


Original article

Contribution of abnormal BMI to adverse health-related quality of life outcomes after a 52-week therapy in patients with SLE

Alexander Borg^{1,2}, Alvaro Gomez^{1,2}, Arvid Cederlund^{1,2}, Flordelyn Cobar^{1,2}, Victor Qiu^{1,2}, Julius Lindblom^{1,2}, Sharzad Emamikia^{1,2}, Yvonne Enman^{1,2}, Susanne Pettersson^{2,3} and Ioannis Parodis ^{1,2}

Abstract

Objectives. To investigate whether abnormal BMI is associated with adverse health-related quality of life (HRQoL) outcome, including severe fatigue, after 52 weeks of standard therapy plus belimumab or placebo in patients with SLE.

Methods. We analysed data from the BLISS-52 (NCT00424476) and BLISS-76 (NCT00410384) trials ($n=1684$). Adverse HRQoL was defined as SF-36 scores \leq the fifth percentile in age- and sex-matched US population-based subjects, and FACIT-F scores <30 . We compared BMI groups using the Pearson's χ^2 test, and assessed independence with multivariable logistic regression analysis.

Results. Overweight (BMI ≥ 25 kg/m²) and obese (BMI ≥ 30 kg/m²) patients showed increased likelihood to exhibit adverse SF-36 physical component summary (OR: 1.8; 95% CI: 1.4, 2.3; $P < 0.001$ and OR: 2.4; 95% CI: 1.8, 3.2; $P < 0.001$, respectively) and FACIT-F (OR: 1.3; 95% CI: 1.1, 1.6; $P = 0.010$ and OR: 1.5; 95% CI: 1.2, 2.0; $P = 0.002$, respectively) scores at week 52. Underweight was associated with adverse SF-36 mental component summary scores, also after adjustment for sex, ancestry, age, disease duration, disease activity, organ damage and prednisone dose during the study period (OR: 2.1; 95% CI: 1.2, 3.6; $P = 0.007$). Addition of belimumab to standard therapy independently protected against adverse SF-36 general health (OR: 0.8; 95% CI: 0.6, 1.0; $P = 0.025$) and FACIT-F < 30 (OR: 0.8; 95% CI: 0.6, 1.0; $P = 0.018$).

Conclusion. Overweight and obesity contributed to adverse physical and mental HRQoL outcomes after therapeutic intervention in SLE patients, and underweight contributed to adverse mental HRQoL outcome. A protective effect of belimumab against adverse general health and severe fatigue was implicated.

Key words: Systemic lupus erythematosus, health-related quality of life, patient-reported outcomes, patient perspective

Rheumatology key messages

- Overweight and obesity contribute to adverse physical health and social functioning after therapy in SLE.
- Underweight contributes to severely impaired mental health despite therapeutic intervention in patients with SLE.
- Addition of belimumab to standard therapy protects against adverse general health and severe fatigue.

¹Division of Rheumatology, Department of Medicine Solna, Karolinska Institutet, ²Department of Gastroenterology, Dermatology and Rheumatology, Karolinska University Hospital and ³Division of Physiotherapy, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden
Submitted 5 October 2020; accepted 30 November 2020

Correspondence to: Ioannis Parodis, Rheumatology, Karolinska University Hospital, SE-171 76, Stockholm.
E-mail: ioannis.parodis@ki.se

Introduction

Despite therapeutic advances during recent decades, patients with SLE experience substantial impairments in physical, mental and social aspects of health-related quality of life (HRQoL) [1–3]. While physician-based assessments and disease-specific outcomes are integrated in composite measures currently used for evaluation of SLE trial interventions, patient-reported HRQoL is omitted. However, patients often value their self-perception of HRQoL higher than disease activity strictly based on physical examination and laboratory tests [4]. It is, therefore, encouraging that the patient perspective receives increasing endorsement within the lupus research community [5]. In fact, as early as in 1998, during the OMERACT IV consensus conference, HRQoL emerged as one of the four important core outcomes for SLE clinical trials along with disease activity, medication side-effects and organ damage [6].

Data from current literature advocate that obesity is associated with higher SLE disease activity [7] and negatively impacts on HRQoL [8, 9]. Recently, we demonstrated that SLE patients' self-reported physical health, fatigue and social functioning were gradually worse with increasing BMI, and that overweight patients experienced clinically important impairments regarding physical aspects of HRQoL and fatigue [10]. Importantly, the impact of high BMI on these HRQoL aspects was greater than that of SLE disease activity. However, less is known about the impact of abnormal BMI on treatment outcome.

The aim of the present *post hoc* analysis of two phase III clinical trials was to investigate whether underweight, overweight or obesity is associated with adverse HRQoL outcome, including severe fatigue, in patients with active SLE after having received a 52-week therapeutic intervention with standard therapy (ST) plus belimumab or placebo.

Patients and methods

Study design

We used longitudinal data from baseline through week 52 deriving from the BLISS-52 (NCT00424476) [11] and BLISS-76 (NCT00410384) [12] clinical trials of belimumab. BLISS-52 comprised 865 and BLISS-76 comprised 819 adult patients with SLE according to the 1997 ACR classification criteria [13], with an ANA titre $\geq 1:80$ and/or a serum anti-dsDNA antibody level ≥ 30 IU/ml, and active SLE defined as a score of ≥ 6 in the Safety of Estrogens in Lupus National Assessment (SELENA)-SLEDAI [14].

Patients were on stable ST for at least 30 days prior to the trial intervention; this included glucocorticoids, antimalarial agents and/or immunosuppressants at tolerable doses. At baseline, patients were randomized to receive belimumab 1 mg/kg, belimumab 10 mg/kg or placebo along with ST, the latter mainly comprising

antimalarials (65.3%), azathioprine (23.1%), methotrexate (13.7%) and mycophenolic acid (11.2%), as summarized in Table 1. Belimumab and placebo were administered as intravenous infusions at baseline, week 2, week 4 and thereafter every fourth week until week 48 in BLISS-52 and until week 72 in BLISS-76. The primary end point was evaluated at week 52 in both trials. Therefore, we studied adverse HRQoL outcomes based on patient reports at week 52.

Data from the BLISS trials were made available by GlaxoSmithKline (Uxbridge, UK) through the Clinical Study Data Request consortium, and were restructured to serve the purpose of this study. Missing values were managed using the last observation carried forward principle for all variables but BMI; for the latter, the mean weight of the previous and next available visits was used to calculate the BMI, and the last observation carried forward principle was used to manage missing weight values when the last visit lacked a valid value. The similar design and identical inclusion and exclusion criteria of the BLISS-52 and BLISS-76 trials facilitated pooling of the data.

The study complied with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all study participants prior to enrolment. The BLISS-52 and BLISS-76 study protocols were reviewed and approved by regional ethics review boards for all participating centres, and the study protocol for this *post hoc* analysis was reviewed and approved by the Swedish Ethical Review Authority (2019–05498).

Adverse HRQoL

Patients reported self-perceptions of HRQoL using the Medical Outcome Study Short Form-36 (SF-36) health survey [15] and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale [16].

The SF-36 health survey is a generic instrument intended to assess perceived well-being in physical, social and mental aspects of life within four weeks preceding the assessment. It consists of 36 questions divided into 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). PF, RP, BP and GH denote physical, and MH, VT, SF and RE denote mental aspects of HRQoL. SF-36 subscale scores are calculated based on weighted formulas, and result into scores that range from 0 to 100 (transformed scores), where higher scores indicate better HRQoL. The eight subscales are weighted into two summary scores, i.e. the mental component summary (MCS) and the physical component summary (PCS), which are norm-referenced scores ranging from 0 to 100 with a mean of 50 and a s.d. of 10. It is worth noting that, albeit negatively, the mental subscales also contribute to the calculation of PCS and the physical subscales to the calculation of MCS. After management of missing values, all patients had available SF-36 data at week 52 ($n = 1684$).

