Systematic Review

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Impact of Obesity on Response Rate for Biological Agents in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis of Cohort Studies

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Background: Existing evidence suggests that obesity has an impact on the onset and development of rheumatoid arthritis (RA) and may also affect the response of patients to different treatments. However, findings from previous studies are controversial. This study aims to obtain evidence-based medical information on the influence of obesity on the response rate of biological agents in patients with RA through a systematic review and meta-analysis.

Methods: A search was performed on Pubmed, Medline, Web of Science, Scopus, and Cochrane Library from their inception to June 2023. Studies that met the inclusion criteria were enrolled. A meta-analysis was used to evaluate remission, response, good European League Against Rheumatism (EULAR) response, moderate EULAR response, retention rate, and clinical disease activity index (CDAI). Subgroup analysis was carried out to identify sources of heterogeneity and sensitivity analysis was performed.

Results: A total of 15 articles met the inclusion criteria and four biological disease-modifying antirheumatic drugs (bDMARDs) were included. The meta-analysis showed that the odds of reaching good EULAR response or achieving CDAI were lower in obese than in non-obese patients treated with bDMARDs. Subgroup analysis revealed significant differences between the two groups. Remission, good EULAR response and retention rate were lower in the obese group than in non-obese patients treated with tumor necrosis factor inhibitors (TNFi). However, there was no significant difference between patients receiving abatacept and tocilizumab treatment. Sensitivity analysis and publication bias confirmed that the results were highly reliable and stable.

Conclusions: Obesity affects the clinical response rate of RA patients receiving TNF inhibitors (TNFi), but it does not have an adverse effect on abatacept and tocilizumab. This suggests that when choosing biological agents for RA patients, the impact of obesity should be considered. Further research is needed to validate these findings.

Keywords: obesity; biological agents; rheumatoid arthritis (RA); meta-analysis; systematic review

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent joint destruction [1]. It manifests as pain and swelling in the joints of the hands and feet, often accompanied by morning stiffness in the affected joints [2]. Given its high rate of disability, it significantly affects the quality of life [3]. Currently, disease-modifying antirheumatic drugs (DMARDs) are considered to be the first-line drugs for the treatment for RA worldwide [4]. Biological DMARDs (bDMARDs) have multiple targets, and hence can be effective treatments for patients who do not respond to standard treatment standards [5]. The bDMARDs used for the targeted treatment of RA primarily encompass tumor necrosis factor inhibitors (TNFi), IL-6 receptor antagonists (anti-IL6), T cell co-stimulation inhibitors, and anti-CD20 monoclonal antibodies [6].

Adipose tissue in individuals with obesity regulates immune and inflammatory reactions associated with metabolic disorders, chronic inflammatory, and autoimmune diseases, thereby increasing the risk of RA [7]. Recent studies have established a link between body mass index (BMI) and chronic inflammation as well as immune responses [8]. In patients with obesity, adipose tissue secretes inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α) and leptin, which induce inflammatory reactions. The levels of these inflammatory markers are elevated before the onset of RA [9]. BMI $\geq$25 kg/m^2 is considered an independent risk factor for RA [10]. With a high BMI significantly increasing the risk of RA [11]. Therefore, BMI is causally related to the increased risk of RA.

Several studies have investigated the impact of obesity on the use rate of bDMARDs [12–26]. However, the find-

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ings from these studies are somewhat controversial. Therefore, we conducted a systematic review and meta-analysis, and subgroup analysis of the types of bDMARDs to identify the impact of obesity. We also analyzed whether the type of bDMARDs was the source of heterogeneity.

Methods

Search Strategy

The systematic literature review and meta-analyses were conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [27] (**Supplementary Table 1**). The protocol for this study is registered on the INPLASY database (https://inplasy.com/) with the identifier INPLASY2023110029. Two researchers (RSL and YZ) independently performed the search using the PICO strategy. Electronic databases were searched to identify relevant trials. Including Pubmed, Medline, Web of Science, Scopus and the Cochrane Library were searched, from inception to June 2023. The following Medical Subject Headings (MeSH) and predefined keywords were used: "obesity" "RA" and "bDMARDs". Following a manual selection process of a reference list, eligible studies were included and supplemented. Redundant articles, meeting abstracts, conference proceedings, reviews, letters, editorials, and comments were excluded. The retrieval strategy is provided in (**Supplementary Data 1**).

Studies Selection

Only studies that met the quality checks were selected to investigate the impact of obesity on the response rate for bDMARDs in RA. Specifically, these studies had to meet the following criteria: 1) The research type is a cohort study (prospective or/and retrospective); 2) Patients met the 1987 American College of Rheumatology ACR [28] or 2010 European League Against Rheumatism (EULAR) criteria for RA [29]; 3) The therapy involved bDMARDs, including TNFi [e.g., infliximab (IFX), adalimumab (ADA), etanercept (ETA)], anti-IL6 [e.g., tocilizumab (TCZ)], T cell co-stimulation inhibitor [e.g., abatacept (ABA)], and anti-CD20 monoclonal antibody [e.g., rituximab (RTX)]; 4) Obesity was defined as a BMI $> 30\ kg/m^2$; 5) The outcomes were evaluated by (a) Disease Activity Score in 28 joints (DAS28) [30] < 2.6; (b) Response decrease in DAS28 > 1.2; (c) Good EULAR response: defined as decrease in DAS28 > 1.2, and with low disease activity (DAS28 ≤ 3.2); (d) Moderate EULAR response: defined as decrease in $0.6 <$ DAS28 ≤ 1.2 and with moderate disease activity ($3.2 <$ DAS28 ≤ 5.1); (e) Retention rate; (f) CDAI Clinical Disease Activity Index (CDAI ≤ 2.8). 6) A comparison was conducted between the baseline and the end of treatment at two distinct times, utilizing complete data. Articles that could not be extracted from raw data were excluded.

