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Original article

The influence of obesity on response to tumour necrosis factor-α inhibitors in psoriatic arthritis: results from the DANBIO and ICEBIO registries

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Abstract

Objectives. To investigate the impact of obesity on response to the first TNF-α inhibitor (TNFI) treatment course in patients with PsA followed in routine care.

Methods. We performed an observational cohort study based on the Danish and Icelandic biologics registries. Kaplan–Meier plots, Cox and logistic regression analyses were performed to study the impact of obesity (BMI $\geqslant 30\,kg/m^2$) on TNFI adherence and response after 6 months (according to 20/50/70% improvement in ACR criteria and EULAR criteria). Subanalyses studied the impact of obesity according to gender, TNFI type and nationality.

Results. Among 1943 PsA patients (193 Icelandic/1750 Danish) identified in the registries, 1271 (65%) had available BMI and 408 (32%) were obese. The median follow-up-time was 1.5 years [interquartile range (IQR) 0.5–3.9]. Obese patients had higher baseline disease activity, for example, 28-joint DAS [mean 4.6 (S.D. 1.2) *vs* 4.4 (1.2)]; CRP [median 9 mg/l (IQR 5–19) *vs* 7 (3–18)] and visual analogue scale-pain [66 mm (IQR 48–76) *vs* 60 (38–74)], compared with non-obese patients (all $P < 0.05$). TNFI adherence was shorter in obese patients, especially among men, where the median TNFI duration was 2.5 years (95% CI 1.7, 3.2) in obese *vs* 5.9 (4.1, 7.7) in non-obese patients ($P < 0.01$). A EULAR good or moderate (EGOM) response was achieved by 55% of obese *vs* 65% of non-obese patients after 6 months ($P = 0.02$). In multivariable analyses, obesity increased the risk of TNFI withdrawal [hazard ratio 1.6 (95% CI 1.3, 2.0)] and reduced odds for EGOM response [odds ratio 0.47 (95% CI 0.29, 0.72)]. The impact of obesity was significant across genders, TNFI types and nationality.

Conclusion: Obesity was associated with higher disease activity and seemed to diminish response and adherence to TNFIs in PsA.

Key words: psoriatic arthritis, obesity, anti-TNF drugs, outcome measures, registry

CLINICAL SCIENCE

Rheumatology key messages

- Obesity is present in one-third of Danish and Icelandic PsA patients initiating TNFIs.
- Obesity is associated with higher disease activity and poorer adherence and response to TNFIs in PsA.
- The negative impact of obesity is evident across genders and TNFI drug types in PsA.

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Introduction

TNF-α inhibitors (TNFIs) have dramatically improved the treatment options for PsA in recent decades [1]. Nevertheless, substantial variability in the efficacy and tolerability of TNFIs exists in routine care, where a sustained response occurs in less than half of PsA patients [2, 3]. Individualized treatment strategies based on insight into prognostic profiles and response-modifying factors could

improve TNFI outcomes and overall care of PsA patients. Obesity is a common co-morbidity in PsA [4] that may exacerbate both the onset and severity of psoriatic disease, possibly due to enhancement of inflammatory processes [5–11]. Studies of SpA, RA and psoriasis have reported a reduced response and adherence to TNFIs in obese patients [12–19]. In PsA, the impact of obesity on TNFI treatment is still unclear since available studies are small, present diverging results and lack long-term follow-up data [18, 20–23].

The Danish (DANBIO) and Icelandic (ICEBIO) rheumatologic registries include nationwide data on patients with rheumatic diseases treated with TNFI in Denmark and Iceland since year 2000. By using these registries, we aimed to investigate the influence of obesity on disease activity and treatment outcomes in PsA patients initiating their first TNFI course in routine care. Additionally, we studied if an impact of obesity differed across gender, TNFI type and nationality (Denmark *vs* Iceland).

Methods

The DANBIO and ICEBIO registries cover >90% of patients with rheumatic diseases treated in routine care with biologics in Denmark and Iceland [24, 25]. Physicians are encouraged to report data prospectively using an online system at least biannually and when medication is changed. Baseline demographics include age, gender, weight, height, smoking habits, disease duration and biologic and conventional synthetic anti-rheumatic disease-modifying treatments. Functional status and peripheral joint disease activity are monitored by the HAQ, the 28-joint DAS (DAS28), CRP and visual analogue scales (VASs) for pain, patient's global and fatigue. Due to sparse and unsystematic registration of axial disease in these registries, we did not include these measures in the study. According to Danish legislation, publication of data from clinical registries does not require patient consent or approval by ethics committees. The study protocol was approved by the Danish Data Protection Agency (no. 03583, BBH-2015-020) and in Iceland by the National Bioethics Committee and the Data Protection Authority (VSN-15-224).

