

Subgroup Analysis of a Randomized Trial of the Effects of Positive Messaging on Patient-Reported Outcomes with Asthma – Effect of Obesity

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Objective: Asthma in obese patients represents a specific phenotype that is associated with increased symptoms, more frequent and severe exacerbations, reduced responsiveness to treatment, and decreased quality of life. Marketing and placebos have been shown to alter subjective responses to interventions in both asthma and obesity. We evaluated obesity as a potential treatment effect modifier of the effects enhanced drug messaging or placebos on subjective asthma outcomes.

Methods: We conducted a secondary analysis of a multicenter, randomized clinical trial that studied the effect of messaging and placebos on asthma outcomes. A total of 601 participants were randomized (1:1:1:1:1) to one of 5 groups: enhanced messaging with montelukast or placebo, neutral messaging with montelukast or placebo, or usual care and followed for 4 weeks after randomization. We compared baseline characteristics by obesity status for 600 participants with data on body weight. Obesity was evaluated as an effect modifier for enhanced messaging (versus neutral messaging) and on placebo effects (versus usual care) in 362 participants assigned to a placebo group or usual care for three asthma questionnaires: Asthma Control Questionnaire, Asthma Quality of Life Questionnaire and Asthma Symptoms Utility Index.

Results: Overall, 227 (37%) of participants were obese. Obese participants were older (mean age 41 vs 34), more likely female (82% vs 67%) and self-identified as Black (44% vs 25%) than non-obese participants. As previously published, enhanced messaging was associated with improvements in patient-reported asthma scores, but there was no evidence for a placebo effect. Obesity status did not influence the message effects nor did it modify responses to placebo.

Conclusion: Obesity has been shown to be an important factor associated with asthma outcomes and an effect modifier of drug treatment effects. We conducted a post hoc, subgroup analysis of data from a multicenter randomized trial of enhanced messaging and placebo associated with drug treatment on asthma outcomes. Our findings suggest that observed differences in treatment effects between obese and non-obese patients sometimes seen in trials of asthma treatments are unlikely to be due to different “placebo” effects of treatment and may reflect differential physiologic effects of active agents.

Keywords: obesity, asthma, asthma questionnaires, messaging

Introduction

Asthma associated with obesity is associated with adverse asthma outcomes including poorer quality of life, more severe disease, increased daily symptoms, and more frequent exacerbations^{2–6} when compared to non-obese asthmatics. It is also well recognized that obese patients with asthma respond differently to treatment interventions,^{5,6} and that subjective and objective asthma measures in obese patients often do not correlate.^{7–9}

We conducted a multicenter randomized study to evaluate the effects of placebos and enhanced messaging on responses to oral drugs (montelukast or placebo) in poorly controlled asthmatics. The primary outcomes were patient-reported outcomes,

questionnaire scores; secondary outcomes were based on diary cards and spirometric measures of lung function. Overall, we found small, inconsistent placebo effects on asthma questionnaire scores and consistent effects of positive messaging on these outcomes in participants assigned to placebo. There were no placebo or messaging effects on lung function outcomes.

In this analysis, we evaluated obesity as a potential effect modifier. We did not include specific messaging targeting body weight or image in the positive messaging intervention for this trial, recognizing that ads emphasizing negative health consequences elicit stronger cognitive and emotional responses from overweight and obese adults and may have unintended impacts.³⁴ We used images of a slender, active adult, which could produce differential responses to the contextual marketing cues (eg, appearance, activities, branding, labeling, price of a product) even if the cues related to obesity were unintentional. Contextual marketing cues can alter a patient's subjective experience of benefit or harm of a medication—including asthma medications.¹ Contextual marketing cues (eg, appearance, branding, labeling, price of a product) combined with placebo effects has been referred to as “marketing placebo effect”^{10,11} and response to marketing cues may be influenced by personal characteristics, like obesity.