Data Extraction

Two researchers (YTL and YZ) independently extracted the data from the article, and cross-checked the results. The retrieved data included: the name of the first author name, year of publication, sample size, the number of subjects (n), number of patients with obesity and non-obesity (n), type of study, duration and outcomes.

Quality of Evidence Assessment

The methodological quality of the included studies and the risk of bias were assessed using The Newcastle-Ottawa Quality Assessment Scale for Cohort Studies [31]. The scale consists of eight items divided into three main sections: selection of exposed and non-exposed cohorts, comparability, and evaluation of outcomes.

Statistical Analysis

The extracted data were analyzed using the Review Manager 5.3 (Cochrane, London, UK) and StataSE 17 software (Stata Corporation, College Station, TX, USA). Pooled statistics were calculated as pooled odds ratios (ORs) with 95% confidence intervals (CIs). The Cochran's Q statistic or I^2 value size was used to analyze heterogeneity. The selection of fixed-effects models or random models was based on the p value (≥ 0.10) and I^2 ($\leq 50\%$) value of statistical tests. Funnel plots and Egger's tests were utilized to evaluate the publication bias. The stability of the research results was validated through sensitivity analysis. p values < 0.05 were considered statistically significant.

Results

Literature Search

The PRISMA flow chart, which illustrates the process of selecting relevant research reviews is presented in Fig. 1. Initially, 2897 potentially eligible studies were identified. After removing 2052 duplicate articles from the five datasets, a further 513 studies were excluded based on the reading of titles and abstracts due to irrelevance. The full text was read and 308 studies were excluded because they did not meet the inclusion criteria. Through further screening of the review studies, two additional articles were included. Finally, 26 articles were included in this review. A total of 11 articles with incomplete data were excluded, and 15 articles were included in the meta-analysis.

Risk of Bias in Included Studies

Table 1 presents the results of bias assessment of bias based on the NOS Quality Assessment Form [31]. Studies for Cohort Studies. Those that met the quality criteria were assigned a rating of one *, which is divided into three segments, resulting in a maximum of nine *. Out of mong the 15 studies, fourteen were assessed as "Good quality", receiving 7–9 *. The remaining one articles were rated as weak in the comparability domain, obtaining 4–6*.

