HHS Public Access

Author manuscript

Curr Sleep Med Rep. Author manuscript; available in PMC 2020 December 18.

Published in final edited form as:

Curr Sleep Med Rep. 2019 December ; 5(4): 234–242. doi:10.1007/s40675-019-00157-8.

Short Sleep, Insomnia, and Cardiovascular Disease

Caleb G. Hsieh, MD, MS [Sleep Medicine Fellow],
University of California, Los Angeles

Jennifer L. Martin, PhD* **[Professor of Medicine]**
VA Greater Los Angeles Healthcare System, University of California, Los Angeles, 16111 Plummer St #200, North Hills, CA 91343

Abstract

Purpose of Review: This review summarizes key findings linking insomnia, short sleep duration, and cardiovascular health.

Recent Findings: Early studies associations between insomnia with short sleep and cardiovascular disease Recent studies have incorporated objective data to assess sleep and identify comorbid sleep disorders (e.g. sleep apnea). Use of objective metrics has facilitated understanding of the impacts of insufficient sleep on autonomic dysregulation, metabolic syndrome, coronary artery disease and overall cardiovascular mortality. Emerging research suggests treatment of insomnia (CBT-I) may be beneficial in terms of reducing cardiovascular disease risk.

Summary: From short term effects on the autonomic nervous system to lasting effects on metabolic syndrome and coronary artery disease, there is growing evidence to support a physiologic pathway by which insomnia with short sleep contributes to cardiovascular disease. More research is needed to understand the effect of insomnia treatment on cardiovascular risk.

Keywords

Insomnia; Short Sleep; Cardiovascular disease; Insomnia; CVD risk

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the United States and worldwide[1], and via one of its many potential manifestations, affects nearly half of all adults over the age of 20 in the US and costs an estimated $351.2 billion annually.[2] These figures are projected to continue rising over time.[2] In recognition of the enormous impact that sleep disturbance has on health, and the ongoing need to address such modifiable risk factors

*Corresponding Author: Jennifer.martin@va.gov.

Conflict of interest
Caleb G. Hsieh declares no conflicts of interest.

Human and Animal Rights Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors

early, the American Heart Association has added a category for “sleep” to its list of core health behaviors and health factors that contribute to cardiovascular health.[2]

Over one-third of Americans report inadequate sleep or regular sleep disturbance.[3] That number is projected to grow as work habits and lifestyles change.[4] In the modern era, the average individual faces an increasing number of daily challenges and potential threats to maintaining healthy sleep. From increasing demands and stressors in the work place,[5,6] to increasing distraction and blue-light disturbance from pervasive electronic devices,[7,8] “poor sleep” is an escalating burden on health and society.[9,10] In this review, we aim to define components of sleep specifically related to insomnia and short sleep duration and to summarize the emerging evidence and pathways through which insomnia and short sleep duration may contribute to cardiovascular disease.

Terminology for Describing Insufficient and Poor-Quality Sleep

When describing “poor sleep”, the umbrella phrase “sleep disturbance” can refer to any number of a heterogeneous components of disease. While sleep-disordered breathing (e.g. obstructive sleep apnea, central sleep apnea) is a crucial component to sleep disturbance, there is emerging evidence that other sleep-related disturbances are worthy of consideration as well. One challenge in drawing conclusions from the many studies on short sleep duration and insomnia may be attributed to inconsistencies in how insomnia and short sleep duration are defined and measured across studies.

In 2013 and 2014, the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) and the International Classification of Sleep Disorders, third edition (ICSD-3) respectively released updated criteria for the diagnosis of insomnia disorder.[11,12] In both nosologies, a diagnosis of chronic insomnia disorder requires dissatisfying sleep (i.e., difficulty initiating, maintaining, or early awakening) that occurs at least 3 nights per week, for at least 3 months. The sleep disruption must be sufficiently severe to cause significant functional impairment or distress. Current classifications also note that insomnia disorder should not be diagnosed if another sleep-wake disorder, substance abuse, comorbid psychiatric illness or medical illness fully explain the sleep complaint;[11,12] however, it is notable that insomnia disorder can still be diagnosed in the context of comorbid conditions. These changes lengthened the time period required for diagnosis (from 1 month to 3 months) and allowed for easier diagnosis of insomnia in the context of comorbid conditions, and this may alter estimates of prevalence and morbidity.

“Short sleep” has been defined by most epidemiological studies as a habitual sleep duration of less than 6 hours.[13] That said, the 2015 American Academy of Sleep Medicine (AASM) and Sleep Research Society (SRS) guidelines jointly recommend at least 7 hours of sleep per night for adults 18 to 65 years of age to “promote optimal health”.[14] This is similar to the recommendation of 7 to 9 hours from the National Sleep Foundation.[15] In addition to this minor terminological difference, there have also been various methodological heterogeneities with regards to how sleep duration and quality are measured. Large epidemiologic studies generally utilize subjective quantification via recall-based questionnaires. Some studies have used daily sleep diaries to compute sleep duration. Although subjective reports are less resource intensive, there may be more susceptibility to

reporting biases. Objective measures of sleep duration (e.g. at-home actigraphy or in-lab polysomnogram (PSG)) are more resource intensive and generally limited to smaller cohorts, although these approaches have the advantages of measuring actual sleep time and are not subject to recall biases. Few studies to date have utilized or compared both subjective and objective measurements,[13,16,17] and more research on meaningful discrepancies between self-reported and objectively measured sleep duration is needed.