The marketing placebo effect is thought to operate through the mesolimbic reward circuit, specifically the ventral tegmental area (VTA) where neurons are thought to play distinct roles in positive and negative reinforcement, decision-making, working memory, incentive salience, and aversion. These are the same brain regions implicated in overeating in the obese.^{12,33} The effective characteristics of marketing advertisements in obese patients, particularly those with asthma, is not well understood, but there is expanding evidence to suggest that marketing strategies can affect food intake and be a risk factor for body mass index.³⁷ In both phenomenon, the stimulus (eg, branding, appearance, consumption of highly palatable food) stimulates dopamine activity and creates the feeling of pleasure and satisfaction.^{13–16} Placebos are reported to improve subjective and objective outcomes in up to 30–40% of patients in many clinical conditions, including asthma, hypertension, myocardial infarction, insomnia, and depression.^{17–19} In asthma, placebo effects have been observed to improve both patient-reported and physiologic outcomes; however, the magnitude of effect has been variable^{15,20–23} and little is known about the role of marketing placebo effects in patients with asthma and how it may differentially affect the response to asthma medication in obese and non-obese patients with asthma. Improving our understanding of the role of obesity and the marketing placebo effect can potentially provide insight into novel approaches to improving asthma outcomes in this hard to treat asthma population.

In this study, we aimed to quantify the effects of obesity on the relationship between enhanced drug messaging (ie, contextual marketing) and subjective asthma outcomes. We conducted a secondary analysis of the Trial of Asthma Patient Education (TAPE) trial¹ that studied enhanced messaging and its effect on asthma outcomes.

Methods

The 20 centers of the American Lung Association Asthma Clinical Research Centers (ALA-ACRC) conducted the trial from December 2003 to December 2005. The ALA-ACRC Coordinating Center collected and analyzed the data. The trial was sponsored by the American Lung Association and NIH. All centers obtained and maintained IRB approval throughout the study. The trial complied with the Declaration of Helsinki. The trial was registered at ClinicalTrials.gov, NCT00148408 under the acronym Trial of Asthma Patient Education (TAPE).

Study Population

We conducted a secondary analysis of the TAPE trial¹ including participants who had data on weight. The TAPE trial was a multicenter, randomized clinical trial conducted by the American Lung Association Asthma Clinical Research Centers from December 2003 to December 2005 at 20 sites across the United States. The methods and results were previously published.¹ Briefly, the TAPE trial enrolled nonsmokers age 15 years or older with a history of physician diagnosed asthma and regular use of asthma medication, post-bronchodilator FEV₁ of greater than 75% of predicted value, and at least one of the following indicators of poor asthma control: Asthma Control Questionnaire (ACQ) score >1.5, use of β -agonists for asthma symptoms > twice per week, or more than one nocturnal awakening per week.

Participants were randomized to one of five groups: enhanced-message and montelukast 10mg, enhanced-message and placebo, neutral-message and montelukast 10mg, neutral-message and placebo, and usual care (no study drug or messaging intervention) (Figure 1). The usual care group received a NIH pamphlet on controlling your asthma. All participants had a two-week run in period for collection of baseline data and during which they documented asthma symptoms in a diary. At the

