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RESEARCH LETTER

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Premorbid weight in pulmonary arterial hypertension

Abstract

Relationships between obesity and outcomes in pulmonary arterial hypertension (PAH) are complex. Previous work suggested obesity, occurring alongside PAH, may be associated with better survival. In our work, we suggest obesity prior to PAH development is associated with worse survival. This may add a novel temporal element to the "obesity-paradox."

KEYWORDS

epidemiology, obesity, pulmonary arterial hypertension, social determinants of lung health and disease

To the editor:

Pulmonary artery hypertension (PAH) is a serious disease characterized by pulmonary vascular remodeling resulting in increased right heart afterload, right heart failure, and death. Patients with PAH and obesity tend to have worse health-related quality of life and many animal models suggest that obesity may contribute to PAH development; however, counter-intuitively, obese patients appear to have *improved* survival.[1–3] Causal inference on clinical research to-date is complicated by the recognition that PAH, once present, may have complex relationships with weight. For example, severe PAH may have myriad effects on nutritional status, diet, and exercise that lead to differences in weight rather than vice versa. To better understand temporal relationships with obesity in PAH, we evaluated relationships between premorbid body mass index (BMI) and mortality in individuals who subsequently developed PAH.

METHODS

We included adult participants from a single-institution PAH cohort.[4] Participants provided informed consent and the University of Washington Institutional Review Board approved the study (#3387). Participants were diagnosed with PAH using the standard definition at the time of enrollment, had PAH diagnosed after age 20, and were followed for up to 3 years or until death.

Exposure

Exposures of interest were current BMI measured at the time of enrollment and self-reported weight at age 20 (used to calculate pre-PAH BMI). Importantly, self-reported weight has good agreement with measured weight even decades later and self-reported weight at age 20 is an established surrogate for measured weight used in other large cohort studies.[5]

Outcome

The outcome was all-cause mortality over 3 years of follow-up. Risk time accrued from the time of enrollment and the outcome was available for all participants.

Statistical analysis

Cox regression and Kaplan–Meier survival curves were used to estimate relationships between BMI (current and historical) with mortality. Unadjusted and adjusted models were considered. All adjusted models accounted

for age, sex at birth, race, and PAH etiology. A second adjusted model also accounted for current BMI (when evaluating premorbid BMI) to explore the possibility that relationships with historical BMI may be dependent on current BMI for some individuals. Additional models also accounted for (1) differences in disease severity at the time of enrollment using the registry to evaluate early and long-term PAH disease management (REVEAL) 2.0 score or (2) age at PAH diagnosis.

RESULTS

Cohort characteristics

Eighty-two participants were included, and baseline characteristics were representative of a typical PAH population. Mean age at enrollment was 54.1 ± 15.0 years and the age at diagnosis was 49.0 ± 15.6 years. Current BMI was 28.2 ± 6.4 kg/m^2 and mean premorbid BMI at age 20 was 23.7 ± 5.0 kg/m^2 with moderate intraindividual correlation (correlation coefficient 0.56). Most individuals were heavier at the time of enrollment into the cohort than they had been at age 20. PAH etiology was idiopathic (43%), toxin-associated (12%), connective-tissue disease associated (21%), congenital heart disease associated (18%), or PAH from other causes (6%). Most participants had intermediate or high-risk disease features (69.5% of participants had a REVEAL 2.0 score ≥7).

Relationships between BMI and mortality

Current BMI at the time of enrollment was not associated with mortality (Figure 1). The absence of a relationship did not change after accounting for potential confounders. The hazard ratio (HR) for death in unadjusted analyses was 1.0 for every 5 kg/m^2 difference in current BMI (95% confidence interval [CI]: 0.7–1.6, $p = 0.87$). After accounting for age, sex at birth, race, and PAH etiology, the HR of death was 1.1 (95% CI: 0.7–1.9, $p = 0.64$). Further accounting for differences in REVEAL score (HR: 1.1, 95% CI: 0.7–1.8, $p = 0.76$) or age at diagnosis (HR: 1.1, 95% CI: 0.6–1.8, $p = 0.86$) did not change this relationship.

Higher BMI at age 20 was associated with a higher hazard of death (Figure 1). This association was similar after accounting for potential confounders in the relationship. The HR for death in unadjusted analyses was 2.0 for every 5 kg/m^2 increase in BMI at age 20 (95% CI: 1.2–3.2, $p = 0.008$). After accounting for differences in age, sex at birth, race, and PAH etiology, the HR was 1.9 (95% CI: 1.1–3.3, $p = 0.02$). Further accounting for a participant's current weight (HR: 2.3, 95% CI: 1.2–4.5, $p = 0.01$), baseline REVEAL score (HR: 2.5, 95% CI: 1.0–6.1, $p = 0.04$), or further adjustment for age at diagnosis (HR: 2.5, 95% CI: 1.1–6.1, $p = 0.04$) did not change the significant association between BMI at age 20 and mortality after PAH developed.

DISCUSSION

To our knowledge, this is the first study to suggest that BMI before PAH develops is associated with an *increased* risk for mortality after one develops PAH. These hypothesis-generating results may suggest a role for obesity or its antecedents in the pathogenesis of PAH or the subsequent ability to tolerate PAH once it develops.

