

LETTER TO THE EDITOR

Effect of anti-IL-5 biologics on weight and body mass index

To the Editor:

Anti-interleukin (IL)-5 biologics are effective in the treatment of severe asthma associated with predominant eosinophilic inflammation. Mepolizumab and benralizumab are anti-IL-5 monoclonal antibodies with a fixed-dose regimen, compared with reslizumab which

is a weight-based regime.¹ All three are very effective in significantly decreasing circulating and airway eosinophil numbers and steroid exposure,¹ suggesting anti-IL-5 therapy could reduce weight and BMI due to steroid reduction. However, eosinophils have recently been recognized to regulate adipocyte homeostasis and energy

TABLE 1 Baseline characteristics

Characteristic	All (N = 134)	Mepolizumab (N = 87)	Reslizumab (N = 28)	Benralizumab (N = 19)	p value
Age (years)	55.6 ± 13.1	55.9 ± 13.6	52.8 ± 12.6	58.4 ± 10.27	.34
Female sex – no. (%)	76 (56.7%)	47 (54.0)	12 (42.9)	17 (89.5)	<.01
FEV ₁					
Value – Liters	1.87 ± 0.72	2.0 ± 0.8	2.0 ± 0.9	1.7 ± 0.57	.45
% Predicted	69.6 ± 24.1	69.5 ± 27.0	77.3 ± 35.4	68.6 ± 19.2	.85
Blood eosinophils pre-therapy – cells/μl	640 ± 465	729 ± 443	1100 ± 990	479 ± 404	.08
Weight pre-therapy (kg)	84.9 ± 18.1	85.1 ± 17.8	90.1 ± 20.5	76.1 ± 11.9	.03
BMI pre-therapy (kg/m ²)	30.4 ± 5.6	30.4 ± 5.9	30.8 ± 4.9	29.3 ± 5.3	.65
Pretreatment BMI groups – no. (%)					
<25	20 (14.9)	15 (17.2)	2 (7.1)	3 (15.8)	
25–29.9	46 (34.3)	29 (33.3)	9 (32.1)	8 (42.1)	
≥30	68 (50.7)	43 (49.4)	17 (60.7)	8 (42.1)	
No. of patients with daily OCS use – no. (%)	80 (59.7)	57 (65.5)	20 (71.4)	3 (15.8)	<.01
Median OCS pretreatment mg/day prednisone*	10.0 (7.5–15.0)	10.0 (7.5–13.8)	10.0 (10.0–20.0)	10.0 (1.3–10.0)	.24
Median OCS post-treatment mg/day prednisone*	4.5 (0–7.5)	5.0 (0–7.5)	2.8 (0.6–6.8)	1.3 (0–1.3)	.56
Median number of hospitalisations or burst steroids/year pretreatment	2 (1–3.25)	2 (0–3)	3 (2–3)	2 (2–4)	.52
Median number of hospitalisations or burst steroids/year post-treatment	0 (0–1)	0 (0–1)	0	0 (0–1)	.39
Median weight change (kg)	0 (–3.0–2.1)	0 (–2.0–2.4)	–0.45 (–3.6–1.9)	0 (–3.2–1.7)	.64
Median weight change (kg)					
Pretreatment daily OCS use	0 (–3–1.9)	0 (–1–1)	–1 (–3.6–3.1)	–0.7 (–2.7–0)	.82
No pretreatment daily OCS use	0 (–2.9–2.3)	0 (–0.5–2.8)	–0.2 (–5.4–0.8)	0.1 (–3.4–2.1)	.67
Median BMI change (kg/m ²)	0 (–1.0–0.9)	0 (–0.8–1.0)	0 (–1.0–0.3)	0 (–1.2–0.7)	.56
Median BMI change					
Pretreatment daily OCS use	0 (–1–0.8)	0 (–2.3–1.9)	0 (–1–0.8)	–0.3 (–0.9–0)	.80
No pretreatment daily OCS use	0 (–1.1–1)	0 (–1.9–1.1)	–0.1 (–1.6–0.3)	0.1 (–1.4–0.9)	.56

Note: Data are presented as No. (%), mean ± SD, or median (interquartile range).

