Association Between Sleep Characteristics and Incident Dementia Accounting for Baseline Cognitive Status: A Prospective Population-Based Study

Kathleen Bokenberger,1 Peter Ström,1 Anna K. Dahl Aslan,1,2 Anna L. V. Johansson,1 Margaret Gatz,1,3 Nancy L. Pedersen,1,3 and Torbjörn Åkerstedt1,4

1Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. 2Institute of Gerontology, School of Health and Welfare, Jönköping University, Sweden. 3Department of Psychology, University of Southern California, Los Angeles. 4Stress Research Institute, Stockholm University, Sweden. 5Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden.

Address correspondence to Kathleen Bokenberger, MSc, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 17177 Stockholm, Sweden. E-mail: kathleen.bokenberger@ki.se

Received June 3, 2015; Accepted June 19, 2016

Decision Editor: Stephen Kritchevsky, PhD

Abstract

Background: Although research has shown that sleep disorders are prevalent among people with dementia, the temporal relationship is unclear. We investigated whether atypical sleep characteristics were associated with incident dementia while accounting for baseline cognitive functioning.

Methods: Screening Across the Lifespan Twin (SALT) study participants were 11,247 individuals from the Swedish Twin Registry who were at least 65 years at baseline (1998–2002). Sleep and baseline cognitive functioning were assessed via the SALT telephone screening interview. Data on dementia diagnoses came from national health registers. Cox regression was performed to estimate hazard ratios for dementia.

Results: After 17 years of follow-up, 1,850 dementia cases were identified. Short (≤6 hours) and extended (>9 hours) time in bed (TIB) compared to the middle reference group (hazard ratio = 1.40, 95% confidence interval = 1.06–1.85; hazard ratio = 1.11, 95% confidence interval = 1.00–1.24, respectively) and rising at 8:00 AM or later compared to earlier rising (hazard ratio = 1.12, 95% confidence interval = 1.01–1.24) were associated with higher dementia incidence. Bedtime, sleep quality, restorative sleep, and heavy snoring were not significant predictors. Findings stratified by baseline cognitive status indicated that the association between short TIB and dementia remained in those cognitively intact at the start.

Conclusions: Short and extended TIB and delayed rising among older adults predicted increased dementia incidence in the following 17 years. The pattern of findings suggests that extended TIB and late rising represent prodromal features whereas short TIB appeared to be a risk factor for dementia.

Keywords: Dementia—Cognitive impairment—Sleep characteristics—Prodromal sign—Risk factor

Research points to a connection between sleep abnormalities and dementia (1). Based mainly on cross-sectional studies, persons with cognitive impairment or dementia have been found to have sleep abnormalities such as extreme sleep durations (1,2), sleep disturbance or poor sleep quality (1,3,4), circadian rhythm dysregulation and delayed phase shifts (5,6), and sleep-disordered breathing (7,8). Although it is established that sleep–wake patterns often reflect physiologic changes with age or underlying neuropathological processes, there is growing attention to the idea that sleep could have a causal impact on cognitive decline and dementia susceptibility. Poor sleep quality and short sleep duration, for example, appear to induce neuropathology similar to that seen in Alzheimer’s disease such as elevated concentrations of amyloid-β in the brain (9). Prospective studies that have the potential to examine characteristics of sleep as risk factors for future dementia development are fewer in number and have yielded mixed findings.

Many recent prospective studies, most of which were based on self-reported measures of sleep, have observed extreme sleep length
to be associated with diminished cognition or dementia (1,10,11), though reports on short or long sleep duration, or both, as significant predictors were inconsistent across these studies. Other studies did not find an association (12–14). Reduced sleep quality predicted impaired cognition (10,15) and increased dementia risk (16–19) in seven prospective studies, but was not linked to cognitive decline in other studies (13,20,21). No previous study seems to have used a measure of restorative sleep (22). Sleep-disordered breathing, characterized by chronic breathing difficulties during sleep which can be indicated by snoring (23), was related to worse cognitive function (12,24,25). Circadian disturbance and risk of cognitive decline represent an understudied area, but one earlier study observed that decreased circadian activity rhythm and delayed phase rhythm were associated with poorer cognitive prognosis after 5-year follow-up (26).

