Comparison of Body Habitus in Patients With Pulmonary Arterial Hypertension Enrolled in the Registry to Evaluate Early and Long-term PAH Disease Management With Normative Values From the National Health and Nutrition Examination Survey

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OBJECTIVE: To investigate the correlation between body mass index (BMI) and pulmonary artery systolic pressure in a large population of patients with pulmonary arterial hypertension (PAH).

PATIENTS AND METHODS: The BMI of patients with group 1 PAH enrolled in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) was compared with that of age- and sex-matched controls in the National Health and Nutrition Examination Survey (NHANES) to clarify whether obesity is linked with PAH. The diagnosis of PAH was defined in REVEAL by right-sided heart catheterization. Differences in BMI and the percentage of patients considered obese (BMI ≥ 30) and underweight (BMI < 18.5) in various subgroups of patients enrolled in REVEAL from March 30, 2006, through September 11, 2007, were determined.

RESULTS: Mean BMI was no different for patients with PAH (n=2141) than for the NHANES normal comparison group; however, the proportion of obese and underweight patients was increased in patients with PAH. Subgroup analysis demonstrated that subgroups with idiopathic PAH and those with PAH associated with drugs and toxins had both higher BMI and percentage of obese patients, whereas 3 other subgroups (those with PAH associated with congenital heart disease, connective tissue disease, and human immunodeficiency virus) had lower mean BMI.

CONCLUSION: Mean BMI of the REVEAL patients was the same as that of the NHANES normal comparison group; however, there were higher percentages of obese and underweight patients in REVEAL. This discrepancy can be explained by the balancing effect of more overweight and underweight patients in different PAH subgroups. The reason for the increased frequency of obesity in idiopathic PAH is unknown, and additional study is needed.

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APAH = associated PAH; BMI = body mass index; CHD-APAH = congenital heart disease-APAH; CTD-APAH = connective tissue disease-APAH; FPAH = familial PAH; HIV-APAH = human immunodeficiency virus infection-APAH; IPAH = idiopathic PAH; LVEDP = left ventricular end-diastolic pressure; NHANES = National Health and Nutrition Examination Survey; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; REVEAL = Registry to Evaluate Early and Long-term PAH Disease Management; RHC = right-sided heart catheterization

Data from the National Health and Nutrition Examination Survey (NHANES) have demonstrated that 35% of US adults are classified as obese (body mass index [BMI], calculated as the weight in kilograms divided by the height in meters squared, ≥ 30).^{1,2} In addition, up to 46% of patients with pulmonary arterial hypertension (PAH) have no clear cause for the disease (ie, idiopathic

PAH [IPAH]).³ Although obesity is epidemic in the United States,^{1,2} comprehensive reviews have listed obesity as an unlikely risk factor for PAH.⁴ However, there are no confirmed reports of a direct correlation of obesity with clinically significant PAH. Although a correlation between BMI and pulmonary artery systolic pressure has been identified in otherwise echocardiographically normal persons (Spearman rank correlation, 0.19; $P < .01$; $N = 3790$),⁵ a retrospective review of 401 patients in the pulmonary hypertension (PH) database of Mayo Clinic in Florida found no correlation between BMI and diagnosis of PH when these patients were compared with controls (n=578).⁶

PAH is characterized by mean pulmonary artery pressure (PAP) of 25 mm Hg or greater and pulmonary capillary wedge pressure (PCWP) of 15 mm Hg or less.^{3,7} Group 1 PH comprises 5 categories: IPAH, familial PAH (FPAH; now referred to as heritable PAH), associated PAH (APAH; including PAH associated with connective tissue disease [CTD-APAH], drugs and toxins-PAH), congenital heart disease [CHD-AP-

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AH], human immunodeficiency virus infection [HIV-APAH], portal hypertension, schistosomiasis, and chronic hemolytic anemia), and persistent PH of the newborn.⁸

The Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) represents a unique opportunity to examine the potential relationship between obesity and PAH. REVEAL is a prospective study initiated to characterize the demographics, clinical course, hemodynamic features, and disease management of about 3500 US patients with group 1 PH.^{3,9} This large database of patients with PAH permits a robust analysis of BMI and the percentage of overweight and underweight patients with PAH. REVEAL also provides an opportunity to identify potential associated risk factors in patients with IPAH, which, if confirmed, may generate hypothesis-based investigations to help determine causal links. In the current study, we compared patients in the REVEAL database with age- and sex-matched controls from NHANES to determine whether a relationship exists between BMI and the presence of PAH.

PATIENTS AND METHODS

This study compared the BMI of REVEAL patients at the time of diagnosis of PAH by right-sided heart catheterization (RHC) with that of an age- and sex-matched group from NHANES. Specifically, differences in mean BMI and the percentage of obese patients (BMI ≥ 30) and underweight patients (BMI < 18.5) both in the entire PAH group and in subgroups of patients with IPAH, FPAH, and APAH were determined.

INCLUSION AND EXCLUSION CRITERIA

The design and baseline characteristics of the patients enrolled in REVEAL have been previously described.^{3,9} Patients with newly diagnosed (diagnosis confirmed by RHC within 3 months before enrollment in REVEAL) or previously diagnosed (diagnosis confirmed by RHC > 3 months before enrollment in REVEAL) group 1 PH who were consecutively enrolled in REVEAL from March 30, 2006, through September 11, 2007, were included in this analysis.

PAH was defined as mean PAP greater than 25 mm Hg at rest or 30 mm Hg with exercise; PCWP or left ventricular end-diastolic pressure (LVEDP) of 18 mm Hg or less; and pulmonary vascular resistance of 240 dynes-sec-cm⁻⁵ or greater. REVEAL used a less restrictive PCWP criterion of 18 mm Hg or less to be more inclusive of patients seen in clinical practice.⁹ Patients with PCWP greater than 15 mm Hg have previously been excluded from such PAH registries and from controlled trials of PAH-specific medications to avoid inadvertent inclusion of patients with PH

due to left-sided heart disease.^{8,10} However, ventricular interdependence may contribute to transient elevations of PCWP, which are unrelated to left-sided heart disease and thus may exclude patients with true PAH.

Nine REVEAL patients (0.4%) in the current analysis cohort qualified for the registry on the basis of elevated PAP with exercise despite normal PAP at rest. They were distributed across multiple groups (3 with IPAH, 3 with drugs and toxins-APAH, 2 with CTD-APAH, and 1 with FPAH). In addition, 3 were obese, and 6 had a normal BMI. Of the 2141 patients in this analysis cohort, 177 (8%) had PCWP greater than 15 mm Hg.

This analysis was restricted to REVEAL patients who were at least 2 years of age at diagnosis (to match the NHANES population) and whose height and weight were available at diagnosis. From a starting population of 2969 REVEAL patients, 43 (1%) were excluded because of age younger than 2 years, and 785 (27%) additional patients were excluded because of missing height or weight at diagnosis (696 [24%] were missing both). The final REVEAL analysis cohort consisted of 2141 patients. Excluded patients were similar to the analysis cohort with respect to age at diagnosis, sex, etiology, and World Health Organization/New York Heart Association functional class at diagnosis.

STATISTICAL ANALYSES

The REVEAL data lock was January 14, 2010. Public use files containing demographic and examination data were downloaded from the National Center for Health Statistics NHANES Web site for the years 2001-2002, 2003-2004, and 2005-2006.¹¹ NHANES sample weights and stratification and cluster variables were incorporated into estimates to produce unbiased national estimates. Using all NHANES patients with available BMI data (includes ages ≥ 2 years), we created age- and sex-matched controls by year of PAH-diagnostic RHC.