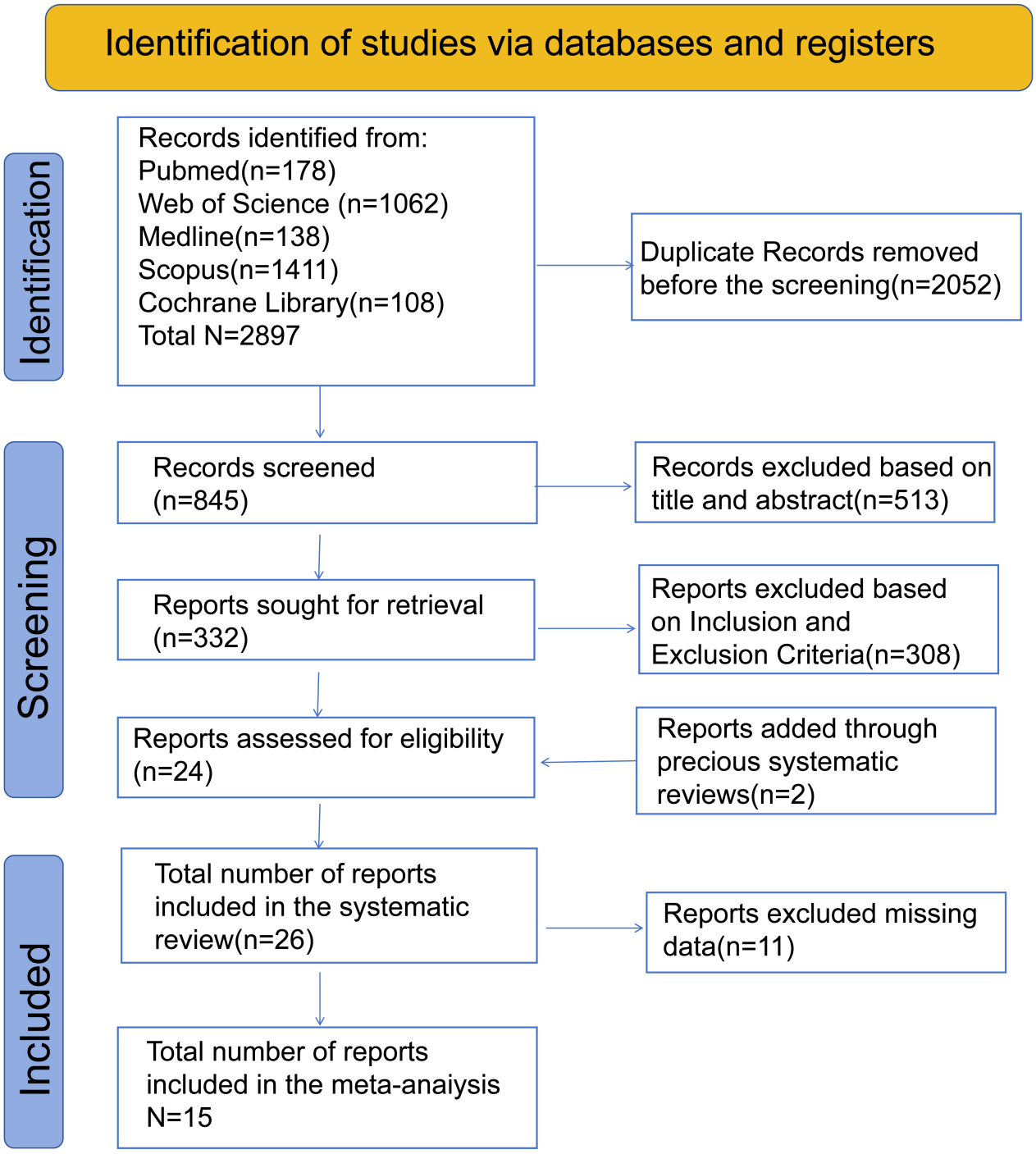

Fig. 1. Flowchart of article identification and selection.

Study Characteristics

The main characteristics of the included studies are summarized in Table 2. Notably, four bDMARDs were recorded in 15 studies [12–26]. Most studies were prospectively carried out [12,13,15–21,24,25], followed by retrospective studies [14,22,23] and pooled analyses [26]. The study duration varied from 2 to 12 months. Frequency of remission, response, good EULAR response, moderate EULAR response, retention rate, and CDAI, were the indicators used to evaluate the clinical response to different bDMARDs. The BMI was categorized based on the World Health Organization's definition: non-obese (BMI < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2). Articles not adhering to these classification criteria were excluded.

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Table 1. Quality assessment of studies by Newcastle–Ottawa Scale, NOS.

References	Selection	Comparability	Outcome	Overall quality
Klaasen *et al*. 2011 [12]	***	**	**	7
Gremese *et al*. 2013 [13]	****	**	***	9
Iannone *et al*. 2015 [14]	***	**	***	8
Novella-Navarro *et al*. 2022 [15]	***	*	***	7
Elalouf *et al*. 2021 [16]	****	*	***	8
Gardette *et al*. 2016 [17]	***	*	***	7
Iannone *et al*. 2017 [18]	***	*	***	7
Mariette *et al*. 2017 [19]	***	*	***	7
D'Agostino *et al*. 2017 [20]	***	*	***	7
Mariette *et al*. 2019 [21]	***	*	***	7
Pers *et al*. 2015 [22]	***	**	**	7
Gardette *et al*. 2016 [23]	***	*	**	6
Hilliquin *et al*. 2021 [24]	****	*	***	8
Pappas *et al*. 2020 [25]	***	**	***	8
Abuhelwa *et al*. 2020 [26]	***	*	***	7

Newcastle-Ottawa Scale: one star represents one point, and the total number of stars represents the number of points scored.