Sufficient follow-up time is an important factor in epidemiologic studies examining sleep as a contributor to risk for cognitive decline and particularly for dementia, for which the most common subtype, Alzheimer’s disease, is suggested to have a preclinical phase extending for many years or even decades (27). Besides the Finnish study that followed participants for a median of 22 years (10), the follow-up period for the aforementioned prospective studies generally ranged between 1 and 10 years.

This study will add to the literature by using a longer follow-up time and by accounting for initial cognitive functioning, and by stratifying by groups with variable baseline cognitive status. This approach may clarify the relationship between sleep duration and diagnosed dementia, as well as that between sleep quality and dementia. We also add a measure of restorative sleep, based on the assumption that not being restored by sleep may be relevant in the prediction of dementia. Specifically, we hypothesized that (a) anomalous sleep characteristics predict greater dementia incidence while taking into consideration baseline cognitive functioning and (b) the association would be moderated by baseline cognitive status because those with poorer baseline status may include preclinical or early dementia cases.

Methods

Participants

This register-based cohort study included individuals who were part of the Swedish Screening Across the Lifespan Twin (SALT) study, which included all twins from the Swedish Twin Registry born in 1958 or earlier (28). Data collection for SALT occurred from March 1998 to December 2002 and was performed with a computer-assisted telephone interview that included questions about sleep as well as screening for cognitive function (28). To obtain follow-up information on dementia, the SALT cohort was linked at the individual level to national health registers using the personal identification number.

The present study included SALT participants who were 65 years or older at the time of interview (n = 12,803, response rate = 71%), as only those 65 and older were given cognitive screening and subsequent clinical dementia workup if they screened poorly. The following were excluded from analysis: persons with missing cognitive screening (n = 340); persons missing all sleep parameters (n = 125); cases of dementia that occurred prior to or at the screening interview that were identified from the patient registers (n = 49) or from the clinical dementia workup (n = 150); and those with less than 3 years of follow-up time after the SALT interview (n = 892), which included 125 dementia cases determined by patient register records. After these exclusions, altogether 11,247 participants were followed until dementia ascertainment, death, or the end of the study period (December 31, 2014). Data collection procedures were reviewed and approved by the Regional Ethics Board at Karolinska Institutet.

Sleep Measures

All sleep measures were based on items from the Karolinska Sleep Questionnaire (29) that was included within the SALT interview. Rise time and bedtime were grouped according to the 75th percentile cut point of the response distribution (rising 8:00 AM or later vs earlier rising; going to bed 11:00 PM or later vs earlier bedtime, respectively) to detect delayed sleep phase. Calculated time in bed (TIB) was assessed as the difference between the reported bedtime and rising time. TIB was categorized into three groups: ≤6 hours (short), between 6 and 9 hours (reference), and >9 hours (extended).

The sleep items included asking participants whether in the past 6 months they experienced the following: premature awakening (waking up too early in the morning), disturbed sleep, difficulties falling asleep, difficulties awakening (having trouble waking up in the morning), repeated nighttime awakenings, not feeling rested upon awakening, and heavy snoring. Response alternatives followed a five-point scale ranging from 0 (never) to 4 (always). The first three listed items as well as rise and bedtime items were given to all participants (N = 11,247 answered at least one of these seven items), whereas the other items were administered by design to a smaller sample, identified randomly, and thus had fewer responses (n = 4,716 answered all sleep items). A validated sleep quality index and restorative sleep index (29) used in sleep research previously (30) were created to capture aspects of sleep disturbance. The sleep quality index was the mean of 4 sleep items (difficulty falling asleep, disturbed sleep, repeated awakenings, and premature awakenings), and the restorative sleep index was the mean of 2 sleep items (difficulties awakening and not feeling rested upon awakening), with higher values indicating poorer or less restorative sleep, respectively. Heavy snoring (yes/no), examined as a separate parameter, was used as a marker of sleep-disordered breathing. A correlation matrix of six sleep parameters is presented in Supplementary Table S1.