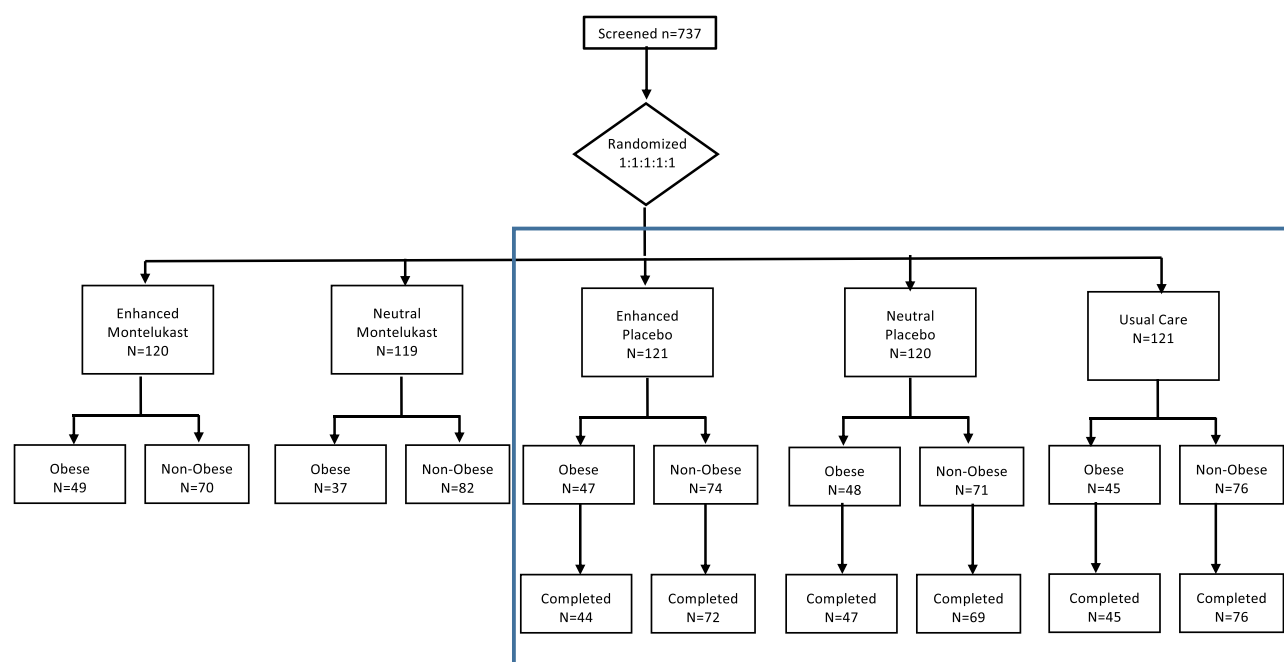


Figure 1 Consort diagram. Data from intervention groups included in blue box were included in the analysis of change in patient-reported outcome.

randomization visit, participants, except for those assigned to usual care, viewed an informational computer-based presentation with enhanced drug messaging or neutral drug messaging. The drug messaging was repeated two weeks later. Outcomes were measured at two and four weeks after randomization.

Messaging Intervention

The message intervention included 3 components: a scripted message, a computer presentation, and the appearance of the study drug capsule containing montelukast or placebo. The enhanced message script and computer presentation emphasized the benefits of the treatment and the likelihood of improved asthma symptoms. The value and potency of the study drug treatment was emphasized by including a television commercial for montelukast. In the enhanced presentation, the study drug was referred to using its brand name, Singulair®. The neutral script and computer presentation were similar to the enhanced but did not have the positive messages about the expected benefits of montelukast, expressed uncertainty about improvement, and did not contain the television commercial. In the neutral presentation study drug was referred to by the generic name, montelukast. The groups also received different colored capsules. The enhanced groups received a two-tone blue capsule containing montelukast or placebo while the neutral group received a monotone off-white capsule containing montelukast or placebo.

Baseline Variables

In this study, baseline BMI (basal metabolic index) ≥ 30 kg/m² was used to define obesity and BMI < 30 kg/m² was used to define the non-obese participants.³² Baseline variables included demographic characteristics (ie, age, self-reported race and ethnicity, gender), body mass index, smoking history, socioeconomic factors (ie, educational attainment, employment status) and asthma characteristics (ie, age of asthma onset, frequency of short-acting beta-agonist use, frequency of inhaled corticosteroid inhaler use).