By 26 January 2015, 2186 patients diagnosed with PsA by their treating rheumatologist had been registered in DANBIO or ICEBIO during treatment with their first biologic drug. We excluded patients participating in clinical trials ($n = 86$), patients with erroneous information at baseline ($n = 66$), patients treated with biologics other than TNFI ($n = 19$) and those not followed from initiation of treatment or without any consecutive clinical registrations ($n = 72$). Consequently, 1943 patients (193 Icelandic, 1750 Danish) were included in the study. Obesity was categorized as BMI $\geqslant 30\,kg/m^2$ according to World Health Organization criteria [26]. In all analyses, obese patients were compared with non-obese patients with BMI $<30\,kg/m^2$.

Treatment adherence

Treatment adherence was calculated as the number of years individual patients maintained treatment with the first TNFI. Start date was the date of the first given dose and stop date was the date of the first missed dose. Temporary treatment interruptions (<3 months) were allowed [2]. All observations were censored on 25 May 2015. Among patients with no follow-up since January 2015, data were censored according to the last visit registered. Reasons for drug discontinuation are registered in pre-specified categories: lack of effect, adverse events, disease remission, pregnancy, surgery, cancer, death, infection, loss to follow-up and other. In the following analyses, reasons for discontinuation were categorized as adverse events (including infection, death or cancer), lack of effect, remission and other (including pregnancy, surgery, loss to follow-up and other reasons for discontinuation).

Treatment response

Disease activity was evaluated at baseline and after 3 and 6 months of TNFI treatment. The baseline visit was defined as a visit from 30 days before to 7 days after initiation of TNFI. The time window for the 3 and 6 month visits were 10–17 and 18–32 weeks, respectively. If more than one visit was available for the given time window, the one closest to the time point was selected. If no visits occurred during the time window, data were registered as missing for the given time point [2]. Patients who stopped treatment within 0–3 months were considered non-responders ($n = 110$). Clinical response was evaluated as achievement of 20, 50 and 70% improvement in ACR criteria (ACR20/50/70), a EULAR good response or a EULAR good or moderate (EGOM) response [27, 28]. We classified patients as responders if they achieved a clinical response at both the 3 and 6 month visit compared with baseline. In case of missing data at either the 3 or 6 month visit, one registration of clinical response was sufficient to characterize the patient as a responder [2].

Statistics

Statistical analyses were performed using SPSS version 22.0 (SPSS, Chicago, IL, USA) and R version 3.2.2 (R Project for Statistical Computing, Vienna, Austria) [29, 30]. Demographics and descriptive data are presented as median [interquartile range (IQR)] or mean (S.D.). Groups were compared by either parametric tests (*t*-test, one-way analysis of variance if data followed a normal distribution) or non-parametric tests (chi-square, Mann–Whitney, Kruskal–Wallis). Statistical significance was defined as $P < 0.05$. Calculations were based on observed data with no imputation of missing data. The influence of obesity on drug adherence was assessed by Kaplan–Meier plots, log rank tests and univariate/multivariate Cox regression analyses. Years since TNFI initiation was used as the underlying time scale in the Cox regression analyses. Covariates were tested for proportional hazards by inspection of Kaplan–Meier plots and log [−log (survival)] *vs* log of survival time graphs. In case of

uncertainty, a test for non-zero slope of Shoenfeld residuals *vs* treatment time was performed. Non-proportional hazards were seen for TNFI drug types, and this variable was not included as a covariate in multivariable Cox regression but was assessed by stratification. In the main analyses, obesity (yes/no) was included as a dichotomous variable. The influence of obesity on discontinuation due to (1) adverse events or (2) lack of response was investigated stepwise by censoring other reasons for withdrawal in Cox regression analyses. The impact of obesity on treatment responses (ACR20/50/70, EULAR good and EGOM response) was analysed by uni- and multivariable logistic regression. Furthermore, changes of individual disease variables (0–3 months and 0–6 months) were calculated. Confounders were selected a priori and included age, gender, disease duration, MTX use (yes/no), smoking (current/non-smokers), VAS-pain, HAQ score, DAS28, year of TNFI initiation (2000–5/2006–15), nationality (Denmark/Iceland) and CRP and in logistic regression also TNFI drugs (adalimumab, certolizumab pegol, etanercept, golimumab or infliximab).

