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Influence of sleep on physiological systems in atherosclerosis

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Abstract

Sleep is a fundamental requirement of life and is integral to health. Deviation from optimal sleep associates with numerous diseases including those of the cardiovascular system. Studies, spanning animal models to humans, show that insufficient, disrupted or inconsistent sleep contribute to poor cardiovascular health by disrupting body systems. Fundamental experiments have begun to uncover the molecular and cellular links between sleep and heart health while large-scale human studies have associated sleep with cardiovascular outcomes in diverse populations. Here, we review preclinical and clinical findings that demonstrate how sleep influences the autonomic nervous, metabolic and immune systems to affect atherosclerotic cardiovascular disease.

As a fundamental and necessary biological process, sleep plays a pivotal role in maintaining health. A growing body of both clinical and preclinical research underscores the intricate interplay between sleep and essential biological processes, including those of the nervous, metabolic and immune systems[1–3]. Sleep insufficiency or disruption has been linked to a myriad of deleterious outcomes, encompassing impaired neuronal function, metabolic dysregulation, a compromised immune system and an increased susceptibility to atherosclerotic cardiovascular disease (ASCVD)[4–6]. As we learn more about the nuanced molecular, cellular and tissue mechanisms governing the relationship between sleep and health, it becomes increasingly evident that prioritizing adequate and quality sleep is key for fostering cardiovascular health.

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Competing interests

The authors declare no competing interests.

Sleep deficiencies are an important public health concern as two-thirds of US adults report insufficient or poor sleep[7,8]. Recently, the American Heart Association (AHA) included sleep as one of 'life's essential 8' factors for cardiovascular health[9] and the American College of Cardiology's top recommendation for primary prevention of heart disease is to adopt a healthful lifestyle that includes sufficient sleep[10]. These guidelines are based on numerous associative studies that have consistently demonstrated the importance of adequate sleep to cardiovascular health. However, limited causal evidence exists for sleep's impact on ASCVD. Experimental and randomization studies in humans and rodents have begun to fill this knowledge gap uncovering mechanistic associations that invariably include the complex interplay between sleep and several bodily systems[11,12].

In this Review, we interweave results from clinical, translational and fundamental studies exploring the role of sleep in ASCVD. The Review synthesizes studies spanning the scientific spectrum, from animal models to humans, highlights the advantages and hurdles of animal models in sleep research (Box 1) and is organized around the idea that sleep affects cardiovascular health by engaging three core systems: the nervous, metabolic and immune (Fig. 1).

Clinical and epidemiological evidence associates sleep and ASCVD

Abundant clinical and epidemiological data link sleep and ASCVD in humans and emerging studies support a causal relationship. Sleep is a multidimensional state, and deviations in its abundance, timing and quality, in addition to sleep disorders such as obstructive sleep apnea (OSA), influence ASCVD risk.

Short and long sleep duration associate with ASCVD

Prospective data demonstrate that self-reported short sleep (<6 h per night) associates with higher rates of acute myocardial infarction (AMI) compared to 6–9 h of sleep per night (hazard ratio (HR) 1.20 (confidence interval (CI) 1.07–1.33))[13]. Applying Mendelian randomization analysis supports a causal effect of short sleep on ASCVD with a 21% increased incidence of AMI (HR 1.21 (CI 1.08–1.37)[13]. These results were confirmed by other Mendelian randomization analyses, thereby demonstrating links between genetically predicted short sleep and ASCVD (including AMI) and hypertension (HTN)[14]. Adding to this evidence are findings of a dose–response relationship between decreasing self-reported sleep duration and ASCVD occurrence (in individuals reporting 7 h, 6 h and <5 h of sleep compared with those reporting 8 h of sleep; relative risk 1.06 (CI 0.89–1.26), 1.30 (CI 1.08–1.57) and 1.82 (CI 1.34–2.41), respectively)[15]. At the other extreme, excessive sleep (>9 h per night) entails elevated risk of ASCVD (relative risk 1.38 (CI 1.03–1.86))[15]. Similar findings have been acquired in diverse cohorts that include men and women across different racial/ethnic backgrounds[16]. The associations between short-versus-long sleep and ASCVD are likely disparate, with long sleepers potentially having greater sleep drive in the setting of underlying illness. This difference is captured in studies evaluating self-reported napping. Although those with short sleep (≤6 h per night) are at higher risk of major adverse cardiac events and death, the addition of self-reported napping does not raise their risk[17]. By contrast, individuals who sleep more than 6 h a night and report requiring daytime naps

are at increased risk of composite CVD events and death[17], a result that suggests that sleep pressure has an important role in the association between sleep and ASCVD. However, these epidemiological studies are limited in their ability to draw causal relationships. It is unknown whether experimentally extending sleep to adequate levels among short sleepers improves atherosclerotic plaques and ASCVD risk. The feasibility of such experimental models of sleep extension in humans and direct analysis of cardiovascular disease remains a challenge among healthy or at-risk participants.