Abbreviations: BMI, Body Mass Index; FEV₁, Forced expiratory volume in one second; OCS, maintenance oral corticosteroid dose.

*Data include patients with pretreatment daily OCS use only. Parametric variables were compared using one-way ANOVA. Nonparametric variables were compared using the Kruskal-Wallis Test.

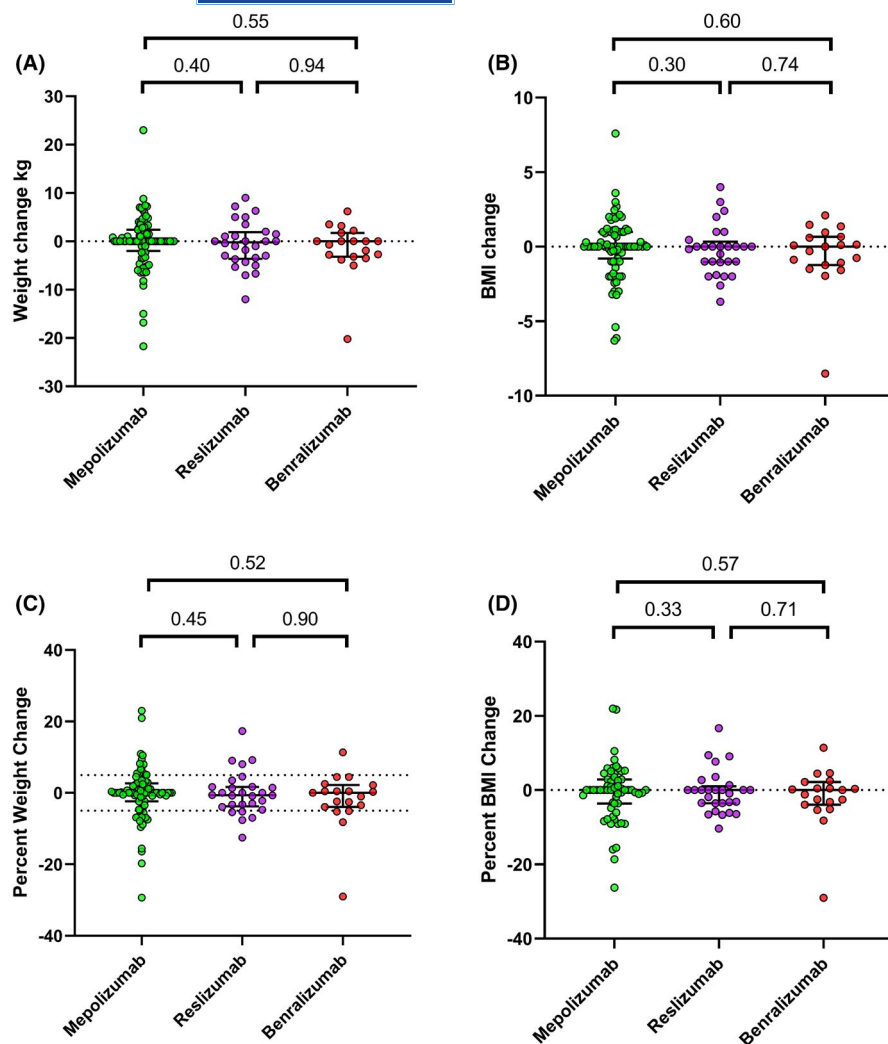


FIGURE 1 Total weight (A) and BMI (B) change and percent weight (C) and BMI (D) change for patients treated with mepolizumab ($n = 87$), reslizumab ($n = 28$) and benralizumab ($n = 19$). Dashed line indicates $\pm 5\%$ change in weight percentage (C). There was no significant difference across all three anti-IL-5 biological therapies for total weight ($p = .64$) or BMI ($p = .56$) change, or percent weight ($p = .57$) or BMI ($p = .66$) change between groups as shown. Data presented as median with IQR and analyzed using Kruskal-Wallis and Mann-Whitney U Tests

expenditure through mechanisms that are not well understood.² It is not known what the effect of anti-eosinophil therapies are on weight and body mass index (BMI).