Within the subset of individuals habitually sleeping less than 6–7 hours a night, there are also some without the sleep insufficiency, dissatisfaction, or functional impairments characteristic of insomnia disorder. These individuals may represent outliers on the spectrum of typical sleep duration and can be difficult to identify in epidemiologic studies due to the lack of symptoms. Conversely, there are also individuals with insomnia that do not necessarily experience short sleep. Combining both subjective and objective elements, Vgontzas and colleagues studying the Penn state cohort were better able to identify the compound effects of insomnia and short sleep duration on medical morbidity and mortality, with findings having since been replicated in several other studies.[16,18–22]

INSOMNIA, SLEEP AND CARDIOVASCULAR DISEASE

Insomnia, Short Sleep and Autonomic Dysregulation

Autonomic dysregulation in insomnia has been implicated in the initiation and propagation of sleep disturbance associated CVD (see Figure 1). Increases in sympathetic tone and decreases in parasympathetic tone portend overall increases in cardiovascular risk.[23] Heart rate variability (HRV) is a complex surrogate for autonomic tone and sympatho-vagal balance that measures the variance of time intervals between consecutive heart beats.[24,25] Fourier transform can be used to convert this information into a frequency spectrum with the high- frequency (HF) domain HRV reflecting vagal activity. Higher HF power indicates increased parasympathetic influence. HF power may often be greater at night and lower during the day. Interpretation of low-frequency HRV remains controversial.[24,25] Although well-accepted in the cardiology literature, use of HRV in studies of sleep insufficiency or sleep disorders has been relatively limited with mixed results.[26]

Grimaldi et al. subjected a small cohort of 26 young, healthy volunteers aged 20–39 years to sleep deprivation and circadian disruption. Participants had normal baseline sleep behavior and schedules as confirmed by baseline PSG and actigraphy. They were then subjected to 3 days of 10-hours bedtimes (22:00h – 08:00h), followed by 8 days with 5-hour bedtimes. The circadian-alignment group slept from 00:30h – 05:30h on all 8 days, while the circadian misalignment group slept from 09:00h −14:00h on days 2,3,5 and 6 and 00:30h – 05:30h on remaining days. HRV and urinary norepinephrine (NE) were measured at regular intervals. They found that the combination of short sleep and circadian misalignment significantly increased urinary NE and decreased HRV, suggesting increased sympathetic and decreased parasympathetic tone.[27] This was similar to earlier studies by Takase et al.[28]

As part of the Multi-Ethnic Study of Atherosclerosis (MESA), Castro-Diehl et al. performed a cross-sectional analysis of baseline HRV and HRV response to additional mental and physical stress challenges. Sleep duration was assessed with 7-day actigraphy manually

adjusted based on data from sleep diaries; Sleep quality was assessed via Women's health initiative insomnia rating scale; and sleep disordered breathing was screened for via 1-night home polysomnogram. With regard to the combined effect of short sleep and insomnia, the authors found greater high-frequency HRV reactivity in response to stress thus implicating higher sympathetic and lower parasympathetic tone.[29]

With regard to chronic insomnia, Jarrin et al. separated a small cross-sectional cohort of 180 patients by objective sleep duration as measured by a 3-night PSG and subjective sleep duration as measured by a 14-day sleep diary, and found that objective short sleepers had dampened parasympathetic activation compared to the near normal sleep duration cohort. Interestingly, there was no significant difference when subjective sleep duration was analyzed.[30]

As a separate measure of autonomic function, systolic blood pressure (SBP) generally decreases by approximately 10% during sleep, a phenomenon referred to as "dipping." Lanfranchi et al compared 13 patient with chronic insomnia to normal sleeping controls and found that self-reported chronic insomniacs had blunted SBP dipping, higher nighttime SBP, and overall higher average 24-hour SBP compared to "good sleepers".[31] Similar to non-dipping HR profiles, elevated nighttime SBP and non-dipping blood pressure may be associated with increased cardiovascular risk[31–33]

Insomnia, Short Sleep and Atrial Fibrillation

Until recently, the effects of insomnia and sleep duration on atrial fibrillation (AF) were largely overshadowed by the association between sleep apnea and AF.[34] Analysis of approximately 18,755 physicians from the Physicians' Health Study found that while self-reported sleep duration of ≤6 hours was associated with higher incidence of AF; however, this effect was nullified when accounting for concomitant sleep apnea.[35] Similarly, Kwon et al. evaluated 2,048 individuals in the MESA cohort with objectively measured sleep duration via actigraphy and found no association between sleep duration and AF.[36] These studies used self- reported sleep duration; however, Genuardi et al. reviewed 31,079 diagnostic polysomnograms and found that every 1-hour decrement in total sleep time was associated with 1.17-fold increased odds for prevalence of AF, and a 1.09-fold increased odds of incidence AF. These associations held even when controlling for SDB.[37] This suggests a relationship between objective sleep time, but not reported sleep time, and AF.

To further evaluate the link between sleep quality and AF independent of SDB, Christensen et al. analyzed cross-sectional data on 4,553 participants in the Health eHeart cohort, longitudinal data from 5,703 participants in the Cardiovascular Health Study (CHS) and clinical data from over 14 million patients in the California HCUP databases. Even after controlling for SDB, they found that longer sleep onset latency and more frequent nighttime awakening were independently associated with prevalent AF in the Health eHeart cohort; frequent nighttime awakening, early morning awakening and decreased REM sleep were associated with increased incident AF in CHS; and a diagnosis of insomnia predicted subsequent diagnosis of AF in clinical settings.[38]

Mechanistically, while the MESA cohort analysis had found a protective effect from increased stage N3 or slow wave sleep time,[36] and analysis of the CHS suggested a protective effect from REM sleep,[38] Genuardi et al. suggest that all stages of sleep were protective.[37]

Insomnia, Short Sleep and Metabolic Syndrome

Hypertension, diabetes, dyslipidemia and obesity are a set of interrelated metabolic disorders that directly promote and increase the risk for cardiovascular disease.[39] While metabolic syndrome is largely influenced by known factors such as genetics, nutrition, physical activity, and more recently, SDB,[40] the role of insomnia and short sleep independent of SDB is not as established.

