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From sleep duration to mortality: implications of meta-analysis and future directions

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Although, to a large extent, the functions of sleep remain elusive, the amount of sleep that humans attain represents a health issue that has received growing attention. Over the past 60 years, accruing evidence demonstrates that self-reported short or long sleep duration (usually <6 or >8 h) is related to mortality risk. Intense interest in the sleep–mortality relationship has paralleled mounting evidence, laboratory-based and epidemiological, implicating sleep duration in a variety of health outcomes including obesity, cardiovascular disease and metabolic dysregulation. The act of sleeping, therefore, is a critical health behavior.

While there have been recent reviews of the sleep duration–mortality relationship (Colten *et al.*, 2006; Grandner and Drummond, 2007; Youngstedt and Kripke, 2004), no published work has attempted to assess the pooled effect of sleep duration on the risk of mortality. A paper in this issue by Gallicchio and Kalesan (2009) presents the first meta-analysis, and this is an important addition to the literature. Using random effects meta-analysis, the authors report that the pooled relative risk (RR) for all-cause mortality for short sleep duration was 1.10 [95% confidence interval (CI) 1.06–1.15], with cardiovascular-related RR at 1.06 (95% CI 0.94–1.30) and cancer-related RR at 0.99 (95% CI 0.88–1.13). For long sleep duration, RR for all-cause mortality was 1.23 (95% CI 1.16–1.30), with cardiovascular RR at 1.38 (95% CI 1.13–1.69) and cancer RR at 1.21 (95% CI 1.11–1.32). Thus, while short sleep carries an increased mortality risk, this is not explained by cardiovascular disease or cancer. For long sleep, the increased risk was greater and the risk associated with cancer and cardiovascular disease was also significant.

Meta-analyses of observational data, still considered controversial, permit assessment of pooled risks of relatively small magnitude but significant public health interest. Attention should be paid to important factors, including exposure definition, variability in study design and data collection, publication bias, differential consideration and treatment of confounding factors and heterogeneity. The authors do well to meet a majority of the checklist proposed by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Working Group (Stroup *et al.*, 2000). Of note, studies included in this meta-analysis varied significantly in the factors for which they adjusted. Presenting results by study design can be insightful in investigating sources of heterogeneity. Although the authors provide formal measures of heterogeneity, these are known to lack statistical power. An important consideration, therefore, would be to compare results from studies of different design, geography or time. Visual grouping of single studies of like kind permit the reader to assess raw heterogeneity. The identification of heterogeneity can be helpful in interpreting and explaining study results as well as the planning of future studies.

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The RRs in this paper may seem small, but evaluation of health issues in the general population, compared with an individual study cohort, requires a different lens – it has been asserted strongly that even small shifts in mean effects are of significant population value (Young, 2008). In addition, sleep duration may be merely a bystander – only a correlate of processes implicated in mortality. While it is unlikely that sleep does not play an important role in survival, it could be that the mortality associated with short and long sleep acts through other processes which are also related to sleep (and should be the target of study and intervention). While this may be the case, this paper at least describes short and long sleepers as easily identifiable groups who are subject to increased mortality risk. This, alone, should justify study.

Our ability to investigate the mechanisms by which sleep duration is linked to mortality risk on a population level has been hampered by limited epidemiological data. Very few, if any, of these large surveys were designed originally to evaluate sleep. Frequently, there has been only one sleep question included in these surveys (estimate of habitual sleep duration). This is not an ideal method for estimating sleep attainment, but it is often the only one available for analysis. Despite the inherent limitations of this approach, a number of studies, reviewed in the current paper, have reached a similar conclusion: too little sleep is bad for you, and too much sleep could be worse. Of note, it is encouraging to see multiple sleep items being included in more recent surveys.

The paper by Gallicchio and Kalesan (2009) makes an important contribution – data from several decades were analyzed to create a new starting point for future research. This paper puts to rest the question of whether self-reported sleep duration is associated with mortality in a U-shaped fashion; in addition, that the various populations sampled for these studies encompass multiple continents and cultures suggests that this phenomenon is a global issue.