TABLE 1 Demographics and clinical data of the entire study population and different BMI groups

	Underweight (n = 73)	Normal weight (n = 850)	Pre-obesity (n = 438)	Obesity (n = 323)	Total (n = 1684)
Demographics					
Age (years)	31.0 ± 9.8	35.3 ± 10.9	39.7 ± 11.3	43.4 ± 11.0	37.8 ± 11.5
Female sex	70 (95.9%)	808 (95.1%)	404 (92.2%)	303 (93.8%)	1585 (94.1%)
Ancestries:					
Asian	32 (43.8%)	237 (27.9%)	71 (16.2%)	15 (4.6%)	355 (21.1%)
Black/African American	6 (8.2%)	43 (5.1%)	49 (11.2%)	50 (15.5%)	148 (8.8%)
Indigenous American ^a	14 (19.2%)	193 (22.7%)	115 (26.3%)	61 (18.9%)	383 (22.7%)
White/Caucasian	21 (28.7%)	377 (44.4%)	203 (46.3%)	197 (61.0%)	798 (47.4%)
Clinical data					
SLE duration at baseline (years)	5.4 ± 6.0	6.3 ± 6.2	6.3 ± 6.4	7.0 ± 6.7	6.4 ± 6.4
Mean BMI (week 0–52)	17.7 ± 0.8	22.0 ± 1.8	27.2 ± 1.4	35.4 ± 4.9	25.8 ± 5.9
SLEDAI-2K score					
Baseline	10.5 ± 4.1	9.8 ± 3.8	10.1 ± 3.7	10.1 ± 4.0	10.0 ± 3.8
week 52	6.8 ± 5.1	6.1 ± 4.1	6.0 ± 4.5	6.2 ± 4.7	6.2 ± 4.4
SDI score					
Baseline	0.7 ± 1.1	0.6 ± 1.1	0.8 ± 1.3	1.1 ± 1.5; N = 322	0.8 ± 1.2; N = 1683
week 52	0.8 ± 1.1	0.7 ± 1.1	0.9 ± 1.3	1.2 ± 1.5; N = 322	0.8 ± 1.3; N = 1683
SDI score >0					
Baseline	0.4 ± 0.5	0.4 ± 0.5	0.5 ± 0.5	0.5 ± 0.5; N = 322	0.4 ± 0.5; N = 1683
week 52	0.4 ± 0.5	0.4 ± 0.5	0.5 ± 0.5	0.6 ± 0.5; N = 322	0.4 ± 0.5; N = 1683
Trial treatment					
Placebo	21 (28.8%)	296 (34.8%)	142 (32.4%)	103 (31.9%)	562 (33.4%)
Belimumab 1 mg/kg	29 (39.7%)	269 (31.6%)	154 (35.2%)	107 (33.1%)	559 (33.2%)
Belimumab 10 mg/kg	23 (31.5%)	285 (33.5%)	142 (32.4%)	113 (35.0%)	563 (33.4%)
Prednisone use	69 (94.5%)	755 (88.8%)	380 (86.8%)	249 (77.1%)	1453 (86.3%)
Prednisone eq. dose (mg/day)	10.6 ± 7.3	11.0 ± 8.5	11.1 ± 9.2	9.9 ± 8.6	10.8 ± 8.7
Immunosuppressant use					
Azathioprine	16 (21.9%)	195 (22.9%)	105 (24.0%)	73 (22.6%)	389 (23.1%)
Methotrexate	8 (11.0%)	112 (13.2%)	52 (11.9%)	59 (18.3%)	231 (13.7%)
Mycophenolic acid	8 (11.0%)	83 (9.8%)	56 (12.8%)	42 (13.0%)	189 (11.2%)
Other Immunosuppressants ^c	1 (1.4%)	17 (2.0%)	9 (2.1%)	6 (1.9%)	33 (2.0%)
Antimalarial agent use ^b	54 (74.0%)	576 (67.8%)	269 (61.4%)	201 (62.2%)	1100 (65.3%)

Data are presented as number (percentage) or mean (s.d.). In case of missing values, the total number of patients with available data is indicated. ^aAlaska Native or American Indian from North, South or Central America. ^bHydroxychloroquine, chloroquine, mepacrine, mepacrine hydrochloride or quinine sulphf. ^cCiclosporin, oral cyclophosphamide, leflunomide, mizoribine or thalidomide. eq.: equivalent; SDI: Systemic Lupus International Collaborating Clinics SLICC/American College of Rheumatology ACR Damage Index; SLE: systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index 2000.

As previously suggested [17], we defined adverse HRQoL outcomes as SF-36 scale scores ≤ the normative fifth percentile (NP5), i.e. the worst 5% of the scores reported from a US population-based control group individually matched for age and sex with the study participants (n=1684). We created this normative control group using summarized values stratified by sex and age categories, provided in user manuals by the creators of SF-36 [18, 19]. The selection of the US population-based norms was guided by early reports of HRQoL outcome in BLISS-52 and BLISS-76 [20]. The NP5 for each SF-36 item was calculated to the following values: PF ≤ 52.5; RP ≤ 29.8; BP ≤ 38.6; GH ≤ 41.0; VT ≤ 25.4; SF ≤ 46.2; RE ≤ 26.6; MH ≤ 43.4; PCS ≤ 36.0; MCS ≤ 34.5.

The FACIT-F scale is a generic index that comprises 13 questions and is intended to assess the degree of fatigue over a period of seven days preceding the assessment. The scores range from 0 to 52, with lower scores representing more severe fatigue. FACIT-F scores <30 denote severe fatigue [16], herein designating adverse FACIT-F outcome. The total number of patients with available FACIT-F registrations at week 52 after management of missing values was 1665.

BMI categories

Patients were stratified into groups based on their mean BMI during the study period (from baseline to week 52) according to the World Health Organization guidelines. BMI

<18.5 kg/m² denoted underweight, BMI ≥18.5 kg/m² and <25 kg/m² denoted normal weight, BMI ≥25 kg/m² denoted overweight, BMI ≥25 kg/m² and <30 kg/m² denoted pre-obesity, and BMI ≥30 kg/m² denoted obesity [21]. We further stratified the obesity group into three subclasses, i.e. obesity class I (BMI ≥30 kg/m² and <35 kg/m²), obesity class II (BMI ≥35 kg/m² and <40 kg/m²) and obesity class III (BMI ≥40 kg/m²).

Clinical assessments

SLE disease activity was evaluated using the SLEDAI-2K [22]. Organ damage was assessed using the SLICC/ACR Damage Index (SDI) [23].

Statistics

Data are presented as number (percentage) or mean (s.d.). The Pearson's χ^2 or Fisher's exact test was used for comparisons between BMI groups in the entire dataset and in calibration and validation sets randomly split into 60% and 40% of the patients, respectively, ensuring similar proportions of BMI categories. For assessment of independence and adjustment for potential confounders, we employed multivariable logistic regression analysis. The accuracy of the models was tested by training the pooled data using a 60% and 40% train and test set, respectively.

The RStudio version 3.6.2 (PBC, MA, USA) and IBM SPSS software version 26 (IBM Corp., NY, USA) were used for data management and statistical analyses. *P*-values <0.05 were considered statistically significant.

Results

Patient characteristics

Demographics and clinical characteristics of the study participants are presented in Table 1 for the entire population and the underweight, normal weight, pre-obesity and obesity groups, and in Table 2 for the obesity class I–III groups. The mean BMI score for the total population was 25.8 (±5.9) kg/m², and the distributions of BMI scores within each BMI group are provided in Table 1 and Table 2. A total of 73 patients were underweight (4.3%), 850 patients had BMI scores within the normal range (50.5%), 438 patients were pre-obese (26.0%) and 323 patients were obese (19.2%).

