQoL diminutions. High BMI was found to particularly impact physical HRQoL aspects, as well as fatigue and social functioning among mental aspects. The observed associations were independent of other factors, including disease activity, organ damage, and current treatment. Notably, the impact of BMI on physical aspects of HRQoL and fatigue was more pronounced than that of SLE disease activity, disease duration and organ damage. Longitudinal investigation to address causality is warranted. As a future perspective, results from such surveys could be a prelude to the implementation of weight control strategies as a complementary intervention to current pharmacological management of lupus patients.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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