Sensitivity and subgroup analyses

Data were divided into groups for sensitivity and subgroup analyses. Baseline characteristics were compared for patients with and without available BMI to assess the risk of selection bias. Assessment of interactions between BMI and smoking/age/gender/CRP and TNFI drug type was performed in the multivariable models. Cox and logistic regression analyses were repeated stratified according to gender and TNFI drug type (adalimumab, etanercept and infliximab), respectively. Patients initiating golimumab ($n = 146$) or certolizumab pegol ($n = 77$) were not included in these subgroup analyses due to small sample sizes. Population-specific effects were assessed by comparing Danish and Icelandic patients at baseline and by analysing the impact of obesity on TNFI outcomes for each nationality, especially to assess how obesity influenced infliximab treatment outcomes, as this is dosed by weight in Denmark but not in Iceland (200 mg fixed dose) [25].

Results

Baseline characteristics

Of the 1943 PsA patients initiating TNFI treatment, 1271 (65%) had available measures of both height and body weight and could be categorized as obese (BMI $\geqslant$30 kg/m^2) or non-obese (BMI $<$30 kg/m^2) (Table 1). Baseline characteristics differed between obese and non-obese patients: obese patients were older, less often smokers and had higher baseline disease activity measured as tender joint count (TJC), DAS28, CRP, HAQ and VAS-global and -pain than non-obese patients. Furthermore, the reason for withdrawal of TNFI was more frequently lack of efficacy and less often remission in obese compared with non-obese patients. Patients with missing registration of BMI began TNFI treatment in later years but had similar baseline disease activity as patients with available BMI, except for higher patient's VAS-global and lower doctor's VAS (Table 1). The distributions of body weight and BMI were equal between TNFI drug types (data not shown). The mean initiation doses of TNFI were comparable between the groups (non-obese *vs* obese patients, respectively): adalimumab 40.18 mg (S.D. 2.36) *vs* 40.10 (0.79) ($P = 0.9$), etanercept 43.65 mg (S.D. 11.22) *vs* 43.52 (11.01) ($P = 0.74$), infliximab 255.92 mg/kg (S.D. 79.23) *vs* 271 (94.96) ($P = 0.1$).

Icelandic patients presented higher median values of BMI [29 kg/m^2 (IQR 26–32) *vs* 27 (24–31)], doctor's VAS [58 mm (IQR 44–67) *vs* 33 (20–49)] and swollen joint count (SJC) [4 (IQR 2–7) *vs* 2 (0–5)] and longer median disease duration [6 years (IQR 2–12) *vs* 4 (1–9)], but lower TJC [4.5 (IQR 2–6) *vs* 6 (2–12)] compared with Danish patients (all $P \leqslant 0.01$). Furthermore, Icelandic patients were more often treated with infliximab (53 *vs* 21%) and less often with adalimumab (8 *vs* 42%) compared with Danish patients ($P < 0.01$).

Obesity and TNFI adherence

The cohort was followed for a total of 5142 person-years and the median follow-up time was 1.51 years (IQR 0.54–3.95). Non-obese patients had a median treatment duration of 2.1 years (IQR 0.60–4.62), which was lower among the obese [1.4 years (IQR 0.53–3.81), $P < 0.01$] and patients with missing BMIs [1.2 years (IQR 0.48–2.94), $P < 0.01$]. The median drug adherence was longer among non-obese compared with obese patients overall and in men and as a tendency in women (Kaplan–Meier plots; Fig. 1A–C and supplementary Table S1, available at *Rheumatology* Online). The difference in median drug adherence between obese and non-obese patients was evident for both etanercept and infliximab and as a tendency for adalimumab (Fig. 2A–C and supplementary Table S2, available at *Rheumatology* Online). In multivariable analyses, obesity was associated with poorer TNFI adherence overall, for each gender and for all three TNFIs (Tables 2 and 3). Kaplan–Meier plots and multivariable Cox regression subanalyses showed that obese patients had an increased risk of treatment withdrawal due to lack of efficacy [HR 1.85 (95% CI 1.38, 2.48)] but not due to adverse events compared with non-obese patients (data not shown).