Adverse HRQoL outcomes

Overall, we observed large proportions of patients with adverse HRQoL outcomes at week 52, with the highest frequency within the entire population documented for SF-36 GH (39.0%) and the lowest frequency documented for RE (10.0%; Supplementary Table S1, available at *Rheumatology* online). Proportions of patients with PCS and MCS scores ≤NP5 at week 52 within different BMI groups are delineated in Fig. 1; actual data are provided in Supplementary Tables S1–S3, available at *Rheumatology* online.

Overweight patients showed increased likelihood compared with normal weight ones to exhibit adverse PCS (odds ratio, OR: 1.8; 95% CI: 1.4, 2.3; *P* <0.001). Increasing proportions of patients with PCS scores ≤NP5 were observed with increasing BMI category, yielding a 1.4 times increased chance in pre-obese (26.0%) compared with normal weight (20.0%) patients (OR: 1.4; 95% CI: 1.1, 1.9; *P* =0.013), a 2.4 times increased chance in obese patients (37.8%; OR: 2.4; 95% CI: 1.8, 3.2; *P* <0.001) and a 4.6 times increased likelihood in patients with obesity class III (53.7%; OR: 4.6; 95% CI: 2.7, 8.1; *P* <0.001). In contrast, higher proportions of MCS scores ≤NP5 were seen among underweight (31.5%; OR: 1.9; 95% CI: 1.1, 3.1; *P* =0.019) and patients with obesity class II (30.0%; OR: 1.7; 95% CI: 1.0, 2.9; *P* =0.033) compared with normal weight (19.9%) patients, while the other abnormal BMI groups did not differ from patients with normal weight (Fig. 1; Supplementary Tables S1–S3, available at *Rheumatology* online).

No difference was seen in proportions of patients with SF-36 subscale scores ≤NP5 at week 52 between the underweight and normal weight groups (Figs. 2 and 3; Supplementary Table S1, available at *Rheumatology* online). Proportions of patients with SF-36 subscale scores ≤NP5 at week 52 were greater among pre-obese vs normal weight patients regarding PF (30.6% vs 24.8%; OR: 1.3; 95% CI: 1.03, 1.7; *P* =0.027), RP (16.0% vs 9.9%; OR: 1.7; 95% CI: 1.04, 2.1; *P* =0.030) and SF (20.3% vs 14.0%; OR: 1.6; 95% CI: 1.2, 2.1; *P* =0.004), but did not differ regarding BP, GH, VT, RE or MH (Figs. 2 and 3; Supplementary Table S2, available at *Rheumatology* online). Proportions of patients with SF-36 subscale scores ≤NP5 were greater among obese vs normal weight patients for all SF-36 subscales but MH (Supplementary Table S2, available at *Rheumatology* online), with the associations being more prominent with increasing obesity category (Figs. 2 and 3; Supplementary Table S3, available at *Rheumatology* online).

Proportions of patients with FACIT-F scores <30 at week 52 were higher within overweight (36.0%) and obese (39.3%) compared with normal weight (30.0%) patients (OR: 1.3; 95% CI: 1.1, 1.6; *P* =0.010 and OR: 1.5; 95% CI: 1.2, 2.0; *P* =0.002, respectively), with this difference being more prominent among patients with obesity class II (51.3%; OR: 2.5; 95% CI: 1.6, 3.9; *P* <0.001) and patients with obesity class III (50.0%; OR: 2.3; 95% CI: 1.4, 4.1; *P* =0.002) (Fig. 1; Supplementary Tables S1–S3, available at *Rheumatology* online).

Similar patterns were observed in the calibration (Supplementary Fig. S1; Supplementary Tables S4–S6, available at *Rheumatology* online) and validation (Supplementary Fig. S2; Supplementary Tables S7–S9, available at *Rheumatology* online) groups.

Results from multivariable logistic regression analysis

We created multivariable logistic regression models with the different adverse HRQoL outcomes at week 52 as the dependent variables. Apart from BMI as a

TABLE 2 Demographics and clinical data of patients within different obesity classes

	Obesity class I (n = 189)	Obesity class II (n = 80)	Obesity class III (n = 54)	Obesity total (n = 323)
Demographics				
Age (years)	43.5 ± 11.7	43.4 ± 9.3	42.8 ± 11.2	43.4 ± 11.0
Female sex	174 (92.1%)	78 (97.5%)	51 (94.4%)	303 (93.8%)
Ancestries:				
Asian	11 (5.8%)	3 (3.8%)	1 (1.9%)	15 (4.6%)
Black/African American	27 (14.3%)	15 (18.8%)	8 (14.8%)	50 (15.5%)
Indigenous American ^a	43 (22.8%)	14 (17.5%)	4 (7.4%)	61 (18.9%)
White/Caucasian	108 (57.1%)	48 (60.0%)	41 (75.9%)	197 (61.0%)
Clinical data				
SLE duration at baseline (years)	7.1 ± 7.0	6.5 ± 6.0	7.5 ± 6.4	7.0 ± 6.7
Mean BMI (week 0–52)	32.3 ± 1.5	36.9 ± 1.4	44.3 ± 3.6	35.4 ± 4.9
SLEDAI-2K score				
Baseline	10.3 ± 3.8	10.0 ± 4.5	9.1 ± 3.7	10.1 ± 4.0
week 52	5.9 ± 4.7	7.3 ± 5.4	5.8 ± 3.2	6.2 ± 4.7
SDI score				
Baseline	1.0 ± 1.4	1.4 ± 1.5; n = 79	1.3 ± 1.8	1.1 ± 1.5; n = 322
week 52	1.0 ± 1.4	1.4 ± 1.6; n = 79	1.3 ± 1.8	1.2 ± 1.5; n = 322
SDI score >0				
Baseline	0.5 ± 0.5	0.6 ± 0.5; n = 79	0.5 ± 0.5	0.5 ± 0.5; n = 322
week 52	0.5 ± 0.5	0.6 ± 0.5; n = 79	0.6 ± 0.5	0.6 ± 0.5; n = 322
Trial treatment:				
Placebo	67 (35.4%)	24 (30.0%)	12 (22.2%)	103 (31.9%)
Belimumab 1 mg/kg	59 (31.2%)	24 (30.0%)	20 (37.0%)	107 (33.1%)
Belimumab 10 mg/kg	63 (33.3%)	32 (40.0%)	22 (40.7%)	113 (35.0%)
Prednisone use	154 (81.5%)	64 (80.0%)	31 (57.4%)	249 (77.1%)
Prednisone eq. dose (mg/day)	10.8 ± 9.2	9.9 ± 7.5	6.8 ± 7.5	9.9 ± 8.6
Immunosuppressant use				
Azathioprine	43 (22.8%)	17 (21.3%)	13 (24.1%)	73 (22.6%)
Methotrexate	31 (16.4%)	16 (20.0%)	12 (22.2%)	59 (18.3%)
Mycophenolic acid	29 (15.3%)	4 (5.0%)	9 (16.7%)	42 (13.0%)
Other immunosuppressants ^c	4 (2.1%)	1 (1.3%)	1 (1.9%)	6 (1.9%)
Antimalarial agent use ^b	113 (59.8%)	54 (67.5%)	34 (63.0%)	201 (62.2%)

Data are presented as number (percentage) or mean (s.d.). In case of missing values, the total number of patients with available data is indicated. ^aAlaska Native or American Indian from North, South or Central America. ^bHydroxychloroquine, chloroquine, mepacrine, mepacrine hydrochloride or quinine sulphf. ^cCiclosporin, oral cyclophosphamide, leflunomide, mizoribine or thalidomide. eq.: equivalent; SDI: Systemic Lupus International Collaborating Clinics SLICC/American College of Rheumatology ACR Damage Index; SLE: systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index 2000.

