Autosomal-dominant, early-onset Alzheimer’s disease (AD) is due to mutations in the processing of the amyloid precursor protein (APP), resulting in excess production of the 42-amino acid form of the beta-amyloid peptide (Aβ1-42). However, the vast majority of sporadic, late-onset AD has no similar causative mutations, although some polymorphisms (apolipoprotein E, SORL1, and clusterin) increase the relative risk of this devastating disease [1]. It is believed that late-onset AD develops secondary to a combination of genetic, environmental, and lifestyle factors. Environmental and lifestyle risk factors that have been proposed to increase risk include midlife hypertension, diabetes or impaired insulin resistance, physical activity, obesity, head injury, socioeconomic status, and level of education. Holtzman and colleagues [2,3] have suggested, on the basis of animal and human studies demonstrating diurnal fluctuations of Aβ levels in cerebrospinal fluid (CSF), adding chronic sleep loss in midlife to this mix. This observation has implications not only for AD pathogenesis but also for the use of CSF for biomarkers in research and clinical management.

Discussion
Bateman and colleagues [2] first observed the fluctuation of both Aβ1-40 and Aβ1-42 in CSF obtained from research subjects with indwelling spinal catheters, which were sampled hourly for 36 hours. The maximum Aβ levels were two to three times the minimum values for the duration of collection. Using in vivo microdialysis, this same group further demonstrated that, in both wild-type and APP transgenic mice, there was diurnal variation in interstitial fluid (ISF) Aβ levels; peaks occurred during periods of greatest physical activity, and the variation was unrelated to light exposure. Moreover, administration of an orexin antagonist, almorexant, abolished the natural diurnal variation of Aβ whereas orexin administration significantly increased interstitial brain Aβ concentrations [3]. Recently, Huang and colleagues [4], from the same group, replicated the observation of diurnal fluctuation in young healthy subjects but found decreased CSF Aβ fluctuation in subjects with brain amyloid accumulation as ascertained by brain positron emission tomography (PET) scanning with an amyloid-binding agent. These observations are important as they have direct implications for the pathogenesis of AD. If Aβ levels in CSF and brain ISF are modulated by sleep-wake activity, then impaired circadian rhythms could cause brain Aβ accumulation and subsequently AD.

Although this is certainly a plausible hypothesis, there are some methodological and conceptual issues that need
to be addressed. In attempts to repeat this important finding, multiple groups looked at diurnal variation of CSF Aβ in humans but could not replicate the findings [5-7]. Although subject selection, the volume of CSF withdrawn, and the interval between collections could account for the lack of fluctuation in some cohorts, Li and colleagues [5] studied the effect of different intervals between CSF sampling and still did not observe diurnal fluctuation synchronous with sleep-wake cycles. In fact, continuously rising levels of Aβ have been observed in several studies, a finding that lacks a good explanation. Other studies have observed that lumbar Aβ levels are higher than ventricular levels [8,9], although this is controversial [10]. In spite of these controversies, the dynamics of Aβ within the various CSF compartments and its exchange with both ISF and blood Aβ remain important subjects of investigation.

Even if the methodological issues are clarified and the finding of diurnal variation in Aβ holds true, there is still the concern that these fluctuations are merely associated with neuronal activity in general and are not related to a specific feature of sleep. Cirrito and colleagues [11] demonstrated that Aβ levels are modulated by neuronal activity, and hence it is plausible that these levels fluctuate with sleep-wake cycles. It is well known that, as we age, sleep gets fragmented and as the circadian rhythm desynchronizes this is exaggerated in several neurodegenerative disorders, including Huntington's disease, Parkinson's disease, and AD [12]. This could explain the recent findings of Bateman and colleagues [2] of significantly depressed fluctuations in older normal adults and patients with AD. While sleep abnormalities are frequent in moderate to late AD, it is not known whether these changes play a role in the pathogenesis of the disease. The circadian rhythm, including the maintenance of sleep and wakefulness, involves a complex network with multiple nuclei and neurotransmitter systems. It is conceivable that the normal circadian rhythm is a marker for general integrity of brain networks and that any pathologic process that affects this intricate network causes disruption of circadian patterns. Sleep abnormalities are detected in patients with synucleinopathies (rapid-eye-movement behavior disorder) and schizophrenia, sometimes decades before the manifestation of the disease [13,14]. In these disorders at least, it is believed that the sleep dysfunction is just an early preclinical biomarker rather than a cause of the disease. Similarly, it is likely that disrupted circadian patterns could be a preclinical marker for AD. In addition, one might expect a lower prevalence of AD pathology in patients with narcolepsy, which is characterized by low or absent levels of orexin. Postmortem neuropathologic assessment in a small sample of patients with narcolepsy did not show evidence of a lower prevalence of AD pathology [15].

Summary
While the data suggesting a causative rather than an associative link between sleep loss and amyloid accumulation are tantalizing, further confirmation of this finding is needed. Prospective cohorts including CSF biomarkers and sleep studies are under way and will help clarify this important observation.

Abbreviations
Aβ, beta-amyloid peptide; AD, Alzheimer's disease; CSF, cerebrospinal fluid; ISF, interstitial fluid.

Competing interests
The authors declare that they have no competing interests.

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