We examined this question in two data sets: 1) a retrospective review of 134 patients at our severe asthma clinics who received an anti-IL-5 between 2016 and 2020 (Table 1) and 2) data from two phase 3 pivotal clinical trials of reslizumab (studies #3082, 3083, BREATHE program) in patients with moderate to severe asthma that are previously published.^{3,4} All patients provided informed consent, and clinical information was extracted from patient charts under protocols approved by the Hamilton Integrated Research Ethics Board for studies related to Airway Inflammatory Database (#11020), and clinical response to anti-IL-5 biologics (#3801 and 11264).

In the real-world series, 134 patients were administered a biologic (87 patients prescribed mepolizumab, 28 reslizumab, and 19 benralizumab). Patient's weight, height, and BMI were recorded at a mean of 47 weeks (SD = 27.1, range 8–109 weeks) after starting biological therapy. A clinically significant change in weight was defined as a change of $\pm 5\%$ body weight from date of commencement of biological therapy.⁵

There was no difference between anti-IL-5 therapies for absolute or percent change in weight or BMI between individual groups (Figure 1A–D), nor a change in weight or BMI pre- and post-treatment for each IL-5 therapy (Figure S1A–F). There was no difference in percent changes in weight ($p = .75$) or BMI ($p = .42$) irrespective of whether patients were obese (BMI ≥ 30 kg/m²) or non-obese (BMI < 30 kg/m²) at baseline. Also, there was no difference between obese and non-obese for absolute or percent change in weight or BMI for each anti-IL-5 therapy (Figure S2A–D). The presence of obesity did not predict anti-IL-5 response ($p = .24$).

Overall, 92 (68.7%) patients had no clinically significant change in body weight percentage, 19 (14.2%) patients had an increase, and 23 (17.1%) patients had a decrease in weight. Patients who gained weight had a significantly lower weight, but not BMI, prior to commencing anti-IL-5 therapy, but there were no other baseline characteristic differences between groups (Table S1). The subgroup of 19 (14.2%) patients who increased their weight by $\geq 5\%$ did so despite a reduction in steroid burden and blood eosinophil level. There were no predictive characteristics for which patients gained or lost weight.

Results from the two phase 3 reslizumab clinical trials provided similar findings with no clinically meaningful (or statistically significant) trend of body weight measurement in terms of mean changes from baseline to study endpoint for the placebo (total 475 patients) and reslizumab (total 477 patients) in either of the two clinical trials (Table S2).

Strengths of our report are that the data include the three anti-eosinophil drugs that are approved for use, and data that were carefully collected in two tertiary severe asthma clinics. Since our clinical practice allows reduction of steroid dosages which might confound measurement of weight, we validated our observation using data from two placebo-controlled clinical trials that did not involve steroid dose reduction. Our observations are consistent with a previous report of 51 patients evaluated over a 6-month period which demonstrated a mean BMI decrease of 1.0 after anti-IL-5 therapy; however, there were significant BMI fluctuations within the mepolizumab group ($n = 29$, range -5.9 to 5.4 , $p = .03$), suggesting a subgroup within their population gained a significant amount of weight.⁶ We recognize the limitations of small sample size particularly to make comparisons between biologics, inherent biases of the retrospective design, and the relatively short period of follow-up. In summary, our data provide reassurance that anti-IL-5 biologics are not generally associated with significant weight gain.

KEYWORDS

asthma, asthma treatment, biologics, clinical immunology, eosinophils

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CONFLICT OF INTEREST

Dr. Cusack reports grants from Ontario Lung Society, grants from MITACS, other from Irish Thoracic Society, outside the submitted work. Ms. Huang has nothing to disclose. Ms. LaVigne has nothing to disclose. Dr. Satia reports personal fees from AstraZeneca, grants and personal fees from Merck Canada, grants from ERS Respire 3 Marie Curie Fellowship, grants from E.J. Moran Campbell Early Career Award, grants and personal fees from GSK, outside the submitted work. Dr. Nair reports grants and personal fees from AZ, grants from Novartis, grants and personal fees from Teva, grants from Sanofi, grants and personal fees from Roche, personal fees from Novartis, personal fees from Merck, personal fees from Equillium, grants from Foresee, outside the submitted work. Dr. O'Byrne reports personal fees from AstraZeneca, personal fees from GSK, personal fees from Chiesi, personal fees from Covis, grants from AstraZeneca, grants from Genentech, grants from Novartis, grants from Merck, grants from Bayer, outside the submitted work.