In short-term laboratory settings, pathophysiologic studies have suggested a mechanistic foundation for an association between short sleep and metabolic syndrome. In animal models used to simulate shift work, circadian misalignment and disruption of normal circadian activity shifted energy homeostasis towards increased feeding, impaired glucose metabolism and obesity.[41] Indeed, similar findings have been demonstrated in human studies.[42] Experimental sleep restriction has been shown to cause hormonal imbalance - decreases in the satiety hormone (Leptin) and increases in the appetite stimulating hormone (Ghrelin) - and inflammatory cascade[43,44] resulting in increased appetite[45,46] and increased insulin resistance.[47]

Longitudinally, a number of meta-analyses have found increased risk for metabolic syndrome among individuals with self-reported short sleep,[48–51] but lack of consideration of SDB and insomnia led Fernandez-Mendoza et al. to analyze the effects of objective short sleep duration amongst individuals within the Penn State Cohort with and without metabolic syndrome. After a mean follow up 16.7 years, the authors found that while differences in mortality among normal (>6h) sleepers with and without metabolic syndrome was essentially negligible, objective short sleepers with metabolic syndrome had a 2-fold increased mortality risk compared to short sleepers without metabolic syndrome. This was largely driven by patients with diabetes and/or hypertension.[52] Thus, in addition to potentially contributing towards development of metabolic syndrome, short sleep may also modify amplify mortality risk.

Insomnia, Short Sleep and Hypertension

An association between insomnia, short sleep and hypertension has been reported for decades, but there remains a significant element of confounding from comorbidities, inconsistent definitions, and study heterogeneity that has limited the interpretation and application of this information. In a thorough systematic analysis and review on this subject, Jarrin et al.[53] found significant heterogeneity across 64 studies in term of definitions for insomnia (e.g. DSM, ICSD, or ICD), subdivisions of insomnia (i.e. onset, maintenance, or early morning awakening), measurement of insomnia (i.e. subjective vs objective), measurements of hypertension (e.g. self-report, physician report, ambulatory monitoring), duration of study, and direction of proposed causality.[53] In a meta-analysis of 11 studies including nearly 60,000 patients and mean follow up of 5.5 years for sleep duration analysis

and 8.2 years for insomnia analysis, Mong et al. found that studies used a mix of subjective and objective sleep duration measurements, subjective and objective hypertension measurements and varying degrees of control for confounding factors. The overall relative risk for short sleep was 1.21 (1.05 – 1.40). There were no statistically significant differences within the various subgroup analyses, however the authors did note that shorter follow-up durations, adjustment for psychological factors, self-reported blood pressures and self-reported sleep durations contributed to a lack of significant findings across studies.[54]

Another large meta-analysis by Wang et al. included data from 13 cross-sectional studies (some overlap with Meng et al.), with approximately 350,000 participants. Adjusting for age and gender, the authors stratified sleep duration by <5h, 6h, 7h, 8h and >9g, and found a U-shaped distribution for the pooled odds ratios for hypertension. Sleep duration of <5h was highest risk for hypertension. In their subgroup analyses, they found that association between shorter sleep and hypertension was stronger for women and weaker for elderly patients. It was also noted that they did not control for sleep disordered breathing or additional comorbidities.[55]

In view of the challenges presented by the above large-scale meta-analyses and reviews, it is worth noting a few studies attempting to address these issues. Fernandez- Mendoza and Vgontzas were among the first to use objective short sleep duration in the study of insomnia and hypertension.[56] In a repeat analysis, 1,741 patients with objectively measured short sleep based on single overnight PSG and mean follow-up of 15.5 years, they found a dose-response pattern with increasing risk of hypertension (and mortality) corresponding to decreased objective duration of sleep.[57] Notable limitations, however, included an oversampling of SDB patients, and lack of consecutive nightly recordings. Thus, Ramos et al. performed a cross sectional study evaluating 2,148 patients who underwent one full week of wrist actigraphy. After accounting for SDB (defined as AHI > 15), there was no significant association between total sleep duration, reported insomnia severity and hypertension; however, patients with hypertension did have significantly increased sleep fragmentation and decreased sleep efficiency compared to those without hypertension.[58] Finally, in an attempt to minimize contribution from covariates, authors of the HUNT-3 trial conducted a large (approximately 50,000) epidemiological study and multivariate analysis adjusting for sociodemographic and lifestyle factors (e.g. physical activity, chronic pain, depression and anxiety), established CVD risk factors (e.g. diabetes an hyperlipidemia) and SDB.[59] In contrast to prior studies, there was a small inverse association between insomnia symptoms and blood pressure which, authors concluded was of limited clinical significance after adjustment for covariates.[59]

From a mechanistic perspective, it has been noted that decreased stage N3 or slow wave sleep may be associated with increased incidence of hypertension.[60,61] Analysis of data from the Sleep Heart Health Study suggested that this association persists even after controlling for SDB, sleep duration, and fragmented sleep.[60] This may be due to increases in parasympathetic activity during slow wave sleep that may be protective and lead to sustained lower blood pressures. That said, if increased total duration of all stages of sleep can be protective with regards to AF,[37] this may also be true for hypertension.

In summary, while strong association between insomnia with short sleep duration and hypertension has been implicated by many cross sectional and prospective studies, the interpretation and implications of these studies is somewhat limited. Future studies would benefit from thorough exclusion of SDB, the use of more objective sleep parameters and blood pressure measurements over longer follow-up periods, and more systematic control of covariates.

Insomnia, Short Sleep, Coronary Artery Disease and Mortality

If insomnia and short sleep does indeed increase risk for autonomic dysfunction, hypertension and metabolic dysregulation as above (see Figure 1), one might expect an association with coronary artery disease, and by corollary, mortality. Early studies focusing on sleep duration alone showed mixed results, which prompted Chandola et al. to evaluate the additive effects of short sleep and "sleep disturbance" in the Whitehall II Cohort – a prospective study of >10,000 individuals with a mean follow up of 15 years.[62] Although SDB was not evaluated, the authors point to a prevalence of 14–21% for sleep disturbance in their study compared to up to 1.5% for OSA in their local population. Even after adjusting for hypertension, diabetes and other potential confounders, short sleep and sleep disturbance contributed to a significantly elevated risk of CAD (HR 1.45, 1.24–1.70).[62]

In the HUNT study cohort, Laugsand et al.[63] separated symptoms of insomnia into difficulty initiating sleep, difficulty maintaining sleep and non-restorative sleep and found a dose dependent relationship between insomnia symptoms and relative risk for acute myocardial infarction. The risk was most notable for those with difficulty initiating sleep and was more pronounced if patients using sleep aids were excluded. Data on mortality was not collected in this study.

