3. Razzouk L, Muntner P. Ethnic, gender, and age-related differences in patients with the metabolic syndrome. *Curr Hypertens Rep* 2009; 11:127–132.

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The Association between Obstructive Sleep Apnea Severity and N-Terminal Pro-B-Type Natriuretic Peptide Levels in Women

To the Editor:

I read with interest the work by Dr. Querejeta Roca and coworkers, which reported that in 1,645 middle-aged and older men and women free of coronary heart disease and heart failure, obstructive sleep apnea (OSA) severity was not associated with N-terminal pro B-type natriuretic peptide (NT-proBNP) levels after adjusting for many potential confounders (1).

Notably, the authors found a negative association between OSA severity and NT-proBNP levels in unadjusted analysis. They explained that body mass index may be a confounder of this relationship. However, the sex difference should be considered to be another potential confounder in this study as well. The proportions of women decreased gradually from 65% of participants without OSA to 35% of those with severe OSA in this report. As is known, women have 1.7 to 1.8 times higher NT-proBNP levels as compared with age-matched men (2), which could explain in part that the baseline NT-proBNP level was paradoxically higher in participants with less severe OSA. In addition, differences in craniofacial morphology and function, body-fat distribution, and sex-hormonal influences may contribute to the sex-specific pathogenesis of OSA (3).

So far, there have been only two studies using a population of only women to investigate the association between OSA severity and NT-proBNP levels. Ybarra and colleagues demonstrated that NT-proBNP levels were independently predicted by sleep-disordered breathing severity defined by the Berlin Questionnaire in 110 asymptomatic morbidly obese young women (4). Furthermore, Ljunggren and colleagues showed a dose-response relationship in 349 healthy women between OSA severity defined by polysomnography and BNP levels (5).

Accordingly, Querejeta Roca and colleagues should do a sex-specific analysis in advance for the associations between OSA severity, NT-proBNP levels, and cardiovascular risk in this study. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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References

1. Querejeta Roca G, Redline S, Punjabi N, Claggett B, Ballantyne CM, Solomon SD, Shah AM. Sleep apnea is associated with subclinical myocardial injury in the community: the ARIC-SHHS study. *Am J Respir Crit Care Med* 2013;188:1460–1465.
2. Luchner A, Behrens G, Stritzke J, Markus M, Stark K, Peters A, Meisinger C, Leitzmann M, Hense HW, Schunkert H, *et al*. Long-term pattern of brain natriuretic peptide and N-terminal pro brain natriuretic peptide and its determinants in the general population: contribution of age, gender, and cardiac and extra-cardiac factors. *Eur J Heart Fail* 2013;15:859–867.
3. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, Kales A. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med* 2001;163:608–613.
4. Ybarra J, Planas F, Navarro-López F, Pujadas S, Pujadas J, Jurado J, Pou JM. Association between sleep-disordered breathing, aminoterminal pro-brain natriuretic peptide (NT-proBNP) levels and insulin resistance in morbidly obese young women. *Eur J Intern Med* 2009;20:174–181.
5. Ljunggren M, Lindahl B, Theorell-Haglöw J, Lindberg E. Association between obstructive sleep apnea and elevated levels of type B natriuretic peptide in a community-based sample of women. *Sleep* 2012;35:1521–1527.

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Reply

From the Authors:

We appreciate Dr. Mirrakhimov's and Dr. Lin's comments regarding our article in the *Journal* (1) studying the association between obstructive sleep apnea (OSA) and serum high-sensitivity troponin (hs-TnT) and N-terminal pro B-type natriuretic peptide (NT-proBNP) in 1,645 community-dwelling subjects free of coronary heart disease and heart failure from the intersection between the Atherosclerosis Risk in the Communities (ARIC) and the Sleep Heart Health Study (SHHS). We agree with Dr. Mirrakhimov that our study's finding may not be generalizable to persons of nonwhite race/ethnicity. As with most previous studies evaluating the relationship between OSA and biomarkers of myocardial injury, the population participating in both ARIC and SHHS was predominantly white. To the best of our knowledge, despite findings of significant race-related differences in the sleep architecture and OSA symptoms (2), there is a lack of robust data on the cardiovascular implications of OSA in several ethnic populations, in particular Hispanics (3). Further studies will be necessary to elucidate whether the association between hs-TnT and OSA severity is also applicable to other ethnic populations and to clarify the cardiovascular implications of OSA more generally in these understudied populations. In this respect, several ongoing NHLBI cohort studies, including the Jackson Heart Study in African Americans (4) and the Study of Latinos (5), offer a unique potential opportunity.