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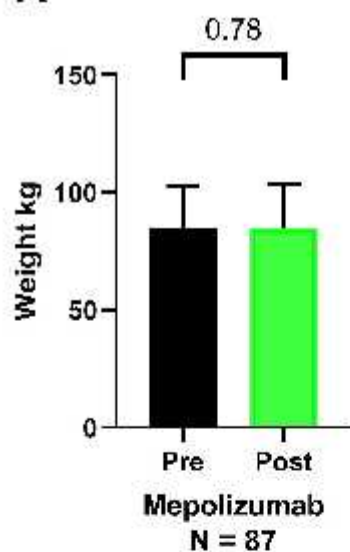
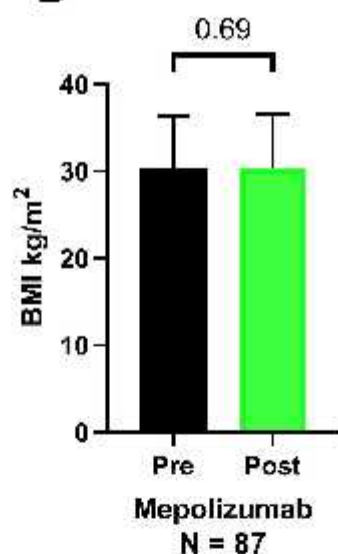
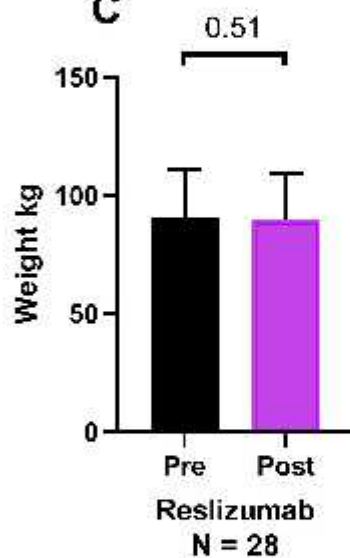
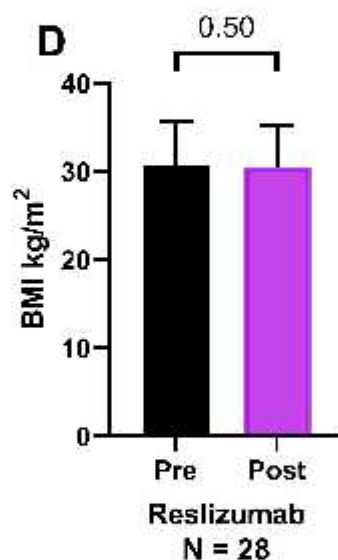
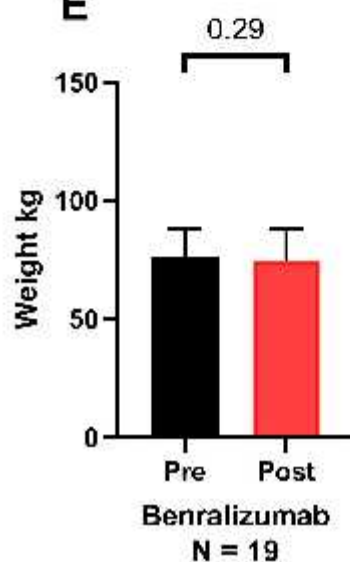
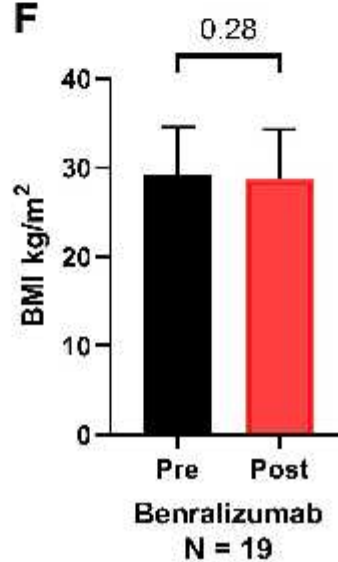