Baseline Cognitive Screening

Cognitive screening administered in the SALT interview included the TELE (31), which provides a score indicating the total number of cognitive items answered correctly. If the participant performed poorly, an informant was interviewed with the Blessed Dementia Rating Scale (BDRS) (31). The TELE and the BDRS were combined into an ordinal cognitive status scale, where a score of 0 indicated no cognitive dysfunction, 1 indicated that there were minor errors, 2 indicated poor cognitive performance but no confirmation of interference with daily functioning, and 3 indicated cognitive dysfunction sufficient to interfere with daily function (32). Participants who screened positive (scored a 3 on the ordinal cognitive status scale) and their twin were referred to a clinical workup for dementia (32). Among those assigned a “3,” 46% were diagnosed with dementia based on a state-of-the-art clinical workup and hence excluded from the present study, with the balance generally having mild cognitive impairment insufficient to meet diagnostic criteria for dementia (32). The analyses used either the TELE score as a quantitative measure of baseline cognitive functioning or the ordinal categories as a measure of baseline cognitive status. For more details on the baseline cognitive screening, see Supplementary Materials.
Diagnoses of Incident Dementia

Three national registers were used to determine dementia ascertainment: the National Patient Register, which includes both inpatient and outpatient records nationwide since 1987; the Cause of Death Register, which records death dates and underlying and contributing death causes since 1952; and the Prescription Drug Register, which began in 2005, wherein individuals with a prescription for dementia medication were defined as demented cases. Dementia diagnoses were identified based on the International Classification of Disease version 10 codes.

Covariates

Covariate measures were based on self-reported data from the SALT interview. Covariates included baseline age, sex, highest educational attainment, night work status, smoking status, habitual alcohol consumption, physical exercise, body mass index, type II diabetes, sleep medication use, cancer history, depression, cardiovascular disease history, and chronic obstructive pulmonary disease (Supplementary Materials).

Statistical Analysis

Differences in baseline characteristics between dementia cases and noncases, as well as between responders and nonresponders, were compared using chi-square tests and F tests assuming equal variances. Cross-sectional associations between sleep parameters and baseline ordinal cognitive status were assessed using ordinal logistic regression with robust standard errors to estimate odds ratios (OR) with 95% confidence interval (CI), including adjustment for age, sex, and education.

Because chi-square tests and F tests do not account for confounding and are not appropriate for assessing the risk of dementia with regard to sleep characteristics, hazard ratios with 95% CI were obtained from Cox proportional-hazards regression models with robust standard errors, with age as the underlying timescale and follow-up time as a time-varying covariate. Hazard ratio point estimates may be interpreted in terms of effect size. The first Cox model was adjusted for age and follow-up time. The second model had additional adjustments for sex, education, and baseline TELE score. A comparison between responders (N = 11,247) and nonresponders (n = 125) for the sleep items showed nonresponders to be older and less educated. Nonresponders also had worse baseline cognitive status, in which 60% scored a 2 (poor cognitive performance) and 30% scored a 3 (cognitive dysfunction) on the ordinal cognitive status scale (p < .05; data not shown).

Sleep Measures and Baseline Cognitive Status

Extended TIB was significantly associated with poorer baseline cognitive status in the adjusted model (OR = 1.13, 95% CI = 1.03–1.23). Short TIB was not related to poorer cognitive status (OR = 1.24, 95% CI = 0.97–1.59). Later rise time (8:00 AM or after) and later bedtime (11:00 PM or after) were related to better baseline cognitive status (OR = 0.88, 95% CI = 0.81–0.96). The association between sleep quality and baseline cognitive status approached significance (OR = 1.05, 95% CI = 0.99–1.13). Baseline cognitive status was not associated with restorative sleep and snoring (Supplementary Table S4).