Population-specific effects

Obesity attenuated TNFI adherence in both Icelandic and Danish patients (data not shown). Multivariable Cox regression of the Danish subset confirmed a negative influence of obesity on adherence overall, across TNFI types and by gender (data not shown). Obesity also hampered the adherence to infliximab (dosed by weight) in Danish patients [HR 1.84 (95% CI 1.14, 2.96), $P = 0.01$]. Multivariable analyses of Icelandic patients were not performed due to small group sizes.

Interactions

No interactions between BMI and smoking, age, gender or CRP appeared in multivariable Cox regression analyses.

Table 1 Baseline characteristics of non-obese and obese PsA patients

Characteristics	Non-obese (BMI <30)	Obese (BMI ⩾30)	*P*-value[a]	Unknown BMI
Total, *n* (%) (*N* = 1943)	863 (68)	408 (32)	<0.01	672 (35)[b]
Icelandic, *n* (%) (*N* = 193)	109 (57)	81 (43)		3 (2)[b]
Danish, n (%) (*N* = 1750)	754 (70)	327 (30)		669 (38)[b]
BMI, mean (S.D.), kg/m^2	25.1 (2.9)	34.6 (4.5)	<0.01	—
Weight, mean (S.D.), kg	75 (12.7)	102 (15.8)	<0.01	82 (20.6)
Age, mean (S.D.), years	47.3 (12.5)	49.4 (11.9)	0.01	48.1 (12.1)
Women, *n* (%)	458 (53)	236 (58)	0.1	347 (52)
Current smoking, *n* (%)	228 (30)	82 (23)	0.01	105 (16)
Disease duration, median (IQR), years	4 (2–10)	4 (1–9)	0.1	3 (1–8)*
CRP, median (IQR), mg/l	7 (3–18)	9 (5–19)	0.01	8 (3–19)
Tender joints, no	5 (2–11)	6 (3–13)	0.01	6 (2–11)
Swollen joints, no	2 (0–6)	3 (0.3–6)	0.1	2 (0–5)
HAQ, median (IQR)	0.9 (0.5–1.4)	1.1 (0.8–1.6)	<0.01	1.2 (0.6–1.5)
DAS28, mean (S.D.)	4.4 (1.2)	4.6 (1.2)	0.01	4.4 (1.3)
VAS-pain (0–100 mm), median (IQR)	60 (38–74)	66 (48–76)	0.01	63 (45–78)
VAS-patient global, median (IQR)	65 (47–81)	72 (54–87)	<0.01	70 (52–86)*
VAS-fatigue, median (IQR)	66 (43–80)	68 (46–84)	0.3	69 (50–82)
Physician's VAS-global, median (IQR)	35 (22–50)	37 (24–53)	0.3	32 (20–48)*
TNFI drug type, *n* (%)				*
Etanercept	192 (22)	95 (23)	0.7	218 (32)
Adalimumab	347 (40)	173 (42)		231 (34)
Infliximab	243 (28)	109 (27)		112 (17)
Certulizumab pegol	21 (2)	6 (2)		50 (8)
Golimumab	60 (7)	25 (6)		61 (9)
TNFI start year, *n* (%)				*
2000–4	111 (13)	47 (12)	0.8	100 (15)
2005–9	336 (42)	163 (40)		169 (25)
2010–15	416 (45)	198 (48)		399 (60)
MTX use, *n* (%)	500 (58)	221 (54)	0.2	291 (44)
Stop reason, *n* (%)[c]				
Lack of efficacy	243 (49)	159 (57)	0.04	202 (55)
Adverse events	125 (25)	68 (24)		81 (22)
Remission	29 (6)	6 (2)		13 (3)
Other	99 (20)	49 (17)		74 (20)

[a]*P*-values: obese *vs* non-obese groups. [b]Percentage of the overall/Icelandic/Danish populations. [c]Percentage of patients who have terminated treatment (within the BMI category). *Significantly different from patients with available BMI.

Obesity and treatment response

The proportion of patients achieving response to TNFI treatment during 6 months was generally lower in the obese than the non-obese group, but the discrepancy was only statistically significant for an EGOM response overall, which was obtained by 284 (65%) non-obese patients compared with 111 (55%) obese patients. No statistically significant differences in response rates appeared between obese and non-obese patients in analyses stratified according to gender or TNFI (data not shown).

