Good night, sleep tight.

Inés García-Lunar[1,2,3], MD PhD; Valentín Fuster[1,5], MD PhD, and Borja Ibanez*[1,2,5], MD PhD;

[1]Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain.
[2]CIBER de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain
[3]Cardiology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain
[4]Icahn School of Medicine at Mount Sinai, New York, USA
[5]Cardiology Dpt, IIS-Fundación Jiménez Díaz University Hospital, Madrid, Spain

*Correspondence to:
Borja Ibanez MD PhD. Clinical Research Director Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC). C/Melchor Fernández Almagro 3. 28029, Madrid, Spain. Tel. 003491 4531200. Fax. 003491 4531240. Email: bibanez@cnic.es

Sweet dreams are made of this, who am I to disagree?
-Annie Lennox and Dave Stewart (1983)-

Human beings spend a substantial fraction (around one third) of their life sleeping and sleep deprivation in some animal species ultimately leads to death. However, it remains largely unknown exactly why sleep is such an essential process for living beings.[1] The normal sleep architecture in humans is characterized by repetitive passage through a specific pattern of sleep cycles, i.e. non-rapid eye movement (NREM) or slow-wave sleep stages I-III followed by rapid eye movement (REM) sleep. Healthy sleep is defined by sufficient sleep duration and quality (usually defined as repetition of 5-7 sleep cycles per night).[2] Historically, there has been a progressive trend towards a reduction in sleeping time over the years. In the US, 21.6% of adults reported sleeping <7 hours/day in 1977 compared with 29.1% in 2009.[3] There are 2 widely recognized reasons why individuals sleep less than recommended: First, sleep time reduction may be a result of a personal decision to comply with personal, professional or social commitments. This profile might additionally be linked to other unhealthy lifestyle habits (psychosocial stress, unbalanced diet, smoking, physical inactivity, electronic device abuse and sedentarism among others). The second cause is the presence of a sleep disorder, such as insomnia (present in 10-15% of the general population) or a sleep-disordered breathing. Among the latter, the most common is obstructive sleep apnea (OSA) with an estimated prevalence of 20-30% in middle-aged adults. OSA is caused by a repeated narrowing of the upper airway during sleep and requires by definition (and in contrast to central sleep apnea [CSA]) a compensatory increase in breathing effort, which is usually assessed using a thoracoabdominal belt.[3,4] Other more infrequent sleep disorders include periodic limb movement and restless leg syndrome.

There is growing evidence linking sleep duration with various medical conditions, namely cardiovascular (CV) risk factors (obesity, hypertension and diabetes mellitus) as well as several cardiovascular diseases (CVD) (pulmonary hypertension, coronary artery disease and arrhythmia) and clinical events.[2] Evidence derived from subjective sleep metrics suggests that the association between sleep duration and CV events follows a J-shaped pattern, since not only short times (<6-7 hours/night) but also excessive sleeping times (>8-9 hours/night) have been linked to increased CV morbidity and mortality.[3,5] However, when measured objectively, only short (but not long) sleep duration has been associated with an increased CVD risk.[2] On top of sleep duration, sleep quality has also been linked to worse CV risk profile and outcomes.[2,3] In the Progression of Early Subclinical Atherosclerosis (PESA) study, (objectively measured) sleep duration and fragmentation were associated with the presence and extension of subclinical atherosclerosis independently of CV risk factors and OSA risk in a middle-aged (mean 46 yo) apparently healthy individuals.[6] More recently, sleep regularity (defined as the day-to-day variability in sleep

duration or time of sleep onset) has been also associated with an increased rate of CVD events in the Multi-Ethnic Study of Atherosclerosis (MESA) population.[7] In OSA patients, treatment with nocturnal continuous positive airway pressure (CPAP) has shown positive results on daytime tiredness and quality of life. However, recent randomized controlled trials in patients with prior CVD or acute coronary syndrome have failed to demonstrate a benefit of CPAP treatment in terms of CV events reduction.[8,9]

The study by Shahrbabaki et al in this issue of European Heart Journal[10] analyzes the prognostic value of sleep fragmentation in three large cohort studies (8000 participants in total, mean age 64-83 years, 38% female), the Osteoporotic Fractures in Men Study (MrOS), the Study of Osteoporotic Fractures (SOF) and the Sleep Heart Health Study (SHHS). Taken together, this constitutes a population at intermediate to high risk for CVD (40-50% of patients were overweight, 40-60% had hypertension, 8-17% had history of coronary artery disease/myocardial infarction and 5-16% prior stroke). The nocturnal arousal burden (measured by in-home overnight polysomnography) was then calculated as the cumulative duration of all arousal events relative to the total sleeping time. Global and CV mortality were evaluated using different standardized protocols across the 3 studies. The authors found that female participants on the fourth quartile (Q4) of arousal burden presented consistently with significantly increased rates of CV as well as all-cause mortality over a 6.5-11 year follow-up. This association between nocturnal arousal burden and (overall and CV) mortality was less clear for men with varying significance across the cohorts. The sex differences in the association between sleep patterns and CVD/adverse events is a controversial matter. In a report from the CARDIA (Coronary Artery Risk Development in Young Adults) study, sleep duration was inversely associated with carotid intima-media thickness in men, but not in women.[11] Conversely, in the study undertaken in the PESA cohort, Domínguez et al. reported that the association between sleep duration and plaque burden was stronger in women than in men.[6] The latter finding is in agreement with data presented in this issue by Shahrbabaki and colleagues.[10]

One major strength of the current study is the use of polysomnography that allows for objective sleep time and fragmentation measurement. By contrast, most of the existing population-based studies have used self-reported sleep parameters that have an inconsistent correlation with polysomnography or actigraphic sleep measurements.[4]

Among others, two very interesting findings from the study by Shahrbabaki et al remain to be further explored from a mechanistic point of view: First, what is the reason for the varying impact of arousal burden on adverse events in men and women; and second, why participants in the Q2 (and not Q1) of arousal burden consistently present lower mortality rates across the 3 cohorts.