In the Sleep Heart Health Study, Bertisch et al.[18] re-produced similar results in a slightly older population (mean age: 64.±11.1 years) of ˜4500 individuals with objectively measured sleep duration and self-reported difficulty initiating sleep, difficulty maintaining sleep, or early morning awakening. In regard to incident CVD (including CVA), neither insomnia nor short sleep alone increased risk of events; however in combination, there was a dose-dependent response with a 29% increase in events (HR 1.29, 1.00–1.66) for <6h and 52% increase (HR 1.52, 1.08–2.14) for <5h. Interestingly, in the mortality analysis, while short sleep alone conferred a modest increased risk of all-cause mortality, insomnia with short sleep did not.[18] This is in contrast to earlier findings from the Penn State Cohort,[64] which noted an increased mortality in men. Authors of both studies suggest that the increased mortality in men within Penn State Cohort may be attributable to an increase in baseline diabetes prevalence (21% in men vs. 8% in women) as the odds ratio was not significant after accounting for diabetes and hypertension[18,64].

In a recent epidemiological study of the Women's Health Initiative Cohort, which incorporated self-reported and subjective measures of sleep duration and insomnia from >150,000 women over a median of 17.8 years, Kabat et al. found that short sleep duration (>5h) was associated with increased CVD related mortality regardless of concomitant insomnia. In fact, the authors reported that insomnia had a small inverse effect on mortality. That said, in addition to the lack of objective sleep measurement, a couple notable

limitations to these findings are that the use of sleep medications or alcohol (i.e. sleep aids) – which did confer an increased mortality risk – was separated from insomnia and that there was no adjustment or information with regards to existing SDB.

Despite using non-standard criteria for insomnia, the above studies suggest that insomnia or sleep disturbance coupled with short sleep duration likely increases the risk for CAD and CVD. The somewhat paradoxical finding that sleep duration alone confers increased risk for CVD mortality, but not necessarily CVD itself supports results published by Cappuccio et al. in a prior meta-analysis.[65] In addition to more objective and standardized assessment of sleep duration and disturbance, the above findings suggest that future studies should attempt to better elucidate the compounding effects of insomnia on CVD-related mortality, better assess the role and effect of sleep medications, and potentially reassess the modifying effects of gender.

TREATMENT OF INSOMNIA AND EFFECTS ON CVD

Beyond interventions that address comorbidities (e.g. treatment of depression/anxiety, encouraging diet and exercise), current therapeutic modalities aimed directly at insomnia and sleep duration utilize cognitive behavioral therapy for insomnia (CBTI), hypnotics, or some combination of the two. While these interventions can be effective in improving sleep iteslf,[66] given the wide array of conditions that contribute to insomnia and short sleep duration and the bidirectional nature of their respective relationships, the end effect of insomnia treatment on cardiovascular risk remains uncertain.

CBTI remains the first-line treatment for chronic insomnia disorder.[67] In 2015, Conley and Redeker revised studies aimed at determining the effect of CBTI on CVD as reviewed by in 2015,[68] and additional work has been published after their review. Jarrin et al. conducted a secondary analysis of a 6 week CBTI program on nocturnal HRV in a cohort of 65 patients with chronic insomnia (based on DSM-IV criteria), excluding individuals with comorbid SDB.[69] Participants kept 2-week sleep diaries and had both pre- and post- intervention PSGs. Contrary to what the authors expected, patients with improved sleep onset latency had reduced HF HRV suggesting less parasympathetic activity. That said, authors acknowledged the small sample size and lack of a control group.[70]

In the Sleep to Lower Elevated blood Pressure trial (SLEPT), McGrath et al[71] conducted a randomized, investigator-blinded trial evaluating the effects of an 8-week self-guided internet- based sleep hygiene and CBTI program on 24-hour ambulatory systolic blood pressure. Volunteers had baseline systolic blood pressure between 130–160 mmHg (mean 141 mmHg), were on one or fewer medications for blood pressure and had self-reported sleeping difficulties. Those with prior sleep-related diagnoses were excluded. Of 67 patients randomized to receive the online intervention, only 58 registered, and of those, only 29 patients completed all sessions. Those that completed the intervention had improved subjective measures of sleep, but no significant difference in blood pressure. Additional studies on this topic are underway.[72]

Finally, Redeker et al.[73] published a pilot randomized control trial evaluating the effect of CBTI on autonomic function and hypothalamic-pituitary axis (as measured by urinary biomarkers) among patients with existing heart failure. Patients with untreated sleep-disordered breathing were excluded. The authors note that while this small pilot study was not powered to detect an effect of CBTI on biomarkers, there were trends for improvements in sleep disturbance, objective sleep characteristics, and biomarkers which may be evaluated in future studies.

SHIFT WORK AND SLEEP DURATION:

Some forms of behaviorally-induced sleep disturbances are more readily identifiable, likely to increase in prevalence, and thus deserve special mention. One seldom discussed cause of insufficient sleep is shift work. The rise of the “24/7 economy” has increased the length of the average working day and the prevalence of so-called “shift workers” whose often dis-circadian work schedules are associated with increased morbidity.[5,74–76]

Data from the Nurses’ Health Study published in 2016 and collected over 24 years found that >5 years of rotating night shift work was associated with an approximately 12% increased risk of CVD. In subgroup analyses, CVD risk decreased after cessation of night shift work, while longer spans of night shift work (5–9 years and >10 years) further increased risks (19% and 27% respectively).[77] Ongoing research on the effects of shift work aims to identify factors that may help predict an individuals’ vulnerability to shift work sleep disturbance or shift work tolerance.[78]

CONCLUSION

The link between insomnia, short sleep and CVD is complex and multidirectional. The relationship remains challenging to study and isolate from comorbid medical, psychiatric, and sleep-related diagnoses. This has resulted in a trend towards incorporation of objective sleep data to exclude SDB and more reliably quantify sleep duration and insomnia. That said, there remains utility in both subjective and objective qualification of sleep in considering the clinical utility of the findings.