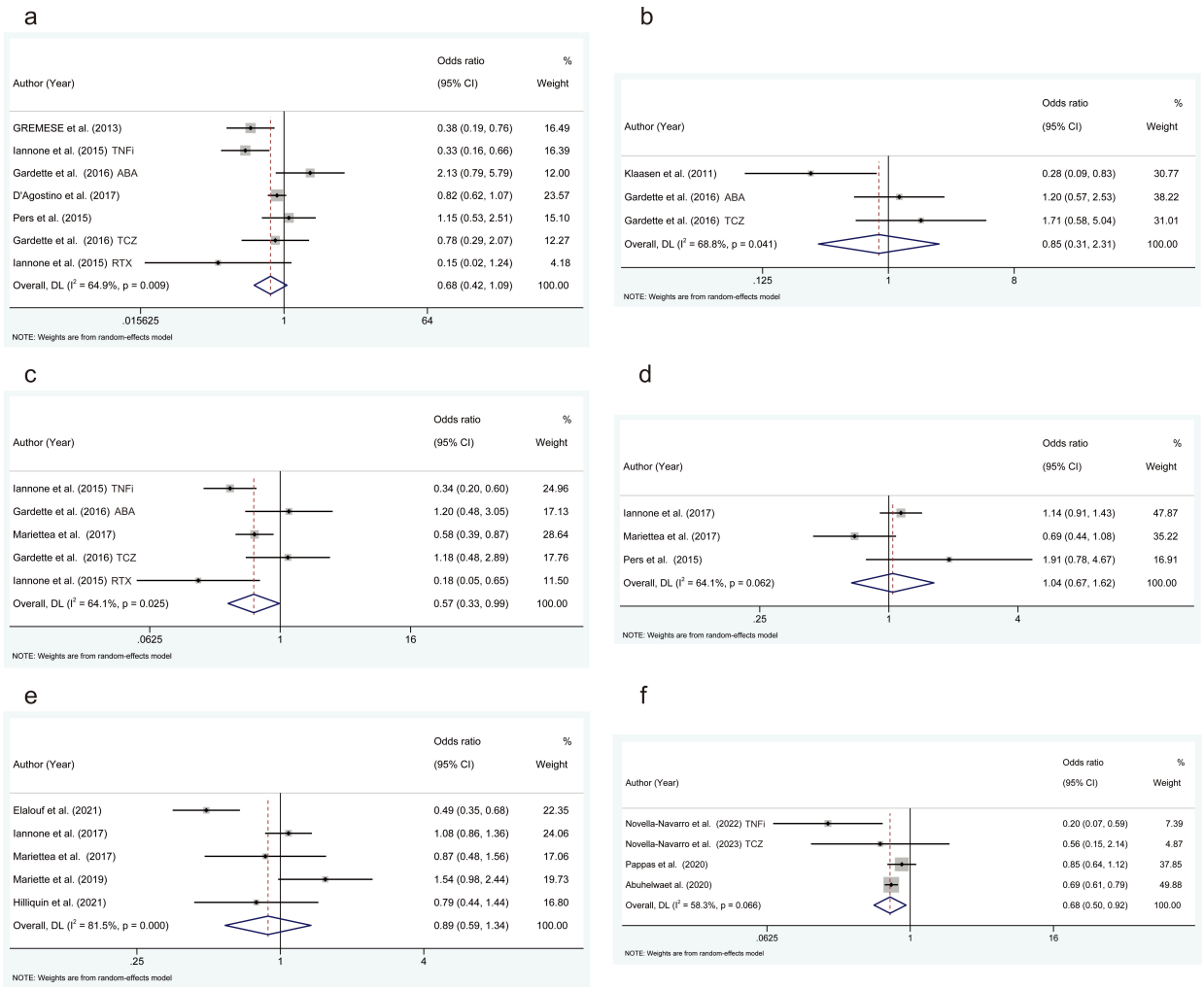

Fig. 2. Forest plot effect of bDMARDs on RA. (a) Frequency of remission. (b) Response. (c) Good EULAR response. (d) Moderate EULAR response. (e) Retention rate. (f) CDAI. TCZ, tocilizumab; ABA, abatacept; RTX, rituximab. TNFi, tumor necrosis factor inhibitors; ABA, abatacept; TCZ, tocilizumab; RTX, rituximab; EULAR, European League Against Rheumatism.

Table 2. Baseline characteristics of the studies included in the meta-analysis.

	Refs	Patients		BMI timing	Therapy:	Groups (n)		Reported Outcomes				Study Design	
		rheumatic disease (n)	obesity%		(n)	obese BMI of >30 kg/m^2	non-obese BMI of <30 kg/m^2	O1: remission%	remission definition clinical remission (DAS28 <2.6)	O2: responders% (Obese vs non-obese)	responder definition	type of study	duration
TNFi													
1	Klaasen *et al.* 2011 [12]	active RA (89)	16.85%	before treatment	IFX (89)	15	74			41.2 vs 71.6 (p = 0.04)	②DAS28 ≥1.2	prospective cohort	4 months
2	Gremese *et al.* 2013 [13]	longstanding RA (641)	10.30%	baseline	IFX (154) ADA (260) ETA (227)	66	575	15.2 vs 32 (p = 0.01)	①DAS28 <2.6			prospective cohort	12 months
3	Iannone *et al.* 2015 [14]	RA (292)	22.60%	baseline	IFX (73) ADA (68) ETA (147) CTZ (4)	66	226	17 vs 38 (p = 0.01)	①DAS28 <2.6	42 vs 68 (p = 0.03)	③good EULAR response	retrospective cohort	12 months
4	Novella-Navarro *et al.*2022 [15]	RA (70)	48.57%	baseline	TNFi (70)	34	36			47 vs 81 (p = 0.004)	⑥CDAI	prospective cohort	6 months
5	Elalouf *et al.* 2021 [16]	RA (818)	27.26%	baseline	TNFi (818)	223	595			59.2 vs 74.8 (p = NA)	⑤Retention Rate	prospective cohort	12 months
ABA													
6	Gardette *et al.* 2016 [17]	RA (141)	27.66%	baseline	ABA (141)	39	102	20.5 vs 10.8 (p = 0.72)	①DAS28 <2.6	①43.6 vs 39.2 (p = 0.24) ②20.5 vs 17.6 (p = 0.86)	②ΔDAS28 ≥1.2 ③good EULAR response	prospective cohort	6 months
7	Iannone *et al.* 2017 [18]	RA (2015)	18.86%	baseline	ABA (2015)	380	1635			③41.8 vs 38.7 (p = 0.49) ④42.9 vs 41 (p = 0.74)	④moderate EULAR response ⑤Retention Rate	prospective cohort	12 months
8	Mariette *et al.* 2017 [19]	RA (643)	24.11%	baseline	ABA (643)	155	488			②25.8 vs 37.5 (p = NA) ③77.4vs 83.2 (p = NA) ④89 vs 90 (p = NA)	③good EULAR response ④moderate response ⑤Retention Rate	prospective cohort	6 months
9	D'Agostino *et al.* 2017 [20]	RA (1456)	29.74%	baseline	ABA (1456)	433	1023	21.9 vs 25.6 (p = NA)	①DAS28 <2.6			prospective cohort	6 months
10	Mariette *et al.* 2019 [21]	RA (444)	22.97%	baseline	ABA (444)	102	342			46.8 vs 36.3 (p = 0.147)	⑤Retention Rate	prospective cohort	2 years
TCZ													
11	Pers *et al.* 2015 [22]	RA (222)	15.46%	baseline	TCZ (207)	32	175	37.5 vs 34.3 (p = 0.34)	①DAS28 <2.6	78.1 vs 65.1 (p = 0.78)	④moderate EULAR response	retrospective cohort	6 months
12	Gardette *et al.* 2016 [23]	RA (115)	21.74%	baseline	TCZ (115)	25	90	28 vs 33.3 (p = 0.66)	①DAS28 <2.6	①80 vs 70 (0.54) ②44 vs 40 (p = 0.82)	②ΔDAS28 ≥1.2 ③good EULAR response	retrospective cohort	6 months
13	Hilliquin *et al.* 2021 [24]	RA (269)	21.19%	baseline	TCZ (269)	57	212			59 vs 65 (p = 0.496)	⑤Retention Rate	prospective cohort	12 months
4	Novella-Navarro *et al.* 2022 [15]	RA (35)	51.43%	baseline	TZC (35)	18	17			44.4 vs 58.8 (p = 0.30)	⑥CDAI	prospective cohort	6 months
14	Pappas *et al.* 2020 [25]	RA (805)	44.22%	baseline	TZC (805)	356	449			49.15 vs 53.14 (p = 0.263)	⑥CDAI	prospective cohort	12 months
15	Abuhelwa *et al.* 2020 [26]	RA (5383)	30.50%	baseline	TZC 5383	1642	3741			27.22 vs 35 (p = NA)	⑥CDAI	pooled analysis cohort	8 weeks
RTX													
3	Iannone *et al.* 2015 [14]	RA patients who failed anti-TNF drug (58)	25.86%	baseline	RTX (58)	15	43	7 vs 33 (p = 0.04)	①DAS28 <2.6	27 vs 67 (p = 0.01)	③good EULAR response	retrospective cohort	12 months