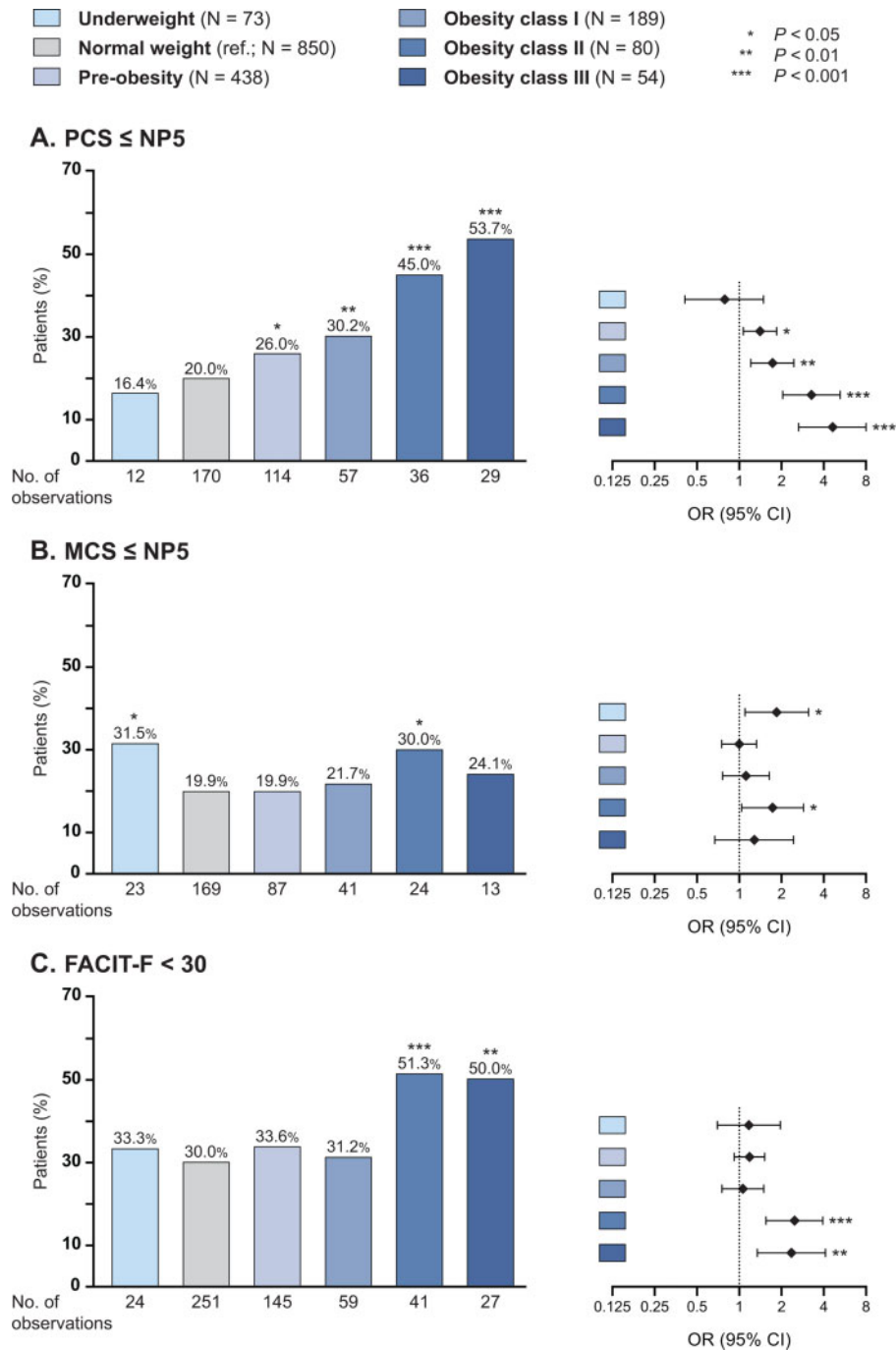
continuous variable or BMI categories, covariates in the models comprised sex, ancestry, age and SLE disease duration at baseline, disease activity burden measured as the area under the curve (AUC) of SLEDAI-2K scores between baseline and week 52 normalized to a scale ranging from the lowest to the highest observed score (0–36), mean SDI scores from baseline to week 52, mean daily prednisone equivalent doses from baseline to week 52, and addition of belimumab to ST (with placebo as the reference comparator).

When BMI was treated as a continuous variable in the models, increasing BMI scores were independently associated with adverse HRQoL in multiple domains. Those included PCS (OR: 1.04; 95% CI: 1.0, 1.1; $P < 0.001$), PF (OR: 1.04; 95% CI: 1.0, 1.1; $P < 0.001$), BP (OR: 1.03; 95% CI: 1.0, 1.1; $P = 0.013$) and GH (OR:

1.02; 95% CI: 1.0, 1.0; $P = 0.027$) among the physical SF-36 items, and VT (OR: 1.03; 95% CI: 1.0, 1.1; $P = 0.011$) and SF (OR: 1.03; 95% CI: 1.0, 1.1; $P = 0.002$) among the mental SF-36 items (Fig. 4; Supplementary Table S10, available at *Rheumatology* online). Notably, addition of belimumab to ST was found to be protective against adverse GH (OR: 0.8; 95% CI: 0.6, 1.0; $P = 0.025$).

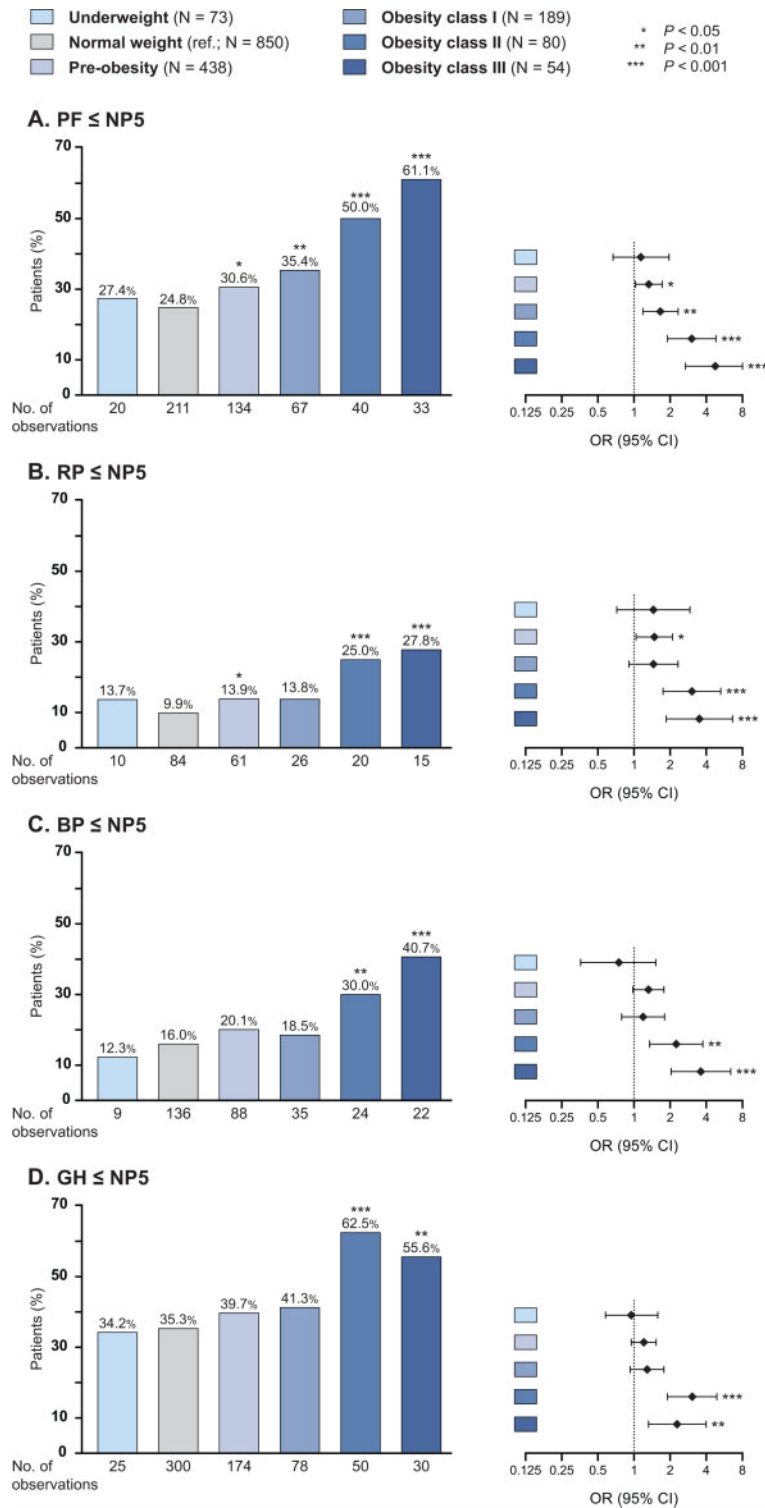
BMI scores corresponding to underweight were associated with SF-36 MCS (OR: 2.1; 95% CI: 1.2, 3.6; $P = 0.007$), RE (OR: 2.1; 95% CI: 1.0, 4.5; $P = 0.048$) and MH (OR: 2.2; 95% CI: 1.1, 4.1; $P = 0.015$) scores \leq NP5 (Fig. 4; Supplementary Table S11, available at *Rheumatology* online). Overweight was associated with adverse PCS (OR: 1.3; 95% CI: 1.0, 1.7; $P = 0.033$) and SF (OR: 1.5; 95% CI: 1.2, 2.0; $P = 0.003$) scores (Fig. 4;