Poor sleep and daytime symptoms and habits affect ASCVD risk

Another key factor is the interaction between short and poor-quality sleep. Self-reported sleep problems associate with CVD, even after controlling for confounders (odds ratio (OR) 1.75 (CI 1.41–2.16))[6]. However, individuals reporting both short and restless/disturbed sleep are at highest risk (relative risk 1.55 (CI 1.33–1.81))[18]. In a prospective observational study using objective measures of sleep duration, insomnia or poor-quality sleep combined with a sleep duration of <6 h per night associates with risk of incident CVD (HR 1.29 (CI 1.00–1.66))[19]. To achieve rigor and granularity for self-reported sleep data, we can apply advanced statistical methods and machine learning to assess sleep phenotypes and interactions. Latent class analysis, which identifies clusters with variable ASCVD risk, reveals that those with dissatisfactory/inefficient sleep and naps are at high risk of CVD (relative risk 1.29 and 1.38, respectively)[20]. Latent class analysis also identifies symptom-based OSA-specific subgroups with high CVD risk. Individuals with OSA who have excessive daytime sleepiness are at highest risk of CVD compared to other symptom subgroups and those without OSA[21], thus highlighting the importance of sleep drive—in this case measured by symptoms rather than requirement for napping—on cardiovascular risk. These findings demonstrate how combining sleep-related symptoms, even when they are daytime symptoms related to quality of life, with formal sleep diagnostics better assesses health risk. Indeed, the effects of short sleep on CVD mortality are amplified when combined with other daytime unhealthy/sedentary behaviors such as limited vigorous activity, excessive time spent watching television and elevated body mass index (BMI, relative risk 1.90 (CI 1.67–2.17))[22].

Impact of sleep timing and variability on ASCVD

Sleep quality, timing, variability and entrainment with circadian rhythm are as influential on ASCVD as sleep duration. Night shift work is associated with increased incidence of ASCVD, and more years working night shifts result in greater CVD risk even after multivariable adjustment (<5-year HR 1.02 (0.97–1.08), 5–9-year HR 1.12 (CI 1.02–1.22), and ≥10-year HR 1.18 (CI 1.10–1.26))[23]. That these results are largely unchanged after adjusting for sleep duration suggests sleeping out of phase with normal circadian rhythm carries an intrinsic risk of ASCVD. Strikingly, it takes more than 24 years after night shift cessation for ASCVD risk to normalize. Even less extreme forms of out-of-phase sleep, like social jetlag with as little as 2–4-h deviation from individualized chronotype, shows a trend toward elevated ASCVD risk[24]. Despite no difference in sleep time, evening chronotype, compared to morning chronotype, is associated with a small but statistically significant rise in CVD prevalence (OR 1.07 (CI 1.04–1.10))[25]. Another consideration intertwined with circadian disorders is variability in sleep schedule, which associates with higher CVD

burden, even after adjustment for chronotype, work schedule, average sleep duration and insomnia symptom scores[26]. Each additional hour in the standard deviation of sleep duration or sleep-onset timing increases the risk of CVD by 39% and 18%, respectively. Individuals with irregular sleep duration and sleep-onset timing are more likely to have high coronary artery calcium burden[27] and are at increased risk of cardiometabolic mortality[28].

Analysis of multidimensional sleep and ASCVD

Principal component analysis (PCA) has been used to generate a sleep score that combines data from polysomnography (PSG), actigraphy and sleep questionnaires[29]. Higher scores—indicating better sleep health—associate with reduced all-cause mortality (HR 0.75 (CI 0.65–0.87) per one standard deviation increase in sleep score). The components of this multidimensional tool that contribute the most to mortality are sleep pattern regularity, sleep duration and apnea–hypopnea index (AHI). These features can represent consequences of OSA; alternatively, however, they can represent an intersection of multiple comorbid sleep conditions and symptoms. Another analysis explored whether adding the same multidimensional sleep data to the AHA's Life's Simple 7 score provided additional information regarding ASCVD risk. Although the Life's Simple 7 score alone does not associate with incident CVD, adding sleep health scores does show an association with CVD incidence (HR 0.53 (CI 0.32–0.89))[30], a result that prompted the AHA to incorporate sleep into Life's Essential 8. Multidimensional sleep scores are also useful when combined with weighted genetic risk. Individuals with poor sleep and high genetic risk scores have the highest risk of ASCVD compared to individuals with better sleep scores and/or lower genetic risk, implying the importance of and interaction between predisposing genetic risk and environmental/lifestyle factors[31]. Advances in machine and deep learning will allow for integration of multidimensional sleep data to capture a myriad of comorbid sleep disease states and thus predict outcomes. For example, a deep neural network trained on 2,500 PSGs from seven studies can estimate mortality from PSG-based age estimation[32]. There is no one single measure of sleep that encapsulates all CVD risk. Therefore, it stands to reason that novel predictive risk scores that assess multiple parameters of sleep health will provide a better understanding of which individuals are at risk of ASCVD. Going beyond risk prediction, novel forms of heterogeneous treatment effects analyses combined with multiple feature domains will enable better estimation of treatment effects on CVD outcomes.