IFX, infliximab; ADA, adalimumab; ETA, etanercept; TCZ, tocilizumab; ABA, abatacept; RTX, rituximab.

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Meta-Analysis

Among the 15 included studies, five investigated the TNFi (n = 1910), five explored the ABA (n = 4699), six examined the TCZ (n = 6829), and only one examined rituximab (n = 58). Multiple bDMARDs were reported in two studies.

Frequency of Remission

Six studies explored the association between obesity and remission [13,14,17,20,22,23]. One of the studies examined both TNFi and RTX [14]. The findings showed that the remission rate was lower in obese patients compared to non-obese patients treated with bDMARDs, but the difference was not statistically significant (OR = 0.68, 95% CI: 0.42, 1.09). Moreover, there was a significant heterogeneity among the studies (I^2 = 64.9%, p = 0.009) (Fig. 2a).

Response

The association between obesity and treatment response was reported in three studies [12,17,23]. The results revealed that the percentage of response was lower in obese patients than in non-obese patients treated with bDMARDs. However, the difference was not significant (OR = 0.85, 95% CI: 0.31, 2.31). Significant heterogeneity was observed between the studies (I^2 = 68.8%, p = 0.041) (Fig. 2b).

Good EULAR Response

The association between obesity and a good EULAR response was reported in four studies [14,17,19,23] with one study describing both TNFi and RTX [14]. An analysis of the studies showed that the percentage of a good EULAR response was lower in obese patients than in non-obese patients treated with bDMARDs, with a significant difference (OR = 0.57, 95% CI: 0.33, 0.99). Notably, a significant heterogeneity was observed between the studies (I^2 = 64.1%, p = 0.025) (Fig. 2c).

Moderate EULAR Response

Three studies have reported the association between obesity and moderate EULAR response [18,19,22]. There was no significant difference in moderate EULAR response between obese patients and non-obese patients receiving bDMARD treatment (OR = 1.04, 95% CI: 0.67, 1.62). There is no significant heterogeneity between studies (I^2 = 64.1%, p = 0.062) (Fig. 2d).

Retention Rate

The association between obesity and retention rate was assessed in five studies [16,18,19,21,24]. Further analysis revealed that the retention rate was lower in obese patients compared to non-obese patients treated with bDMARDs, but the difference was not statistically significant (OR = 0.89, 95% CI: 0.59, 1.34). There was a significant heterogeneity observed among the studies (I^2 = 81.5%, p = 0.000) (Fig. 2e).

CDAI

The association between obesity and CDAI was reported in three studies [15,25,26], with one study describing both TNFi and TCZ [15]. The results revealed a significantly lower percentage of CDAI in obese patients compared to non-obese patients treated with bDMARDs, with a significant difference (OR = 0.68, 95% CI: 0.50, 0.92). There was no significant heterogeneity between the studies (I^2 = 58.3%, p = 0.066) (Fig. 2f).

Subgroup Analysis

Further exploration of sources of heterogeneity through subgroup analysis involved the selection of different types of bDMARDs as subgroups for further analysis.