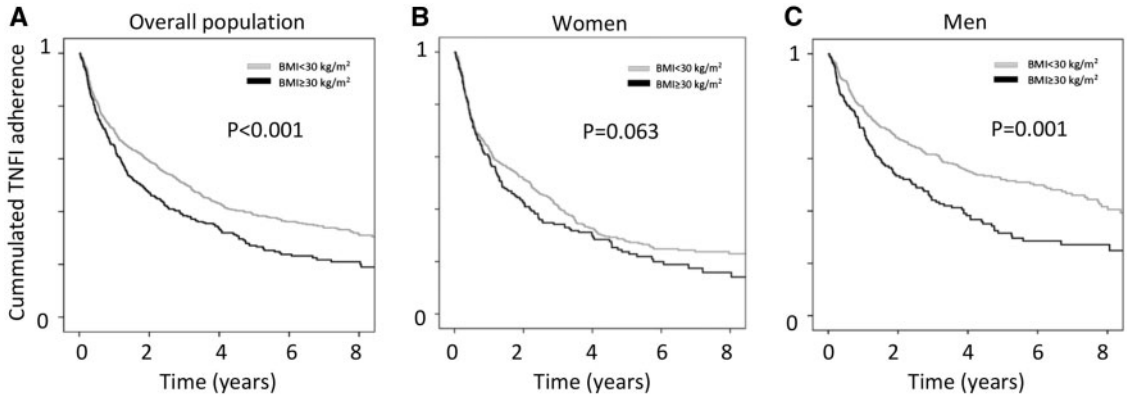
The chance of achieving an EGOM response after 6 months was significantly reduced among obese compared with non-obese patients, both overall, in both genders and for adalimumab and infliximab and as a tendency for etanercept ($P = 0.05$) (Table 4). The impact of obesity was strongest among men and patients on adalimumab.

Delta values were calculated for changes in the following variables between baseline and after 3 and 6 months of treatment: CRP, VAS-global, VAS-fatigue, VAS-pain, SJC, TJC, DAS28 and HAQ. No statistically significant differences between obese and non-obese patients were seen for any of the delta values, either overall or according to gender or TNFI drug type The mean changes of DAS28 in obese *vs* non-obese patients were −1.49 (S.D. 1.48) *vs* −1.47 (1.37) ($P = 0.82$) after 3 months and −1.65 (S.D. 1.49) *vs* −1.59 (1.42) ($P = 0.72$) after 6 months (other delta values are not shown).

Population-specific effects

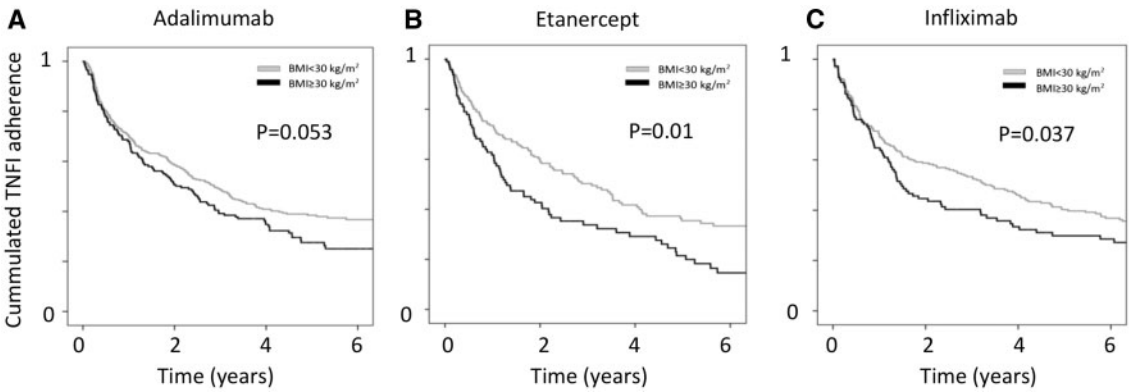
In Danish patients, the impact of obesity was consistent with the results reported for the overall population (data not shown); of note, obesity impaired the EGOM response to infliximab (dosed by weight) in Danish patients [OR 0.37 (95% CI 0.14, 0.99), multivariable analyses, $P = 0.049$].

Fig. 1 Drug adherence in obese and non-obese patients overall and by gender



Kaplan–Meier plots of TNFI adherence in obese and non-obese patients depicted for (**A**) the overall population, (**B**) women and (**C**) men. *P*-values by log rank test.