Sleep Measures and Incident Dementia

TIB exhibited a U-shaped association with incident dementia, wherein short and extended TIB were related to higher incident dementia in multivariable adjusted models (Table 1). Later rise time, but not bedtime, was related to higher dementia risk. Differences between prospective and cross-sectional findings are discussed below. Other sleep measures were not associated with incident dementia.

Table 1. Associations Between Sleep Measures and Incident Dementia Taking Into Account Baseline Cognitive Functioning, Based on Cox Regression

<table>
<thead>
<tr>
<th>Sleep Measure</th>
<th>Cases/Person-Years</th>
<th>Model* HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in bed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6 h</td>
<td>1,844/138,137</td>
<td>1.40 (1.06–1.85)</td>
</tr>
<tr>
<td>&gt;6 h</td>
<td>52/3,043</td>
<td>0.99 (0.80–1.26)</td>
</tr>
<tr>
<td>Reference</td>
<td>1,235/101,864</td>
<td>1.00</td>
</tr>
<tr>
<td>Rise time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Earlier than 8 AM</td>
<td>1,304/100,109</td>
<td>1.00</td>
</tr>
<tr>
<td>8 AM or later</td>
<td>540/38,027</td>
<td>1.12 (1.01–1.24)</td>
</tr>
<tr>
<td>Bedtime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Earlier than 11 PM</td>
<td>1,201/84,216</td>
<td>1.00</td>
</tr>
<tr>
<td>11 PM or later</td>
<td>643/53,920</td>
<td>0.99 (0.89–1.09)</td>
</tr>
<tr>
<td>Sleep quality index</td>
<td>980/66,669</td>
<td>0.93 (0.85–1.01)</td>
</tr>
<tr>
<td>Restorative sleep index</td>
<td>984/66,962</td>
<td>0.94 (0.80–1.09)</td>
</tr>
<tr>
<td>Heavy snoring</td>
<td>861/59,615</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>500/31,853</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>361/27,761</td>
<td>0.92 (0.80–1.06)</td>
</tr>
</tbody>
</table>

Notes: CI = confidence interval; HR = hazard ratio. Higher scores on the sleep quality index and restorative sleep index indicate poorer quality and less restorative sleep, respectively.

*Model is adjusted for follow-up time, sex, education, and baseline cognitive functioning (TELE score), with age as the underlying timescale, with robust standard errors.
dementia. Findings were similar (change in estimates of association were less than 10%) even in additional analyses that were adjusted for additional covariates. Sensitivity analyses based on samples with different inclusion criteria yielded similar results.

Table 2 presents results from stratified analyses examining the effect of the sleep measures on dementia rates within the four ordinal cognitive strata. Within the group with no baseline cognitive dysfunction, both short and extended TIB remained predictive of greater dementia incidence. Among those with poorest baseline cognition, extended TIB and later rising were associated with higher rates of subsequent dementia.

Lastly, a co-twin control analysis was performed that included all twin pairs as well as only MZ pairs to assess possible confounding due to familial influences (Supplementary Table S5). We did not observe any significant associations, perhaps due to inadequate sample size.

Discussion

In this population-based study prospectively examining the association of sleep-related characteristics during late adulthood and subsequent dementia up to 17 years later, higher rates of incident dementia were associated with short (≤6 hours) and extended (>9 hours) TIB as well as with rise time at 8:00 AM or later. Upon examination of the associations as a function of baseline cognitive status, short and extended TIB remained significant predictors of greater dementia risk among those cognitively intact at the start while late rise time was predictive only for the group with poorest baseline cognition. We did not find evidence of an association of increased dementia risk with bedtime, sleep quality, restorative sleep, or heavy snoring.