The remission rate was lower in obese than non-obese patients treated with TNFi (OR = 0.35, 95% CI: 0.21, 0.58; I^2 = 0.0%, Pheterogeneity p = 0.761). However, no significant difference was found among patients treated with ABA (OR = 1.16, 95% CI: 0.47, 2.89; Pheterogeneity p = 0.068, I^2 = 69.9%), TCZ (OR = 0.99, 95% CI: 0.54, 1.82; Pheterogeneity p = 0.54, I^2 = 0.0%), or RTX (OR = 0.15, 95% CI: 0.02, 1.24; only one study) (Fig. 3a).

Similarly, among RA patients treated with TNFi, the good EULAR response was lower in obese patients compared to non-obese patients (OR = 0.34, 95% CI:0.20, 0.60; only one study). Among RA patients treated with RTX, the good EULAR response in obese patients was lower than that in non-obese patients (OR = 0.18, 95% CI: 0.05, 0.65; only one study). However, no significant differences were found among patients receiving ABA treatment (OR = 0.74, 95% CI: 0.38, 1.45 Pheterogeneity p = 0.157, I^2 = 50.0%) and among patients receiving TCZ treatment (OR = 1.18, 95% CI: 0.48, 2.89; only one study) (Fig. 3b). The retention rate was also lower in obese than non-obese patients treated with TNFi (OR = 0.49, 95% CI: 0.35, 0.68; only one study). However, no significant difference was found among patients receiving ABA treatment (OR = 1.14, 95% CI: 0.88, 1.47 Pheterogeneity p = 0.254, I^2 = 27.0%) and TCZ treatment (OR = 0.79, 95% CI: 0.44, 1.44; only one study) (Fig. 3c). The results of remission rate, good EULAR response, and retention rate indicated that obesity does not affect the response rate of RA patients receiving ABA and TCZ treatment, but it does influence the use of TNFi.

Regarding response outcomes, such as moderate EULAR and CDAI, the analysis is limited by a small number of articles that provide data on only two types of drug usage. Consequently, subgroup analysis is not feasible. However, the observed trend in the results is consistent across the articles. In addition, we conducted subgroup analyses of intervention time, research design, and sample size. The results are presented in **Supplementary Fig. 1**.

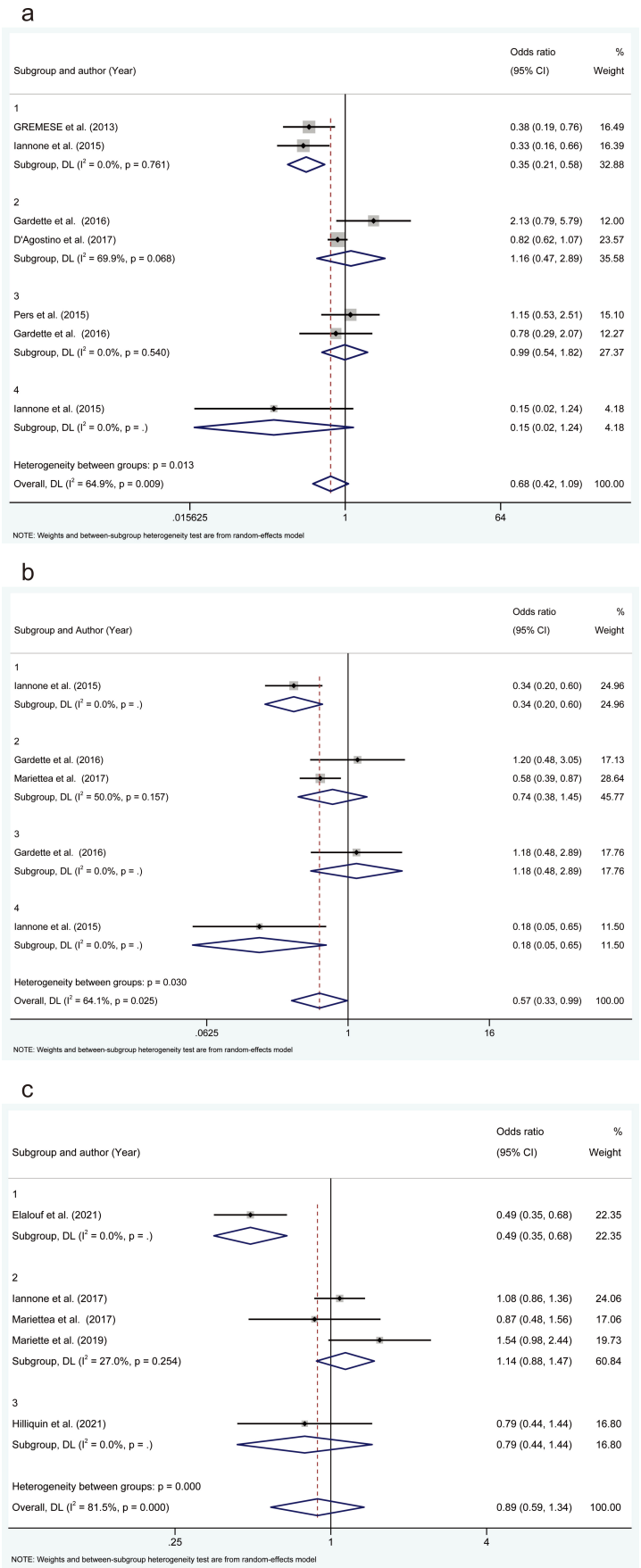

Fig. 3. Subgroup analysis forest plot effect of bDMARDs on RA. (a) Remission. (b) Good EULAR response. (c) Retention rate.