Means and standard errors were computed, accounting for the complex sampling scheme of the NHANES. Means and standard errors were separately computed using the unweighted REVEAL cohort. The standard error of the difference in means could be calculated directly as the square root of the sum of the squared errors because the 2 means were computed from independent populations with large sample sizes. *P* values were then calculated from the standard *z* score, the difference divided by the standard error of the difference, under the null hypothesis of no difference between NHANES and REVEAL BMI. Statistical significance was determined on the basis of *P* $< .05$.

REVEAL patients in the IPAH subgroup who were obese (BMI ≥ 30) were compared with REVEAL patients with IPAH who were not obese (BMI < 30) across several demographic characteristics, hemodynamic mea-

asures, comorbid conditions, and concomitant medications. Means and standard deviations were calculated for continuous variables, and *P* values for descriptive comparisons were computed from the *t* test. For categorical variables, the number and percentage of patients with nonmissing data were computed, and *P* values were calculated from the χ^2 test.

RESULTS

PATIENT CHARACTERISTICS AT DIAGNOSIS IN THE REVEAL COHORT

Of the 2141 REVEAL patients included in this analysis, 1680 (78%) were female, 935 (59%) were in World Health Organization/New York Heart Association functional class III, and 441 (22%) had a history of obstructive sleep apnea. The mean age at diagnosis was 48 years. The cohort included 117 pediatric patients (5%) aged 2 to 18 years at diagnosis. Descriptive characteristics in the total REVEAL cohort and by PAH subtype are shown in Table 1. Hemodynamics at the time of diagnostic RHC are provided in Table 2. The pattern of drug use in the 114 patients in the drugs and toxins–APAH group was as follows: anorexigens, 64 (56%); stimulants (methamphetamine, amphetamine, and cocaine), 48 (42%); and other, 2 (2%). Two patients took both an anorexigen and a stimulant.

COMPARISON OF BMI IN REVEAL AND NHANES POPULATIONS

There was no significant difference in mean BMI between the overall REVEAL and NHANES cohorts (28.4 and 28.2, respectively; Table 3). However, there were significant differences in the REVEAL and NHANES populations when evaluated by PAH subtype (Table 3; Figure, A). Patients with CHD-APAH or CTD-APAH were more likely to have a lower BMI than were NHANES controls, whereas patients with IPAH or drugs and toxins–APAH were more likely to have a higher BMI than were NHANES controls. Although the difference was not statistically significant (*P*=.06), BMI was also lower in the HIV-APAH subgroup than in NHANES controls.

COMPARISON OF OBESITY AND UNDERWEIGHT IN REVEAL AND NHANES POPULATIONS

As previously mentioned, obesity was defined as BMI of 30 or more and underweight as BMI less than 18.5. Overall, there were significantly more obese (36.5% vs 33.0%; *P*=.004) and underweight (5.7% vs 4.1%; *P*=.003) patients in REVEAL compared with NHANES controls (Table 3). Compared with NHANES controls, IPAH and drugs and toxins–APAH groups had significantly more patients considered obese (32.5% vs 40.1% and 35.0% vs 59.6%, respectively; both *P*<.001) (Table 3; Figure, B). In contrast, the higher proportion of underweight patients in REVEAL