Outcomes

The primary outcomes for these analyses were change from baseline for three patient-reported asthma outcomes measured at baseline and two and four weeks after randomization: the Asthma Control Questionnaire (ACQ),²⁴ the Asthma Symptom Utility Index (ASUI),^{25,26} and the Asthma Quality of Life Questionnaire (AQLQ).^{27–29} All

questionnaires were previously validated and widely used in asthma research. ACQ assesses asthma control over one week; AQLQ and ASUI have a 2 week recall.^{24–29} The 6 item version of the ACQ score that does not include percent predicted FEV₁ was calculated for this analysis.

Statistical Analysis

All trial participants were included in the comparison of baseline characteristics by obesity status (Figure 1). We used descriptive statistics to summarize participants baseline characteristics and Chi-square and Kruskal–Wallis tests to evaluate differences in characteristics between obese and non-obese participants.

Data from participants assigned to placebo with either an enhanced or neutral message were analyzed to evaluate whether obesity was a treatment modifier of message effects on patient-reported outcomes (Figure 1, blue box). Study outcomes were analyzed as change from baseline values at two visits (2 and 4 weeks post randomization) in linear regression, mixed effects models. Participant ID was modeled as a random effect in all models; the intervention (neutral versus enhanced), obesity and visit were fixed effects in unadjusted models; age, gender and race were included as fixed effects in adjusted models. Effect modification was evaluated by inclusion of interaction terms for intervention assignment and obesity status at follow-up visits.¹

In the TAPE trial, the “placebo effect” was estimated by comparing those assigned to placebo with a neutral message versus the usual care group (Figure 1, blue box). Data from participants assigned to placebo with a neutral message or usual care were compared to evaluate obesity as a treatment modifier of the placebo effect on patient-reported outcomes. Mixed effects models as described previously were used to evaluate obesity as a treatment modifier of the placebo effect. In these models, the intervention was defined as neutral-placebo or usual care. Analyses were performed with SAS V9.

Results

A total of 601 study participants were enrolled in the trial between December 2003 and December 2005, 600 with data on weight at baseline were included in this analysis (Figure 1). Baseline characteristics are shown in Table 1. Overall 37% of participants were obese. Obese participants were on average older with higher proportions of Blacks and females compared to the non-obese participants, who were more likely to be students. Obese participants had worse scores on asthma questionnaires and a lower percent predicted FVC.

Participants assigned to placebo with a neutral message (N = 120) or to placebo with an enhanced message (N = 121) were evaluated to determine whether obesity modified the effect of message intervention. Participants assigned to montelukast with neutral or enhanced messages were not included in this analysis because the effects of montelukast on these outcomes regardless of assigned message were significant,¹ so the potential for effect modification related to obesity was fundamentally different in the groups receiving active drug versus placebo groups.

All participants assigned to placebo, obese and non-obese, had improvements in asthma scores during follow-up regardless of the message type. As reported for the TAPE trial, overall the ACQ6 score improvement in the enhanced message-placebo group was larger than in the neutral message-placebo group.¹ The mean changes in the AQLQ and ASUI were also larger in the enhanced message-placebo group compared to improvements in the neutral message-placebo group, although the effects of message type on these two outcomes did not reach statistical significance of <0.05.¹

Similar proportions of participants were classified as obese in the enhanced message-placebo group (47 [40%]) as were in the neutral message-placebo group (47 [39%]) (Figure 1, blue box). In obese participants, the mean change in ACQ6 scores adjusted for age, gender and race was –0.6 (95% CI –0.8, –0.5) in enhanced message-placebo group versus –0.4 (95% CI –0.6, –0.2) in the neutral message-placebo group. In non-obese participants, the adjusted mean changes were –0.6 (95% CI –0.7, –0.4) in participants assigned to enhanced messaging with placebo versus –0.2 (95% CI –0.4, –0.1) in those assigned to the neutral message (Figure 2A and Supplemental Table 1). So, although there was an overall effect of messaging on change in ACQ6 scores (enhanced versus neutral message p-value=0.005) which exceeded the MCID of 0.5,³⁶ there was no evidence of a difference in that effect by obesity status (interaction p-value=0.76). There also was no evidence to support the hypotheses that obesity status influenced the message effect on changes in AQLQ or ASUI scores (Figures 2B and C, and Supplemental Table 1).