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Sensitivity Analysis

Sensitivity analysis indicated that the exclusion of any study did not significantly alter the effect of obesity on the response rate of outcome indicators in RA patients (**Supplementary Fig. 2–7**). These findings further support the high stability and reliability of the results.

Publication Bias

Funnel plots and Egger's regression test were used to investigate potential publication bias. Visual observation of the funnel plot indicated no asymmetry (**Supplementary Fig. 8**). This observation was further confirmed by Egger's regression test (intercept = – 0.70; standard error = 1.23; 95% CI: – 3.88, 2.47; t = – 0.57; two-tailed p value = 0.595); Response Egger's regression test (intercept = – 3.33; standard error = 7.32; 95% CI: – 96.32, 89.65; t = – 0.45; two-tailed p value = 0.728); Good EULAR response Egger's regression test (intercept = 0.25; standard error = 2.19; 95% CI: – 6.74, 7.25; t = 0.12; two-tailed p value = 0.915); Moderate EULAR response Egger's regression test (intercept = 0.07; standard error = 2.92; 95% CI: – 37.06, 37.02; t = 0.02; two-tailed p value = 0.984); Retention rate Egger's regression test (intercept = – 0.41; standard error = 3.24; 95% CI: – 10.73, 9.90; t = – 0.13; two-tailed p value = 0.907) and CDAI Egger's regression test (intercept = – 0.94; standard error = 1.28; 95% CI: – 6.44, 4.60; t = – 0.74; two-tailed p value = 0.538).

Discussion

Obesity significantly affects the clinical response rate of RA patients receiving bDMARDs. However, there is a lack of evidence-based medical research demonstrating the impact of obesity on the response rate. Therefore, there is a need to conduct well-designed systematic reviews and meta-analyses to search for evidence-based medical data.

The novelty of our study lies in exploring whether the clinical efficacy of bDMARDs in obese RA patients is lower than that of non-obese patients based on evidence from several cohort studies. Our findings reveal no substantial difference in overall efficacy between obese and non-obese groups when analyzing bDMARDs collectively. However, we have identified a significant source of heterogeneity. Subsequent subgroup analysis on distinct bDMARD types indicates that the variability stems from the types of bDMARDs. Specifically, obesity alters the clinical efficacy of TNFi, while it has no significant impact on the efficacy of ABA and TCZ. Consequently, we will investigate the individual bDMARD types separately. Sensitivity analysis suggests that our results are relatively robust. This meta-analysis demonstrates that the use of TNFi is influenced by obesity, which is consistent with findings from previous studies.

In clinical practice, TNFi is used clinically to relieve symptoms of RA. It is a class of bDMARDs with a well-studied mechanism of action. Currently, IFX, ETA, and ADA are the most widely used TNFi. Klaasen *et al*. [12] performed a study to determine whether or not BMI affects the response of patients with RA to IFX. The researchers measured the body weight of 89 patients with active RA before IFX treatment. After 16 weeks, changes in DAS28 indicated that patients with RA with a high BMI had a poorer response to IFX despite the weight-based IFX dose. Similarly, Gremese *et al*. [13] administered TNFi therapy to 611 outpatients with longstanding RA (260 cases with ADA, 227 cases with ETA, and 154 cases with IFX). After 12 months, 15.2% of patients in the obese group, 30.4% in the overweight group, and 32.9% in the normal group exhibited DAS28 $<$2.6. This demonstrates that obesity is an independent risk factor for a high remission rate in RA patients receiving long-term TNFi therapy. Another cohort study comprising 292 RA patients who received TNFi therapy found that patients with obesity who discontinued the first TNFi drugs exhibited the highest risk and lowest DAS28-based remission rate at 12 months [14]. The study by Novella-Navarro [15] suggested that obesity can affect the extent of LDA/remission in TNFi treated patients, but it does not influence TCZ, indicating that the differential source is the potential mechanism of pro-inflammatory adipokines production. Research by Offr Elalouf's [16] further supported that TNF-α blocker retention is lower in morbidly obese RA patients compared to those with a normal BMI. Additionally, Ottaviani *et al*. [32] conducted a retrospective study to investigate the potential association between BMI and the response to IFX in 76 RA patients. The primary outcome measured was a reduction in DAS28 by $\geq$1.2. The study by Heimans *et al*. [33] confirmed that high BMI was an independent risk factor for failure to achieve DAS $\leq$2.4 on primary therapy through a relative risk regression analysis. Huvers *et al*. [34] conducted an open-label prospective study involving eight patients with chronic inflammatory diseases but without diabetes who were started on IFX and followed-up for 6 weeks. They found that the TNFi therapy-mediated improvement in insulin sensitivity mediated by TNFi therapy was negatively affected by BMI and obesity at the start of treatment. Therefore, these results imply that obesity attenuates the beneficial effects of these drugs on RA-related metabolic syndrome, and the efficacy of TNFi therapy in reversing inflammation-related insulin resistance may be influenced by the body weight. A previous study reported no reduction in TNFi efficacy in patients with obesity [35]. In this retrospective cohort study, a significant association was observed between severe obesity and the initial subcutaneous injection, independent of any interruption in TNFi therapy. Conversely, patients with a low/normal BMI demonstrated a higher likelihood of interrupting TNFi compared to those with an overweight BMI. However, confounding factors persisted, and the level of evidence remained low. This suggests that obesity could potentially have an adverse impact on the response to TNFi drugs, particularly IFX.

