Editorial

Sleep and mortality: cause, consequence, or symptom?

Epidemiologic studies of self-reported sleep and health status began to appear more than 40 years ago. However, in the last 15 years there has been an explosion of population science on the relationships between sleep quantity and quality as well as a variety of health outcomes, and the implications for public health have become apparent [1]. There is sufficient evidence to support the idea that disturbances of quantity and quality of sleep, however and wherever measured, are associated with increased likelihood of developing conditions, including neurobehavioral difficulties, obesity, hypertension, diabetes mellitus, coronary heart disease, stroke, some forms of cancer, and crucially early mortality [1]. In particular, for mortality the collective evidence from prospective population studies performed worldwide in more than 1.3 million participants, with more than 110,000 events, and over a follow-up varying from 4 to 25 years suggests the presence of a U-shaped relationship between duration of self-reported sleep and all-cause mortality; the risk is considered significantly higher by 12% and 30% in short and long sleepers, respectively [2]. The pooled estimates included multiple adjusted models from each individual study, most of them including various comorbidities. There was no publication bias but a significant heterogeneity, which could be explained for long sleep but not short sleep by age (individuals older than 60 years were at greater risk), duration of follow-up (greater risk over 10 years of follow-up), geographic locations (greater risk in East Asia), and definition of long sleep (>10 h/d being associated with the greater risk).

Observational epidemiology is unable to answer one fundamental question: is sleep a cause, a consequence, or a symptom? This is the question Sir Michael Marmot set in the opening of the book, *Sleep, Health, and Society* [1], where he clearly and succinctly explained sleep as all three (cause, consequence, and symptom) and further explained that they all can interact. Furthermore, when relying on observational epidemiology, the task of assessing causality goes beyond the exclusion of the role of chance, bias, and confounding. It relies on criteria such as strength, specificity, and consistency of the association; temporal sequence, biologic gradient, and reversibility of the effect; and biologic plausibility, coherence, and analogy [3].

In this context, the objective of the paper by Magee et al. [4] was to quantify the likely impact of residual confounding due to poor health status on the association between sleep duration and mortality using a large (>200,000 participants and >8500 events) Australian cohort. The study relied on self-reported sleep duration and self-assessed anthropometry from mailed questionnaires, preexisting illness through self-reported doctor diagnoses, and functional capacity measured with a 10-item subscale equivalent to the Short Form 36. The response rate was 18%, and a further 10% of the sample had missing values. The mean follow-up was 2.8 years, and other preexisting conditions, including depression, self-rated health, other mental health concerns, and regular use of hypnotics, were not included. In an adjusted model, the primary analysis confirmed a significantly greater mortality in both short (13%) and long (26%) sleepers, consistent with previous collective estimates [2]. However, when stratified by health status, the relationship was only present in those with poor baseline health status. The authors concluded that the study provided evidence against causal mechanisms, and they suggested that the relationship between sleep duration and mortality was due to residual confounding with poor health at baseline.

The study contributes to the current debate, and it raises more questions than it provides answers, as often is the case. The authors appropriately addressed the strengths and limitations of their approach. From one perspective large sample sizes and longitudinal approaches undoubtedly are necessary requirements in this field of research, and the present study is adequate. The authors are correct in emphasizing that researchers need to pay special attention to assess and consider preexisting health conditions and functional limitations in multivariate or stratified analyses, as they likely are confounders. However, it is unfortunate that the authors missed important known confounders in their otherwise careful approach. Some of the confounders included the presence of depression, self-rated health, other mental health concerns, and crucially the use hypnotics, which are a cause for concern, given their growing use (up to 10%) and their potential association with mortality [5].

The authors correctly acknowledged the limitations of the study. The response rate was low (18%), and beyond the lack of generalization the low response rate may conceal important self-selection bias in those with more sleep concerns. Further, those with associated ill health would be more likely to have responded to the invitation and to participate. This suspicion is corroborated in part by the results of the stratified analysis by health status. The less healthy group comprised 50% more events, with a ratio of 3:1 and 4.5:1 in the short and long sleep groups, respectively (Table 3). Finally, although not statistically significant in the healthy group, a U-shaped association was apparent in both groups (Fig. 1). Moreover, it is possible that the lack of statistical power partly contributed to these findings. Another limitation was the short follow-up of just 2.8 years. It is conceivable that any effect of short or long sleep on a final event such as death might have a long lag time. Additionally, it would be mediated through an increase of intermediate risk factors from the activation of inflammatory [6], metabolic [7], and neurohormonal processes [8]; from the development of conditions such as obesity, diabetes mellitus, hypertension, and mental health; or from the development of cardiovascular disease, cancer, or other chronic debilitating conditions

[1]. If this model were true, the short average follow-up would help to explain the current results. Moreover, the present study reported "diagnosed" preexisting conditions. This word is not synonymous to the "presence of underlying conditions", which very often are undiagnosed. Therefore, the stratified analysis does not adequately consider the potential risk for reverse causality. Customarily one would remove events in the first few years of follow-up from the analysis, hoping to remove such a risk. This analytical approach was prevented by the short mean follow-up. Sleep duration is only one of the dimensions of sleep disturbances, with quality being the other important aspect. For example, there is evidence that cardiovascular mortality mainly is greater in short sleepers, who also experience poor sleep quality [9,10]. Finally, it has been argued that a single self-reported measurement of sleep may not well represent sustained sleep patterns in an individual and that better measurements, either self-reported or objective, would increase our ability to detect more meaningful associations and interactions [11].

The question of whether or not sleep disturbances predict mortality through causal mechanisms and ensuing public health implications will have to be determined through a refinement of methods of observational epidemiology, as the question cannot be resolved using intervention trials.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.04.001.

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