CHEST

BMI and Treatment Response in Patients With Pulmonary Arterial Hypertension

A Meta-analysis

Breanne E. McCarthy, MD; Robyn L. McClelland, PhD; Dina H. Appleby, MS; Jude S. Moutchia, MD; Jasleen K. Minhas, MD; Jeff Min, MD; Jeremy A. Mazurek, MD; K. Akaya Smith, MD; Jason S. Fritz, MD; Steven C. Pugliese, MD; Ryan J. Urbanowicz, PhD; John H. Holmes, PhD; Harold I. Palevsky, MD; Steven M. Kawut, MD; and Nadine Al-Naamani, MD

BACKGROUND: Obesity is increasingly prevalent in pulmonary arterial hypertension (PAH) but is associated with improved survival, creating an "obesity paradox" in PAH. It is unknown if the improved outcomes could be attributable to obese patients deriving a greater benefit from PAH therapies.

RESEARCH QUESTION: Does BMI modify treatment effectiveness in PAH?

STUDY DESIGN AND METHODS: Using individual participant data, a meta-analysis was conducted of phase III, randomized, placebo-controlled trials of treatments for PAH submitted for approval to the U.S. Food and Drug Administration from 2000 to 2015. Primary outcomes were change in 6-min walk distance (6MWD) and World Health Organization (WHO) functional class.

RESULTS: A total of 5,440 participants from 17 trials were included. Patients with overweight and obesity had lower baseline 6MWD and were more likely to be WHO functional class III or IV. Treatment was associated with a 27.01-m increase in 6MWD (95% CI, 21.58-32.45; $P < .001$) and lower odds of worse WHO functional class (OR, 0.58; 95% CI, 0.48-0.70; $P < .001$). For every 1 kg/m^2 increase in BMI, 6MWD was reduced by 0.66 m ($P = .07$); there was no significant effect modification of treatment response in 6MWD according to BMI (P for interaction = .34). Higher BMI was not associated with odds of WHO functional class at end of follow-up; however, higher BMI attenuated the treatment response such that every 1 kg/m^2 increase in BMI increased odds of worse WHO functional class by 3% (OR, 1.03; P for interaction = .06).

INTERPRETATION: Patients with overweight and obesity had lower baseline 6MWD and worse WHO functional class than patients with normal weight with PAH. Higher BMI did not modify the treatment response for change in 6MWD, but it attenuated the treatment response for WHO functional class. PAH trials should include participants representative of all weight groups to allow for assessment of treatment heterogeneity and mechanisms.

CHEST 2022; 162(2):436-447

KEY WORDS: BMI; meta-analysis; obesity; pulmonary arterial hypertension

ABBREVIATIONS: 6MWD = 6-min walk distance; FDA = US Food and Drug Administration; PAH = pulmonary arterial hypertension; WHO = World Health Organization

AFFILIATIONS: From the Department of Medicine (B. E. McCarthy, J. K. Minhas, J. Min, J. A. Mazurek, K. A. Smith, J. S. Fritz, S. C. Pugliese, H. I. Palevsky, S. M. Kawut, and N. Al-Naamani) and the Department of Biostatistics, Epidemiology, and Informatics (D. H. Appleby and J. S. Moutchia), Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; and the Department of Biostatistics

Take-home Points

Study Question: Does BMI modify treatment effectiveness in PAH?

Results: Higher BMI did not modify the treatment response to change in 6MWD but attenuated the odds of a treatment response on WHO functional class.

Interpretation: The survival benefit observed for patients with obesity and PAH ("obesity paradox") cannot be explained by differences in treatment response.

Pulmonary arterial hypertension (PAH) is characterized by pathologic remodeling of the small muscular pulmonary arteries, right ventricular dysfunction, and reduced functional capacity.[1-3] Increasingly, patients diagnosed with PAH are older and overweight or obese, paralleling the rising prevalence of obesity in the United States and other regions.[4–11] Some studies have shown that obesity is associated with PAH, not only related to prior use of appetite suppressants leading to drug/toxin-related PAH.[12-14] Interestingly, obesity may be associated with worse health-related quality of life and possibly increased hospitalizations but also better survival in patients with PAH.[7] The increased prevalence of obesity in PAH but greater survival is often termed the "obesity paradox."[7,8,15-18]

Obesity may contribute to PAH through mechanisms that can include inflammation, oxidative stress, endothelial dysfunction, increased leptin and decreased adiponectin, or altered estrogen metabolism.[19-24] In an observational multicenter cohort of patients with PAH, we found that overweight and obesity were associated with shorter 6-min walk distance (6MWD) and worse World Health Organization (WHO) functional class.[7] There are currently five approved classes of PAH-specific treatments.[25] Notably, in addition to promoting pulmonary vasodilation, these agents are also antiinflammatory and antiproliferative, and they reduce oxidative stress.[26-31] Patients with obesity might derive a greater benefit from these therapies, explaining the obesity paradox.

Using individual participant data from 18 phase III randomized clinical trials in PAH, we examined the associations of BMI with demographic and clinical characteristics, hemodynamics, and exercise capacity at baseline/randomization. We then assessed for heterogeneity in treatment response to pulmonary vasodilators according to BMI and weight status. We hypothesized that patients with overweight and obesity with PAH would exhibit greater improvement in 6MWD and have a greater likelihood of improving their WHO functional class with PAH-targeted therapies than would patients without obesity.

Study Design and Methods

This study used individual participant data from 18 phase III randomized placebo-controlled trials of therapies for PAH submitted to the U.S. Food and Drug Administration (FDA) for approval from 2000 to 2015 (Table 1).[32-47] The raw data from these trials were provided to the University of Pennsylvania by the FDA. All trials of PAH medications for which FDA approval was sought were received, including trials for sitaxentan, which ultimately was not granted approval. The current study included all participants randomized in these trials who had a diagnosis of PAH (Fig 1). The following were excluded: (1) participants without recorded BMI (which included all participants from the Oral Treprostinil in Combination With an endothelin receptor antagonist (ERA) and/or a phosphodiesterase-5 inhibitor (PDE-5I) for the Treatment of PAH [FREEDOM-C] trial,[40] which did not record BMI); (2) participants who were randomized to treatment but never received the active treatment or placebo to which they were allocated; and (3) participants who were underweight.