Fig. 2 Drug adherence in obese and non-obese patients according to TNFI drug type



Kaplan–Meier plots of TNFI adherence in obese *vs* non-obese patients treated with (**A**) adalimumab, (**B**) etanercept and (**C**) infliximab. *P*-values by log rank test.

Interaction terms

No interactions between BMI and smoking, age, gender or CRP appeared in multivariable logistic regression analyses.

Discussion

Using registry data for >1000 patients from Denmark and Iceland, we analysed the impact of obesity on TNFI treatment outcomes in PsA from 2000 to 2015. One-third of the PsA patients were obese (BMI $\geqslant 30\,kg/m^2$) compared with 14% of the general Danish population [31] and 22% of the Icelandic population [32], reflecting the recognized link between PsA and adiposity [33–35]. Obese patients had higher disease activity at baseline and obesity was associated with poorer treatment response and drug adherence.

The negative influence of obesity on TNFI outcomes has previously been reported in RA [15, 17–19], psoriasis [12–14], SpA [16] and PsA [20–23], although most of these studies are limited by rather short follow-ups and small sample sizes. In a prospective study of 135 obese and 135 normal weight PsA patients treated with TNFI, di Minno *et al*. [20, 23] found obesity to be an independent predictor of not achieving minimal disease activity (MDA) after 1 year and not maintaining MDA until 24 months. The same authors reported that weight loss improved TNFI response rates among obese PsA patients. In a Canadian cohort study of 557 PsA patients initiating mostly conventional synthetic DMARDs, overweight and obesity were associated with a reduced chance of achieving sustained MDA over 1 year [22]. In contrast, a retrospective registry study of 135 TNFI-treated PsA patients from Italy reported that BMI neither influenced the chance of a good EULAR response nor remission according to DAS28 or the Simplified Disease Activity Index [21].

Our results add to the increasing evidence of obesity as a negative predictor of TNFI treatment success, but the

Table 2 Impact of obesity on TNFI adherence for all patients and by gender

	All patients HR (95% CI)	Male HR (95% CI)	Female HR (95%CI)
Univariable analyses			
BMI $\geqslant$30 kg/m^2[a]	1.37 (1.18, 1.58)*	1.60 (1.27, 2.02)*	1.19 (0.99, 1.44)
Multivariable analyses			
BMI $\geqslant$30 kg/m^2[a]	1.64 (1.32, 2.03)*	1.78 (1.26, 2.50)*	1.50 (1.10, 2.02)*
Age, years	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
HAQ	1.15 (0.94, 1.42)	1.41 (0.98, 2.02)	1.09 (0.84, 1.41)
DAS28	1.03 (0.92, 1.15)	1.21 (1.01, 1.45)*	0.94 (0.82, 1.08)
PsA duration, years	0.98 (0.96, 0.99)*	0.95 (0.93, 0.98)*	0.99 (0.97, 1.01)
TNFI start 2006–15[a]	1.37 (1.02, 1.84)*	1.44 (0.90, 2.29)	1.39 (0.93, 2.06)
CRP, mg/l	0.99 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Current smoker[a]	1.20 (0.96, 1.50)	1.20 (0.83, 1.74)	1.15 (0.88, 1.57)
VAS-pain (0–100 mm)	1.01 (1.00, 1.01)	0.99 (0.99, 1.00)	1.01 (1.00, 1.02)*
MTX use[a]	1.02 (0.83, 1.24)	1.03 (0.74, 1.45)	1.07 (0.82, 1.40)
Women[a]	1.48 (1.20, 1.84)*	–	–
Danish nationality[a]	1.86 (1.18, 2.96)*	1.12 (0.60, 2.10)	2.65 (1.29, 5.43)*

Results of Cox regression analyses. [a]References (HR = 1) for the categorical variables included in the analyses are as follows: BMI $<$30 kg/m^2, TNFI start year 2000–5, non-smoker, no MTX, men, Icelandic nationality. *P-values < 0.05.