Fig. 1 Associations between BMI and adverse PCS, MCS and FACIT-F outcome



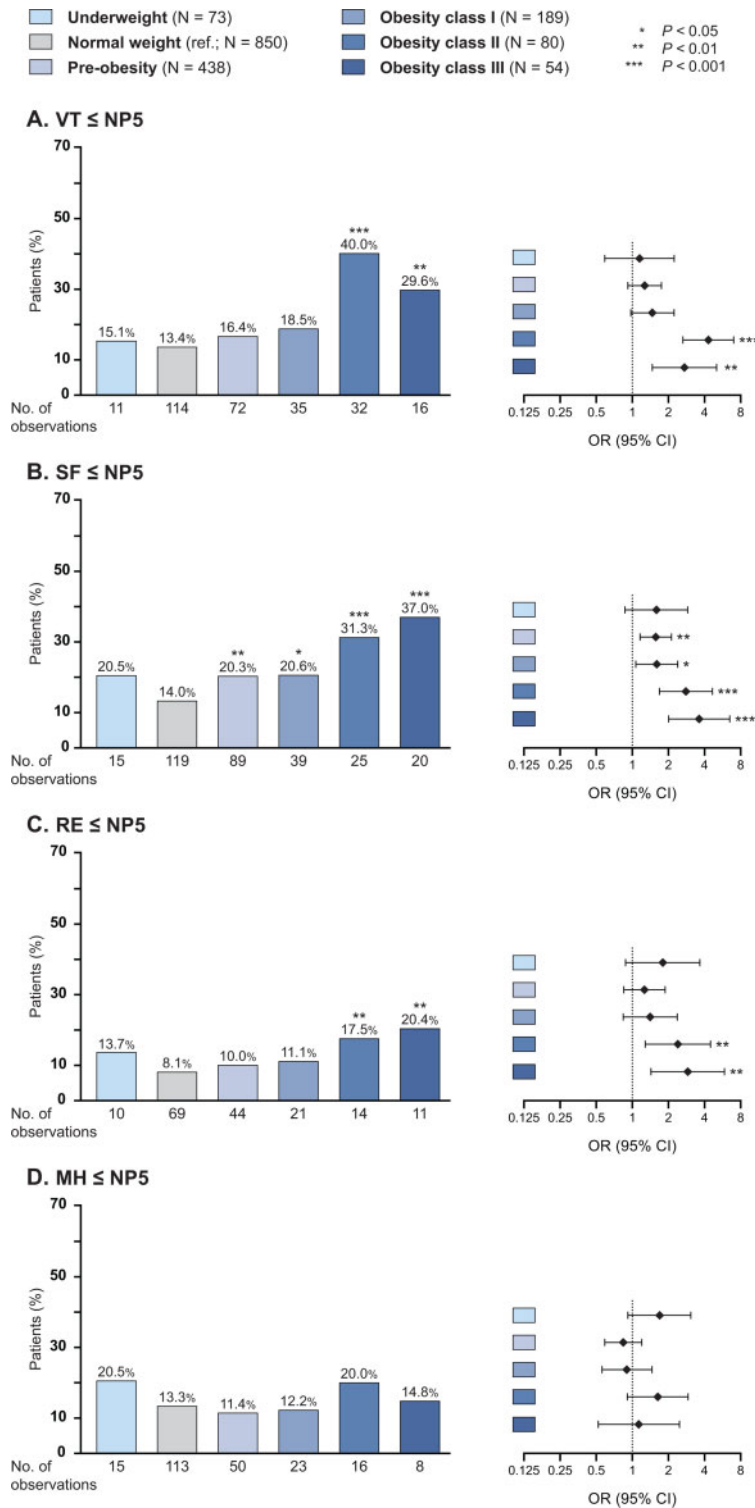
The bars delineate proportions of patients with adverse SF-36 PCS (A), SF-36 MCS (B) and FACIT-F (B) at week 52 from treatment initiation, stratified by BMI categories. Comparisons between abnormal BMI groups and normal weight patients were conducted using Pearson's χ^2 tests. The number of patients within the different BMI categories is indicated below the corresponding chart. The forest plots illustrate the corresponding unadjusted ORs and 95% CIs, with normal weight patients as comparators. Significant P -values are indicated with asterisks. FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; MCS: mental component summary; NP5: normative fifth percentile; OR: odds ratio; PCS: physical component summary.

Fig. 2 Associations between BMI and adverse HRQoL outcome within physical SF-36 domains