These trials studied nine drugs belonging to five drug classes: (1) endothelin receptor antagonists (bosentan, ambrisentan, sitaxentan, and macitentan); (2) guanylate cyclase stimulators (riociguat); (3) phosphodiesterase inhibitors (sildenafil and tadalafil); (4) prostacyclin analogues (treprostinil and iloprost); and (5) prostacyclin receptor agonists (selexipag). All trials except for A Randomised, Multicenter Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects With Pulmonary Arterial Hypertension (AMBITION) trial[34] randomized patients to receive one investigational drug or placebo, and many trials allowed participants to be on background therapy. Even though both ambrisentan and tadalafil were approved therapies, for this analysis, we considered the combination arm (tadalafil and ambrisentan) as the "investigational arm" in the AMBITION trial and the monotherapy arms (tadalafil alone or ambrisentan alone) as control or "placebo arms." All investigational treatments were combined into a single active arm for the purpose of this analysis.

(R. L. McClelland, R. J. Urbanowicz, J. H. Holmes, and S. M. Kawut), University of Washington School of Public Health, Seattle, WA.

Some of these data were previously presented in abstract form at the American Thoracic Society Meeting, May 18-23, 2018, San Diego, CA, and the American Thoracic Society Meeting, May 15-20, 2020, Philadelphia, PA.

CORRESPONDENCE TO: Nadine Al-Naamani, MD; email: Nadine.Al-Naamani@pennmedicine.upenn.edu

DOI: https://doi.org/10.1016/j.chest.2022.02.041

TABLE 1] Description of the 17 Clinical Trials and Number of Participants From Each Included in Analysis

Author, Year	Study	Medication	No. of Participants	Primary Outcome	Secondary Outcomes
Galie et al,[37] 2008	ARIES-1	Ambrisentan	199	Δ From baseline to Wk12 in 6MWD	TTCW, Δ from baseline to Wk12 in BNP, dyspnea score, WHO FC, and QoL
Galie et al,[37] 2008	ARIES-2	Ambrisentan	187	Δ From baseline to Wk12 in 6MWD	TTCW, Δ from baseline to Wk12 in BNP, dyspnea score, WHO FC, and QoL
Galie et al,[34] 2015	AMBITION	Ambrisentan/ tadalafil	486	TTCW	Δ from baseline to Wk24 in NT-proBNP, 6MWD, WHO FC, and Borg dyspnea index
Rubin et al,[43] 2002	BREATHE-1	Bosentan	198	Δ From baseline to Wk16 in 6MWD	Δ from baseline to Wk16 in Borg dyspnea score, WHO FC, and TTCW
Olschewski et al,[41] 2002	AIR	Iloprost	143	10% Increase in 6MWD and improvement in WHO FC at Wk12	Δ from baseline to Wk12 in 6MWD, WHO FC, Mahler dyspnea score, hemodynamic variables, QoL, and TTCW
Pulido et al,[42] 2013	SERAPHIN	Macitentan	686	TTCW	Δ from baseline to 6 mo in 6MWD and WHO FC
Ghofrani et al,[38] 2013	PATENT-1	Riociguat	428	Δ From baseline to Wk12 in 6MWD	Δ from baseline to Wk12 in PVR, NT-proBNP, WHO FC, Borg dyspnea score, QoL, and TTCW
Galie et al,[36] 2005	SUPER	Sildenafil	270	Δ From baseline to Wk12 in 6MWD	TTCW, Δ from baseline to Wk12 in mPAP, Borg dyspnea score, and WHO FC
Sitbon et al,[46] 2015	GRIPHON	Selexipag	1,149	TTCW	Δ from baseline to Wk26 in 6MWD and WHO FC
Barst et al,[33] 2004	STRIDE-1	Sitaxsentan	173	Δ From baseline to Wk12 in percent predicted peak VO2	Δ from baseline to Wk12 in 6MWD, WHO FC, VO2 at AT, hemodynamic variables, QoL, and TTCW
Barst et al,[32] 2006	STRIDE-2	Sitaxsentan	240	Δ From baseline to Wk18 in 6MWD	Δ from baseline to Wk18 in WHO FC, Borg dyspnea score, and TTCW
Sandoval et al,[44] 2012	STRIDE-4	Sitaxsentan	92	Δ From baseline to Wk18 in 6MWD	Δ from baseline to Wk18 in WHO FC and TTCW
Galie et al,[35] 2009	PHIRST	Tadalafil	86	Δ From baseline to Wk16 in 6MWD	TTCW, Borg dyspnea score, WHO FC, hemodynamics, and QoL
McLaughlin et al,[40] 2010	TRIUMPH	Inhaled treprostinil	225	Δ From baseline to Wk12 in 6MWD	TTCW, Borg dyspnea score, WHO FC, and QoL
Jing et al,[39] 2013	FREEDOM-M	Oral treprostinil	145	Δ from baseline to Wk12 in 6MWD	TTCW, Borg dyspnea score, NT-proBNP, WHO FC, and dyspnea-fatigue index
Tapson et al,[47] 2013	FREEDOM-C2	Oral treprostinil	291	Δ From baseline to Wk16 in 6MWD	TTCW, Borg dyspnea score, NT-proBNP, WHO FC, and QoL
Simonneau et al,[45] 2002	…	Subcutaneous treprostinil	442	6MWD at Wk12	Δ from baseline to Wk6 and Wk12 in Borg dyspnea score, hemodynamics, and QoL

