Peer Review Report

Review Report on Self-reported sleep disturbance is an independent predictor of all-cause mortality and respiratory disease mortality in US adults: a population-based prospective cohort study

Original Article, Int J Public Health

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EVALUATION

Q 1 **Please summarize the main findings of the study.**

Authors report that participants with self-defined sleep dysfunction tend to have higher all-cause mortality, higher chronic lower respiratory disease mortality, but not CVD-specific mortality and cancer mortality. The finding that CVD mortality was not significantly increased is contrary to the literature.

Q 2 **Please highlight the limitations and strengths.**

The limitations of this study are not different from the general literature on the topic. For instance, the largest analysis (not cited in the paper), based on 42 prospective studies in 35 distinct study populations worldwide, concluded that the evidence for a robust U-shaped association is still lacking [https://pubmed.ncbi.nlm.nih.gov/23622956/]. The investigators of this study cited many similar limitations in the existing epidemiological data, including measurement bias (only three of the studies measured sleep objectively with actigraphy or EEG), the inability to fully adjust for confounding demographic, social, or health factors, and inconsistency in the definition of short (<6 or 7 hours) and long (>8, 9, or 10 hours) sleep. The strength of the study is its prospective design, powered to adjust for many confounders and the large sample size (n>40,000). The findings though apply only for US adults. Authors should discuss such aspects of the literature to put into the context their findings and limitations. Another limitation is the nature of the "dysfunction". We do not know whether it is insufficiency, circadian misalignment, poor sleeping quality, insomnia, chronic vs. transient, etc. This is vaguely mentioned in the limitations, but a more clear statement is needed for the interested reader. Another strength is the stratified analysis.

Q 3 **Please provide your detailed review report to the authors. The editors prefer to receive your review structured in major and minor comments. Please consider in your review the methods (statistical methods valid and correctly applied (e.g. sample size, choice of test), is the study replicable based on the method description?), results, data interpretation and references. If there are any objective errors, or if the conclusions are not supported, you should detail your concerns.**

Line 15: After adjusting "for" all sociodemographic variables (add for). In the abstract and the whole manuscript try to add the word "risk", because when i read statements like "...participants had higher all cause mortality" the word risk is not here. Otherwise you can use 'associations' if you want to soften the language, due to the self-reported data. In the conclusions you have done this.

Lines 160-165: There is no such resolution on the information you describe here in Table 2. The whole paragraph seems out of context.

In the results, I see that being an older adult (>60) have no association with risk of all-cause mortality. This is interesting, as among healthy middle-aged adults, sleep dysfuntion (type of duration) has been associated with a higher burden of subclinical noncoronary atherosclerosis. In one large cross-sectional study that included nearly 4000 adults 40 to 54 years of age without a history of CVD or obstructive sleep apnea, those with the shortest sleep duration on seven-day actigraphy (<6 hours per night) had increased atherosclerotic

plaque burden as measured by carotid and femoral vascular ultrasound, independent of conventional CVD risk factors [https://pubmed.ncbi.nlm.nih.gov/30654884/].

In the Discussion you miss important references in the field. For instance, sleep dysfunction (of the type short sleep duration) has been associated with a variety of adverse cardiovascular outcomes and a 2016 scientific statement from the American Heart Association, such dysfunction is recognized as a risk factor for adverse cardiometabolic profiles and outcomes, and healthy sleep behavior is recommended to promote ideal cardiac health, along with efforts to address other established risk factors including blood pressure, cholesterol, diet, blood glucose, physical activity, weight, and smoking cessation (https://pubmed.ncbi.nlm.nih.gov/27647451/). In your stratified analysis (Fig.3) you have such information which you can relate.

Possible mechanisms should be mentioned. For instance, inflammation is one plausible mechanism for the observed relationship between sleep dysfunction and CVD risk. In laboratory experiments, acute sleep loss is associated with the induction of several proinflammatory markers, including C-reactive protein [https://pubmed.ncbi.nlm.nih.gov/21112025/, https://pubmed.ncbi.nlm.nih.gov/23901303/]. Even a relatively mild restriction of sleep (eg, from eight to six hours for eight days) increases the level of pro-inflammatory cytokines.

It would be interesting to discuss that dysfunction of sleep may have arrhythmogenic effects on the heart as well, although the evidence is not entirely consistent. In a large retrospective cohort study of over 31,000 adults undergoing diagnostic polysomnography, a one-hour reduction in sleep duration during PSG (used as a proxy for chronic sleep insufficiency) was associated with increased odds of both prevalent (odds ratio [OR] 1.17) and incident (OR 1.09) atrial fibrillation, independent of age, sex, body mass index, hypertension, CHD, heart failure, and sleep apnea severity [https://pubmed.ncbi.nlm.nih.gov/30825445/]. In a 2018 meta-analysis of 10 observational studies in over 14 million individuals, self-reported insomnia and frequent awakenings were risk factors for atrial fibrillation (OR 1.3 and 1.4, respectively), whereas the association between short sleep duration and atrial fibrillation was not statistically significant (OR 1.20, 95% CI 0.93-1.55) [https://pubmed.ncbi.nlm.nih.gov/29460411/]. Such mechanisms would be interesting to be discussed, despite your negative findings and acknowledgment of the possible confounder.

Conclusions: Re-write the first sentence to be clearer as follows: "Self-reported sleep dysfunction is associated with higher risk of ..."

PLEASE COMMENT

Q 4 **Is the title appropriate, concise, attractive?**

The title is appropriate, concize and attractive

Q 5 **Are the keywords appropriate?**

Yes

Q 6 **Is the English language of sufficient quality?**

Yes

Q 7 **Is the quality of the figures and tables satisfactory?**

Yes.

Q 8 Does the reference list cover the relevant literature adequately and in an unbiased manner?)

Not really, but I have pointed out to the authors some relevant resources.

QUALITY ASSESSMENT

Q 9	Originality	
Q 10	Rigor	
Q 11	Significance to the field	
Q 12	Interest to a general audience	
Q 13	Quality of the writing	
Q 14	Overall scientific quality of the study	

REVISION LEVEL

Q 15 Please make a recommendation based on your comments:

Major revisions.