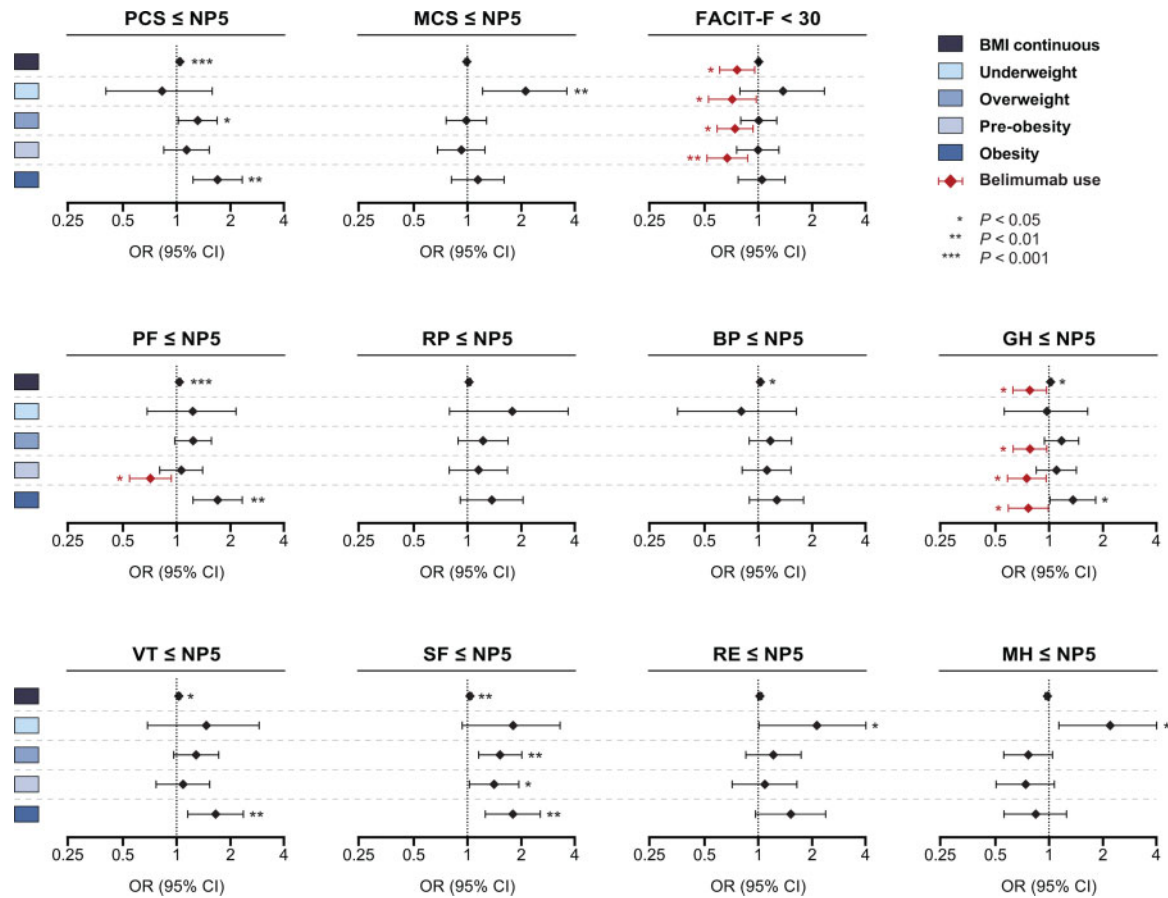
The bars delineate proportions of patients with adverse SF-36 PF (A), SF-36 RP (B), SF-36 BP (C) and SF-36 GH (D) at week 52 from treatment initiation, stratified by BMI categories. Comparisons between abnormal BMI groups and normal weight patients were conducted using Pearson's χ^2 tests. The number of patients within the different BMI categories is indicated below the corresponding chart. The forest plots illustrate the corresponding unadjusted ORs and 95% CIs, with normal weight patients as comparators. Significant P -values are indicated with asterisks. BP: bodily pain; GH: general health; NP5: normative fifth percentile; OR: odds ratio; PF: physical functioning; RP: role physical.

Fig. 3 Associations between BMI and adverse HRQoL outcome within mental SF-36 domains



The bars delineate proportions of patients with adverse SF-36 VT (A), SF-36 SF (B), SF-36 RE (C) and SF-36 MH (D) at week 52 from treatment initiation, stratified by BMI categories. Comparisons between abnormal BMI groups and normal weight patients were conducted using Pearson's χ^2 tests. The number of patients within the different BMI categories is indicated below the corresponding chart. The forest plots illustrate the corresponding unadjusted ORs and 95% CIs, with normal weight patients as comparators. Significant P-values are indicated with asterisks. MH: mental health; NP5: normative fifth percentile; OR: odds ratio; RE: role emotional; SF: social functioning; VT: vitality.

Fig. 4 Associations between BMI and adverse HRQoL



The forest plots illustrate ORs and 95% CIs, generated from multiple logistic regression analyses, in models where apart from the different BMI categories, age, sex, ancestry, SLE duration, disease activity burden, organ damage and prednisone equivalent dose during the study period and belimumab treatment were included as covariates. In models where use of belimumab displayed a significant independent association with adverse HRQoL outcome, the corresponding result has been plotted in red. Significant *P*-values are indicated with asterisks. BP: bodily pain; GH: general health; MH: mental health; NP5: normative fifth percentile; OR: odds ratio; PF: physical functioning; RE: role emotional; RP: role physical; SF: social functioning; VT: vitality.

Supplementary Table S12, available at *Rheumatology* online); again, addition of belimumab to ST protected patients against adverse GH (OR: 0.8; 95% CI: 0.6, 1.0; *P* =0.017).

Pre-obesity was associated with SF-36 SF scores ≤NP5 at week 52 (OR: 1.4; 95% CI: 1.0, 1.9; *P* =0.034), while add-on belimumab was found to protect patients against adverse PF (OR: 0.7; 95% CI: 0.6, 0.9; *P* =0.014) and GH (OR: 0.8; 95% CI: 0.6, 1.0; *P* =0.024) (Fig. 4; Supplementary Table S13, available at *Rheumatology* online). Obesity was associated with adverse PCS (OR: 1.7; 95% CI: 1.2, 2.3; *P* =0.001), PF (OR: 1.6; 95% CI: 1.2, 2.2; *P* =0.003), GH (OR: 1.4; 95% CI: 1.0, 1.8; *P* =0.041), VT (OR: 1.7; 95% CI: 1.2, 2.4; *P* =0.006) and SF (OR: 1.8; 95% CI: 1.3, 2.6; *P* =0.001) scores (Fig. 4; Supplementary Table S14, available at *Rheumatology* online); add-on belimumab protected against adverse GH (OR: 0.8; 95% CI: 0.6, 1.0; *P* =0.045).

Finally, while no significant association between increasing BMI and FACIT-F scores <30 at week 52 was documented in multivariable logistic regression analysis (OR: 1.01; 95% CI: 1.0, 1.0; *P* =0.492), addition of belimumab to ST was protective against severe fatigue in multiple models (Fig. 4; Supplementary Table S15, available at *Rheumatology* online).

No interaction between mean BMI scores or BMI category and disease activity burden was noted, with the exception of an interaction between underweight and normalized SLEDAI-2K AUC with regard to adverse SF-36 GH (OR: 0.9; 95% CI: 0.8, 0.9; *P* =0.003); the associations of underweight and SLEDAI-2K AUC with adverse GH were still significant after inclusion of their interaction in the model. The model accuracy ranged from 0.64–0.92.

Increasing age and SLEDAI-2K AUC were independently associated with adverse HRQoL outcome in

multiple domains, as was increasing organ damage within physical but not mental HRQoL. Increasing disease duration was inversely associated with adverse PF, BP, VT, SF and FACIT-F scores <30. Using White/Caucasian individuals as the reference due to their highest prevalence in the study population, Asian ancestry was inversely associated with adverse HRQoL outcome in multiple physical and mental domains, including severe fatigue, while Indigenous American patients showed inverse associations with adverse HRQoL outcome mainly within mental domains and severe fatigue (Supplementary Tables S10–S15, available at *Rheumatology* online).

Discussion

We demonstrated overall high frequencies of adverse patient-reported HRQoL in patients with active SLE given a 52-week long standard therapy along with belimumab or placebo. The lowest frequency of adverse HRQoL outcome in the entire BLISS study population was documented for role emotional (10%) and the highest for general health (39%). Overweight and obesity exerted a negative impact on patient-reported HRQoL outcome, particularly within physical aspects; however, also regarding vitality and social functioning. Moreover, a negative impact of underweight on HRQoL outcome was implied within mental aspects; to our knowledge, this finding is novel for patients with SLE. Lastly, we demonstrated that addition of belimumab to standard therapy protected against adverse general health and severe fatigue.