6MWD = 6-min walk distance; AIR = Aerosolized Iloprost Randomized Study; AMBITION = A Randomised, Multicenter Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects With Pulmonary Arterial Hypertension; ARIES-1 and ARIES-2 = Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study 1 and 2; AT = anaerobic threshold; BNP = brain natriuretic peptide; BREATHE = Bosentan Randomized trial of Endothelin Antagonist Therapy for PAH; FREEDOM-M = Oral Treprostinil as Monotherapy for the Treatment of Pulmonary Arterial Hypertension (PAH); FREEDOM-C = Oral Treprostinil in Combination With an ERA and/or a PDE-5I for the Treatment of PAH; GRIPHON = Prostacyclin (PGI_2) Receptor Agonist In Pulmonary Arterial Hypertension; mPAP = mean pulmonary artery pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; QoL = quality of life; PATENT = Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial; PHIRST = Pulmonary Arterial Hypertension and Response to Tadalafil; PVR = pulmonary vascular resistance; SERAPHIN = Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome; STRIDE = Sitaxsentan To Relieve Impaired Exercise; SUPER = Sildenafil Use in Pulmonary Arterial Hypertension; TRIUMPH = Double Blind Placebo Controlled Clinical Investigation Into the Efficacy and Tolerability of Inhaled Treprostinil Sodium in Patients With Severe Pulmonary Arterial Hypertension; TTCW = time to clinical worsening; VO2 = maximal oxygen consumption; WHO FC = World Health Organization functional class; Wk = week.

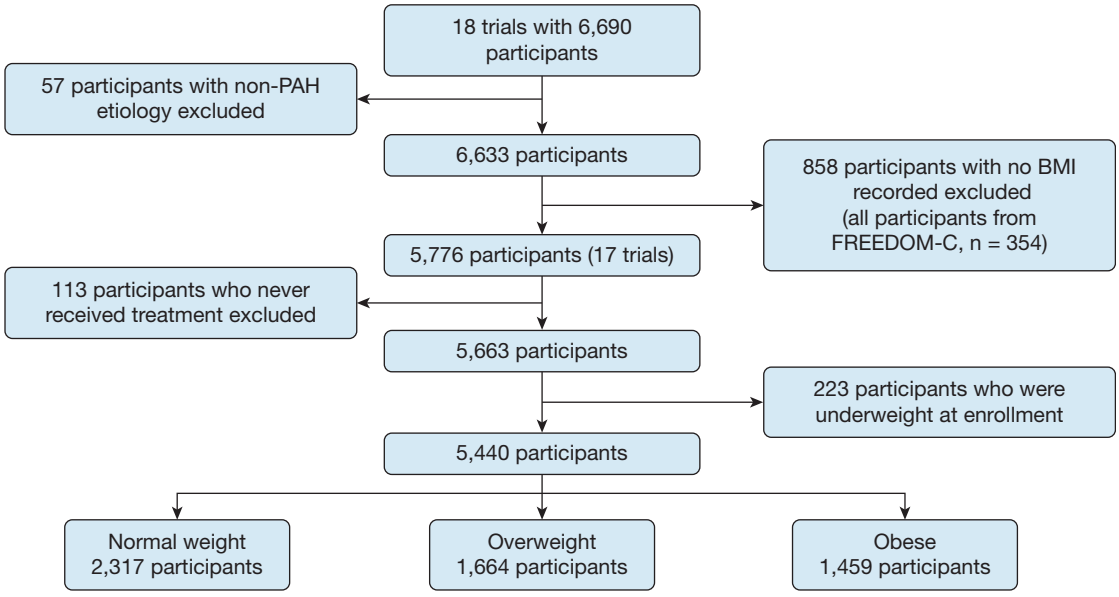

Figure 1 – *Participant inclusion flowchart. FREEDOM-C = Oral Treprostinil in Combination With an ERA and/or a PDE-5I for the Treatment of PAH; PAH = pulmonary arterial hypertension.*

Data Harmonization

Demographic and clinical data, including age, sex, race, ethnicity, PAH etiology, and hemodynamics from right heart catheterization (available from 12 trials), were harmonized by using the Study Data Tabulation Model (Version 1.4) as described in the Study Data Tabulation Model Implementation Guide: Human Clinical Trials, Version 3.2, adding nonstandard variables where necessary. Details of data harmonization are provided in e-Appendix 1. Harmonization and analysis of these data were exempted from review by the University of Pennsylvania Institutional Review Board.

BMI

Weight status was defined according to BMI recorded at the time of the participant's randomization in the trial. Underweight was defined as a BMI < 18.5 kg/m^2, normal weight as BMI ≥ 18.5 and < 25.0 kg/m^2, overweight as BMI ≥ 25.0 and < 30.0 kg/m^2, and obese as BMI ≥ 30.0 kg/m^2.

Study Outcomes

All studies included multiple 6-min walk tests at baseline and over the duration of the trials, which differed in length of follow-up ranging from 12 to 96 weeks (median follow-up, 12 weeks). Our primary study efficacy outcome was the change in 6MWD from baseline to end of trial, which was calculated as follows:

$$\text{Change in 6MWD} = 6\text{MWD}_{\text{end}} - 6\text{MWD}_{\text{baseline}}$$

We did not account for the time of follow-up for our primary end point because change in 6MWD over duration of the trial represents the overall effect of active treatment. The secondary outcome of interest was WHO functional class. For this analysis, the WHO functional class at final follow-up was treated as an ordinal outcome.

Statistical Analysis

Baseline data were summarized by weight strata as number and percentages, means and SD, or medians and interquartile range, as appropriate. Baseline characteristics were compared by using an analysis of variance, Kruskal-Wallis test, or χ^2 test, as appropriate. Bonferroni-adjusted pairwise comparisons were then performed.

