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Ⓞ The Challenges of Estimating Causal Effects of Continuous Positive Airway Pressure Therapy from Observational Data

To the Editor:

We read with great interest the recent work by Gervès-Pinquieré and colleagues seeking to estimate the causal effect of continuous positive airway pressure (CPAP) on long-term outcomes among patients with obstructive sleep apnea (1). Obtaining unbiased causal estimates from observational data is challenging, and Gervès-Pinquieré and colleagues are to be congratulated for their efforts. Nevertheless, we had several concerns about interpreting the findings from this work.

First, the authors identified a stronger impact of CPAP on lowering the relative risk of major adverse cardiovascular events (MACEs) in those without preexisting cardiovascular disease compared with those with prior history of cardiovascular disease. In considering the clinical implications of this finding, it is important to recognize that the potential benefit of CPAP therapy is based on the absolute risk reduction rather than the relative risk

reduction. Given that those with a prior history of cardiovascular disease are at a much higher baseline risk, a smaller relative risk reduction can still translate into a larger absolute risk reduction. It would be helpful if the authors could estimate the absolute risk reduction (with confidence intervals) for MACEs to be obtained from CPAP therapy in the primary and secondary prevention subgroups.

Second, while we congratulate the authors for reporting E-values, we disagree with their interpretation. E-values estimate the necessary effect size that unmeasured confounders would need to explain a given finding's point estimate and upper confidence interval (2). For the comparison of CPAP use of 7 hours or more relative to less than 4 hours in Table 2 of their manuscript, Gervès-Pinquieré and colleagues estimate an impact on incident MACEs with a relative risk of 0.78 with an upper confidence interval of 0.93, translating to E-values of 1.88 and 1.36, respectively (1). Based on these estimates, the authors conclude there is a “low risk” that their findings stem from residual confounding. However, the healthy adherer effect is known to impact mortality with effect sizes in this range. In a meta-analysis of eight randomized trials, nonadherence to placebo medications was associated with a 1.79-fold increase in mortality (3). While the authors accounted for adherence to common medications in their analyses, concern for residual confounding remains. Adherence to medications does not fully predict CPAP adherence (4), and residual confounding by the healthy adherer effect is difficult to address. For instance, even after accounting for demographics, socioeconomic status, comorbidities, and healthy behaviors such as physical activity and diet, randomized trials in both women and men have estimated the risk of mortality is 50% greater in those who are nonadherent to placebo medications compared to those who are adherent (5, 6). Further research is needed to better understand how CPAP adherence is related to the general healthy adherer effect and to develop robust methods to account for these effects. Until then, efforts need to continue to develop feasible strategies for the conduct of long-term randomized trials of CPAP in patients with obstructive sleep apnea. ■

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Reply to Donovan and Patel

From the Authors:

We appreciate the correspondence from Drs. Lucas M. Donovan and Sanjay R. Patel about our study recently published in the *Journal* (1). On the basis of real-life clinical data from the Pays de la Loire Sleep Cohort linked to health administrative data, we demonstrated an inverse dose–response relationship between positive airway pressure (PAP) adherence and incident major adverse cardiovascular (CV) events (MACEs; composite outcome of mortality, stroke, and cardiac diseases), after adjustment for major confounding factors including CV active drug adherence.

Table 1. Incidence of Major Adverse Cardiovascular Events According to Positive Airway Pressure Daily Usage in Patients without and with Prior History of Cardiovascular Diseases

	n	Incidence Density Rate (95% CI), Events per 1,000 Person-Years			
		0–4 h	4–6 h	6–7 h	≥7 h
History of CVD					
No	4,491	25.6 (22.1–29.4)	24.3 (21.0–28.1)	20.8 (17.3–25.0)	25.9 (22.5–29.6)
Yes	647	96.1 (75.3–122.6)	76.9 (59.4–99.4)	75.3 (55.6–101.9)	86.0 (69.9–105.8)

Definition of abbreviations: CI = confidence interval; CVD = cardiovascular diseases.

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The first comment from Donovan and Patel concerns the finding of our subgroup analysis showing a stronger impact of PAP on lowering the relative risk of MACEs in patients without overt CV disease compared with those with prior history of CV events (P value for interaction < 0.0001). This finding is consistent with a *post hoc* analysis of the ISAACC (Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome) trial. The effect of intervention with CPAP shows that among patients with nontreated obstructive sleep apnea (OSA) and recent acute coronary syndrome, only those with no previous heart disease on admission had an increased risk of a recurrent CV event compared with the non-OSA group (2). It may contribute to explaining the lack of association between PAP therapy and CV outcomes in randomized controlled trials focusing on secondary prevention (3–6). However, as we mentioned in the discussion section, subgroup analyses should be interpreted with caution because of unbalanced sample sizes. Among 5,138 patients included in our study, only 647 had a prior history of CV events and were therefore in secondary prevention. The remaining 4,491 patients with no overt CV disease belonged to the primary prevention group. To better evaluate the potential CV benefit of PAP therapy in both primary and secondary prevention, Donovan and Patel suggest considering not only the relative risk reduction but also the absolute risk reduction (ARR). In the overall population, the overall incidence density rate of MACEs was 30.1 events per 1,000 person-years (95% confidence interval, 28.2–32.1). As expected, the incidence of MACEs was markedly lower in the primary prevention group (24.4 events per 1,000 person-years [22.4–26.7]) than in the secondary prevention group (84.0 events per 1,000 person-years [74.3–95.0]). Table 1 shows the incidence of MACEs according to PAP daily usage in patients without and with a history of CV diseases. Among patients with no overt CV disease, the incidence of MACEs was 25.6 events per 1,000 person-years (22.1–29.4) in the nonadherent group (PAP use less than 4 h per night) and 24.0 events per 1,000 person-years (21.9–26.2) in

adherent users (PAP use 4 h or more per night) resulting in a raw ARR of 1.6 events per 1,000 person-years (1.4–1.7) in the adherent group. Among patients with prior history of CV diseases, the incidence of MACEs was 96.1 events per 1,000 person-years (73.3–122.6) in the nonadherent group and 80.6 events per 1,000 person-years (69.8–92.9) in adherent users, resulting in a raw ARR of 15.5 events per 1,000 person-years (13.7–17.6) in the adherent group.

Real-world observational data represent a promising method for overcoming the sample selection biases that have been recently