Poor sleep affects many independent factors of cardiovascular health. Over time, autonomic dysregulation and sympathetic-parasympathetic imbalance are likely to increase incidence of arrhythmia, hypertension, metabolic syndrome, coronary artery disease and cardiovascular events. Non-pharmacologic treatment of insomnia, namely CBTI, may help improve subjective perceptions of sleep and improve sleep duration; however, more studies are needed to detect any potential impact on CVD, both in terms of reducing risk for subsequent disease, and in improving symptoms in those with diagnosed CVD.

As the awareness and understanding of insomnia, short sleep, and sleep disturbance improves, so hopefully will the ability to address the resulting burden on society. Future studies could benefit from measurements of HRV, biomarkers, and potentially integration of wearable technology as it may become more feasible to both quantify and track objective sleep duration during intervention studies. It may also be important for future studies to further evaluate which particular aspects of insomnia have the greatest impact on CVD.

Support:

This work was supported by K24 HL143055 (PI: Martin) and VA Greater Los Angeles Healthcare System, Geriatric Research, Education and Clinical Center.

Jennifer Martin reports a grant from NIH/NHLBI during the conduct of the study.

REFERENCES

1. Xu J, Murphy SL, Kochanek KD, Bastian B, Arias E. Deaths: Final Data for 2016. Natl Vital Stat Rep. 2018;67(5):1–76.
2. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019;139(10):e56–e528. [PubMed: 30700139] * American Heart Association adds sleep to its several important components of cardiovascular health
3. Data and Statistics: Short Sleep Duration Among US Adults. CDC. https://www.cdc.gov/sleep/data_statistics.html. Published 2017 Accessed April 29, 2019.
4. Bin YS, Marshall NS, Glozier N. Secular trends in adult sleep duration: a systematic review. Sleep Med Rev. 2012;16(3):223–230. [PubMed: 22075214]
5. Bannai A, Tamakoshi A. The association between long working hours and health: A systematic review of epidemiological evidence. Scand J Work Env Hea. 2014;40(1):5–18.
6. St-Onge MP, Grandner MA, Brown D, et al. Sleep Duration and Quality: Impact on Lifestyle Behaviors and Cardiometabolic Health A Scientific Statement From the American Heart Association. Circulation. 2016;134(18):E367–E386. [PubMed: 27647451]
7. Chang AM, Aeschbach D, Duffy JF, Czeisler CA. Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness. Proceedings of the National Academy of Sciences of the United States of America. 2015;112(4):1232–1237. [PubMed: 25535358]
8. Emens JS, Burgess HJ. Effect of Light and Melatonin and Other Melatonin Receptor Agonists on Human Circadian Physiology. Sleep Medicine Clinics. 2015;10(4):435–453. [PubMed: 26568121]
9. Hossain JL, Shapiro CM. The prevalence, cost implications, and management of sleep disorders: an overview. Sleep Breath. 2002;6(2):85–102. [PubMed: 12075483]
10. Daley M, Morin CM, LeBlanc M, Gregoire JP, Savard J, Baillargeon L. Insomnia and its relationship to health-care utilization, work absenteeism, productivity and accidents. Sleep Medicine. 2009;10(4):427–438. [PubMed: 18753000]
11. American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington, D.C.: American Psychiatric Association; 2013.
12. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146(5):1387–1394. [PubMed: 25367475]
13. Grandner MA, Patel NP, Gehrman PR, Perlis ML, Pack AI. Problems associated with short sleep: bridging the gap between laboratory and epidemiological studies. Sleep Med Rev. 2010;14(4):239–247. [PubMed: 19896872]
14. Watson NF, Badr MS, Belenky G, et al. Recommended Amount of Sleep for a Healthy Adult: A Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society. Sleep. 2015;38(6):843–844. [PubMed: 26039963]
15. Hirshkowitz M, Whiton K, Albert SM, et al. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. Sleep Health. 2015;1(1):40–43. [PubMed: 29073412]
16. Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. Sleep Med Rev. 2013;17(4):241–254. [PubMed: 23419741]
17. Hausler N, Marques-Vidal P, Heinzer R, Haba-Rubio J. How Are Sleep Characteristics Related to Cardiovascular Health? Results From the Population-Based HypnoLaus study. J Am Heart Assoc. 2019;8(7):e011372. [PubMed: 30898062] * One of relative few large scale (n=1826) studies to use

objective measurements with PSG in addition to subjective questionairres. Outcomes, however, focused more on the effects of OSA and thus objective data was not used to isolate effects of insomnia associated with short sleep.