Several previous investigations have considered relationships between contemporaneous BMI and outcomes in patients with PAH. While BMI in these studies is associated with worse health-related quality of life, obesity is also associated with modestly increased survival.[3,6,7] This phenomenon is known as the "obesity

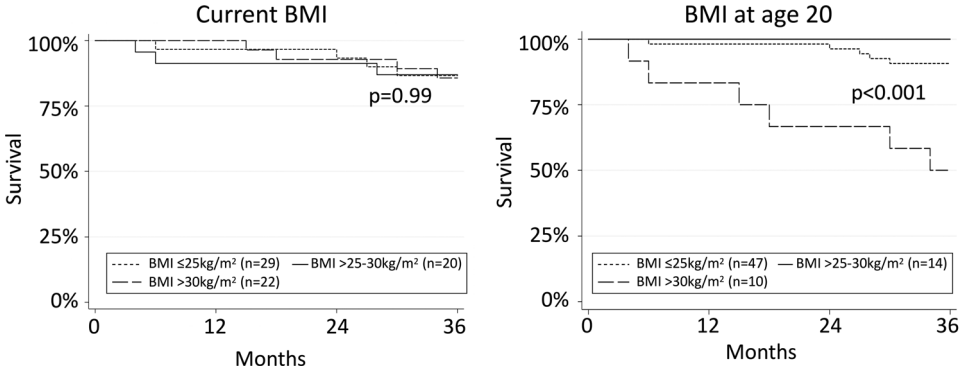

FIGURE 1 Survival among patients with pulmonary arterial hypertension (PAH) as estimated by Kaplan–Meier survival curves and stratified by current body mass index (BMI) or BMI at age 20 before the development of PAH.

paradox" and is not fully understood. One might speculate that heavier patients present with symptoms earlier in their disease course which would give the impression of "longer" survival. Alternatively, severe PAH may drive weight loss, such that the observed association reflects the impact of PAH on weight rather than the impact of weight on PAH (reverse causation–also known as confounding by pre-existing disease).[8] In fact, once PAH is present, multiple factors complicate the relationship between the disease state, BMI, and outcomes including malnutrition, cardiac cachexia, lack of exercise, and change in overall body composition including lower muscle mass, higher total body fat content, and changes in epicardial fat volume.[9–12]

By using predisease BMI at age 20, we preserve the temporal sequence of events and limit the possibility for PAH itself to cause the differences in weight. This approach allows focus on the relationships between high BMI or the drivers of high BMI and subsequent outcomes in PAH. Our findings suggest that obesity or its antecedents, before the onset of PAH, may lead to worse disease or limit the ability of patients to tolerate PAH once it develops. This may better align with results from several PAH animal models suggesting that obesity is a disease driver.[2] Importantly, while obesity at age 20 may have several health-related consequences (such as insulin resistance and changes in adipose signaling), it also corresponds with a suite of exposures during an individual's formative years that may independently drive health outcomes including health behaviors, diet, and underlying differences in metabolism and comorbidity.[5,13,14] The impact of early obesity on outcomes does not appear to be specific to PAH. Self-reported obesity at age 20 is also associated with a threefold increase in left heart failure later in life among other worrisome associations.[5] Nevertheless, this lack of specificity need not imply a lack of relevance as obesity or its antecedent may be important across a range of diseases complicated by heart failure.

Limitations

The small sample size provided sufficient power to detect the large association between premorbid BMI and mortality; however, limited power and a small sample size may have limited the ability to detect smaller associations between current BMI and mortality such as have been described in other cohorts. In addition, self-report may misclassify premorbid weight. Previous work supports the validity of self-report, nondifferential misclassification would be expected to bias results toward the null, and it is unclear why a participant's misremembered higher weight would be systematically associated with worse mortality; nevertheless, *measured* weight before PAH would be a better measure of the exposure of interest and validation in future cohorts with directly measured weight is needed to reinforce or refute these findings.[5] In addition, it is quite possible that the trajectory of weight change is important. While we did not collect an estimate of weight immediately before the onset of PAH symptoms, such a measure would be key to understand the relationships between predisease weight and weight trajectory with outcomes.

In conclusion, this is the first study to examine temporal relationships between premorbid obesity and PAH outcomes. We report a significant association between premorbid BMI and PAH mortality which may inform a novel temporal aspect of the "obesity paradox." This should be considered in subsequent obesity-oriented work in PAH.

AUTHOR CONTRIBUTIONS

Laura J. Oppegard, Jeffrey C. Robinson, and Peter J. Leary take responsibility for the content of this manuscript, including the data and analysis and were involved in each step of development. Lia M. Barros, Hongyang Pi, James Kornfield, Catherine L. Hough, and Samuel G. Rayner contributed to study design and data interpretation. All authors drafted and revised the manuscript.

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CONFLICTS OF INTEREST STATEMENT

All authors report no direct conflict of interest related to this manuscript. Dr. Leary receives research support from the NHLBI, AHA, and Bayer; salary support from the Cystic Fibrosis Therapeutic Development network; and has consulting fees from Bayer. Dr. Rayner receives research funding from the NHLBI, AHA, Bayer, and United Therapeutics. Dr. Pi receives research funding from the NHLBI. Dr. Robinson receives research funding from Janssen Pharmaceuticals, Gossamer Bio, Acceleron/Merck, and United Therapeutics; and consulting fees from Janssen Pharmaceuticals and Bayer. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

Participants provided informed consent and the University of Washington Institutional Review Board approved the study (#3387).

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