Table I Baseline Characteristics

Characteristic	Total (N= 600)	Non-Obese (N= 373)	Obese (N= 227)	P-value*
Age, Median(IQR)	37 (26, 48)	34 (24, 47)	41 (30, 50)	<0.001
Male, N (%)	164 (27%)	123 (33%)	41 (18%)	<0.001
Race or ethnic group, N (%)				
White	349 (58%)	242 (65%)	107 (47%)	<0.001
Black	196 (33%)	95 (25%)	101 (44%)	
Hispanic	37 (6%)	23 (6%)	14 (6%)	
Other	18 (3%)	13 (3%)	5 (2%)	
BMI, Median(IQR)	27 (24, 34)	24 (22, 27)	36 (33, 41)	<0.001
Former smoker, N(%)	88 (15%)	45 (12%)	43 (19%)	0.021
Socioeconomic				
Education, N(%)				
<High school	49 (8%)	28 (8%)	21 (9%)	<0.001
High school or equivalent	86 (14%)	42 (11%)	44 (19%)	
Some college	260 (43%)	148 (40%)	112 (49%)	
Bachelor's Degree	113 (19%)	86 (23%)	27 (12%)	
Some post graduate studies	36 (6%)	25 (7%)	11 (5%)	
Post graduate degree	56 (9%)	44 (12%)	12 (5%)	
Employment, N(%)				
Student	99 (17%)	81 (22%)	18 (8%)	<0.001
Not working outside the home	62 (10%)	32 (9%)	30 (13%)	
Currently employed full time	294 (49%)	184 (49%)	110 (48%)	
Currently employed part time	70 (12%)	42 (11%)	28 (12%)	
Retired	29 (5%)	18 (5%)	11 (5%)	
Disabled, unable to work	24 (4%)	6 (2%)	18 (8%)	
Other	22 (4%)	10 (3%)	12 (5%)	
Combined household income				
<\$20,000	127 (21%)	71 (19%)	56 (25%)	0.389
\$20,000-\$50,000	184 (31%)	110 (29%)	74 (33%)	
>\$50,000-\$75,000	68 (11%)	45 (12%)	23 (10%)	
>\$75,000	66 (11%)	46 (12%)	20 (9%)	
Declined to answer	114 (19%)	74 (20%)	40 (18%)	
Unknown	41 (7%)	27 (7%)	14 (6%)	
Asthma Characteristics				
Age of asthma onset, Median (IQR)	13 (4, 29)	12 (4, 25)	18 (5, 35)	0.007
Use inhaled short-acting beta-agonist ≥ 2 x per week	505 (84%)	319 (86%)	186 (82%)	0.243
Daily use of ICS or ICS/LABA	325 (54%)	192 (51%)	133 (59%)	0.090
Asthma Questionnaires, Median (IQR)				
ACQ6 Score (\downarrow range: 0–6)	1.5 (0.8, 2.0)	1.3 (0.8, 1.8)	1.7 (1.0, 2.3)	<0.001
AQLQ Score (\uparrow range: 0–7)	5.1 (4.1, 5.9)	5.4 (4.4, 6.0)	4.7 (3.9, 5.4)	<0.001
ASUI Score (\uparrow range: 0–1)	0.80 (0.69, 0.88)	0.83 (0.73, 0.89)	0.77 (0.64, 0.84)	<0.001
Spirometry, Median(IQR)				
Pre-BD FEV ₁ [‡]	2.68 (2.23, 3.19)	2.82 (2.40, 3.33)	2.41 (2.00, 2.91)	<0.001
Pre-BD %Predicted FEV ₁ [‡]	86 (77, 94)	86 (78, 95)	86 (75, 93)	0.172
Post-BD FEV ₁ [‡]	2.90 (2.43, 3.42)	3.07 (2.61, 3.59)	2.59 (2.18, 3.06)	<0.001
Post-BD % Predicted FEV ₁ [‡]	92 (84, 101)	93 (85, 102)	91 (81, 99)	0.004
% change FEV ₁ from BD [‡]	6.2 (3.0, 12.5)	6.5 (3.4, 12.8)	5.9 (2.2, 11.6)	0.057
Pre-BD FVC [‡]	3.55 (2.92, 4.27)	3.75 (3.15, 4.53)	3.19 (2.69, 3.84)	<0.001
Pre-BD % Predicted FVC [‡]	94 (85, 103)	95 (87, 105)	91 (83, 101)	<0.001
Post-BD FVC [‡]	3.65 (3.07, 4.43)	3.87 (3.24, 4.61)	3.29 (2.78, 3.99)	<0.001
Post-BD % Predicted FVC [‡]	96 (89, 106)	98 (90, 107)	94 (86, 103)	<0.001
% change FVC from BD [‡]	2.1 (–0.5, 5.3)	1.8 (–0.2, 4.8)	2.4 (–0.7, 6.5)	0.602