TABLE 1. Characteristics of REVEAL Population at Diagnosis^a

	Overall ^b (N=2141)	IPAH (n=921)	FPAH (n=54)	CHD-APAH (n=234)	CTD-APAH (n=507)	D&T-APAH (n=114)	HIV-APAH (n=32)	PoPH-APAH (n=109)
Age at diagnosis (y), mean ± SD	47.9±16.8	47.0±17.4	35.3±14.4	35.7±17.3	55.3±14.1	46.9±10.2	42.2±8.3	48.4±11.0
Female, No. (%)	1680 (78.5)	722 (78.4)	39 (72.2)	173 (73.9)	460 (90.7)	93 (81.6)	11 (34.4)	59 (54.1)
Race, No. (%) ^c								
White	1569 (74.3)	689 (75.7)	44 (83.0)	171 (73.4)	358 (71.9)	90 (80.4)	13 (40.6)	81 (74.3)
Black	268 (12.7)	110 (12.1)	1 (1.9)	10 (4.3)	89 (17.9)	9 (8.0)	15 (46.9)	9 (8.3)
Hispanic	188 (8.9)	70 (7.7)	6 (11.3)	33 (14.2)	39 (7.8)	8 (7.1)	4 (12.5)	17 (15.6)
Other	88 (4.2)	41 (4.5)	2 (3.8)	19 (8.2)	12 (2.4)	5 (4.5)	0 (0.0)	2 (1.8)
WHO/NYHA FC at PAH diagnosis, No. (%) ^d								
I	66 (4.2)	29 (4.1)	3 (7.3)	11 (6.6)	11 (2.9)	2 (2.3)	3 (11.5)	4 (4.9)
II	382 (24.1)	153 (21.6)	12 (29.3)	52 (31.1)	88 (23.3)	16 (18.4)	7 (26.9)	28 (34.1)
III	935 (59.0)	417 (59.0)	23 (56.1)	92 (55.1)	239 (63.2)	54 (62.1)	10 (38.5)	43 (52.4)
IV	203 (12.8)	108 (15.3)	3 (7.3)	12 (7.2)	40 (10.6)	15 (17.2)	6 (23.1)	7 (8.5)
History of sleep apnea, ^e No. (%)	441 (21.6)	227 (26.0)	12 (23.1)	34 (15.3)	68 (14.0)	30 (27.5)	4 (12.9)	19 (17.8)

^a CHD-APAH = congenital heart disease–associated PAH; CTD-APAH = connective tissue disease–associated PAH; D&T-APAH = drugs and toxins–associated PAH; FPAH = familial PAH; HIV-APAH = human immunodeficiency virus–associated PAH; IPAH = idiopathic PAH; PAH = pulmonary arterial hypertension; PoPH-APAH = portopulmonary hypertension–associated PAH; REVEAL = Registry to Evaluate Early and Long-term PAH Disease Management; WHO/NYHA FC = World Health Organization/New York Heart Association functional class.

^b Analysis cohort includes patients enrolled in REVEAL through September 11, 2007, who were at least 2 years of age and had height and weight data available at the time of the diagnostic right-sided heart catheterization. Group 1 subgroup numbers do not add up to the overall number because some patients were missing data at diagnosis and some patients were in smaller diagnostic subgroups not included here.

^c Due to missing race data at PAH diagnosis, percentage denominators were smaller than column n's.

^d Due to missing WHO/NYHA FC data at PAH diagnosis, percentage denominators were smaller than column n's.

^e History of sleep apnea is reported at the time of enrollment. Due to missing data, percentage denominators were smaller than column n's.

TABLE 2. Hemodynamic Variables at Diagnosis of Pulmonary Arterial Hypertension by Right-Sided Heart Catheterization^a

Variable ^b	Overall ^c	IPAH	FPAH	CHD-APAH	CTD-APAH	D&T-APAH	HIV-APAH	PoPH-APAH
mPAP (mm Hg)	2140 51.6±14.4	921 53.6±13.8	53 57.6±15.4	234 61.1±17.4	507 44.6±11.2	114 52.6±13.2	32 49.8±10.7	109 48.5±10.6
Mean RAP (mm Hg)	1966 9.5±5.7	840 10.3±5.8	50 9.6±4.9	221 7.4±4.0	460 8.9±5.7	108 10.9±5.7	27 10.2±5.5	103 9.4±6.9
Fick or thermodilution CI (L/min × m ²)	2137 2.4±0.9	921 2.3±0.9	53 2.0±0.7	NA ^d	507 2.5±0.7	114 2.1±0.7	32 2.1±0.5	109 2.8±0.8
PVR (Wood units) ^e	2137 11.6±7.3	920 12.6±7.5	53 14.9±6.7	232 14.2±10.7	507 9.3±5.0	114 11.8±5.9	32 10.6±4.7	109 8.2±4.1