18. Bertisch SM, Pollock BD, Mittleman MA, et al. Insomnia with objective short sleep duration and risk of incident cardiovascular disease and all-cause mortality: Sleep Heart Health Study. Sleep. 2018;41(6).** Data from the Sleep Heart Health Study, which included 4994 patients with questionairres and at home PSGs, finding an increased risk for incidenct cardiovascular disease for the combination of insomnia and short sleep, but not with either component individually. This was in agreement with prior studies suggesting that insomnia with objective short sleep represents a more severe phenotype. It should be noted, however, that authors did not exclude participants with elevated AHIs from analysis.
19. D'Aurea C, Poyares D, Piovezan RD, Passos G, Tufik S, Mello MT. Objective short sleep duration is associated with the activity of the hypothalamic-pituitary-adrenal axis in insomnia. Arq Neuropsiquiatr. 2015;73(6):516–519. [PubMed: 26083888]
20. Hausler N, Lisan Q, Van Sloten T, et al. Cardiovascular health and sleep disturbances in two population-based cohort studies. Heart. 2019.
21. Helbig AK, Stockl D, Heier M, Ladwig KH, Meisinger C. Symptoms of Insomnia and Sleep Duration and Their Association with Incident Strokes: Findings from the Population-Based MONICA/KORA Augsburg Cohort Study. PloS one. 2015;10(7):e0134480. [PubMed: 26230576]
22. Kabat GC, Xue X, Kamensky V, et al. The association of sleep duration and quality with all-cause and cause-specific mortality in the Women's Health Initiative. Sleep Med. 2018;50:48–54. [PubMed: 29982090] * Very large epidemiological study of 158,203 women (no objective data) that found increase in mortality amongs those with insomnia and short sleep. In this study, there was a stronger independent association between short sleep and mortality, although again, sleep duration was subjectively assessed.
23. Schuster AK, Fischer JE, Thayer JF, Mauss D, Jarczok MN. Decreased heart rate variability correlates to increased cardiovascular risk. Int J Cardiol. 2016;203:728–730. [PubMed: 26587729]
24. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health. 2017;5:258. [PubMed: 29034226]
25. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996;93(5):1043–1065. [PubMed: 8598068]
26. Dodds KL, Miller CB, Kyle SD, Marshall NS, Gordon CJ. Heart rate variability in insomnia patients: A critical review of the literature. Sleep Med Rev. 2017;33:88–100. [PubMed: 28187954] * A recent review summarizing findings from 22 papers evaluating HRV in insomnia patients. Found that studies have many inconsistencies in design that make meta-analysis challenging. Thus, indivating a need to have more standardized assessments.
27. Grimaldi D, Carter JR, Van Cauter E, Leproult R. Adverse Impact of Sleep Restriction and Circadian Misalignment on Autonomic Function in Healthy Young Adults. Hypertension. 2016;68(1):243–250. [PubMed: 27271308]
28. Takase B, Akima T, Satomura K, et al. Effects of chronic sleep deprivation on autonomic activity by examining heart rate variability, plasma catecholamine, and intracellular magnesium levels. Biomed Pharmacother. 2004;58 Suppl 1:S35–39. [PubMed: 15754837]
29. Castro-Diehl C, Diez Roux AV, Redline S, et al. Sleep Duration and Quality in Relation to Autonomic Nervous System Measures: The Multi-Ethnic Study of Atherosclerosis (MESA). Sleep. 2016;39(11):1927–1940. [PubMed: 27568797]
30. Jarrin DC, Ivers H, Lamy M, Chen IY, Harvey AG, Morin CM. Cardiovascular autonomic dysfunction in insomnia patients with objective short sleep duration. J Sleep Res. 2018;27(3):e12663. [PubMed: 29493063] * One of the first studies comparing heart rate variability in patients with insomnia and objective short sleep duration showing decreased parasympathatic and increased sympathetic tone in this cohort. It is also important to note that patients with significant sleep apnea were excluded.
31. Lanfranchi PA, Pennestri MH, Fradette L, Dumont M, Morin CM, Montplaisir J. Nighttime blood pressure in normotensive subjects with chronic insomnia: implications for cardiovascular risk. Sleep. 2009;32(6):760–766. [PubMed: 19544752]

32. Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Predictors of all-cause mortality in clinical ambulatory monitoring: unique aspects of blood pressure during sleep. Hypertension. 2007;49(6):1235–1241. [PubMed: 17389258]

33. Tsioufis C, Andrikou I, Thomopoulos C, Syrseloudis D, Stergiou G, Stefanadis C. Increased nighttime blood pressure or nondipping profile for prediction of cardiovascular outcomes. J Hum Hypertens. 2011;25(5):281–293. [PubMed: 21124340]

34. Kwon Y, Koene RJ, Johnson AR, Lin GM, Ferguson JD. Sleep, sleep apnea and atrial fibrillation: Questions and answers. Sleep Med Rev. 2018;39:134–142. [PubMed: 29029984]

35. Khawaja O, Sarwar A, Albert CM, Gaziano JM, Djousse L. Sleep duration and risk of atrial fibrillation (from the Physicians' Health Study). Am J Cardiol. 2013;111(4):547–551. [PubMed: 23218998]

36. Kwon Y, Gharib SA, Biggs ML, et al. Association of sleep characteristics with atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. Thorax. 2015;70(9):873–879. [PubMed: 25986436]

37. Genuardi MV, Ogilvie RP, Saand AR, et al. Association of Short Sleep Duration and Atrial Fibrillation. Chest. 2019.** Very large scale study with 30,061 patients undergoing PSG finding increased incidence and prevalence of atrial fibrillation in patients with objective short sleep independent of sleep apnea and other confounders.

38. Christensen MA, Dixit S, Dewland TA, et al. Sleep characteristics that predict atrial fibrillation. Heart Rhythm. 2018;15(9):1289–1295. [PubMed: 29958805] * A three stage study showing that poor sleep evaluated in three unique databases were each associated with increased risk for atrial fibrillation.

39. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome - An American Heart Association/National Heart, Lung, and Blood Institute scientific statement - Executive summary. Circulation. 2005;112(17):E285–E290.

40. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation. 2008;118(10):1080–1111.

41. Huang W, Ramsey KM, Marcheva B, Bass J. Circadian rhythms, sleep, and metabolism. J Clin Invest. 2011;121(6):2133–2141. [PubMed: 21633182]

42. Gangwisch JE. Epidemiological evidence for the links between sleep, circadian rhythms and metabolism. Obes Rev. 2009;10 Suppl 2:37–45. [PubMed: 19849800]

43. Vgontzas AN, Zoumakis E, Bixler EO, et al. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. J Clin Endocrinol Metab. 2004;89(5):2119–2126. [PubMed: 15126529]

44. Venancio DP, Suchecki D. Prolonged REM sleep restriction induces metabolic syndrome-related changes: Mediation by pro-inflammatory cytokines. Brain Behav Immun. 2015;47:109–117. [PubMed: 25532784]

45. Kjeldsen JS, Hjorth MF, Andersen R, et al. Short sleep duration and large variability in sleep duration are independently associated with dietary risk factors for obesity in Danish school children. Int J Obes (Lond). 2014;38(1):32–39. [PubMed: 23924757]

46. Broussard JL, Kilkus JM, Delebecque F, et al. Elevated ghrelin predicts food intake during experimental sleep restriction. Obesity (Silver Spring). 2016;24(1):132–138. [PubMed: 26467988]

47. Broussard JL, Ehrmann DA, Van Cauter E, Tasali E, Brady MJ. Impaired insulin signaling in human adipocytes after experimental sleep restriction: a randomized, crossover study. Ann Intern Med. 2012;157(8):549–557. [PubMed: 23070488]

48. Kruisbrink M, Robertson W, Ji C, Miller MA, Geleijnse JM, Cappuccio FP. Association of sleep duration and quality with blood lipids: a systematic review and meta-analysis of prospective studies. BMJ Open. 2017;7(12):e018585.* A meta-analysis of 13 studies finding insufficient data to support a definitive link between poor sleep quality and dyslipidemia.