Obstructive sleep apnea and cardiovascular disease

OSA and CVD are closely connected. Large-scale epidemiological studies demonstrate that OSA positively associates with CVD and, on long-term follow-up, with CVD mortality[33–36]. These observations were preceded by smaller studies[37–39], confirmed by other single-center cohorts[40], and replicated in diverse cohorts[41,42]. Studies have found that adherence to OSA treatment with continuous positive airway pressure (CPAP) therapy benefits CVD[43–46]. However, randomized controlled trials (RCTs) evaluating CPAP for primary and secondary CVD prevention consistently show neutral findings[47]. This discrepancy may be due to a 'healthy user' bias within observational data or the inherent limitations of RCTs including restrictive inclusion criteria and poor adherence to therapy. OSA affects almost one billion people worldwide[48]; therefore, it is unlikely that all CVD risk within this group is attributable to OSA. Endotyping and phenotyping OSA can achieve a precision approach

to treatment for specific disease outcomes[49] including CVD endpoints. Endotypic processes that underlie OSA pathophysiology, including arousal threshold, loop gain, airway muscle compensation and pharyngeal collapsibility, have been suggested as targets for specific and novel treatments[50] that would challenge the current one-size-fits-all approach. How treatment algorithms targeting these specific axes impact ASCVD outcomes needs to be fully assessed in future studies.

A critical deficiency in RCTs evaluating OSA treatment on ASCVD is the lack of inclusion of important symptom-based phenotypes. Individuals with OSA who have excessive daytime sleepiness are known to be at increased CVD risk[21,51] and, conversely, OSA without excessive daytime sleepiness may have the same CVD risk as no OSA[51]. Additionally, OSA must be evaluated as part of a holistic, multidimensional approach to sleep. For example, outcomes for individuals with comorbid insomnia and OSA are much worse than for either condition alone[52–55]. As underlying mechanisms differ between OSA endophenotypes and ASCVD, future work must rigorously collect data to analyze OSA cohorts by their heterogeneous individualized subgroups. Clinicians must be vigilant in obtaining detailed history and objective evidence of comorbid sleep disorders to better understand sleep's comprehensive impact on ASCVD. Through this lens, we will be able to explore intermediate endpoints that may represent the fundamental autonomic, metabolic and inflammatory pathways through which sleep disruption causes ASCVD.

Effects of sleep on the autonomic nervous system

The autonomic nervous system is composed of two branches, the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). The SNS and PNS highly innervate organs and arterial adventitia[56] to modulate function through neurotransmitters, such as catecholamines and acetylcholine (ACh), respectively. While the SNS is considered a quick response, 'fight-or-flight' system, the PNS exerts slowly activated complementary effects to dampen bodily functions. When humans transition from the waking state to progressively deeper stages of sleep, SNS tone decreases and PNS vagal tone increases. Non-rapid eye movement (NREM) sleep, most notably slow-wave sleep, can be considered a phase that allows autonomic stability and metabolic recovery due to parasympathetic dominance[57]. This is in contrast to rapid eye movement (REM) sleep where SNS tone and neurotransmitter release rises, enhancing heart rate variability and elevating systolic and diastolic blood pressure[58]. These changes in SNS and PNS parallel the activity of the hypothalamic–pituitary–adrenal (HPA) axis, which is a vital neuroendocrine system connecting perceived stress to physiological reactions via glucocorticoids[59]. Individuals with OSA[60], narcolepsy[61] and chronic insomnia[62] have higher sympathetic nerve activity, during both sleep and wakefulness, which may be caused by disturbed chemoreflex and baroreflex activity, altered cardiac electrophysiology, endothelial dysfunction or increased neural cardiovascular responsiveness. A persistent increase in SNS activity can favor the emergence of permitted local inflammatory zones. In chronic inflammatory settings and sleep-related hyperarousal states, this has detrimental effects that lead to comorbidities such as high blood pressure, cardiovascular mortality or insulin resistance[63–65]. These observations suggest interplay between the autonomic nervous system and sleep in the regulation of inflammation, which may be able to be harnessed therapeutically (Box 2). In

addition, sleep disruption may modulate changes in adrenal and gonadal androgen levels that in turn promote a pro-inflammatory state, thereby perpetuating sleep disturbance[66]. Moreover, signals through gonadal steroids together with inputs from the paraventricular hypothalamic nucleus can be integrated in the preoptic area of the hypothalamus, where activation of glutamatergic neurons elicits microarousals and subsequent sleep fragmentation[67]. Heightened autonomic activity together with sleep disruption may instigate the underlying causes of ASCVD by simultaneously affecting the interconnections between cardiac physiology, local inflammation and hormonal balance (Fig. 2).