(Continued)

Table 1 (Continued).

Characteristic	Total (N= 600)	Non-Obese (N= 373)	Obese (N= 227)	P-value*
Pre-BD Peak Flow [‡]	380 (330, 450)	390 (340, 460)	370 (320, 430)	0.023
Pre-BD FEV ₁ /FVC ratio [‡]	0.76 (0.69, 0.81)	0.75 (0.69, 0.81)	0.77 (0.71, 0.82)	0.069
Post-BD FEV ₁ /FVC ratio [‡]	0.79 (0.74, 0.85)	0.79 (0.73, 0.85)	0.80 (0.75, 0.84)	0.859
% change from BD FEV ₁ /FVC ratio [‡]	4.16 (1.63, 7.94)	4.89 (2.01, 8.84)	3.22 (1.34, 5.97)	<0.001

Notes: *P-values are based upon Chi-squared and Kruskal–Wallis tests for categorical and continuous characteristics, respectively. † High scores indicate better health. ‡ Low scores indicate better health. ‡Predicted values for FEV₁ and FVC are taken from: Hankinson JL et al.²²

Abbreviations: SD, standard deviation; DI, metered dose inhaler; Neb, nebulizer; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; ACQ6, Asthma Control Score; ASUI, Asthma Symptom Utility Index; AQLQ, Asthma Quality of Life; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; BD, bronchodilator.

In the TAPE trial, participants assigned to placebo with a neutral message (N = 120) were compared to those assigned to usual care (N = 121) to evaluate the placebo effect. Overall, there was no evidence to support a placebo effect on these patient-reported outcomes.¹ Approximately equal proportions of participants were obese in the neutral message group (47 [39%]), as were in the usual care group (45 [37%]) (Figure 1). The adjusted mean changes in ACQ6 scores for obese participants were −0.3 (95% CI −0.5, −0.1) for participants assigned to the neutral message-placebo group versus −0.2 (95% CI −0.4, −0.0) in the usual care group. In non-obese participants, the adjusted mean changes were even more