49. Deng HB, Tam T, Zee BC, et al. Short Sleep Duration Increases Metabolic Impact in Healthy Adults: A Population-Based Cohort Study. Sleep. 2017;40(10).** A large prospective

epidemiologic study with 162,121 patients finding subjective short sleep (regardless of insomnia) was associated with an increased risk of multiple components of metabolic syndrome. Sleep apnea was not controlled for.

50. Iftikhar IH, Donley MA, Mindel J, Pleister A, Soriano S, Magalang UJ. Sleep Duration and Metabolic Syndrome. An Updated Dose-Risk Metaanalysis. Ann Am Thorac Soc. 2015;12(9):1364–1372. [PubMed: 26168016]
51. Grandner MA, Chakravorty S, Perlis ML, Oliver L, Gurubhagavatula I. Habitual sleep duration associated with self-reported and objectively determined cardiometabolic risk factors. Sleep Med. 2014;15(1):42–50. [PubMed: 24333222]
52. Fernandez-Mendoza J, He F, LaGrotte C, Vgontzas AN, Liao D, Bixler EO. Impact of the Metabolic Syndrome on Mortality is Modified by Objective Short Sleep Duration. J Am Heart Assoc. 2017;6(5).* Retrospective analysis of the Penn State Cohort finding that among patients with metabolic syndrome, objective short sleep duration was significantly associated with increased mortality. Within metabolic syndrome, hypertension and impaired glucose tolerance were drivers of this interaction.
53. Jarrin DC, Alvaro PK, Bouchard MA, Jarrin SD, Drake CL, Morin CM. Insomnia and hypertension: A systematic review. Sleep Med Rev. 2018;41:3–38. [PubMed: 29576408] ** A thoroughly extensive systematic review of the relationship between insomnia and hypertension. Small section is dedicated also to additional contributions from short sleep.
54. Meng L, Zheng Y, Hui R. The relationship of sleep duration and insomnia to risk of hypertension incidence: a meta-analysis of prospective cohort studies. Hypertens Res. 2013;36(11):985–995. [PubMed: 24005775]
55. Wang Y, Mei H, Jiang YR, et al. Relationship between Duration of Sleep and Hypertension in Adults: A Meta-Analysis. J Clin Sleep Med. 2015;11(9):1047–1056. [PubMed: 25902823]
56. Fernandez-Mendoza J, Vgontzas AN, Liao DP, et al. Insomnia With Objective Short Sleep Duration and Incident Hypertension The Penn State Cohort. Hypertension. 2012;60(4):929-+. [PubMed: 22892811]
57. Fernandez-Mendoza J, He F, Vgontzas AN, Liao DP, Bixler EO. Objective short sleep duration modifies the relationship between hypertension and all-cause mortality. Journal of Hypertension. 2017;35(4):830–836. [PubMed: 28253221] * Similar to reference 52, analysis of the Penn State Cohort finding dose dependent relationship between sleep duration and risk of mortality associated with hypertension.
58. Ramos AR, Weng J, Wallace DM, et al. Sleep Patterns and Hypertension Using Actigraphy in the Hispanic Community Health Study/Study of Latinos. Chest. 2018;153(1):87–93. [PubMed: 28970105] * Unique study utilizing 5-day actigraphy alongside unattended home polysomnogram to evaluate sleep in a primarily hispanic-american population. In this study, sleep duration did not have as much of a role in prevalent hypertension, but sleep fragmentation, efficiency and naps did.
59. Hauan M, Strand LB, Laugsand LE. Associations of Insomnia Symptoms With Blood Pressure and Resting Heart Rate: The HUNT Study in Norway. Behav Sleep Med. 2018;16(5):504–522. [PubMed: 27726451]
60. Javaheri S, Zhao YY, Punjabi NM, Quan SF, Gottlieb DJ, Redline S. Slow-Wave Sleep Is Associated With Incident Hypertension: The Sleep Heart Health Study. Sleep. 2018;41(1).** One of the first studies to compare differences in duration of sleep stage with cardiovascular health. Prospective evaluation of 6441 patients finding an increased odds of incident hypertension in patients with decreased percentage stage N3 sleep. True significance of percentage N3 sleep, however, has not yet been shown to be a reliable indicator of sleep quality.
61. Fung MM, Peters K, Redline S, et al. Decreased slow wave sleep increases risk of developing hypertension in elderly men. Hypertension. 2011;58(4):596–603. [PubMed: 21876072]
62. Chandola T, Ferrie JE, Perski A, Akbaraly T, Marmot MG. The effect of short sleep duration on coronary heart disease risk is greatest among those with sleep disturbance: a prospective study from the Whitehall II cohort. Sleep. 2010;33(6):739–744. [PubMed: 20550013]
63. Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the risk of acute myocardial infarction: a population study. Circulation. 2011;124(19):2073–2081. [PubMed: 22025601]
64. Vgontzas AN, Liao D, Pejovic S, et al. Insomnia with short sleep duration and mortality: the Penn State cohort. Sleep. 2010;33(9):1159–1164. [PubMed: 20857861]

65. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Heart J. 2011;32(12):1484–1492.

66. Smith MT, Perlis ML, Park A, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. Am J Psychiatry. 2002;159(1):5–11. [PubMed: 11772681]

67. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med. 2008;4(5):487–504. [PubMed: 18853708]

68. Conley S, Redeker NS. Cognitive Behavioral Therapy for Insomnia in the Context of Cardiovascular Conditions. Curr Sleep Med Rep. 2015;1(3):157–165. [PubMed: 26500835]

69. Morin CM, Vallieres A, Guay B, et al. Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial. JAMA. 2009;301(19):2005–2015. [PubMed: 19454639]

70. Jarrin DC, Chen IY, Ivers H, Lamy M, Vallieres A, Morin CM. Nocturnal heart rate variability in patients treated with cognitive-behavioral therapy for insomnia. Health Psychol. 2016;35(6):638–641. [PubMed: 27054300] * One of the first of only a few studies to evaluate the impact of CBTI on cardiovascular disease. Cohort is small (65 patients) but provide preliminary evidence of possible effects of non-pharmacologic treatment for insomnia.