Sleep and hypertension

SNS activation is a predominant contributor to HTN. OSA-related respiratory events increase sympathetic nerve activity[68], drive nocturnal non-dipping of blood pressure[69] and lead to daytime HTN[70], while CPAP treatment for OSA reduces nocturnal[71] and daytime[72,73] blood pressure. The influence of sleep on HTN can be characterized more effectively when multiple dimensions of sleep are combined. For example, systolic blood pressure is highest among those with moderate-to-severe OSA and a morning chronotype, as compared with intermediate OSA or evening chronotypes[74]. Short sleep and insomnia also associate with HTN. Compared to those sleeping >6 h a night, individuals with insomnia and <5 h of nightly sleep have elevated risk of HTN (OR 5.1 (CI 2.2–11.8))[75]. Short sleep (<6 h versus 7–8 h) raises the risk of HTN (OR 1.66 (CI 1.35–2.04)), an effect that persists even after adjusting for confounding variables[76]. These dynamics are not limited to short sleepers; those reporting >9 h of sleep per night also have increased HTN risk (OR 1.30 (CI 1.04–1.62))[76]. These findings have been validated in prospective cohorts, in which reporting ≤5 h of sleep per night associates with greater risk of developing HTN compared to sleeping 7 h per night (HR 1.20 (CI 1.09–1.31)), an effect that obesity partially mediates[77]. Although they do not prove causation, prospective incidence data provide stronger evidence that sleep modulates autonomic and vascular function. For example, studies using actigraphy to assess objective sleep duration and consolidation demonstrate higher rates of both HTN and incident HTN over 5 years (OR 1.37 (CI 1.05–1.78))[78]. Experimental studies strengthen this association by revealing a causal relationship between sleep restriction (that is, 4-h time-in-bed restriction for 9 days) and 24-h blood pressure, increased morning plasma norepinephrine and attenuated vasodilatory capacity[79].

Sleep and circadian regulation also have central roles in modulating diurnal blood pressure[80]. Evening chronotypes have a 1.3-fold OR for arterial HTN than morning types[81]. Derangements in blood pressure are regulated by wake–sleep states with significantly elevated systolic, diastolic and mean blood pressure during wakefulness compared to NREM sleep and these oscillations are accentuated in obesity-prone leptin-deficient (ob/ob) mice compared to wild-type controls[82]. In experimental manipulations, 30 days of sleep fragmentation impairs neurovascular coupling and decreases whisker-stimulated cerebral blood flow in normotensive and hypertensive mice[83]. Furthermore, sleep-fragmented mice have expanded vascular network density but unaltered arteriole vascular remodeling[83]. In genetic models of insufficient sleep, hypocretin-ataxin3 transgenic and hypocretin-deficient mice (both are models of human narcolepsy) display elevated blood pressure during NREM and REM sleep and blunted sleep–wake blood pressure changes[84,85].

Sleep and heart rate

Many aspects of cardiovascular physiology, including heart rate variability, are orchestrated by circadian rhythmicity. Accordingly, circadian misalignment leads to internal desynchronization of the HPA axis and can subsequently result in altered cardiac electrophysiology in mice[86] and humans[87]. Perturbations in sleep-dependent cardiovascular sympathetic control also occur in narcoleptic hypocretin-deficient mice[88]. Mistimed sleep and unsynchronized behavior disrupt sinoatrial node rhythms and atrioventricular node activity in humans and mice[89]. In perfused heart preparations, susceptibility to ventricular tachycardia is increased at ZT12, compared to ZT0, and mice prone to catecholamine-induced arrhythmogenesis elicit bidirectional ventricular tachycardia at ZT12, but not ZT0, upon caffeine or adrenaline administration[89]. These findings align with increased incidence of early morning sudden cardiac deaths in humans[90]. It is not yet fully understood whether mistimed or irregular sleep can predispose humans to arrhythmia or other cardiac events. However, a recent large-scale, longitudinal sleep study using wearable devices found inverse associations between REM and deep sleep and the odds of atrial fibrillation incidence[91]. Moreover, irregular shift workers showed prolonged correlated QT (QTc) interval and more frequent conduction or repolarization disorders compared to regular shift workers[92,93].