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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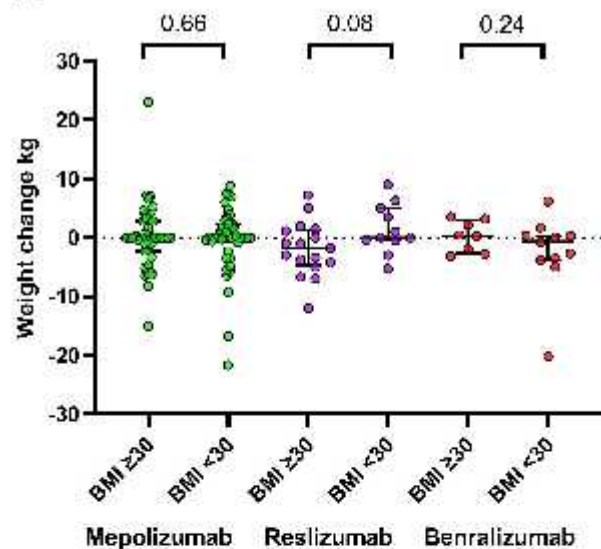
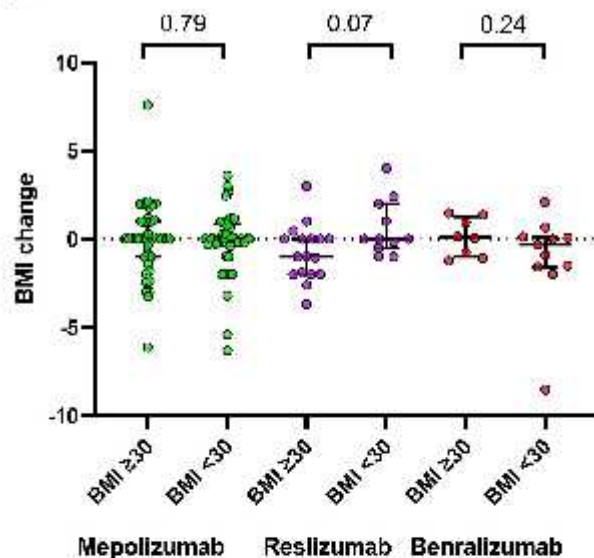
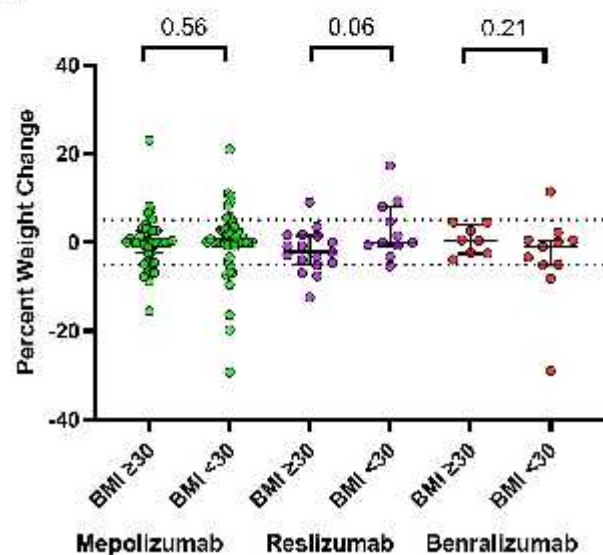
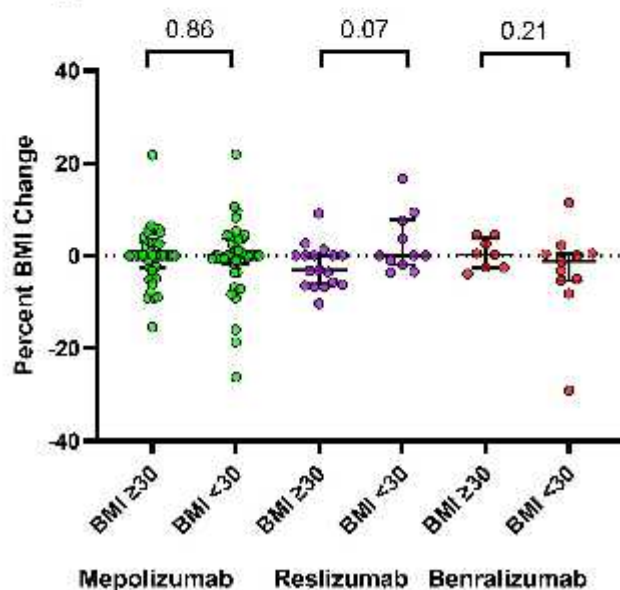
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Figure S1