^a CHD-APAH = congenital heart disease–associated PAH; CI = cardiac index; CTD-APAH = connective tissue disease–associated PAH; D&T-APAH = drugs and toxins–associated PAH; FPAH = familial PAH; HIV-APAH = human immunodeficiency virus–associated PAH; IPAH = idiopathic PAH; mPAP = mean pulmonary artery pressure; NA = not available; PAH = pulmonary arterial hypertension; PoPH-APAH = portopulmonary hypertension–associated PAH; PVR = pulmonary vascular resistance; RAP = right atrial pressure.

^b Number of patients followed by mean ± SD value unless otherwise specified.

^c Analysis cohort includes patients enrolled in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) through September 11, 2007, who were at least 2 years of age and had height and weight data available at the time of the diagnostic right-sided heart catheterization. Group 1 subgroup numbers do not add up to the overall number because some patients were missing data at diagnosis and some patients were in smaller diagnostic subgroups not included here.

^d Because of incomplete data for patients without repair or with partial repair at time of analyses.

^e SI conversion factor: To convert PVR values (Wood units) to dynes·sec·cm⁻⁵, multiply by 80.

TABLE 3. Comparison of Body Mass Index in REVEAL and NHANES Populations^a

Comparison of mean BMI by group 1 subtype	No.	Mean REVEAL BMI	Mean NHANES BMI	P value ^b
Overall ^c	2141	28.4	28.2	.28
IPAH	921	29.1	28.1	<.001
FPAH	54	27.8	26.8	.13
CHD-APAH	234	24.5	26.8	<.001
CTD-APAH	507	27.6	28.7	<.001
D&T-APAH	114	32.7	28.8	<.001
HIV-APAH	32	26.7	28.7	.06
PoPH-APAH	109	29.0	28.8	.75
Comparison of obese (BMI ≥30) proportions	No.	REVEAL % obese	NHANES % obese	P value ^b
Overall ^c	2141	36.5	33.0	.004
IPAH	921	40.1	32.5	<.001
FPAH	54	31.5	27.6	.55
CHD-APAH	234	22.2	27.7	.05
CTD-APAH	507	31.4	35.3	.08
D&T-APAH	114	59.6	35.0	<.001
HIV-APAH	32	28.1	34.6	.43
PoPH-APAH	109	36.7	36.1	.90
Comparison of underweight (BMI <18.5) proportions	No.	REVEAL % underweight	NHANES % underweight	P value ^b
Overall ^c	2141	5.7	4.1	.003
IPAH	921	4.9	4.5	.61
FPAH	54	5.6	10.0	.16
CHD-APAH	234	18.4	9.8	<.001
CTD-APAH	507	4.1	2.0	.02
D&T-APAH	114	0.0	1.4	NA
HIV-APAH	32	6.3	1.6	.28
PoPH-APAH	109	2.8	2.2	.75

^a BMI = body mass index; CHD-APAH = congenital heart disease–associated PAH; CTD-APAH = connective tissue disease–associated PAH; D&T-APAH = drugs and toxins–associated PAH; FPAH = familial PAH; HIV-APAH = human immunodeficiency virus–associated PAH; NA = not available; NHANES = National Health and Nutrition Examination Survey; PAH = pulmonary arterial hypertension; PoPH-APAH = portopulmonary hypertension–associated PAH; REVEAL = Registry to Evaluate Early and Long-term PAH Disease Management.

^b P values were calculated from the standard z score, under the null hypothesis of no difference between the NHANES and REVEAL BMI. The standard error for the difference was computed as a function of the standard errors for the 2 independent populations.

^c Analysis cohort includes patients enrolled in REVEAL through September 11, 2007, who were at least 2 years of age and had height and weight data available at the time of the diagnostic right-sided heart catheterization.