However, what is the nature of this phenomenon? What is driving it? Most importantly, what should we do? Documentation alone is no longer sufficient; we must explore the mechanisms for this relationship so that we can hopefully begin to flatten this U-shaped curve. If we can reduce the mortality risk associated with sleep duration in a significant proportion of the population, is it possible that the deaths of millions of people may be postponed by this work? If so, a few research directions will be necessary for this to happen.

First, we believe it is important to recognize that, as others have asserted, there is a ‘tale of a two-tailed hypothesis’ regarding mortality associations with short and long sleepers (Foley, 2004). Much attention has focused upon sleep insufficiency, sending the implicit and explicit message that: ‘the more sleep the better, because we live in a sleep-deprived society’, although a more accurate prescription might be: make sure you get enough sleep, of good quality, although not too much. As with diet, the problems associated with ‘too little’ may be different from those associated with ‘too much’. Although some of the same pathways may be implicated, the path from short sleep to mortality risk is likely to be different to that for long sleep. Therefore, we need to examine these relationships separately and develop separate (although possibly overlapping) models.

Second, we need to explore possible causal mechanisms and pathways. For the long sleep–mortality association, several have been proposed recently (Grandner and Drummond, 2007): (1) sleep fragmentation, (2) fatigue, (3) immune function, (4) photoperiodic abnormalities, (5) lack of physiological challenge, (6) depression or (7) an underlying disease process such as (a) sleep apnea, (b) heart disease or (c) failing health. Regarding short sleep duration, a number of possible mechanisms have been postulated, including capitalism and a 24 × 7 society. Socioeconomic factors may play a significant role for long sleep (Hale, 2005; Patel *et al.*, 2006) as well as short sleep (Gellis *et al.*, 2005; Hale, 2005;

Stamatakis *et al.*, 2007). We must, however, be cautious in deducing relationships involving socioeconomic factors measured at one point in time, as lower socioeconomic status disadvantages many from an early age, placing them at increased risk of mortality and disease (Mackenbach and Howden-Chapman, 2003). It is plausible that the driving force behind the relationship between short sleep duration and mortality could be socioeconomic disadvantage, as those from such social strata report habitual short sleep (Hale, 2005; Lauderdale *et al.*, 2006). Other factors may also play a role. Studies report that short sleep and sleep deprivation may disrupt a number of physiological regulatory mechanisms, including those that control metabolism and cardiovascular health, which may explain the increased risk of diabetes and heart disease in short sleepers (Hall *et al.*, 2008; Knutson and Van Cauter, 2008). Finally, anxiety and depression may play a significant role, as both are associated very strongly with shortened sleep and may contribute to mortality risk. Further research needs to clarify the contributions of these factors to the relationships between mortality and both short and long sleep.

Third, research needs to address the role of individual differences regarding sleep duration preferences. We need to differentiate between natural (possibly healthy) short/long sleep and insufficient/overextended sleep. If sleep duration is to be our metric, then we must develop improved methods to measure this and then link it to functioning. It is very challenging to accept a ‘one size fits all’ approach, as sleep needs and the functional consequences thereof can be quite different; for example, 6 h of nightly sleep may be adequate for some but grossly insufficient for others. Current investigations into individual differences associated with susceptibility to sleep loss (Balkin *et al.*, 2008; Van Dongen *et al.*, 2005) are beginning to clarify this issue.

Fourth, we need to conduct community-based intervention studies to assess the effect of modifying sleep times on health outcomes and mortality. These studies should include strategies that would clarify the respective relationships between long and short sleep with mortality.

While, to a extent, these issues are outside the scope of the current paper, they are addressed. The finding that all-cause mortality is not explained completely by specific-cause mortality suggests that other mechanisms are at play. The paper also demonstrates that the pathways to mortality risk may differ between men and women. Finally, in demonstrating that this issue is a problem facing the global population, we can deduce that local factors are not solely responsible for the relationship.

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