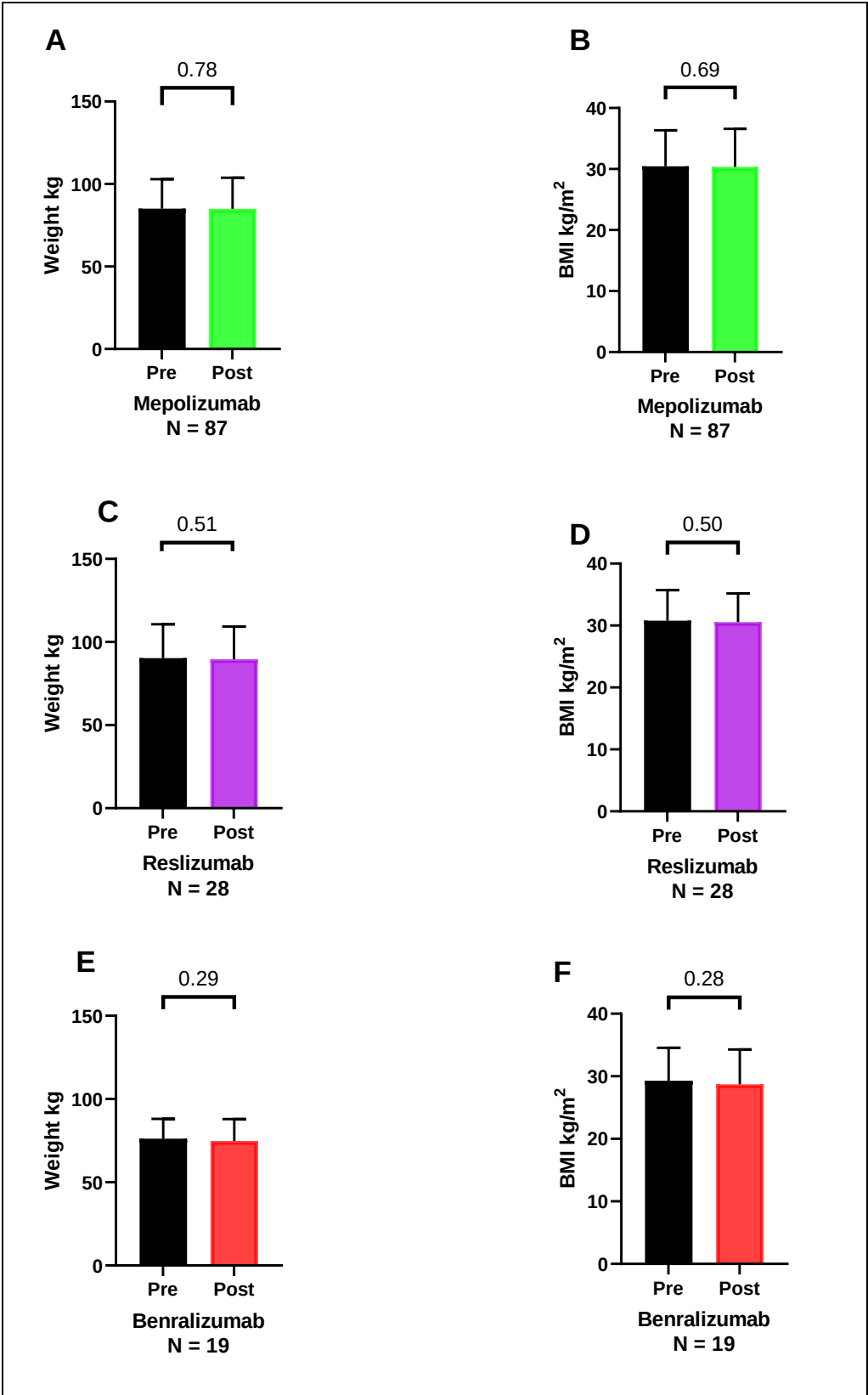


Figure S1: Weight (A) and BMI (B) pre and post treatment with mepolizumab (n = 87), reslizumab (n = 28) and benralizumab (n = 19). Data presented as mean with S.D. and analysed using paired t-tests.