FIGURE. Comparison of body mass index (BMI) in Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) and National Health and Nutrition Examination Survey (NHANES) populations. A, Differences in mean BMI for the REVEAL cohort compared with the NHANES cohort, by pulmonary arterial hypertension (PAH) subtype. B, Differences in percentage of patients (pts) who are obese (BMI ≥ 30) in the REVEAL and NHANES cohorts, by PAH subtype. C, Differences in percentage of patients who are underweight (BMI, <18.5) in the REVEAL and NHANES cohorts, by PAH subtype. Error bars represent 95% confidence interval. Asterisk (*) indicates significant difference between REVEAL and NHANES populations. CHD = congenital heart disease; CTD = connective tissue disease; FPAH = familial PAH; HIV = human immunodeficiency virus; IPAH = idiopathic PAH; PortoPH = portopulmonary hypertension.

TABLE 4. **Characteristics of Obese and Nonobese Patients With Idiopathic Pulmonary Arterial Hypertension Enrolled in REVEAL^a**

	Obese (BMI ≥30)	Nonobese (BMI <30)	P value ^b
Group 1 IPAH ^c patients, No.	369	552	
Age at PAH diagnosis (y), mean ± SD	49.7±13.7	45.2±19.3	<.001
Race, No. (%)			
White	288 (79.1)	401 (73.4)	.02
Black	46 (12.6)	64 (11.7)	
Hispanic	24 (6.6)	46 (8.4)	
Asian/Pacific Islander	4 (1.1)	22 (4.0)	
Native American/Native Alaskan	1 (0.3)	2 (0.4)	
Other ^d	1 (0.3)	11 (2.0)	
WHO/NYHA FC at PAH diagnosis, No. (%)			
I	7 (2.4)	22 (5.2)	.009
II	48 (16.7)	105 (25.0)	
III	184 (64.1)	233 (55.5)	
IV	48 (16.7)	60 (14.3)	
Hemodynamics at PAH diagnosis, No. and mean ± SD unless specified otherwise			
mPAP (mm Hg)	369	552	.45
Mean RAP (mm Hg)	54.0±13.3	53.3±14.1	
Fick or thermodilution CO (L/min)	339	501	<.001
Fick or thermodilution CI ^e (L/min × m ²)	11.8±6.1	9.2±5.3	
PVR (Wood units)	369	552	<.001
PVRI (Wood units × m ²)	4.5±1.4	3.9±1.4	
Proportion PCWP or LVEDP ^f at PAH diagnosis, No. (%)	369	552	<.001
≤15 mm Hg	2.2±0.7	2.4±1.0	
16-18 mm Hg	369	551	<.001
History of sleep apnea, ^g No. (%)	11.3±6.0	13.5±8.3	
Diabetes at enrollment, ^g No. (%)	369	551	.14
Hypertension at enrollment, ^g No. (%)	23.7±12.3	22.5±13.2	
Renal insufficiency at enrollment, ^g No. (%)	336 (91.1)	503 (91.5)	.83
Use of statins at enrollment, ^g No. (%)	33 (8.9)	47 (8.6)	
Use of diuretics at enrollment, ^g No. (%)	146 (42.0)	81 (15.5)	<.001
Diabetes at enrollment, ^g No. (%)	81 (22.9)	37 (6.8)	<.001
Hypertension at enrollment, ^g No. (%)	176 (49.7)	161 (29.7)	<.001
Renal insufficiency at enrollment, ^g No. (%)	20 (5.7)	20 (3.7)	.17
Use of statins at enrollment, ^g No. (%)	77 (21.8)	58 (10.7)	<.001
Use of diuretics at enrollment, ^g No. (%)	267 (75.4)	338 (62.4)	<.001

^a BMI = body mass index; CI = cardiac index; CO = cardiac output; IPAH = idiopathic pulmonary arterial hypertension; LVEDP = left ventricular end-diastolic pressure; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; PVRI = PVR index; RAP = right atrial pressure; REVEAL = Registry to Evaluate Early and Long-term PAH Disease Management; WHO/NYHA FC = World Health Organization/New York Heart Association functional class.