Emerging metrics of sympathetic activation in sleep

Given early evidence demonstrating sympathetic activation in OSA[68] and its ill effects on CVD[94], a noninvasive measure of autonomic surges using PSG would help to improve risk stratification of patients. One such metric is the relationship between the pulse-rate response and OSA-related respiratory events (that is, apneas and hypopneas). Individuals with OSA who have high pulse-rate response are at increased risk of both CVD mortality and all-cause mortality (HR 1.68 (CI 1.22–2.30) and 1.29 (1.07–1.55), respectively), as compared to those with a pulse-rate response within the 25th–75th percentiles[95]. A clinical trial of CPAP for secondary CVD prevention shows CPAP has a protective effect among individuals with OSA who have an increased pulse-rate response[96]. While this novel approach is encouraging, evaluating the pulse-rate response represents more complex physiology than just autonomic function as it requires healthy cardiac conduction system responses and is limited by medications that interfere with chronotropy (for example, beta blockers). Another OSA-related metric is the respiratory event duration. Individuals with OSA who have shorter average respiratory event duration have an increased risk of all-cause mortality (1.31 (CI 1.11–1.54))[97]. While this measure likely represents a combination of factors including arousal threshold, it may suggest higher autonomic tone. Short sleep duration, insomnia and poor sleep quality also contribute to lower high-frequency heart rate variability, another marker of imbalance between sympathetic and parasympathetic tone[98].

The role of sleep in obesity and lipid metabolism

Sleep and its disorders shape metabolic function, including effects on obesity, diabetes and insulin sensitivity[99,100], and lipid metabolism[101]. These metabolic syndrome components are important contributors to the development and progression of ASCVD (Fig. 3). Here, we give particular attention to obesity and lipid metabolism.

Suboptimal sleep drives obesity and emergence of the metabolic syndrome

The associations between sleep, food consumption, obesity and energy balance in humans are numerous and have been reviewed in detail[102]. Sleep insufficiency both increases food consumption via alterations in the appetite hormones leptin and ghrelin, and alters meal timing and food choices, which can lead to obesity[103–105]. Sleep duration is shortest and most variable among obese children and associates with changes in insulin, low-density lipoprotein cholesterol (LDL-c), and C-reactive protein (CRP)[106]. These phenomena highlight the importance of early-life sleep habits for future metabolic and ASCVD health. Night-to-night variability in sleep duration and daytime napping are independently associated with obesity in older men and women[107]. Other studies have validated these findings and further shown that irregular sleep–wake timing correlates with increases in obesity, fasting glucose and diabetes, 10-year CVD risk and comorbid metabolic abnormalities[108]. Recent human intervention experiments indicate that sleep restriction increases caloric intake without a commensurate rise in energy expenditure, thereby resulting in weight gain and added subcutaneous and visceral fat[109]. Importantly, among overweight adults who sleep fewer than 6.5 h per night, a randomized control trial of sleep extension reverses excess energy intake and reduces weight[110]. Weight and BMI cannot be viewed in isolation, and more granular measures such as lipid accumulation product, which accounts for both waist circumference and triglyceride levels, strongly associate with sleep disorders[111]. For example, lipid accumulation product was helpful in predicting risk of diabetes in individuals with OSA and, when combined with high-density lipoprotein cholesterol (HDL-c), heart disease.

Sleep and obesity in experimental studies

Sleep and obesity have a bidirectional relationship. A high-calorie diet enhances sleep pressure, as obese mice have reduced wakefulness in both the dark and light cycles and spend more time in NREM sleep with higher slow-wave activity[112]. Wake episode duration decreases following high-fat diet feeding, and body weight positively correlates with NREM sleep and negatively associates with wakefulness[113,114]. Sleep disruption also worsens in diet-induced obesity and leptin-deficient mice[115,116], leading to sleep-disordered breathing characterized by increased flow-limited breathing and hypoxemia[117] and more circadian variation in respiratory rate and diaphragmatic bursts during REM sleep[118]. However, obese female mice are less susceptible than males to sleep-disordered breathing and sleep fragmentation[119]. Importantly, dietary change and weight loss reverse obesity-dependent sleep alterations[120]. Regarding the effect sleep has on obesity onset and progression, 10 days of sleep deprivation in mice heightens food intake and elevates weight gain, with the effects mitigated by melatonin[121]. When fed a high-fat diet, mice with a history of persistent sleep deprivation experience weight gain, insulin resistance, expanded heightened fat mass and more adipose tissue inflammation[122], whereas prolonged sleep fragmentation leads to increased food intake, higher body weight gain[123] and glucose intolerance[124]. Sleep-fragmented animals also develop larger subcutaneous and visceral fat depots, have more adipocyte progenitor cells in the visceral white adipose tissue and greater adipose tissue inflammation[125]. In a mouse model of shift work, timed sleep restriction leads to prolonged metabolic reprogramming of white adipose tissue and early leptin resistance in a *Per1*- and *Per2*-dependent manner[126]. Recurrent circadian disruption in mice fed a high-fat

diet results in increased weight gain, higher body fat mass, impaired glucose tolerance and insulin sensitivity[127]. In genetic models, ablation of wake-promoting hypocretin neurons in hypocretin/ataxin3 mice combined with high-fat diet promotes weight gain[128,129]. Consistent with this, daily light-phase, but not dark-phase, administration of suvorexant, a hypocretin antagonist, for 2–4 weeks ameliorates glucose tolerance in leptin-deficient mice and improves hepatic glucose metabolism[130]. In summary, the collective empirical evidence derived from human and animal studies underscores the detrimental effects insufficient and irregular sleep has on obesity development and progression.