Table 3 Impact of obesity on TNFI adherence according to drug type

	Adalimumab HR (95% CI)	Infliximab HR (95% CI)	Etanercept HR (95% CI)
Univariable analyses			
BMI $\geqslant$30 kg/m^2[a]	1.25 (0.99, 1.56)	1.33 (1.02, 1.74)*	1.65 (1.22, 2.22)*
Multivariable analyses			
BMI $\geqslant$30 kg/m^2[a]	1.60 (1.16, 2.23)*	1.63 (1.07, 2.48)*	2.03 (1.26, 3.29)*
Age, years	1.00 (0.99, 1.01)	1.00 (0.99, 1.02)	1.01 (0.99, 1.04)
HAQ	1.01 (0.72, 1.41)	1.12 (0.75, 1.65)	1.23 (0.75, 2.23)
DAS28	1.10 (0.93, 1.30)	1.06 (0.84, 1.32)	0.79 (0.62, 1.02)
PsA duration, years	0.98 (0.96, 1.00)	0.97 (0.94, 1.00)	0.98 (0.93, 1.02)
TNFI start 2006–15[a]	1.27 (0.74, 2.17)	1.37 (0.84, 2.22)	1.46 (0.76, 2.82)
CRP, mg/l	1.00 (0.99, 1.01)	0.99 (0.98, 1.00)	1.01 (0.93, 1.02)
Current smoker[a]	1.25 (0.89, 1.76)	1.11 (0.72, 1.69)	1.54 (0.93, 2.54)
VAS-pain (0–100 mm)	1.01 (0.99, 1.02)	1.00 (0.99, 1.01)	1.02 (1.00, 1.03)*
MTX use[a]	1.21 (0.88, 1.65)	0.55 (0.36, 0.83)*	1.19 (0.75, 1.90)
Women[a]	1.51 (1.09, 2.06)*	1.55 (1.02, 2.35)*	1.13 (0.66, 1.92)
Danish nationality[a]	1.11 (0.26, 4.67)	2.76 (1.49, 5.09)*	1.89 (0.55, 6.50)

Results of Cox regression analyses. [a]References (HR = 1) for the categorical variables included in the analyses are as follows: BMI $<$30 kg/m^2, TNFI start year 2000–5, non-smoker, no MTX, men, Icelandic nationality. *$P < 0.05$

underlying mechanisms are still unclear and may be multifactorial. Our subanalyses indicated that obesity was a risk factor for TNFI withdrawal due to poor response, while no association between obesity and TNFI termination due to adverse events was found. Impaired response to TNFI could arise due to insufficient dosing of TNFI in obese patients, and our data confirmed that similar (standard) initiation doses of TNFI were used in obese and non-obese patients. Obesity causes a greater volume of distribution, resulting in decreased overall TNFI concentration [14, 36]. Reduced bioavailability of TNFI in obese patients could also occur as a result of impaired drug absorption from excess s.c. fat layers [36]. However, our results do not confirm this theory, since obesity impaired response to infliximab (infused intravenously) as well as adalimumab, but only as a trend to etanercept, where the latter two are administrated by s.c. injections.

Adipose tissue secretes hormones and pro-inflammatory cytokines like TNF-α and IL-6 that simultaneously act as key players in the immune response of psoriatic diseases [6, 8, 37]. It seems plausible that synergistic, immunological processes of PsA and obesity can lead to a more severe inflammatory state that is less responsive to TNFI [38]. Furthermore, drug elimination may be accelerated in obese patients since (i) their higher TNF-α levels mediate faster TNFI clearance [39] and (ii) renal

Table 4 Impact of obesity on treatment response according to ACR and EULAR definitions

6 month response	Overall, OR (95% CI)	Women, OR (95% CI)	Men, OR (95% CI)	Adalimumab, OR (95% CI)	Infliximab, OR (95% CI)	Etanercept, OR (95% CI)
EULAR good, obese	0.75 (0.50, 1.15)	0.92 (0.50, 1.69)	0.53* (0.29, 0.99)	0.70 (0.37, 1.34)	0.59 (0.26, 1.37)	0.99 (0.31, 3.21)
EGOM[a], obese	0.47* (0.30, 0.74)	0.50* (0.27, 0.92)	0.36* (0.17, 0.79)	0.45* (0.21, 0.97)	0.39* (0.17, 0.92)	0.30 (0.09, 1.00)
ACR20, obese	0.65 (0.40, 1.06)	0.83 (0.41, 1.69)	0.40* (0.19, 0.86)	0.44* (0.21, 0.96)	0.76 (0.28, 2.02)	1.28 (0.39, 4.15)
ACR50, obese	0.71 (0.42, 1.18)	1.17 (0.53, 2.60)	0.43* (0.21, 0.91)	0.42* (0.19, 0.94)	0.97 (0.33, 2.82)	2.02 (0.51, 8.01)
ACR70, obese	0.80 (0.43, 1.48)	1.37 (0.46, 4.16)	0.59 (0.27, 1.30)	0.63 (0.24, 1.65)	1.35 (0.33, 5.52)	1.19 (0.15, 8.96)