Figure S2

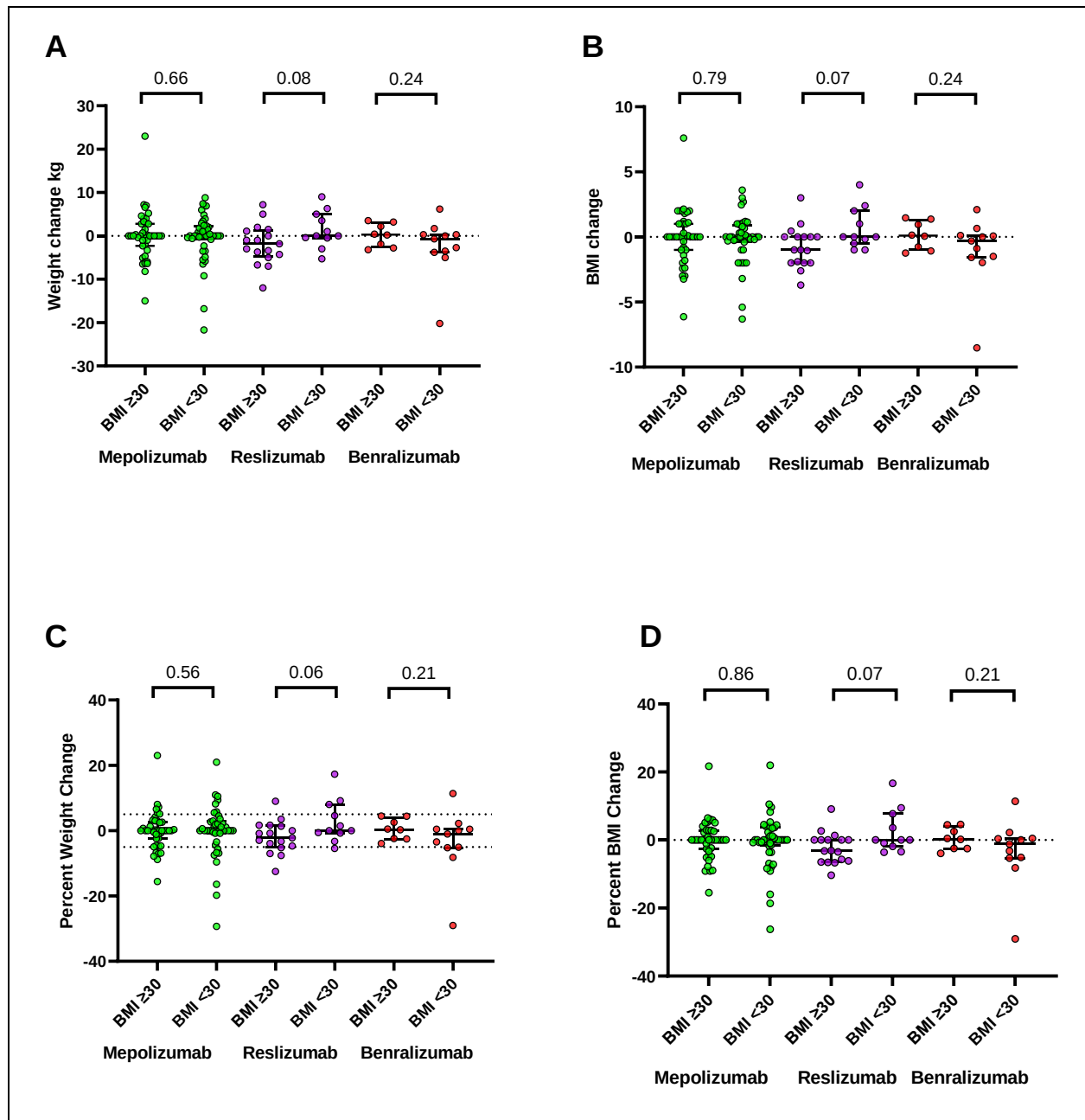


Figure S2: Total weight (A) and BMI (B) change and percent weight (C) and BMI (D) change for patients with BMI ≥ 30 and BMI < 30 , treated with mepolizumab (n = 87), reslizumab (n = 28) and benralizumab (n = 19). Dashed line indicates $\pm 5\%$ change in weight percentage (Figure S2C). There was no significant difference between BMI ≥ 30 and BMI < 30 for total weight or BMI change, or percent weight or BMI change for each anti-IL-5 therapy. Data presented as median with IQR, and analysed using Mann-Whitney U Tests.