^b Calculated using the χ^2 test for categorical data and *t* test for continuous data.

^c This table includes the subset of patients with BMI measurements in group 1 subgroup IPAH at the time of PAH diagnosis.

^d Includes 5 patients of South-Asian descent, 2 patients of Middle-Eastern descent, 4 mixed-race patients, and 1 patient for whom other was checked without additional information.

^e CI calculated on the basis of a hierarchy in which Fick values are used if available; otherwise, thermodilution values are used.

^f The minimum of PCWP or LVEDP at PAH diagnosis is reported.

^g Data were not available at the time of PAH diagnosis.

DISCUSSION

appears to be due to patients with CHD-APAH or CTD-APAH (Figure 1, C; Table 3).

When REVEAL patients with IPAH who were obese (BMI ≥30) were compared with REVEAL patients with IPAH who were not obese (BMI <30), there were significant differences in age, race, functional class, hemodynamics, comorbidities, and therapies (Table 4). There were similar proportions of patients with traditional PCWP values of 15 mm Hg or less in the obese and non-obese subgroups.

The mean BMI in the REVEAL (group 1 PH) patients was the same as in the normal NHANES comparison group; however, the percentages of both obese and underweight patients were increased in the PAH group as a whole. The large database of the REVEAL registry provided a unique opportunity to examine subgroups of patients with PAH according to diagnostic group. The higher proportion at either end of the weight spectrum was attributable to the

characteristics of specific subgroups: IPAH and drugs and toxins–APAH subgroups had a higher percentage of obese patients compared with NHANES controls, whereas CHD-APAH and CTD-APAH subgroups had a higher percentage of underweight patients. The Figure demonstrates the averaging effect on the BMI of the various subgroups. The U-shaped distribution highlights the potential hazard of using only the BMI in examining the relationship of PH to obesity, a likely explanation for the results in a prior negative study.⁶

The reason for the increased frequency of obesity in patients with IPAH (Table 3) is unknown, and further research is needed. Avenues to explore include the hypothesis of an association in the IPAH population with metabolic syndrome¹² and reports that metabolic syndrome is an independent predictor of impaired lung function.¹³ Indeed, the obese group had higher prevalences of statin use, diabetes mellitus, and systemic hypertension. In addition, the associated comorbidities may represent independent risk factors for PAH. Such an association is well established with obstructive sleep apnea^{14,15} but less so with systemic hypertension.⁴

Another possibility is that the distribution of obese and nonobese patients may be due to disease severity or progression. Disproportionately more patients among the obese than the nonobese group were in functional class III or IV (Table 4). The hemodynamic variables also indicate slightly more impairment; the obese IPAH group had higher right atrial pressure and pulmonary vascular resistance index as well as lower cardiac index. In addition, more obese patients were taking diuretics (n=267 [75%]) compared with nonobese patients (n=338 [62%]; $P<.001$). Obese patients may have been heavier because of more fluid retention due to right-sided heart dysfunction. Finally, the obese patients with IPAH were slightly older, which may represent longer disease duration or a higher prevalence of obesity seen in older patients.^{1,2}

The increased prevalence of obstructive sleep apnea, diabetes mellitus, and systemic hypertension in the obese group might lead to speculation that diastolic dysfunction may be an important confounding variable. Indeed, the REVEAL registry included patients with PCWP or LVEDP of 18 mm Hg or less, in contrast to the newly updated recommendations that define PAH as PCWP or LVEDP of 15 mm Hg or less.^{3,7} However, the difference does not seem to be explained by diastolic dysfunction, as evidenced by the lack of differences between patients with PCWP or LVEDP of 15 mm Hg or less and those with PCWP or LVEDP of 16 to 18 mm Hg.