Patients with SLE experience substantial impairments in HRQoL compared with the general population. In several aspects, e.g. perceptions of general health, bodily pain and social functioning, these impairments have been shown to be more prominent in SLE than in more common chronic illnesses such as congestive heart failure and diabetes mellitus [2]. It is known that obesity has a negative impact on SLE disease activity [7] and HRQoL in the general population [8, 9, 24, 25]. We recently showed that self-reported physical health, fatigue and social functioning were gradually worse with increasing BMI. In the same report, we showed that pre-obese and obese patients with SLE experienced more prominent impairments in physical aspects of HRQoL and more prominent fatigue than normal weight patients, with these divergences exceeding cut-offs for clinically important differences [10]. In the present study, we demonstrated a detrimental effect of overweight and obesity on the efficacy of a 52-week intervention with ST plus belimumab or placebo with regard to physical aspects of HRQoL, vitality and social functioning. In subgroup analysis of patients within different BMI categories, a prominent and manifold negative impact was observed in gradually higher BMI categories. For instance, pre-obesity was primarily associated with higher frequencies of adverse social functioning while greater proportions of obese vs normal weight patients reported

adverse outcomes in multiple HRQoL domains, i.e. general health, physical and social functioning, pain and vitality.

An interesting and, to our knowledge, novel finding was that underweight was independently associated with adverse SF-36 MCS. This association held true for role emotional and mental health among the mental SF-36 subscales. It is known that patients with SLE suffer an impaired mental HRQoL compared with healthy individuals [1]. Our results suggest that abnormally low BMI may have an additive negative impact on how SLE patients perceive their mental health status, also after therapeutic intervention. Possible explanations could be traced to comorbidities of psychiatric nature or neuropsychiatric affliction as a part of the clinical disease phenotype, resulting in e.g. an aberrant perception of self-image, potentially contributing to a negative impact on the body weight, mental health, or both. This study was not designed to address a potential causal relationship between underweight and adverse mental health or, if present, its direction. Neither was it possible to explore comorbid conditions as potential confounders. Nevertheless, further investigation of this association in future studies has merit.

Increasing age and burden of SLE disease activity during the study period were independently associated with adverse HRQoL outcome in multiple domains, as was increasing organ damage within physical albeit not mental HRQoL aspects. Compared with White/Caucasian individuals, Asian ancestry was protective against adverse HRQoL outcome in multiple physical and mental domains, including severe fatigue, and Indigenous American patients were protected against adverse mental HRQoL outcome and severe fatigue. A finding of particular interest was that increasing disease duration was inversely associated with adverse physical functioning and bodily pain, as well as adverse social functioning and severe fatigue, the latter both based on SF-36 vitality scores <NP5 and FACIT-F scores <30. A reasonable explanation underlying this association could be that patients show a gradual acceptance of living with a chronic disease and its consequences over time, and find ways to cope with practical problems and accrued disability. In support of this notion are associations between disease duration and an increasing level of acceptance in e.g. inflammatory bowel disease [26] and multiple sclerosis [27]. Using the example of pain, coping strategies have been shown to be associated with improved well-being, reduced anxiety and depression, and less physical and psychosocial disability [28, 29]. Collectively, complementary trajectories in disease management along with conventional pharmacotherapy, such as cognitive, emotional and behavioural intervention, may have merit for patients with SLE.

In the BLISS-52 and BLISS-76 trials, the patients were treated with ST plus belimumab or placebo. An important observation in the present *post hoc* analysis was that addition of belimumab to ST was an independent protective factor against adverse general health and

severe fatigue after 52 weeks of treatment. Belimumab use also displayed a protective effect against adverse physical functioning in pre-obese patients; no such association was, however, seen in obese patients, possibly due to the low number of patients in this group, abating the power in statistical analysis. In early studies, belimumab was shown to be superior over placebo in inducing HRQoL improvements within physical, mental and social aspects [11, 12, 20, 30–32], especially in patients showing clinical improvement [33]. However, the documentation of a protective effect of belimumab against adverse HRQoL outcomes is novel. Adverse HRQoL outcome despite treatment, persistent pain in particular, has been shown to be a frequent problem in RA [34], while addition of a biological agent to conventional disease-modifying therapy reduced the risk of this outcome by >30%, yielding a greater amelioration than triple therapy with non-biological agents [35]. Such observations support the notion that molecular explanations are underlying patient perceptions of health state and HRQoL outcomes, at least partly, and that selective modulation is likely to exert a benefit that is superior to that of broad immunosuppression. Collectively, biological therapy might partially reverse the negative impact of overweight.

Dysregulation of the lipid profile has been shown to correlate with SLE disease activity [36, 37], and SLE is known to increase the risk of cardiovascular comorbidities and cardiovascular mortality, especially in patients with specific genetic cargo, antiphospholipid antibodies and exposure to tobacco smoking [38–41]. It is reasonable to assume that a proportion of patients with aberrant BMI also have a dysregulated lipid profile, with SLE *per se* and/or SLE disease activity likely potentiating this dysregulation. In our models, SLE disease activity and aberrant BMI were independent contributors to adverse HRQoL outcomes, also after accounting for a potential interaction between them. However, prospective studies specifically designed to address this question are warranted to further support weight control strategies as a complementary intervention along with pharmacotherapy for the management of patients with SLE. Identification of such influenceable factors that are associated with adverse outcome after therapy is important, and may have direct implications in clinical practice.

The study may have been underpowered for some analyses, as the initial BLISS-52 and BLISS-76 trials were not designed to address our questions. Thus, no safe implications can be gleaned regarding potential causalities between aberrant BMI and adverse HRQoL, or their direction. The exclusion criteria of the BLISS trials limit the generalisability of the results; for instance, the findings may not be applicable to severe active LN populations or SLE patients with active severe CNS involvement. Moreover, we lacked data on economic and educational background of the patients, and were therefore unable to adjust for their impact on HRQoL outcomes. The clinical significance of the cut-offs used to

define adverse HRQoL in SF-36 items has yet to be determined; however, the concept was borrowed from another rheumatic disease, i.e. RA [17], which along with their stringency provides reassurance. The large number of participants allowed for stratification into BMI categories and adjustments in multivariable regression models, contributing to a deeper understanding of the observed associations.

Conclusion

Patients with active SLE who received standard therapy plus belimumab or standard therapy alone for 52 weeks displayed a high frequency of adverse self-reported HRQoL, especially regarding general health. Overweight and obesity exerted a negative impact on treatment outcome with regard to physical HRQoL aspects, vitality and social functioning. Underweight was associated with adverse HRQoL outcome within mental aspects. Addition of belimumab to standard therapy was shown to protect against adverse general health and severe fatigue. Our findings suggest that molecular aetiologies may underlie failure of pharmacotherapy to induce satisfactory HRQoL outcomes, while weight control and selective immune modulation may exert independent benefits.

Acknowledgements

The authors would like to thank GlaxoSmithKline (Uxbridge, UK) for sharing the data from the BLISS-52 (NCT00424476) and BLISS-76 (NCT00410384) trials with the Clinical Study Data Request (CSDR) consortium, Dimitris Ladakis, Joaquin Matilla and Martin Pehr for their contribution in data management, as well as all participating patients. Conception and design of the work: A.B., A.G., Y.E., S.P., I.P. Data management: A.B., A.G., A.C., F.C., V.Q., J.L., S.E., I.P. Statistical analysis and interpretation of data: A.B., A.G., F.C., S.P., I.P. Manuscript draft: A.B., I.P. Critical revision of the manuscript for important intellectual content: all authors. All authors reviewed and approved the final version of the manuscript prior to submission, and agree to be accountable for all aspects of the work.

Funding: This work was supported by the GlaxoSmithKline Investigator-Sponsored Studies (ISS) programme, and grants from the Swedish Rheumatism Association (R-932236), King Gustaf V's 80-year Foundation (FAI-2019-0635), Professor Nanna Svartz Foundation (2019-00290), Ulla and Roland Gustafsson Foundation (2019-12), Region Stockholm and Karolinska Institutet. The funders had no role in the design of the study, the analyses or interpretation of data, the writing of the manuscript, or the decision to publish the results.