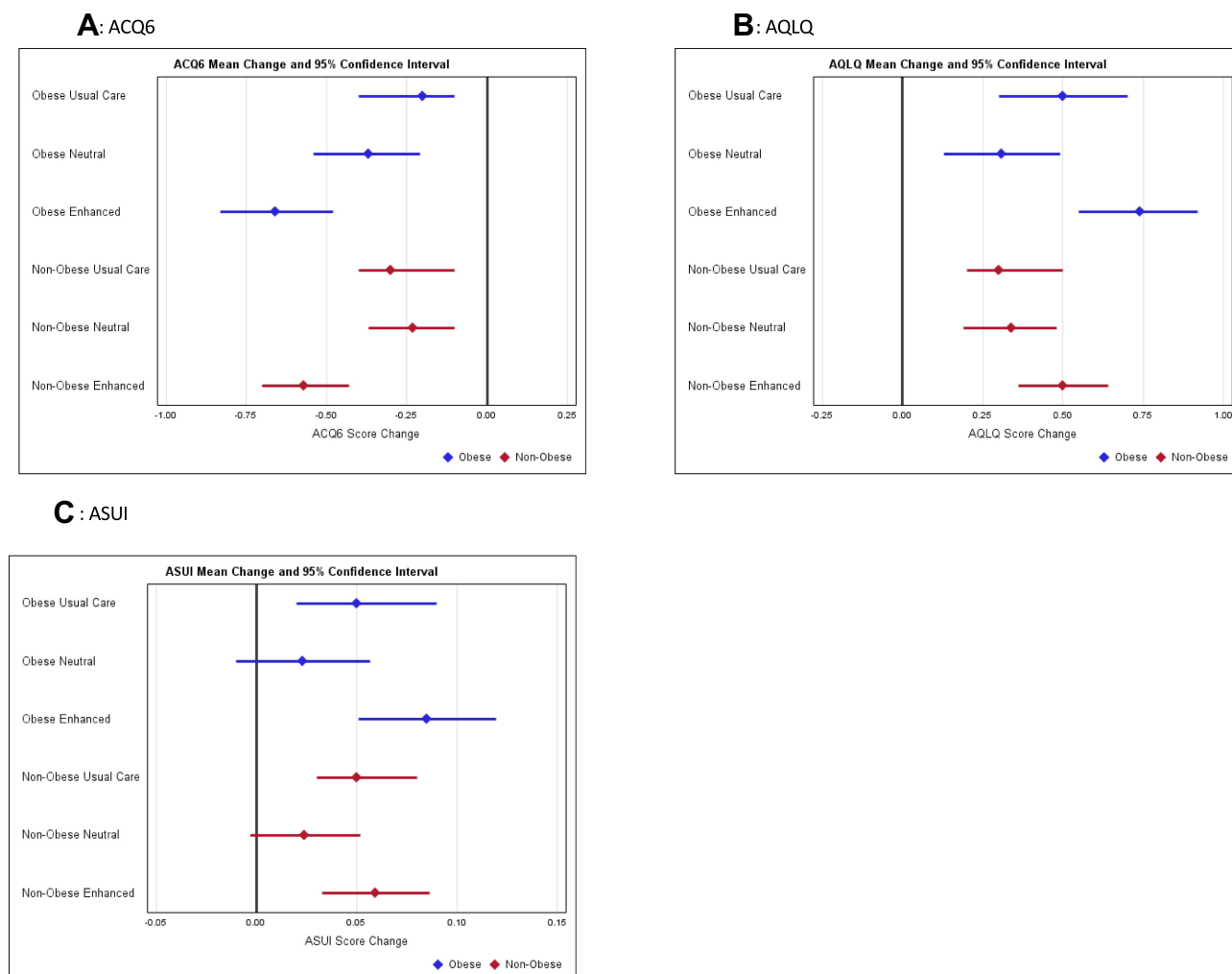


Figure 2 Change in scores by intervention group and obesity status, mean and 95% confidence intervals by messaging and obesity for (A) ACQ6, (B) AQLQ and (C) ASUI. Estimates of change from baseline values at two visits (2 and 4 weeks post randomization) from linear regression, mixed effects models.

similar, -0.2 (95% CI $-0.4, -0.1$) in the neutral message-placebo group versus -0.2 (95% CI $-0.3, -0.0$) in the usual care group (Figure 2A and Supplemental Table 2). There was no evidence supporting effect that obesity status modified placebo effects on ACQ6, AQLQ nor ASUI scores (Figure 2A–C, Supplemental Table 2).