A two-stage meta-analysis was used. In the first stage, linear regression models were run within each trial, with the change in 6MWD as the dependent variable and BMI and treatment assignment as the main exposures, to obtain beta-coefficients and their SEs. We also adjusted the models for potential confounders selected a priori, including age, sex, etiology of PAH, baseline 6MWD, baseline WHO functional class, and history of diabetes mellitus or systemic hypertension. In the second stage, the inverse variance-weighted random effects model was used to allow for between-trial heterogeneity in the true treatment effect to combine the adjusted effect estimates from the first stage and produce summary results and forest plots. The random effects models were fitted with a restricted maximum likelihood estimation with CIs derived by using the Hartung-Knapp-Sidik-Jonkman approach to calculate the between-study variance Tau2.[48] We then followed the same two-stage approach with models that included an interaction term for BMI and treatment assignment and generated summary results and forest plots for the interaction terms. For the WHO functional class analysis, ordinal logistic regression models were initially run in each trial to obtain the OR and CIs prior to combining the adjusted effect estimates in a second stage. These models were also adjusted for age, sex, etiology of PAH, baseline 6MWD, baseline WHO functional class, and history of diabetes mellitus or systemic hypertension.

Sensitivity analyses were run by using a one-stage approach meta-analysis in which BMI was centered at the mean within each trial, and an interaction term between the treatment arm, and the mean BMI of the trial was added to the model. All one-stage models were adjusted for the same variables as the two-stage models.

In addition, the nonlinearity of the interaction between BMI and treatment was tested. Nonlinear interaction was assessed by fitting a restricted cubic spline model with four knots at the 10th, 35th, 65th, and 90th percentiles of BMI. The *P* value for nonlinear interaction was obtained from a likelihood ratio test that compared the linear model without an interaction term vs the nonlinear model with treatment $\times$ BMI interaction terms (interaction between treatment and three BMI spline terms). Finally, we tested for an interaction between BMI and treatment class (endothelin receptor antagonists, vs guanylate cyclase stimulator vs phosphodiesterase inhibitors vs prostacyclin analogues and receptor agonists vs placebo). All analyses were conducted in R version 4.0.4 and RStudio version 1.4.1106 and R packages metaphor.[49]

Results

The study sample included 5,440 participants from 17 trials (participants from one trial were excluded because of no recorded BMI) (Fig 1). Baseline characteristics grouped according to weight strata are shown in Table 2. The majority of the patients were female (> 70%), and patients with overweight and obesity were on average 6 years older than patients with normal weight (52 years vs 52 years vs 46 years for overweight, obesity, and normal weight, respectively; $P < .001$ for both). Patients with overweight were more likely to be male (26%) compared with patients with normal weight (21%; $P < .001$), whereas patients with obesity were slightly more likely to be female (82%) compared with patients with normal weight (79%; $P = .008$). Patients with overweight and obesity were more likely to be White (72% and 77%, respectively), and patients with obesity were more likely to be Black (6%) and less likely to be Asian (3%), compared with patients with normal weight (59% White, 3% Black, and 25% Asian; overweight vs normal weight, $P = .002$; obese vs normal weight, $P = .002$).

Patients with obesity were more likely to have idiopathic PAH or drug- and toxin-associated PAH, whereas patients with normal weight were more likely to have connective tissue disease-associated PAH or congenital heart disease-associated PAH ($P = .002$). There were no differences in the prevalence of HIV-associated PAH, portopulmonary hypertension, or heritable PAH across weight groups. Patients with overweight and obesity were more likely to have diabetes and systemic hypertension compared with patients with normal weight ($P < .001$ for both). There was no difference in treatment assignment across weight strata, with similar proportions assigned to the active treatment and control groups.

Hemodynamics

Twelve of the clinical trials collected right heart catheterization data,[33-38,41-43,45,46] seven of which performed right heart catheterization as part of the study protocols.[33,35,36,38,41,42,45] Right atrial pressure was higher in heavier weight strata ($P < .001$ for all pairwise comparisons). Mean pulmonary artery pressure and cardiac output were similar between patients with overweight and obesity but higher than in patients with normal weight ($P < .001$ for both). Conversely, the cardiac index was similar between patients with overweight and obesity but lower than in patients with normal weight ($P < .001$ for overweight vs normal weight and obesity vs normal weight). Pulmonary vascular resistance was lower with heavier weight strata ($P < .001$ for all pairwise comparisons); pulmonary vascular resistance index was lowest for patients with obesity, which was statistically significantly different from that of patients with normal weight and overweight ($P = .002$ for both).

Baseline Functional Status

6MWD was significantly lower in patients with overweight and obesity compared with patients with normal weight, with patients with obesity having the lowest 6MWD ($P < .001$ for all pairwise comparisons). Patients with obesity were more likely to be WHO functional class III or IV (73%) compared with patients with normal weight who were more likely to be WHO functional class I or II (41%; $P = .004$).

Change in 6MWD

The placebo-adjusted treatment effect was a 27.01-m increase in 6MWD (95% CI, 21.58 to 32.45; $P < .001$) (Table 3). Higher BMI may have been associated with a smaller difference in 6MWD, but this was not statistically significant. For every 1 kg/m^2 increase in BMI, the change in 6MWD was reduced by 0.66 m (95% CI, −1.37 to 0.05; $P = .07$) (Fig 2A, Table 3). The improvement in 6MWD associated with treatment was not affected by BMI (P for interaction = .34) (Fig 2B, Table 3). To better illustrate the theoretical magnitude of the BMI by treatment interaction, a hypothetical group of individuals with a BMI of 22 kg/m^2 would have a treatment effect of a 21.6-m increase in 6MWD compared with a 17.9-m increase in a hypothetical group of individuals with a BMI of 27 kg/m^2, holding all other covariates constant. A group of individuals with a BMI of 32 kg/m^2 would have a treatment effect of a 14.3-m increase. There was moderate heterogeneity present among trials for the association of BMI with change in 6MWD ($I^2 = 60\%$). There was minimal heterogeneity present among trials for the association of BMI by treatment interaction and change in 6MWD ($I^2 = 0\%$). Sensitivity analysis yielded similar results (e-Table 1).