Table S1: Baseline characteristics of patients as grouped by percent weight change (n = 134)

Characteristic	Increased $\geq 5\%$ Body Weight (N = 19)	Stable Body Weight % (N = 92)	Decreased $\geq 5\%$ Body Weight (N = 23)	P value
Age (years)	52.8 $\pm$ 12.7	55.5 $\pm$ 13.3	58.0 $\pm$ 12.6	0.44
Biological therapy no. (%):				
mepolizumab	14 (73.7)	59 (64.1)	14 (60.9)	
reslizumab	4 (21.1)	19 (20.7)	5 (21.7)	
benralizumab	1 (5.2)	14 (15.2)	4 (17.4)	
Female sex – no. (%)	13 (68)	47 (51)	16 (70)	0.15
Pre-treatment weight	75.8 $\pm$ 18.3	87.7 $\pm$ 18.4	81.4 $\pm$ 13.9	0.02
Pre-treatment BMI	28.3 $\pm$ 5.7	30.9 $\pm$ 5.6	29.9 $\pm$ 5.4	0.16
Pre-treatment FEV ₁ % predicted	74.7 $\pm$ 27.1	71.4 $\pm$ 22.2	61.25 $\pm$ 28.3	0.45
Pre-treatment FVC % predicted	91.8 $\pm$ 27.2	86.0 $\pm$ 26.1	87.5 $\pm$ 19.9	0.87
Pre-treatment blood eosinophils, cells/ μ L	816.7 $\pm$ 643.2	624.1 $\pm$ 446.5	580.0 $\pm$ 342.5	0.60
Post-treatment blood eosinophils, cells/ μ L	60.0 $\pm$ 54.8	126.1 $\pm$ 350.6	22.2 $\pm$ 44.1	0.63
Median OCS pre- treatment mg/day prednisone	8.2 (0 – 10)	5 (0 – 10)	7.5 (0 – 10)	0.88
Median OCS post- treatment mg/day prednisone	0 (0 – 7)	0 (0 – 5)	0 (0 – 5)	0.66
Median number of hospitalisations or burst steroids/year pre- treatment	1 (0 – 2.25)	2 (1 – 3)	3.5 (0 – 4.25)	0.21
Median number of hospitalisations or burst steroids/year post- treatment	0 (0 – 1)	0 (0 – 1)	0 (0 – 2.25)	0.69

Data are presented as No. (%), mean $\pm$ SD, or median (interquartile range). Parametric variables were compared using one-way anova. Nonparametric variables were compared using kruskall-wallis test. BMI = body mass index, FEV₁ = forced expiratory volume in one second, OCS = maintenance oral corticosteroid dose.

Table S2: Data from two phase III studies of reslizumab in patients with moderate to severe asthma

Study	Drug/placebo	Weight Baseline*	Weight Change at End of Treatment [#]	Special consideration
C38072/3082 - Phase III parallel group, randomized, placebo-controlled trial	Placebo (n = 243)	76.2 (18.29)	0.4 (3.38)	No clinically significant change in weight was observed during study
	Reslizumab 3mg/kg IV (n = 245)	75.6 (19.05)	0.8 (3.95)	
C38072/3083 – Phase III parallel group, randomized, placebo-controlled trial	Placebo (n = 243)	73.8 (15.96)	0 (3.86)	No clinically significant change in weight was observed during study
	Reslizumab 3mg/kg IV (n = 245)	74.8 (15.78)	0.6 (3.38)	One subject discontinued study drug due to weight increase

*: Mean weight at baseline in kg (SD). #: Mean change of weight in kg (SD) at study endpoint (end-of-treatment visit or early withdrawal visit).