ABA can reduce cell infiltration and interaction among T cells and macrophages, as well as the release of downstream cytokines by inhibiting T-cell costimulation to suppress the generation of osteoclasts [36,37]. In a multicenter retrospective study, Gardette *et al*. [17] reported that obesity was not a limiting factor for ABA use in patients with RA. Iannone *et al*. [18] carried out a prospective cohort clinical study to evaluate the effect of BMI on ABA use. The results showed that ABA drug retention was the primary endpoint, and the EULAR/LUNDEX response rate was the secondary endpoint. Among the patients, 380 (18.9%) were classified as obese. Patients with obesity exhibited more severe dysfunction and a lower radiofrequency positive rate. The risk of discontinuation of ABA in patients with overweight or obesity was not significantly different compared to those with normal weight. Mariette *et al*. [19] investigated the clinical response of baseline BMI to subcutaneous or intravenous ABA. Specifically, they reported hazard ratios (HRs) of 0.46 for patients with overweight and 0.69 for patients with obesity, suggesting that BMI does not significantly impact the response or retention rates of ABA in these patients. The presence of positive rheumatoid factors was associated with a decreased risk of discontinuation of ABA, whereas previous biological agent therapy was positively associated with discontinuation. Notably, they observed no reduction in drug retention or clinical response rates to ABA in patients with obesity. Furthermore, both subcutaneous and intravenous ABA demonstrated comparable clinical efficacies, independent of baseline BMI, when strict remission criteria were used. Regardless of the method of administration, most patients achieved a therapeutic level of ABA in their plasma [20]. A 2-year French ACTION cohort study found that 44% of patients maintained this level, and it was not linked to their BMI [21]. Another study by Carlo *et al*. [38] retrospectively analyzed the data from 130 RA patients who participated in the ultrasound clinical arthritis activity (US-CLARA) study to investigate whether BMI affected the clinical response to ABA. The analysis showed that patients achieved a clinical response regardless of their weight status. Therefore, ABA may be an effective treatment for RA patients, irrespective of their BMI.

Tocilizumab is the first biological agent that targets the IL-6 receptor antagonist, significantly controlling the inflammatory response and preventing joint injury [39,40]. A retrospective study of 222 patients with RA reported that obesity (BMI >30 kg/m^2) in 222 patients with RA could not predict the efficacy of tocilizumab. Some responses to tocilizumab were similar between patients with obesity and controls. Initially, the infusion dose of tocilizumab is determined by the patient's body weight. Consequently, individuals with obesity should receive a higher dose of tocilizumab. When assessing the correlation between obesity and clinical response to weight-based bDMARDs like tocilizumab and abatacept, weight may provide a more distinct and potentially more meaningful metric than BMI. Additionally, individuals with obesity often exhibit elevated cortisol levels. The increased production of the inflammatory cytokine IL-6 by abundant adipose tissue triggers systemic inflammatory responses, and the interplay with factors such as tocilizumab dosage and hormonal responses could potentially counterbalance it. Gardette *et al.* [23] and Pascal Hilliquin *et al.* [24] found no correlation between the patient's profile (BMI) and TCZ-SC use. Similarly, in real-world analysis, the effectiveness of TCZ was not affected by obesity status [25]. However, Abuhelwa *et al.* [26] postulated that regardless of RA treatment, baseline BMI should be regarded as a stratification factor in future RA trials, although there is no confirmation that obesity affects the response rate of bDMARDs. Kim *et al*. [41] reported that the BMI was not associated with the EULAR clinical response. Based on the above research results, we speculated that BMI is not an index influencing the clinical efficacy of TCZ. Currently, there are no data to demonstrate the impact of obesity on the response indices to RTX (an antibody targeting the B-cell receptor CD20). Ottaviani *et al.* [42] retrospectively analyzed 114 RA patients treated with RTX. Through a multivariate analysis, they confirmed that there was no correlation between BMI and response indices of RTX.

In the conducted meta-analysis, the focus was primarily on examining the influence of bDMARDs on obese RA patients. This study aimed to standardize the definition of obesity and categorize bDMARDs. The analysis was conducted in line with current guidelines, which included the use of extensive sensitivity analysis to evaluate the results and updated evaluation tools to investigate the risk of bias. Therefore, the findings of our analyses are highly credible. However, our review is subject to potential limitations. First, the exclusion of a considerable amount of literature due to missing data restricts the supporting evidence for our research outcomes. Second, the absence of a hierarchical assessment of bDMARD use in RA patients might influence the effectiveness results.

Conclusions

The results of the included studies revealed that obesity affects the clinical response rate of RA patients receiving TNFi, but it does not have an adverse effect on ABA and TCZ. However, the ineffectiveness of TNFi biological category selectivity in patients with obesity remains unclear and warrants further investigation. This discovery has the potential to inform clinical diagnosis and treatment. Moreover, our results indicate that personalized medication should be tailored to individual body weight.

Availability of Data and Materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

RSL: data curation. YZ: formal analysis, meta-analysis, methodology. YTL: writing original draft. JZ: conceptualization, supervision. SR: methodology. FYM: literature collection. QC: formal analysis. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.23812/j.biol.regul.homeost.agents.20243805.290.

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