We found no significant nonlinearity with respect to BMI and the BMI by treatment interaction and change in 6MWD (Fig 3). No significant interaction was found between BMI and treatment class and change in 6MWD (data not shown) (P for interaction = .76). In addition,

TABLE 2] Baseline Characteristics of Study Participants

Characteristic	Normal Weight (n = 2,317)	Overweight (n = 1,664)	Obese (n = 1,459)	*P* Value
Age, y	46 ± 16	52 ± 15[a]	52 ± 13 [a]	< .001
Male	484 (20.9)	433 (26.0)[a]	265 (18.2)[a]	< .001
Race				< .001
White	1,371 (59.2)	1,191 (71.6)[a]	1,127 (77.2)[a]	
Black	62 (2.7)	54 (3.2)	83 (5.7)[a]	
Asian	587 (25.3)	158 (9.5)[a]	39 (2.7)[a]	
American Indian/Alaska Native/Native Hawaiian/Pacific Islander	3 (0.1)	3 (0.2)	8 (0.5)	
Multiple/other	21 (0.9)	17 (1.0)	11 (0.7)	
Unknown	273 (11.8)	241 (14.5)	191 (13.1)	
Ethnicity				< .001
Hispanic or Latino	230 (9.9)	194 (11.7)	132 (9.0)	
Not Hispanic or Latino	2,024 (87.4)	1,395 (83.8)	1,239 (84.9)	
Unknown	63 (2.7)	75 (4.5)	88 (6.0)[a]	
Etiology				< .001
Idiopathic	1,254 (54.1)	1,004 (60.3)	985 (67.5)[a]	
Heritable	27 (1.2)	25 (1.5)	12 (0.8)	
Drug and/or toxin	20 (0.9)	27 (1.6)	52 (3.6)[a]	
Connective tissue disease	733 (31.6)	483 (29.0)	332 (22.8)[a]	
Congenital heart disease	250 (10.8)	101 (6.1)	62 (4.2)[a]	
HIV infection	27 (1.2)	17 (1.0)	11 (0.8)	
Portopulmonary hypertension	3 (0.1)	5 (0.3)	5 (0.3)	
Other	3 (0.1)	2 (0.1)	…	
BMI, kg/m^2	22.0 ± 1.8	27.3 ± 1.4	35.2 ± 4.9	< .001
Comorbid conditions				
Diabetes mellitus	138 (6.0)	191 (11.5)	286 (19.6)[a]	< .001
Hypertension	447 (19.3)	579 (34.8)	731 (50.1)[a]	< .001
Hemodynamics				
Right atrial pressure, mm Hg (n = 4,111)	7 [4-11]	8 [5-11][a]	9 [6-13][a,b]	< .001
Mean pulmonary artery pressure, mm Hg (n = 4,436)	52 [42-64]	51 [42-60][a]	51 [41-60][a]	< .001
Pulmonary artery wedge pressure, mm Hg (n = 4,254)	8 [6-11]	9 [7-12][a]	10 [7-12][a,b]	< .001
Cardiac output, L/min (n = 3,191)	3.80 [3.02-4.70]	4.10 [3.40-4.90][a]	4.50 [3.70-5.50][a,b]	< .001
Cardiac index, L/min/m^2 (n = 3,596)	2.40 [1.90-2.90]	2.28 [1.90-2.79][a]	2.22 [1.82-2.70][a,b]	< .001
Pulmonary vascular resistance, Wood units (n = 4,301)	11.3 [7.6-16.6]	10.0 [6.9-14.0][a]	8.8 [6.0-12.4][a,b]	< .001
Pulmonary vascular resistance index, Wood units.m^2 (n = 3,532)	27.4 [20.6-34.3]	23.2 [18.2-29.0][a]	20.9 [16.2-25.4][a,b]	.04
Baseline 6-min walk distance, m (n = 5,438)	360 ± 81	349 ± 84[a]	331 ± 87[a,b]	< .001
WHO functional class				< .001
I	21 (0.9)	9 (0.5)	4 (0.3)	
II	916 (39.6)	548 (32.9)	390 (26.8)[a]	
III	1,304 (56.3)	1,049 (63.0)	1,009 (69.3)[a]	
IV	74 (3.2)	58 (3.5)	54 (3.7)	

(Continued)

TABLE 2] *(Continued)*

Characteristic	Normal Weight (n = 2,317)	Overweight (n = 1,664)	Obese (n = 1,459)	*P* Value
Treatment assignment in trial				.18
Control arm	911 (39.3)	702 (42.2)	600 (41.1)	

Data are presented as mean ± SD, No. (%), or median [interquartile range]. WHO, World Health Organization.
[a]Bonferroni-adjusted *P* value for pairwise comparison indicating significant difference from normal weight.
[b]Bonferroni-adjusted *P* value for pairwise comparison indicating significant difference from overweight.

when the data set was limited to patients with idiopathic PAH (n = 3,243), the findings were similar (data not shown).

WHO Functional Class

On average, receiving active treatment was associated with lower odds of being in a worse WHO functional class at the end of the study compared with those receiving placebo (OR, 0.58; 95% CI, 0.48-0.70; $P <$ .001) (Table 4). BMI was not associated with odds of WHO functional class at the end of the study (Fig 2C, Table 4). The odds of WHO functional class worsening on treatment was slightly affected by BMI although it did not reach statistical significance (OR, 1.03; 95% CI, 1.00-1.06; $P = .06$). Every 1 kg/m^2 increment in BMI attenuated the treatment effect by 3% (*P* for interaction = .06) (Fig 2D). For example, for hypothetical patients with a BMI of 25 kg/m^2, the OR of being in a worse WHO functional class for active treatment vs control was 0.53, whereas for patients with BMI of 35 kg/m^2, the OR for active treatment vs control was 0.70 (all other covariates identical). Sensitivity analysis yielded similar results (e-Table 1).