Sleep and lipids

Poor sleep leads to dysfunctional lipid metabolism. Large epidemiological studies report increases in hepatic triglyceride content among the shortest sleepers (<5th percentile, average 5 hour per night) and elevated serum triglyceride among those with poor sleep quality. These associations are tempered after adjustment for BMI and OSA, suggesting more complex dynamics between sleep time, obesity and comorbid sleep disorders[131]. Poor sleep hygiene during transition from childhood to adolescence associates with an atherogenic lipid profile including lower HDL-c and increased triglyceride levels, an effect more prominent in adolescent girls[132]. Sleep architecture also affects dyslipidemia, as the ratio of slow-wave sleep to total sleep time correlates independently with triglyceride and total cholesterol levels, and microarousal index also independently associates with HDL-c and LDL-c[133]. Despite the highlighted studies, a systematic meta-analysis of 13 prospective studies found no significant relationship between sleep duration or quality and the emergence of dyslipidemia[134].

A meta-analysis assessing lipid profiles of individuals with OSA found higher total cholesterol, LDL-c and triglyceride as well as lower HDL-c than in individuals without OSA[135]. Moreover, there is a dose–response relationship between OSA severity and total cholesterol, LDL-c and triglycerideTG, such that oxygen desaturation index associates with total cholesterol while AHI better predicts LDL-c and triglyceride[136]. These findings indicate mechanisms involved in lipid metabolism may depend on the underlying sleep abnormality. In contrast to these large epidemiological studies, an experimental study found that a 5-h time-in-bed restriction for 4 nights suppresses postprandial triglyceride, which returned to baseline after one night of recovery sleep[137]. Interestingly, sleep-restriction participants in this study also reported feeling less full or satiated after meals.

In mice, chronic intermittent hypoxia, a feature of OSA, modulates sterol regulatory element binding protein 1 and stearoyl-coenzyme A desaturase 1 to increase total cholesterol, phospholipids, LDL-c, triglyceride and atherosclerosis[138]. In humans, however, oxidized LDL-c associates with OSA and overall dyslipidemia[139]. Among individuals with severe OSA, CPAP therapy to alleviate apnea events improves the clearance rate of radiolabeled lipids[140]. This study also presents an inverse correlation between cholesteryl ester clearance rate and hypoxemia (that is, total sleep time with oxygen saturation < 90% (T90%)), and carotid intima–media thickness. Some studies have validated these findings, showing CPAP therapy reduces total cholesterol[141] and LDL-c[142], but other studies have observed no meaningful changes[143]. Another interesting consideration is that disruption in different

sleep stages results in different effects on lipids. A clinical cohort study reveals that AHI in NREM specifically associates with elevated total cholesterol, LDL-c and apolipoprotein B, while REM AHI does not[144]. Sleep stage-specific impacts on metabolism are apparent throughout the metabolome. For example, while fatty acid oxidation rises during stage N3 sleep and drops during wakefulness, the tricarboxylic acid cycle and glycolysis seem to be more active during REM sleep[145].

The effects of sleep manipulation on lipids in murine models

Mouse sleep disruption increases serum cholesterol and LDL-c, decreases HDL-c and very low-density lipoprotein (VLDL)[146], and mediates liver cholesterol through the circadian rhythm genes *NR1D1* and *CYP7A1* (ref. 147). Additionally, short-term (5 days) sleep deprivation suppresses the circadian expression of lipid metabolism genes in the liver and lowers daily peaks in serum cholesterol and triglyceride[148]. In long-term models, chronically shifting the light–dark cycle exacerbates atherosclerosis in female, but not male, apolipoprotein E-deficient ($Apoe^{-/-}$) mice, a change that associates with heightened total serum cholesterol and atherogenic VLDL/LDL particles, independently of food intake[149]. In APOE*3-Leiden mice, however, the same method produced no obvious changes in lipid levels, although these mice exhibit lower total cholesterol levels than $Apoe^{-/-}$ mice[150]. Long-term sleep fragmentation does not impact body weight, total cholesterol or triglyceride in western-diet-fed $Apoe^{-/-}$ and LDL receptor-deficient ($Ldlr^{-/-}$) mice[12]. Together, these results indicate that, in mice, while acute sleep disruption may engender short-term fluctuations in lipid levels, chronic poor sleep does not seem to modulate plasma cholesterol levels.