One limitation to this and most of the existing studies addressing the effect of sleep patterns on clinical outcomes is the observational nature of the examinations, that allows evaluation for association but not causality. Indeed, in the present study, subjects on the Q4 of arousal burden presented a higher prevalence of conventional CV risk factors, prior CVD and increased apnea-hypopnea index compared to Q1-Q3 participants. Despite extensive adjustment for factors potentially influencing clinical outcomes, the presence of residual confounders cannot be fully excluded. A number of pathophysiological mechanisms have been reported to occur under short sleep conditions (such as sympathetic overactivation, inflammation, oxidative stress, endothelial dysfunction, insulin resistance and prothrombotic state).[4] One mechanism potentially explaining the association between sleep fragmentation and mortality is circadian rhythm disruption or misalignment, that has been found to affect leukocyte and lipid supply into the circulation and to alter cellular behavior in atherosclerotic lesions.[12] To overcome the difficulties to address causal inference, a prior study used Mendelian randomization analysis to confirm the causal relationship between short sleep duration and a higher risk of incident myocardial infarction.[13] Precisely, the increased presence and extension of subclinical atherosclerosis in participants with the shortest and most fragmented sleep in the PESA study[6] may explain the higher incidence of clinical CVD events thereafter (Figure).[5,7,10]

Even though many knowledge gaps on the relationship between sleep and CVD remain to be studied in the coming years, this study provides solid evidence supporting the importance of sleep quality for a better CV health. Further evidence combining comprehensive sleep evaluation with biological sampling and long-term follow-ups will be desirable. From this standpoint, as a part of the PESA study follow-up (http://www.estudiopesa.org/en/index.php), the approximately 4000 participants constituting this CV cohort will undergo a cardiorespiratory polysomnography in the next 3 years to clarify the longitudinal associations between sleep patterns, CV risk factors, subclinical atherosclerosis, biological mediators and incident CV events.

In summary, cumulative evidence shows that sleep quality (duration and fragmentation) is associated with adverse cardiovascular events. What remains to be determined is whether an intervention aiming at improving sleep quality is able to reduce the incidence of CV events and mortality. While awaiting these trials, we wish you sweet dreams.

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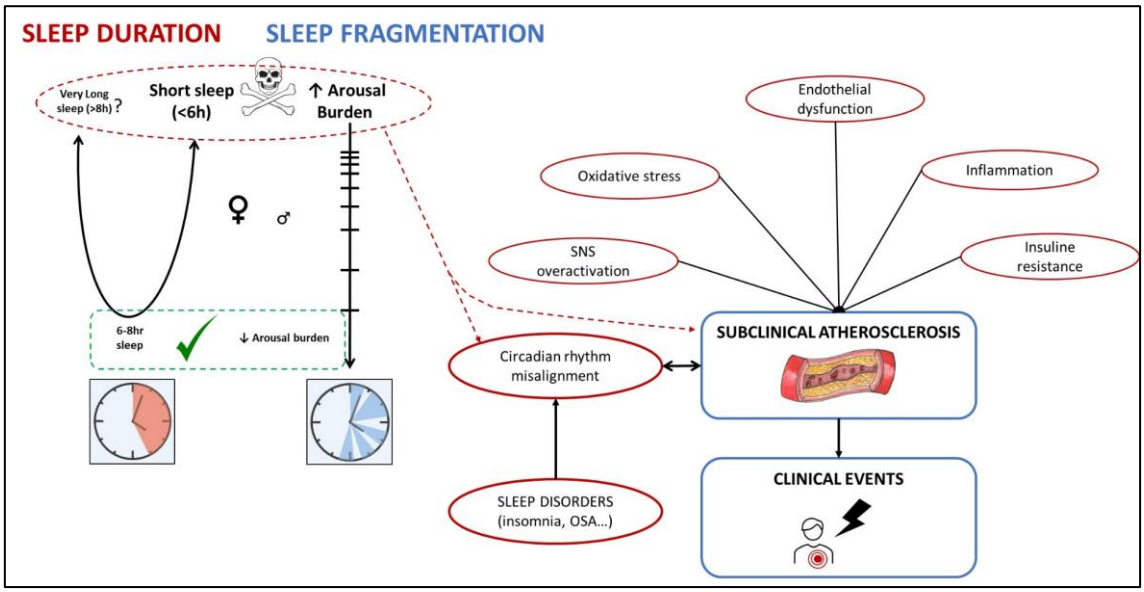
Figure: Potential mechanisms driving the association between sleep duration and fragmentation with incident CVD events.



OSA: Obstructive sleep apnea; SNS: Sympathetic nervous system.