Discussion

In this secondary analysis of the TAPE trial,¹ we confirmed findings of other researchers indicating obesity is associated with worse asthma scores and some measures of the lung function.^{2–6} The majority of obese participants in our study were Black, female, had late onset asthma, and a lower %predicted FVC than non-obese participants. Regardless, the effects of enhanced messaging on patient-reported asthma outcomes were similar in obese and non-obese participants. Neither obese nor non-obese participants showed evidence for placebo effects on these outcomes.

Consistent with earlier reports describing asthma in the obese population, our patients tended to have lower lung function and had higher asthma symptom scores than their non-obese counterparts.^{5,30,31} Despite these differences, obesity did not influence the placebo or message effects on patient-reported outcomes. There was no evidence to support a placebo effect on subjective asthma outcomes in either obese or non-obese patients. Nor was the effect of the enhanced message different in obese versus non-obese participants; both obese and non-obese participants assigned to the enhanced message had improved scores.

Our results seem to be in contrast to work by Peters-Golden in which 3073 individuals with moderate asthma enrolled in four studies were pooled. They demonstrated that although all individuals assigned to placebo improved in a pre-post comparison, the magnitude of the responses (asthma control days) in the placebo groups correlated negatively with increasing BMI.⁶ We also showed that obese and non-obese participants improved during follow-up regardless of treatment assignment, however we did not see evidence of a greater response in obese participants. Our analysis was more conservative than Peter-Golden since we used a dichotomous classification of obesity rather evaluate correlations between continuous measures. In addition, their study included relatively fewer obese patients (16%), fewer Black patients (3% overall and 6% of obese group), and almost half of study participants were non-USA citizens (45% overall and 58% of obese group). Another difference is the relatively short follow-up in our study.

However, they also demonstrated that placebo effects were more likely to modify the treatment effect of inhaled beclomethasone than of oral montelukast,⁶ which is consistent with our results of no intrinsic effect of obesity on treatment response. Hence, the need to consider obesity when designing controlled trials for asthma treatments or selecting treatments for asthmatics may depend more on the physiologic effects of the agents than systematic differences in treatment response due to obesity.

Additional limitations to this study include the post-hoc nature of the analysis and relatively small numbers as this was an exploratory secondary analysis. In addition, our sample only included asthmatics with mild airway obstruction and poorly controlled symptoms, and therefore, our findings may not be generalizable to the overall asthma population. However, this ensured we used strict criteria to define our patient population. Our follow-up period was short, 4 weeks, but we did observe improvements in asthma scores in all groups. We do not think that additional exposure to an enhanced message or placebo would have increased the observed effects. In a sub-study of 99 participants followed with electronic monitoring, enhanced messaging had a negative effect on treatment adherence when paired with an ineffective treatment (placebo) indicating that participants are less likely to continue ineffective treatments.³⁵

In conclusion, our findings found that obesity did not influence the susceptibility to the effects of enhanced drug messaging on asthma-related symptoms and quality of life. Furthermore, we found no evidence to support a placebo effect on subjective asthma outcomes regardless of obesity status. Our findings suggest that addressing treatment needs for asthma patients with obesity—a hard to treat asthma phenotype—and highlight the need for future investigation.

Ethics and Consent Statement

The trial protocol, individual interventions and informed consent statements were reviewed and approved by local IRBs at all participating sites, including the Data Coordinating Center. No deception was used in the conduct of the trial. The informed consent document stated that “The purpose of this research study is to investigate the way that educational approaches and presentation of a drug may affect the response to montelukast and placebo (an inactive medication) in

subjects with asthma. You are being asked to join this research study because you have asthma that causes you symptoms with your current treatment.”

Disclosure

Dr Anne M Mathews was affiliated with Duke University during the conduct of the study and is now affiliated with CU-Anschutz. Dr Robert A Wise reports personal fees from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers, Chemerx, Chiesi, Puretech, Contrafect, FSD Pharma, Merck, GSK, Savara, Vaxart, Galderma; grants and/or personal fees from Verona, Sanofi, GSK, 4Dx, AbbVie, outside the submitted work. The authors report no other conflicts of interest in this work.

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