Sleep modulates inflammation and the immune system

Inflammation contributes to ASCVD. Following retention in the arterial wall, apolipoprotein B-containing lipoproteins undergo structural modifications and become immunogenic, thus inciting inflammation and the recruitment of circulating monocytes to the growing atheroma. Hematopoiesis is enhanced and contributes to the circulating monocyte pool, exacerbating vascular inflammation and atherogenesis. Inflammatory mediators like cytokines and growth factors perpetuate inflammation leading to atheroma growth and instability. Although our knowledge of the influence of sleep at each stage of plaque growth is incomplete, studies have begun to identify important mechanistic links (Fig. 4).

The effect of sleep on cytokines

Cytokines orchestrate many inflammatory processes in ASCVD including activating endothelial cells, recruiting and programming leukocytes in atheroma, and destabilizing plaque. Persistent sleep disruption, such as chronic insomnia[151] or circadian misalignment[152], promotes prolonged pro-inflammatory cytokine responses that instigate chronic health complications such as ASCVD.

Although the contributions of interleukin-6 (IL-6) and tumor necrosis factor (TNF) to atherosclerosis are complex, several human and animal studies have documented increased plasma IL-6 and TNF after prolonged sleep deprivation. Sleep inconsistency measured over

seven nights associates with heightened IL-6 and CRP[153]. Furthermore, increased levels of circulating IL-6 and TNF correlate with sleep irregularity in older adults[154]. Importantly, individuals experiencing an acute cardiovascular event combined with preexisting OSA have higher serum levels of IL-6 than individuals without OSA[155]. Persistent sleep fragmentation in mice raises plasma IL-6, which normalizes with recovery sleep[11]. By contrast, sleep fragmentation does not affect plasma TNF levels in humans[156,157] or rodents[158]. In a murine model, complete sleep deprivation induces a cytokine storm before death[159]. Increased wakefulness after sleep onset, a measure of insomnia, associates with increased IL-6 and CRP[160]. After a single night of forced prolonged (4 h) wakefulness after sleep onset in healthy individuals, monocytes produce more IL-6 and TNF[161]. Additionally, inflammatory responses to sleep disruption vary by sex as women experiencing wakefulness after sleep onset have greater immune and cytokine activation[162]. A large epidemiological study of short sleepers confirmed these sex differences in cytokine levels[163]. Serial 24-h evaluation of plasma IL-6 and TNF among individuals with chronic insomnia found that although average 24-h levels of these fatigue-inducing cytokines are consistent, their major peaks shift significantly[151], a result that suggests dysregulated circadian rhythm and highlights the importance of sample collection timing in epidemiological and experimental studies. Interestingly, as with ASCVD risk, habitual sleep time of more than 7–8 h per night also associates with higher levels of IL-6 and CRP[164]. However, the association between sleeping more than 7–8 h per night and inflammation remains to be fully determined, is experimentally difficult to test and is likely influenced by comorbidities, which themselves associate with ASCVD.

The IL-1 cytokine family is influential to immune responses. IL-1 is either increased[165] or unchanged[157] upon acute sleep deprivation, whereas IL-1Ra, an atheroprotective natural inhibitor of IL-1, is increased after sleep disruption[165,166], which may be a homeostatic response to higher IL-1 levels. It has been shown that five nights of sleep restriction increases peripheral blood mononuclear cell production of IL-6 and IL-1β[167]. IL-1β maturation and production are controlled by the NLR family pyrin domain containing 3 (NLRP3) inflammasome, which can be promoted by cholesterol crystals in atherosclerotic lesions[168]. While information is scarce regarding how prolonged sleep disruption impacts NLRP3 activation in innate immune cells, a recent report showed that plasma exosomes isolated from sleep-fragmentated animals trigger NLRP3 activation in endothelial cells, resulting in more deposition of IL-1β and IL-18 in atherosclerotic lesions[169].

Obstructive sleep apnea and pathways of inflammation

The underlying pathobiology by which the sequelae of obstructive respiratory events lead to ASCVD is unclear, although many theories exist. Many studies have demonstrated an association between OSA and elevated systemic inflammatory biomarkers, including CRP, IL-6 and TNF, among others[170,171], and levels of these cytokines are highest after an acute cardiovascular event among those with OSA, relative to those without it[155]. To assess how treating OSA affects systemic inflammation, a study evaluated composite serum proteomic inflammatory scores based on 92 inflammatory proteins before and 3 months after CPAP initiation. Among participants with OSA who have elevated baseline inflammatory scores, there is significantly decreased inflammatory protein expression after OSA treatment[172].