Disclosure statement: I.P. has received research funding from GlaxoSmithKline and Eli Lilly and Company, and honoraria from Gilead Sciences, GlaxoSmithKline and

Novartis. The other authors have declared no conflicts of interest.

Data availability statement

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

- Choi ST, Kang JI, Park IH *et al.* Subscale analysis of quality of life in patients with systemic lupus erythematosus: association with depression, fatigue, disease activity and damage. *Clin Exp Rheumatol* 2012; 30:665–72.
- Jolly M. How does quality of life of patients with systemic lupus erythematosus compare with that of other common chronic illnesses? *J Rheumatol* 2005;32:1706–8.
- Waldheim E, Elkan AC, Pettersson S *et al.* Health-related quality of life, fatigue and mood in patients with SLE and high levels of pain compared to controls and patients with low levels of pain. *Lupus* 2013;22:1118–27.
- Sanderson T, Morris M, Calnan M, Richards P, Hewlett S. Patient perspective of measuring treatment efficacy: the rheumatoid arthritis patient priorities for pharmacologic interventions outcomes. *Arthritis Care Res* 2010;62:647–56.
- Annapureddy N, Devilliers H, Jolly M. Patient-reported outcomes in lupus clinical trials with biologics. *Lupus* 2016;25:1111–21.
- Strand V, Gladman D, Isenberg D *et al.* Endpoints: consensus recommendations from OMERACT IV. Outcome Measures in Rheumatology. *Lupus* 2000;9: 322–7.
- Teh P, Zakhary B, Sandhu VK. The impact of obesity on SLE disease activity: findings from the Southern California Lupus Registry (SCOLR). *Clin Rheumatol* 2019; 38:597–600.
- Kolotkin RL, Andersen JR. A systematic review of reviews: exploring the relationship between obesity, weight loss and health-related quality of life. *Clin Obes* 2017;7:273–89.
- Kolotkin RL, Crosby RD, Williams GR, Hartley GG, Nicol S. The relationship between health-related quality of life and weight loss. *Obes Res* 2001;9:564–71.
- Gomez A, Hani Butrus F, Johansson P *et al.* Impact of overweight and obesity on patient-reported health-related quality of life in systemic lupus erythematosus. *Rheumatology* 2020;doi: 10.1093/rheumatology/keaa453.
- Navarra SV, Guzman RM, Gallacher AE *et al.* Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011;377:721–31.
- Furie R, Petri M, Zamani O *et al.* A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011;63:3918–30.
- Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40: 1725.
- Petri M, Kim MY, Kalunian KC *et al.* Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med* 2005;353:2550–8.
- Ware J, Sherbourne C. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
- Webster K, Cella D, Yost K. The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications, and interpretation. *Health and Quality of Life Outcomes* 2003;1:79.
- Druce KL, Jones GT, Macfarlane GJ, Basu N. Patients receiving anti-TNF therapies experience clinically important improvements in RA-related fatigue: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Rheumatology* 2015;54:964–71.
- Ware J, Snow K, Kosinski M, Gandek B. SF-36 Health Survey: Manual and Interpretation Guide. Boston: Health Institute, New England Medical Center, 1993.
- Ware J, Kosinski M, Keller S. SF-36 physical and mental health summary scales: a user's manual. Boston: New England Medical Center, 1994.
- Strand V, Levy RA, Cervera R *et al.* Improvements in health-related quality of life with belimumab, a B-lymphocyte stimulator-specific inhibitor, in patients with autoantibody-positive systemic lupus erythematosus from the randomised controlled BLISS trials. *Ann Rheum Dis* 2014;73:838–44.
- Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;894:1–253.
- Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002;29:288–91.
- Gladman D, Ginzler E, Goldsmith C *et al.* The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996;39:363–9.
- Busutil R, Espallardo O, Torres A *et al.* The impact of obesity on health-related quality of life in Spain. *Health Qual Life Outcomes* 2017;15:197.
- Hopman WM, Berger C, Joseph L *et al.* The association between body mass index and health-related quality of life: data from CaMos, a stratified population study. *Qual Life Res* 2007;16:1595–603.
- Kiebles JL, Doerfler B, Keefer L. Preliminary evidence supporting a framework of psychological adjustment to inflammatory bowel disease. *Inflamm Bowel Dis* 2010;16: 1685–95.

- 27 Wilski M, Gabryelski J, Broła W, Tomasz T. Health-related quality of life in multiple sclerosis: links to acceptance, coping strategies and disease severity. *Disabil Health J* 2019;12:608–14.
- 28 McCracken LM. Learning to live with the pain: acceptance of pain predicts adjustment in persons with chronic pain. *Pain* 1998;74:21–7.
- 29 McCracken LM, Eccleston C. Coping or acceptance: what to do about chronic pain? *Pain* 2003;105:197–204.
- 30 Bangert E, Wakani L, Merchant M, Strand V, Touma Z. Impact of belimumab on patient-reported outcomes in systemic lupus erythematosus: review of clinical studies. *Patient Relat Outcome Meas* 2019;10:1–7.
- 31 Parodis I, Sjøwall C, Jonsen A *et al*. Smoking and pre-existing organ damage reduce the efficacy of belimumab in systemic lupus erythematosus. *Autoimmun Rev* 2017;16:343–51.
- 32 Parodis I, Lopez Benavides AH, Zickert A *et al*. The impact of belimumab and rituximab on health-related quality of life in patients with systemic lupus erythematosus. *Arthritis Care Res* 2019;71:811–21.
- 33 Furie R, Petri MA, Strand V *et al*. Clinical, laboratory and health-related quality of life correlates of Systemic Lupus Erythematosus Responder Index response: a post hoc analysis of the phase 3 belimumab trials. *Lupus Sci Med* 2014;1:e000031.
- 34 Altawil R, Saevarsdottir S, Wedren S *et al*. Remaining pain in early rheumatoid arthritis patients treated with methotrexate. *Arthritis Care Res* 2016;68:1061–8.
- 35 Olofsson T, Wallman JK, Joud A *et al*. Pain over 2 years after start of biological versus conventional combination treatment in early rheumatoid arthritis: results from the randomised controlled SWEFOT trial. *Arthritis Care Res* 2020;doi: 10.1002/acr.24264.
- 36 Durcan L, Winegar DA, Connelly MA *et al*. Longitudinal evaluation of lipoprotein variables in systemic lupus erythematosus reveals adverse changes with disease activity and prednisone and more favorable profiles with hydroxychloroquine therapy. *J Rheumatol* 2016;43:745–50.
- 37 Zhou B, Xia Y, She J. Dysregulated serum lipid profile and its correlation to disease activity in young female adults diagnosed with systemic lupus erythematosus: a cross-sectional study. *Lipids Health Dis* 2020;19:40.
- 38 Gustafsson JT, Gunnarsson I, Kallberg H *et al*. Cigarette smoking, antiphospholipid antibodies and vascular events in Systemic Lupus Erythematosus. *Ann Rheum Dis* 2015;74:1537–43.
- 39 Gustafsson JT, Simard JF, Gunnarsson I *et al*. Risk factors for cardiovascular mortality in patients with systemic lupus erythematosus, a prospective cohort study. *Arthritis Res Ther* 2012;14:R46.
- 40 Lundstrom E, Gustafsson JT, Jonsen A *et al*. HLA-DRB104/13 alleles are associated with vascular disease and antiphospholipid antibodies in systemic lupus erythematosus. *Ann Rheum Dis* 2013;72:1018–25.
- 41 Svenungsson E, Gustafsson J, Leonard D *et al*. A STAT4 risk allele is associated with ischaemic cerebrovascular events and anti-phospholipid antibodies in systemic lupus erythematosus. *Ann Rheum Dis* 2010;69:834–40.