Dr. Lin's letter raises the possibility that the negative association between NT-proBNP and OSA severity noted in our unadjusted analysis may be confounded by the differential distribution of sex by OSA severity. We agree with Dr. Lin that there are important sex-based differences in both the pathophysiology of OSA (6) and the cardiac response to insult and

altered loading conditions (7). In our study, the association between OSA and NT-proBNP remained negative and strongly significant ($P = 0.007$), even after adjusting for sex and age. After further adjusting for body mass index, this association was no longer significant ($P = 0.05$). Similarly, in our dataset, sex did not modify the association between respiratory disturbance index and NT-proBNP level (P for interaction = 0.21). An exploratory sex-stratified analysis found a negative association in women of marginal significance ($P = 0.05$) and a null association in men. Our findings indicate a need for further research to address potential sex differences in cardiovascular biomarker responses to OSA-related stresses. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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References

- Querejeta Roca G, Redline S, Punjabi N, Claggett B, Ballantyne CM, Solomon SD, Shah AM. Sleep apnea is associated with subclinical myocardial injury in the community: the ARIC-SHHS study. *Am J Respir Crit Care Med* 2013;188:1460–1465.
- O'Connor GT, Lind BK, Lee ET, Nieto FJ, Redline S, Samet JM, Boland LL, Walsleben JA, Foster GL; Sleep Heart Health Study Investigators. Variation in symptoms of sleep-disordered breathing with race and ethnicity: the Sleep Heart Health Study. *Sleep* 2003;26:74–79.
- Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008;5:136–143.
- Taylor HA, Wilson JG, Jones DW, Sarpong DF, Srinivasan A, Garrison RJ, Nelson C, Wyatt SB. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. *Ethn Dis* 2005;15:S6–4–17.
- Sorlie PD, Avilés-Santa LM, Wassertheil-Smoller S, Kaplan RC, Daviglius ML, Giachello AL, Schneiderman N, Raji L, Talavera G, Allison M, et al. Design and implementation of the Hispanic Community Health Study/Study of Latinos. *Ann Epidemiol* 2010;20:629–641.
- Lin CM, Davidson TM, Ancoli-Israel S. Gender differences in obstructive sleep apnea and treatment implications. *Sleep Med Rev* 2008;12:481–496.
- Krumholz HM, Larson M, Levy D. Sex differences in cardiac adaptation to isolated systolic hypertension. *Am J Cardiol* 1993;72:310–313.

Nonlinear Weight and Chronic Obstructive Pulmonary Disease Effect Modeling to Improve Data Fitting

To the Editor:

We read with interest the article by Sood and colleagues (1) reporting that weight gain affects respiratory outcomes differently between obese and normal-weight smokers, with a nonlinear relationship suggesting that the effect of excess weight is unlikely to be mechanical alone. Although we agree with the authors' conclusion, some cautions should be urged with the methodology performed.

First, it is stated that “35, 23, and 17% of smokers in the normal-weight, overweight, and obese categories, respectively, had spirometry-defined COPD” and “the remainder was considered at risk for COPD.” This statistically significant heterogeneous repartition of patients with chronic obstructive pulmonary disease (COPD) may be a source of potential confounding factors because patients with COPD and non-COPD individuals have distinct phenotypes, especially when the effects of obesity or weight gain are concerned (2). This implies that the three groups used by the authors cannot be as easily compared as stated. For many years (since the famous curves from Fletcher and Peto [3]), accelerated lung function decline has been regarded as a critical hallmark of COPD. Even though conflicting data exist (4), smokers should not have been considered as a whole, especially because some had documented COPD and others did not. Therefore, we suggest the author should have taken the effect of COPD by itself into account.

Besides considering cross-sectional analyses, the authors suggested a nonlinear relationship between baseline weight and spirometric function and health status. Logistic and linear regression techniques were performed overall and after stratification into the three baseline weight categories. This implies a clinical *a priori* to determine the threshold used to construct the groups. A data-driven analysis would avoid this and still model the nonlinear relationship; a possible approach is a generalized regression spline with optimized knot locations. Splines are defined to be piecewise of polynomials of degree d whose function values and first $d - 1$ derivatives agree at the points where they join. The abscissas of these joint points are called knots, and the number and position of knots and the degrees of polynomial pieces may vary. The use of spline functions in simple or multiple regression models allows the investigation of nonlinear effects. The B-spline base functions, which represent one of several ways to write spline models, would be appropriate because they are numerically well conditioned and achieve local sensitivity to the data (5).

In the paper, when considering categorical dependent variables, the authors performed logistic models, but a spline model would be able to remove the linear restriction on logit function. By considering knot locations as free variables, spline approximation of data would be improved, and the number of knots and the degree of the spline functions would be determined by using a model selection procedure.

However, using optimal knot locations requires considering that the models are not nested, and the classical maximum likelihood ratio test cannot be used. Moreover, a knot, seen as a free parameter for a piecewise linear spline, represents a break point in the logit function that may be interpreted as a data-driven threshold value (6). Model selection criteria (Akaike or