Discussion

Using individual participant data from 17 randomized clinical treatment trials in PAH, we found that patients with overweight were more likely to be male, and patients with obesity were more likely to be female. Patients with obesity were more likely to have idiopathic PAH or drug/toxin-related PAH and less likely to have connective tissue disease- or congenital heart disease-related PAH compared with patients with normal weight. At baseline, patients with overweight and obesity had lower 6MWD and worse WHO functional class compared with patients with normal weight. Higher BMI was possibly associated with lower 6MWD at the end of follow-up, independent of treatment assignment, although no modification of the treatment effect in the setting of higher BMI was noted (ie, no interaction). The impact of active therapy vs control in preventing worsening WHO functional class was of lesser magnitude in those with higher BMI, although this finding was not statistically significant.

Overweight and obesity in patients with PAH in clinical trials between 1998 and 2013 were less common than in a contemporary cohort of patients from the Pulmonary Hypertension Association Registry (PHAR) (33.8% overweight and 39.6% obese)[7] but similar to the prevalence from European and Chinese registries (30% obese in the French registry[10] and 35.7% obese in the Scottish Pulmonary Vascular Unit[50]). The lower prevalence of overweight and obesity in these clinical trials could be due to secular trends.[51] However, it is also possible that patients with overweight and obesity were excluded from these clinical trials due to inclusion/exclusion criteria. Some trials had lower cutoffs for 6MWD, which may have led to selection bias, excluding predominantly patients with overweight and obesity who were noted to have shorter 6MWD. Alternatively, the lower prevalence of obesity in these trials, which are multinational, could reflect the lower prevalence of obesity in other regions compared with the US population. Similar to prior reports, we found that

TABLE 3] Results of the Meta-analysis for Change in 6-Min Walk Distance in Meters With BMI as a Continuous Variable

Variable	β	95% CI	*P* Value
BMI, per 1 kg/m^2 increase	−0.66	−1.37 to 0.05	.07
Active vs control (treatment effect)	27.01	21.58 to 32.45	< .001
BMI × treatment effect[a]	−0.39	−1.24 to 0.46	.34

Adjusted model includes BMI, treatment, age, sex, pulmonary arterial hypertension etiology, history of diabetes, history of systemic hypertension, baseline 6-min walk distance, and baseline World Health Organization functional class.
[a]Adjusted model + BMI × treatment interaction.

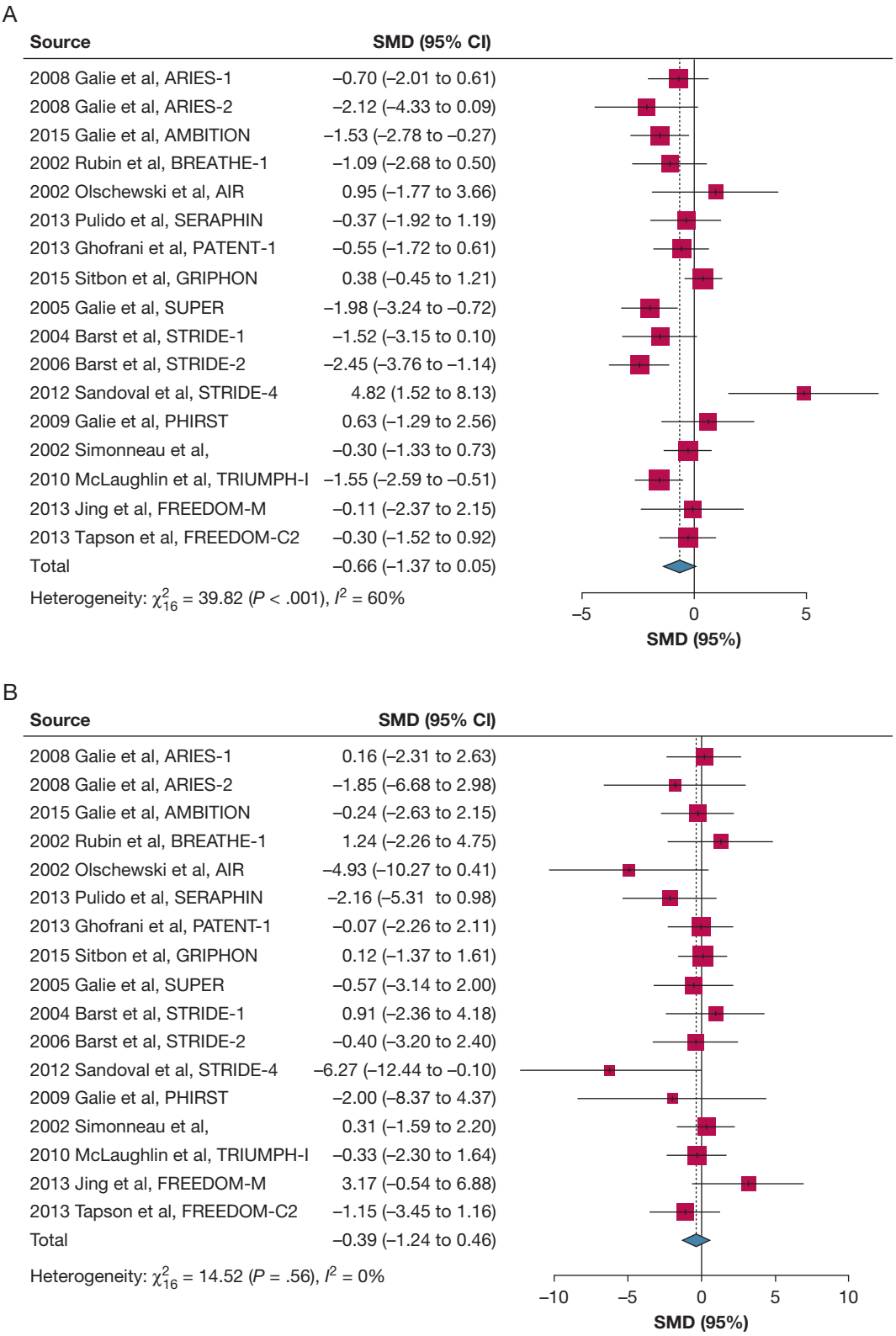

Figure 2 – *A, Forest plot for the association of BMI with change in 6-min walk distance from baseline to end of follow-up. B, Forest plot for the association of BMI by treatment interaction terms with change in 6-min walk distance from baseline to end of follow-up. C, Forest plot for the association of BMI with World Health Organization functional class at end of follow-up. D, Forest plot for the association of BMI by treatment interaction terms with World Health Organization functional class at end of follow-up. See Table 1 for expansion of study names. RE = random effects; SMD = standardized mean difference.*