Results of multivariable logistic regression with adjustment for age (years), CRP (mg/l), DAS28, MTX (yes/no), smoking (yes/no), VAS-pain (0–100 mm), nationality (Danish/Icelandic), disease duration (years) and TNFI initiation year (2000–5/2006–15) as well as gender and TNFI drug types (all five). ORs and 95% CIs with non-obese (BMI <30) as reference (OR = 1). [a]EGOM: EULAR good or moderate response. *$P < 0.05$.

impairment due to obesity-related co-morbidities (e.g. diabetes) may enable glomerular filtration or leak of IgG (most TNFI) into the urine [36].

Data from randomized controlled studies of psoriasis and RA suggest that dose escalation is likely to improve TNFI efficacy in obese patients [36, 40]. Nevertheless, we found that obesity also impaired response to infliximab dosed by weight in Danish patients. Furthermore, our drug adherence analyses illustrated that obesity had a negative influence on long-term TNFI adherence, which could reflect reasons beyond primary failure due to, for example, insufficient dosing. Some TNFI-treated patients develop anti-drug antibodies (ADAs) that neutralize the treatment effect over time [41]. The risk of ADA formation is reduced by sufficient TNFI levels and MTX co-medication [42]. In obese patients, lower peak TNFI levels and cautious dosing of MTX due to increased hepatotoxic risk could increase ADA formation [40]. However, in our study we adjusted for MTX co-medication in multivariable analyses and found equal MTX prescription rates between obese and non-obese patients at baseline. We are not aware of any prior studies investigating ADA levels in obese *vs* non-obese patients.

Our results showed an influence of obesity on TNFI outcomes in both genders, most prominently in men. Pharmacokinetic differences exist between the genders, as men with RA seem to have ~40% increased clearance of adalimumab compared with women [43]. The combination of an increased volume of distribution and higher drug clearance may result in subclinical TNFI levels, especially in men, but hormonal and behavioural factors could influence results.

In our study, obese patients had higher DAS28 scores and CRP levels at baseline than non-obese patients. Higher CRP levels could reflect the pro-inflammatory activity of obesity *per se* [44] and not necessarily PsA severity, since other objective disease measures (SJC, physicians' VAS) did not diverge between obese and non-obese patients.

An important limitation of this study is the use of a 28-joint count, which seems insufficient for PsA assessment. Adherence to the 66-/68-joint count could have revealed differences in the distribution of joint activity between BMI groups, which may have influenced the results. However, we are not aware of studies that provide evidence for a different PsA pattern in obese patients. On the contrary, one might speculate that weight-bearing joints are more tender in obese patients due to mechanical stress (weight overload) and OA.

We did not have information on co-morbidities, and conditions such as osteoarthrosis, depression and chronic pain [45–47] could partly explain the increased patient-reported disease measures (HAQ, VAS-pain, VAS-global) among obese patients at baseline. However, we did not find patient-reported outcomes to be less responsive to TNFI treatment in obese patients and the relative change in disease parameters (from 0 to 3 to 6 months) did not differ between obese and non-obese patients. This also underscores that no single DAS28 or ACR variable is responsible for the poorer response profile among obese individuals.

Our study is based on observational data from a large PsA cohort, which strengthens the external validity of the results. Regression analyses were adjusted for several baseline factors, including smoking status, demography and disease activity, but the risk of residual confounding still exists as we lacked information on, for example, enthesitis, spinal involvement, psoriasis, co-morbidities, alcohol consumption and physical activity. Information on psoriasis could have been valuable in order to clarify differences in skin and joint response among obese and non-obese patients. If obese patients had a poorer skin response than the non-obese, they might stop treatment due to lack of effect on psoriasis and not necessarily due to a poor joint response.

BMI was available for approximately two-thirds of the study population. However, baseline characteristics were comparable between patients with and without BMI registration. Measures of weight and height were retrieved by the treating physician at the start of TNFI treatment and weight changes during TNFI treatment were not taken into account. These limitations may have influenced our understanding of the association between disease activity, obesity and TNFI outcomes.

In conclusion, obesity was associated with higher baseline disease activity and seemed to decrease the chances

of response as well as adherence to TNFI treatment in Danish and Icelandic patients with PsA.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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