Cross-sectional findings showed that extended but not short TIB was associated with poorer baseline cognition. This corresponds with the prospective findings showing that the impact of extended TIB on dementia risk was more pronounced among those with poorest baseline cognition, and that short TIB was shown to be a risk factor for dementia only among those with best baseline cognition. Our prospective findings on short and extended TIB being associated with increased dementia risk are in line with previous reports from some prospective studies (1,10,11), but depart from findings in other studies (12–14). The mechanism underlying the risk conferred by short TIB may be inefficient interstitial clearance of metabolic waste associated with insufficient time asleep, resulting in higher levels of extraneuronal β-amyloid (9,33). This argument, however, does not explain the adverse effect of extended TIB. Given that the pattern of findings point to long TIB likely being a prodromal sign of dementia, it is plausible that different mechanisms underlie the link between short and long TIB with dementia. Long TIB may reflect existing neuropathological processes or be a sign of residual confounding due to comorbidity that is influencing such processes. Moreover, long sleep has been shown to be associated with impaired mobility (34) and increased mortality (35), but there have not been any studies demonstrating compelling evidence of a mechanism explaining the link between long sleep and poorer health status.

Late rise time and bedtime were associated with better baseline cognition since the cognitively intact group had the highest proportion of late risers and bedtime goers compared to the other groups with cognitive impairment. When we add dementia to the picture, the relative hazard of late versus early risers becoming demented was lowest in the baseline cognitively intact group and highest in the group with baseline dysfunction. Considering many of the late risers who converted to dementia had baseline cognitive impairment, late rising appears to be a dementia prodrome. There is a biological tendency to shift from eveningness to morningness with age, with older persons generally experiencing an internal circadian phase advance that is accompanied by a 1-hour advance in body temperature increase in the early morning due to changes in the circadian pacemaker (36). Late rising, which may imply delayed circadian rhythm, represents an atypical feature in the cognitively impaired elderly. Prior cross-sectional studies suggesting circadian timing irregularities (5), including phase-delayed circadian activity rhythm (6) in patients with Alzheimer’s disease compared to controls, support our finding of late rising as prodromal of dementia. Similarly, increased odds of mild cognitive impairment and dementia

Table 2. Associations Between Sleep Measures and Incident Dementia, Stratified by Baseline Cognitive Status

<table>
<thead>
<tr>
<th></th>
<th>Cognitively Intact</th>
<th>Minor Cognitive Problems</th>
<th>Poor Cognitive Function</th>
<th>Cognitive Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 6,568</td>
<td>n = 2,728</td>
<td>n = 1,332</td>
<td>n = 619</td>
</tr>
<tr>
<td>Time in bed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6 h</td>
<td>1.74 (1.19–2.55)</td>
<td>1.09 (0.61–1.93)</td>
<td>1.45 (0.72–2.90)</td>
<td>1.00 (0.47–2.13)</td>
</tr>
<tr>
<td>Reference</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;9 h</td>
<td>1.18 (1.01–1.38)</td>
<td>1.02 (0.83–1.25)</td>
<td>0.90 (0.71–1.16)</td>
<td>1.47 (1.08–2.00)</td>
</tr>
<tr>
<td>Rise time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Earlier than 8 AM</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>8 AM or later</td>
<td>1.05 (0.90–1.21)</td>
<td>1.13 (0.93–1.38)</td>
<td>1.10 (0.84–1.43)</td>
<td>1.59 (1.15–2.20)</td>
</tr>
<tr>
<td>Bedtime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Earlier than 11 PM</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>11 PM or later</td>
<td>0.97 (0.85–1.12)</td>
<td>1.00 (0.83–1.21)</td>
<td>0.96 (0.74–1.24)</td>
<td>1.14 (0.80–1.62)</td>
</tr>
<tr>
<td>Sleep quality index</td>
<td>0.97 (0.86–1.09)</td>
<td>0.97 (0.81–1.14)</td>
<td>0.89 (0.73–1.09)</td>
<td>0.81 (0.63–1.04)</td>
</tr>
<tr>
<td>Restorative sleep index</td>
<td>0.97 (0.78–1.20)</td>
<td>0.95 (0.70–1.28)</td>
<td>0.88 (0.60–1.28)</td>
<td>0.95 (0.56–1.39)</td>
</tr>
<tr>
<td>Heavy snoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>0.94 (0.77–1.15)</td>
<td>0.94 (0.71–1.25)</td>
<td>0.83 (0.58–1.18)</td>
<td>0.90 (0.55–1.48)</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval; HR = hazard ratio. All models adjusted for follow-up time, sex, and education with age as the underlying timescale, with robust standard errors.
development associated with delayed rhythms were observed in a cohort free of baseline cognitive impairment or dementia when there was only a short follow-up time (26). Dementia incidence did not differ based on bedtime, contrary to expectations, and warrant further exploration.