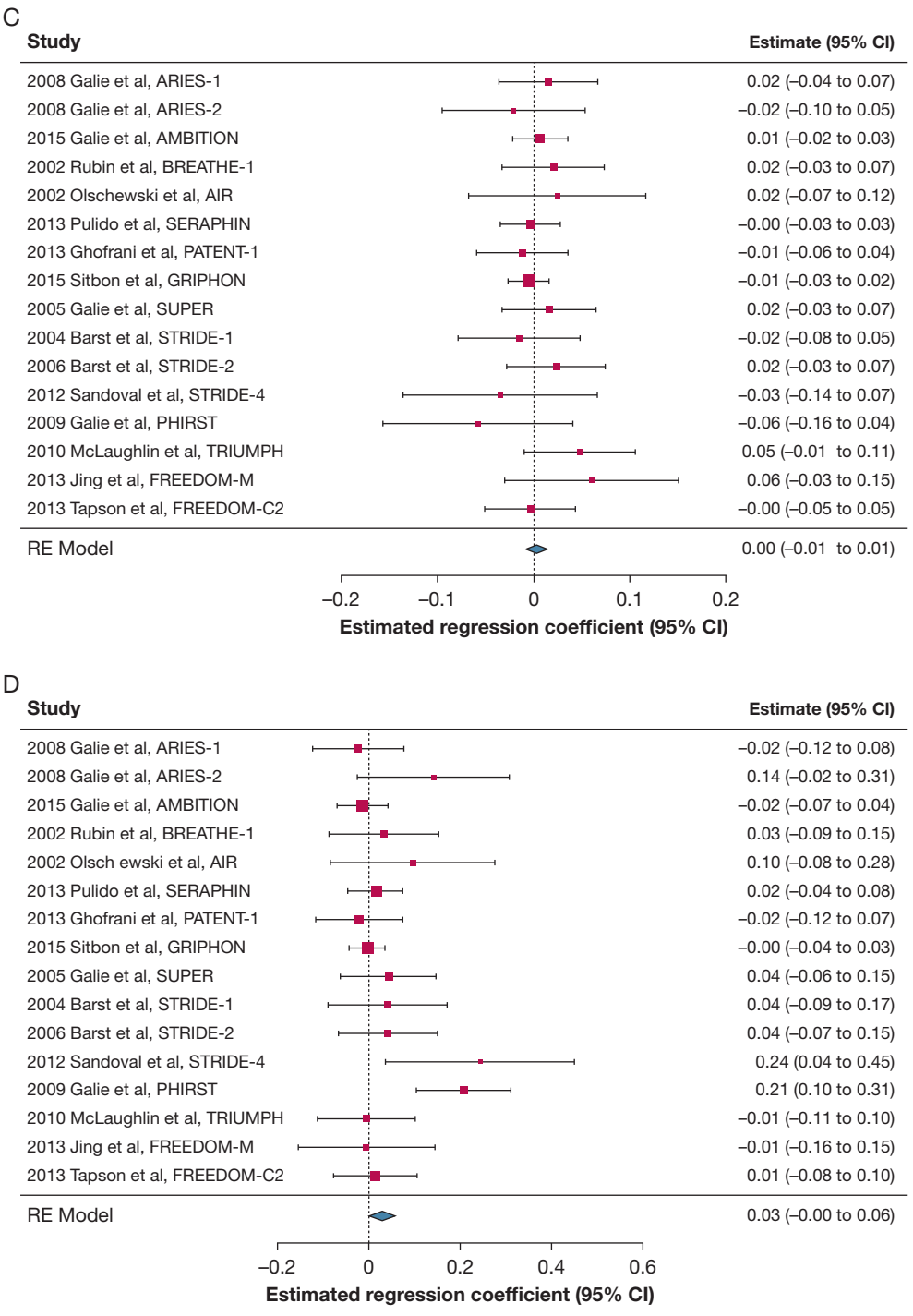

Figure 2 – *Continued*

patients with PAH who were obese had shorter 6MWD and were more likely to be WHO functional class III or IV compared with patients with normal weight with PAH.[7,10] Comorbid conditions such as diabetes mellitus, systemic hypertension, and hypothyroidism were more frequent among patients with obesity,[10] which may contribute to the shorter 6MWD and worse functional class. Patients with overweight and obesity had lower cardiac indices, which could also contribute to impaired exercise tolerance.

Observational studies in PAH have reported what appears to be an obesity paradox whereby obesity is common in pulmonary hypertension but patients with

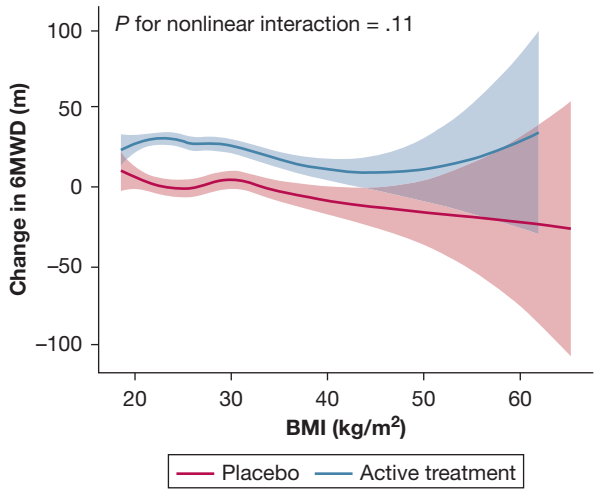

Figure 3 – *Nonlinear interaction between BMI and BMI by treatment with change in 6-min walk distance.*

obesity have a better survival than their normal weight counterparts.[7,8,15-19,52] Possible explanations for this observed improved survival among patients with obesity with PAH have not been previously explored. We hypothesized that patients with higher BMI would derive greater benefit from active PAH treatment; however, we found no interaction between treatment and BMI in terms of 6MWD. If anything, we found that in heavier patients, active treatment had less of an impact on decreasing the odds of worsening functional class compared with placebo.

