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Rapid Eye Movement–related Sleep-disordered Breathing and Cardiovascular Risk: Additional Clarity or More Questions?

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Previous prospective cohort studies have reported an increased risk of cardiovascular disease in participants who receive a diagnosis of sleep-disordered breathing (SDB) when the apnea–hypopnea index (AHI) in both rapid eye movement (REM) and non-REM (NREM) sleep is taken into account (1, 2). Recently, additional analyses of these cohorts have identified that the REM-related AHI is independently associated with cardiovascular, neurocognitive, and metabolic risks (3–5). This observation is biologically plausible because of the unique features of REM-related SDB, such as lower lung volumes, increased upper airway collapsibility, increased sympathetic tone, and decreased respiratory drive, that results in longer obstructive events, greater desaturation, and an increased rise in blood pressure at the termination of the obstructive events (6).



In this issue of *AnnalsATS*, Aurora and colleagues (pp. 614–620) report the natural history of REM-related AHI, predictors of disease progression, the evolution of REM-related SDB into NREM sleep, and its association with incident cardiovascular events in the SHHS (Sleep Heart Health Study) cohort (7). The analyzed data included two unattended home polysomnography studies in conjunction with a detailed health interview and measurements of blood pressure and anthropometry ~5 years apart. Participants (n = 1,908) with an NREM AHI of <5 events per hour at baseline and >15 min of REM sleep at baseline as well as at follow-up were included in the analysis. The population included women (n = 1224) and men (n = 684) who were predominantly white. The overall AHI at baseline was 2.7 ± 2.9 for men and 3.0 ± 2.6 for women. Neither group was obese at baseline, with a body mass index (BMI) of 28.0 ± 5.4 (women) and 27.6 ± 3.9 (men), and did not differ with regard to age (60.7 ± 10.3 yr [women] and 60.9 ± 10.0 yr [men]).

Most of the participants progressed to an AHI of >5 events per hour in NREM at follow-up. A higher baseline REM AHI increased the likelihood of developing NREM SDB at follow-up. SDB in REM did not progress in most of the study population. A higher baseline BMI and an increase in the BMI predicted progression of the AHI in NREM and REM sleep only in men. Only women with REM-related SDB at baseline who developed an NREM AHI of >5 events per hour exhibited an increased relative risk of cardiovascular events at follow-up.

The limitations of this report relate to the relatively short time interval between the two assessments (~5 yr) and the limited number of participants with a severe REM-related AHI at baseline (6.1% women and 4.5% men). Body position was measured using a mercury gauge that cannot assess head position. Milder degrees of REM AHI may be associated with the "normal physiology" of REM that is related to inhibition of the diaphragm in phasic REM sleep (8). The chosen 15-minute minimum period needed to assess REM SDB may also be an overestimation, because two single apneas or hypopneas during a 15-minute-long REM sleep (in the whole night) correspond to a REM AHI of 8 events per hour (i.e., REM-related SDB by definition). Subjective sleepiness, an endotype associated with cardiovascular risk, was not reported (7). Finally, there is uncertainty regarding the best definition of hypopnea as part of a composite AHI (9). This is particularly relevant for determining cardiovascular risk. In this data set, a hypopnea was defined as a 30% reduction in airflow assessed by either an oronasal thermocouple or uncalibrated inductance plethysmography for at least 10 seconds and a 4% oxyhemoglobin desaturation by pulse oximetry. As opposed to measuring the number of 4% oxyhemoglobin desaturations, better characterization of the exposure to the hypoxic burden (i.e., the area under the curve), defined as % min/h, was recently reported using the SHHS and MrOS (Outcomes of Sleep Disorders in Older Men) cohorts (10). This measure predicts cardiovascular mortality and may be more precise and adaptable to home testing devices.

Despite the uncertainty and the reproducibility regarding defining events to predict cardiovascular risk in individuals with SDB, Aurora and colleagues should be commended for this work. Using the previously accepted criteria for diagnosing SDB, they identified that women with predominantly REM-related SDB may be at greater risk for adverse cardiovascular

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outcomes. Additional studies are needed to determine how this finding relates to hormonal changes in the menopausal and postmenopausal status of women in this age group, and how we assess this difference using current approaches to home-based testing for SDB (11–13). In the meantime, focusing on fitness in conjunction with weight loss would be a prudent approach for anyone with REM-related SDB, and, as these data suggest, especially women. ■

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

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Bye-Bye Gender Bias? The Promise of a New Generation

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"In conclusion, I recommend Dr. Smith, an ambitious researcher with seven first-authored papers and an excellent communicator, without reservation."

"In conclusion, I recommend Dr. Smith, a hard-working and compassionate physician, without reservation."

The first recommendation is longer and emphasizes abilities, whereas the second emphasizes effort and communal traits. Which fictional Dr. Smith is male and which is female? Although these statements lack *explicit* gender cues, they are representative of the widespread *implicit* gender bias that plagues academic medicine. It has been shown that recommendation letters for men are longer and more likely to have descriptions of assertive, self-oriented behaviors, whereas the letters for women are more likely to reference personal life and describe communal behaviors (1, 2). Gendered differences in the way we evaluate and reward performance extend beyond letters of reference. A recent study showed that women are less likely than men to be invited as Grand Rounds speakers (3), and introductions of female Grand Rounds speakers by male faculty were less likely to include a professional title (4). After being shown identical curriculum vitae, both male and female science faculty were less likely to hire a female as a lab manager than a male, and would offer her a lower salary (5).



In the past, these gender differences either went unnoticed or were dismissed as harmless. However, these biases contribute

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