Regarding characteristics of sleep disturbance, we noted that the association between sleep quality and baseline cognitive status approached significance, which agrees with previous cross-sectional findings (3). However, sleep quality was not predictive of subsequent risk for dementia, which is in line with reports from some studies (13,20,21), but not in others (16–19). Restorative sleep and heavy snoring were also not related to greater dementia incidence in this study. As previously mentioned, nonresponders compared to responders of sleep items tended to be older, lower educated, and had poorer baseline cognitive scores. Had the study sample included individuals with poorer cognition and worse sleep behavior, we may have seen more pronounced effects. Altogether, the pattern of findings demonstrates that tendencies of older adults to stay in bed longer and rise later may reflect prodromal features, and short TIB appeared to represent a risk factor of dementia.

Strengths and Limitations

One limitation of the study is that self-reported sleep may be prone to bias; however, polysomnography, which is considered the gold standard for measuring sleep, is not easily accessible in a clinical setting, while informant questionnaires on sleep history are diagnostically pragmatic. Sleep measures and other covariates were assessed at only one occasion at baseline, which meant that the values for the variables were assumed as fixed over time in our models. As such, we were unable to measure intraindividual changes in sleep experiences across time. We note that measuring snoring via self-report is not ideal since people may be unaware that they snore (29), which may explain why heavy snoring did not predict dementia in this paper. Relatedly, self-reported bedtime may not have been optimal for detecting tendencies for delayed sleep phase. There may have been problems with reliability of data obtained from those with baseline cognitive impairment, which would result in associations biased toward the null. However, results from a sensitivity analysis based on a sample that excluded persons with severe cognitive problems did not depart from the full cohort findings. One might argue that including individuals with initial poor cognitive status in the study may undermine arguments for causality between sleep behavior and dementia. Instead of excluding those cognitively impaired at baseline, we excluded participants who developed dementia within 3 years (or within 1, 2, or 4 years in sensitivity analyses) proximal to baseline since all persons with cognitive impairment do not necessarily become dementia cases. Finally, multiple testing may have increased the probability of deriving a significant finding due to chance.

Strengths of this study include the long follow-up period of 17 years, the large study sample size, the use of a population-based prospective design utilizing registers with essentially complete follow-up and individual level data, the exclusion of persons who developed dementia soon after baseline, and the various sensitivity analyses done based on cohorts with different inclusion criteria to determine robustness of findings. Moreover, we had the possibility of adjusting for baseline cognitive function and examining if the association between sleep and subsequent dementia was dependent on baseline cognitive status.

Conclusions

Short and extended TIB (≥6 hours and >9 hours) and late rising (8:00 AM or later) among older adults predicted increased dementia incidence in the following 17 years, even when accounting for initial cognitive functioning. Upon examination of the associations by baseline cognitive status, extended TIB and late rising seemed to be prodromal, whereas short TIB appeared to be a risk factor for dementia. Future prospective studies with sufficient follow-up on rise and bedtime in relation to dementia susceptibility are needed. Recognition of patients’ sleep characteristics preceding and during the prodromal stage of dementia may allow for appropriate treatment earlier on and potentially delay cognitive impairment.

Supplementary Material

Please visit the article online at http://biomedgerontology.oxfordjournals.org/ to view supplementary material.

Funding

This work was supported by grants from the National Institute on Aging (R01-AG08724) and the Swedish Research Council for Health, Working Life and Welfare (FORTE).

Conflict of Interest

The authors have no conflicts of interest to declare.

References