Several potential explanations for the potentially smaller benefit derived from active treatment could be postulated. First, patients with overweight and obesity may be underdosed, as most of the pulmonary vasodilator medications studied have fixed dosing, which assumes that drug metabolism does not change with body size.[53] Second, the presence of comorbidities such as systemic hypertension or diabetes mellitus may negatively affect the response to treatment in patients who are overweight or obese; however, our results were not affected by adjusting for hypertension and diabetes. Finally, the systemic inflammation associated with obesity may also negatively affect the efficacy of treatments. These findings highlight the need for inclusion of patients at the extremes of the weight continuum in drug treatment trials to ensure dose efficacy across the spectrum.

To our knowledge, this is the largest individual participant data meta-analysis in PAH exploring the effect of obesity on treatment response. We harmonized data across 17 trials, adjusted for confounders, and used the change in 6MWD from trial start to end of follow-up to maximize the use of available data despite the differential length of follow-up of the trials. The trials included in our analysis were multicenter international studies, which should increase the generalizability of our findings. In addition, there was minimal heterogeneity across trials for the effect of BMI on treatment response, supporting the accuracy of this meta-analysis. Finally, our sensitivity analysis using a one-stage approach found no significant impact of BMI on treatment response (similar magnitude), consistent with our primary analysis suggesting robustness of our findings.

The current study also had several limitations. This analysis only included trials submitted to the FDA for drug approval, which is almost certainly a biased sample. We excluded a trial that did not record BMI. In addition, there was a small amount of missing BMI data in the other trials, and these patients were excluded. We did not stratify our analysis according to drug class as the study was not sufficiently powered for such analyses; however, this topic would be of interest in future studies. Although this study is the largest collection of individual participant data from randomized clinical trials for PAH treatment, it still may not have sufficient power to detect an interaction between treatment response and BMI. This interaction may also have required more follow-up time to detect than was possible using the available randomized clinical trials (many of which were around 12 weeks of follow-up). Future PAH trials should include participants of all weight groups and provide

TABLE 4] Results of the Meta-analysis for WHO Functional Class at End of Follow-Up With BMI as a Continuous Variable

Variable	OR	95% CI	*P* Value
BMI, per 1 kg/m^2 increase	1.00	0.91-1.01	.63
Treatment effect, active arm	0.58	0.48-0.70	< .001
BMI × treatment effect[a]	1.03	1.00-1.06	.06

Adjusted model includes BMI, treatment, age, sex, pulmonary arterial hypertension etiology, history of diabetes, history of systemic hypertension, baseline 6-min walk distance, and baseline World Health Organization (WHO) functional class.
[a]Adjusted model + BMI × treatment interaction.

BMI data to allow for ongoing assessment of treatment heterogeneity, and more long-term PAH clinical trials are needed to increase the likelihood of detecting differences in treatment response. Finally, our primary analysis used a two-stage approach for ease of interpretation of results using forest plots[48,54,55]; however, we confirmed our findings using a one-stage approach in sensitivity analyses.

Interpretation

We found that the proportion of patients with overweight or obesity enrolled in randomized clinical trials of PAH was lower than in contemporary PAH registries. Overweight and obese individuals with PAH experienced a reduced 6MWD and increased odds of worse WHO functional class compared with those with normal weight. Notably, higher BMI did not modify the treatment response for change in 6MWD, although it did seem to attenuate the treatment response in terms of WHO functional class (with a borderline *P* value). This study shows that the survival benefit observed for patients with obesity and PAH (obesity paradox) may not be explained by differences in treatment response. Our findings emphasize the need for inclusion and representation of patients across the weight spectrum in PAH.

Acknowledgments

Author contributions: N. A.-N., the corresponding author, had full access to all of the data in the study and contributed to the study design, data collection, data analysis and interpretation, and the writing of the manuscript, and had the final decision to submit for publication. B. E. M. and R. L. M. provided data analysis and interpretation and contributed to writing of the manuscript; D. H. A, J. S. M., J. K. M., J. M., R. J. U., and J. H. H. contributed to data collection and data organization; J. A. M., K. A. S., J. S. F., S. C. P., and H. I. P. provided critical revision of the manuscript for important intellectual content; and S. M. K. contributed substantially to the study design, data interpretation, and the writing of the manuscript.

Funding/support: Support was provided by the Cardiovascular Medical Research and Education Fund (S. M. K.), the National Institutes of Health [K24HL103844, S. M. K.; K23HL141584, N. A.-N.; and T32HL007891, J. K. M. and J. M.], and the Aldrighetti Research Award for Young Investigators (N. A.-N.).

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: In the past 36 months, J. H. H. has received payments in the form of grants or contracts and travel from the University of Pavia; and served on the Advisory Board for the Clinical Data to Health (CD2H) External Advisory Board. R. L. M. has served on the Observational Study Monitoring Board for the RURAl study. J. A. M. has received payments from United Therapeutics for serving on an Advisory Board. H. I. P. has received honoraria from Actelion/Janssen, Acceleron, Phase Bio, and United Therapeutics. S. M. K. has received payments from United Therapeutics for serving as the Data Safety Monitoring Board Chair, from Acceleron for serving on an Advisory Board, from Vivus for serving on an Advisory Board, and from the *European Respiratory Journal* for serving on the Editorial Board. None declared (B. E. M., D. H. A., J. S. M., J. K. M., J. M., K. A. S., J. S. F., S. C. P., R. J. U., N. A.-N.)

Additional information: The e-Appendix and e-Table are available online under "Supplementary Data."

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