Other possibilities are more speculative. For example, patients with PAH also have diminished exercise capacity and decreased caloric use and thus have a metabolic disadvantage and may be more prone to obesity. The difference

in race between the obese and nonobese groups indicates a possible relationship, but the reason is unclear.

The reasons for the subtype differences in BMI, percentage overweight, and percentage underweight (Table 3) are also unknown, but potential explanations may include anorexigen use or the long-term effects of systemic disease. Anorexigen (fenfluramine and dexfenfluramine) use has been shown to contribute to the development of PAH, although such patients are generally classified as having drugs and toxins–APAH.^{16–18} Indeed, most patients in the drugs and toxins–APAH subgroup of the REVEAL cohort used anorexigens. Presumably, most patients with PAH in association with anorexigen use were obese before exposure. Many, if not most, of those patients probably remained obese until they developed PAH. Two additional concerns that cannot be adequately addressed in the current study include the possibility that recall bias resulted in patients being included in the IPAH rather than the drugs and toxins–APAH subgroup. Such a bias, if prevalent, could produce a false-positive finding of an association between IPAH and obesity. Conversely, if obesity is a risk factor for PH, the more severe obesity in the drugs and toxins–APAH subgroup could have contributed to the development of PH. The patients with coexisting CTD or HIV have systemic disease that may independently predispose them to a lower BMI. Patients with HIV have been shown to have lower BMI than controls, regardless of whether PAH was also diagnosed.^{19,20} In contrast, obesity is a common comorbidity seen in pediatric and adult patients with CHD (perhaps due to decreased exercise capacity),^{21–23} and decreasing BMI in this patient population may be a warning sign of development of right-sided heart failure and PAH.

As previously noted, 15% to 20% of patients with obstructive sleep apnea also have PH.¹⁵ Although the coexistence of chronic obstructive pulmonary disease was originally suggested as the cause, PAH has also been shown to occur in patients with sleep apnea without chronic obstructive pulmonary disease.¹⁴ Moreover, sleep apnea has been shown to correlate with obesity.^{14,15} Interestingly, the obese patients with IPAH in our study were more likely to have a history of sleep apnea (n=146 [42%]) than the nonobese patients with IPAH (n=81 [16%]; $P<.001$). Although the small sample size precludes statistical comparison, the patients with subtypes of PAH that were associated with greater BMI (IPAH and drugs and toxins–APAH) also tended to have a history of sleep apnea, whereas those PAH subtypes associated with a lower BMI than in the NHANES controls (CHD-APAH, CTD-APAH, and HIV-APAH) had lower proportions of patients reporting sleep apnea. The relationship of PAH subtype to sleep apnea requires further exploration.

Our analysis has several limitations. Because it is a prospective registry, most patients in REVEAL received their

diagnosis of PAH before enrollment. We do not have BMI data at the time of first symptom onset, and therefore we cannot determine causality or how symptoms of PAH may have affected BMI. Moreover, although there are some differences between obese and nonobese patients enrolled in REVEAL, the number of patients in each PAH subtype category (aside from IPAH) was small, and therefore performing the obese and nonobese analyses in the PAH subtypes was not recommended. Another limitation is the location of the study; this is a US-based registry and, although the incidence of obesity is rising worldwide, the United States has the highest incidence in the developed world.²⁴ Furthermore, the REVEAL inclusion criteria do not conform to the recommendations of the 4th World Symposium on Pulmonary Hypertension because the registry was initiated before their issuance.³ Finally, REVEAL uses a less-restrictive PCWP criterion of 18 mm Hg or less to be more inclusive of patients seen in clinical practice, although this did not appear to bias the results of our study.

CONCLUSION

We have shown that, although mean BMI was no different, patients with PAH enrolled in REVEAL are more likely to be obese or underweight than the NHANES controls. However, the likelihood of a patient with PAH being obese primarily depends on the subtype of PAH. The factors influencing the relationship between obesity and PAH subtype are currently unknown and require additional study.

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