71. McGrath ER, Espie CA, Power A, et al. Sleep to Lower Elevated Blood Pressure: A Randomized Controlled Trial (SLEPT). Am J Hypertens. 2017;30(3):319–327. [PubMed: 28391289] ** A randomized control trial evaluating the effect of an online CBTI program on sleep and blood pressure. In general there are few studies evaluating cardiovascular outcomes after CBTI and even fewer are RCTs. Unfortunately, with small sample size and short follow-up duration, a significant effect on blood pressure was not readily evident. That said, this was a strong demonstration of proof of concept.

72. Levenson JC, Rollman BL, Ritterband LM, et al. Hypertension with unsatisfactory sleep health (HUSH): study protocol for a randomized controlled trial. Trials. 2017;18(1):256. [PubMed: 28587609] * This is the protocol for an ongoing RCT evaluating the effect of BBTI/CBTI on hypertension. The study has finished enrollement and is estimated to be completed by 7/2020.

73. Redeker NS, Conley S, Anderson G, et al. Effects of Cognitive Behavioral Therapy for Insomnia on Sleep, Symptoms, Stress, and Autonomic Function Among Patients With Heart Failure. Behav Sleep Med. 2018:1–13.* This is the pilot study for a larger RCT evaluating effects of CBTI on autonomic function in patients with heart failure. The larger study is still actively recruiting as of 7/2019.

74. Tobaldini E, Pecis M, Montano N. Effects of acute and chronic sleep deprivation on cardiovascular regulation. Arch Ital Biol. 2014;152(2–3):103–110. [PubMed: 25828682]

75. Hermansson J, Gillander Gadin K, Karlsson B, Reuterwall C, Hallqvist J, Knutsson A. Case fatality of myocardial infarction among shift workers. International archives of occupational and environmental health. 2015;88(5):599–605. [PubMed: 25261317]

76. Wang A, Arah OA, Kauhanen J, Krause N. Shift work and 20-year incidence of acute myocardial infarction: results from the Kuopio Ischemic Heart Disease Risk Factor Study. Occupational and environmental medicine. 2016;73(9):588–594. [PubMed: 27032692]

77. Vetter C, Devore EE, Wegrzyn LR, et al. Association Between Rotating Night Shift Work and Risk of Coronary Heart Disease Among Women. Jama. 2016;315(16):1726–1734. [PubMed: 27115377]

78. Booker LA, Magee M, Rajaratnam SMW, Sletten TL, Howard ME. Individual vulnerability to insomnia, excessive sleepiness and shift work disorder amongst healthcare shift workers. A systematic review. Sleep Med Rev. 2018;41:220–233. [PubMed: 29680177]

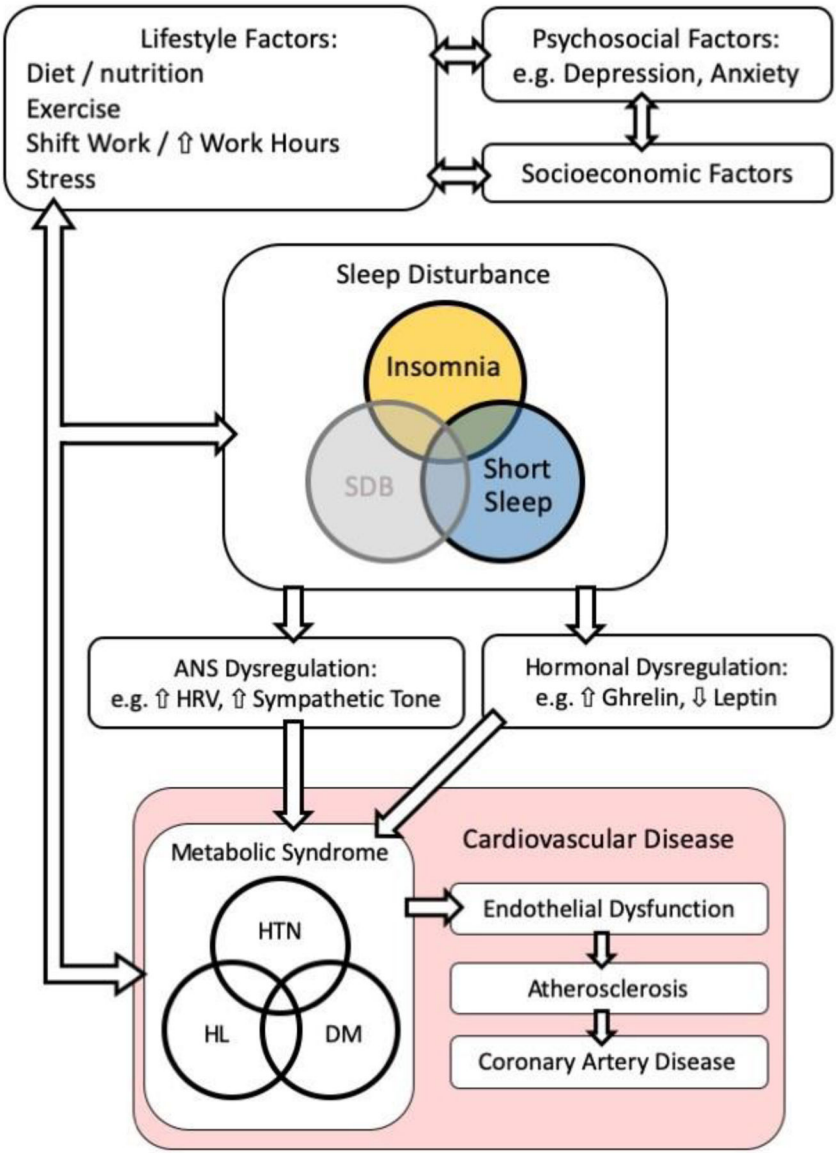

Figure 1:

The relationship between insomnia, short sleep duration and cardiovascular disease is complex with many overlapping and interacting components.