Studies with more limited panels of systemic inflammatory markers[173,174] or oxidative stress markers[175] do not show similar benefits from CPAP. Monocytes from individuals with severe OSA display higher NLRP3 inflammasome activity, which correlates with hypoxemia indices and is mediated by hypoxia-inducible factor-1α (HIF-1α)[176]. This increase in HIF-1α among individuals with OSA has been validated[177], although others have found that intermittent hypoxemia selectively activates nuclear factor kappa B (NF-κB), rather than HIF-1α[178].

Another hypothesis is that immune priming results from local pharyngeal inflammation due to mechanical trauma and strain related to OSA airway collapse. Among individuals with OSA, ^{18}F-fluorodeoxyglucose uptake on positron emission tomography with magnetic resonance imaging (PET/MRI) of the pharyngeal mucosa correlates with a composite proteomic inflammatory score from nasal lavage samples[179]. In a cluster of individuals with high baseline inflammation, application of CPAP—which stabilizes the upper airway—results in significant reductions in monocyte chemoattractant protein 4 (MCP-4), transforming growth factor beta 1 (TGFβ1) and vascular endothelial growth factor-α (VEGFα). Others have also shown decreases in pharyngeal lavage cytokines (that is, IL-6 and IL-8) and leukocytes one year after initiation of CPAP[180]. This local inflammatory response and immune cell priming may perpetuate systemic inflammation and ASCVD progression.

Sleep-dependent changes in leukocyte abundance and generation

Emerging data have revealed that sleep modulates leukocyte abundance and production. Short-term sleep restriction results in changes in tissular and circulating immune cell abundance, likely due to redistribution of cells between organs and peripheral blood rather than alterations in generation[181]. For example, in animals, 1–3 days of sleep deprivation leads to a stress-induced increase in splenic and bone marrow B cells without impacting cell production[182]. Similarly, short paradoxical sleep deprivation redistributes leukocytes by releasing cells from the bone marrow, resulting in decreased bone marrow cellularity and elevated blood monocytes and neutrophils[183]. In a skin allograft model, both $CD4^+$ and $CD8^+$ T cells exited the spleen and lymph nodes of mice undergoing short sleep restriction[184]. However, most of these short-term studies have not directly profiled hematopoietic stem and progenitor cells (HSPCs) or their proliferation and differentiation. More work is needed to understand how short-term insufficient or disrupted sleep manipulates HSPC programming, proliferation, differentiation and lineage commitment.

Growing evidence suggests that long-term sleep disruption or insufficiency modifies immune cell production, a process known as hematopoiesis. Long-term (16 weeks) sleep fragmentation in atherogenic mice compromises hypothalamic control over medullary hematopoiesis, resulting in heightened hematopoietic stem cell proliferation in the bone marrow[12]. The underlying mechanism involves a sleep fragmentation-induced decrease in hypocretin production in the lateral hypothalamus, a change that dampens hypocretin signaling to pre-neutrophils in the bone marrow, thereby leading to elevated colony-stimulating factor 1 production and myeloid-biased hematopoiesis. Consequently, sleep-fragmented mice display monocytosis that leads to expanded aortic immune cell infiltration

and augmented atherosclerotic lesion formation in western-type diet-fed, atherosclerosis-prone *Apoe*$^{-/-}$ mice; these findings are phenocopied in hypocretin-deficient *Apoe*$^{-/-}$ mice. There are conflicting data on how extended sleep restriction influences lymphocyte generation[167,185,186]. Whether sleep recovery can reverse the adverse effects of persistent sleep disruption on hematopoiesis and inflammatory recall is understudied and warrants further investigation (Box 3).

In humans, chronically restricting sleep by 1.5 h every night for 6 weeks increases the numbers of circulating CD14^{+}CD16^{-} classical monocytes, CD14^{-}CD16^{+} non-classical monocytes, and Lin^{-}CD34^{+} HSPCs, changes that suggest enhanced hematopoietic activity[11]. HSPCs retrieved from participants after 6 weeks of sleep restriction display altered epigenetic programming and myeloid-biased differentiation cues[11]. Other studies similarly report that one week of sleep restriction is sufficient to expand circulating blood monocytes and neutrophils[187,188]. Indeed, in humans, healthful and sufficient sleep curtails hematopoiesis and reduces circulating monocytes[189], neutrophils[190], B cells and T cells[157,191], the precursors of mature dendritic cells[192] and natural killer cells[187], while basophil and eosinophil numbers are unaffected. Accordingly, self-reported insufficient sleep boosts circulating monocytes, neutrophils, and total and memory CD4^{+} T cells[193]. Similar findings were reported in a study of young adults, in whom irregular sleep patterns (incorporating sleep duration and sleep onset) correlate with increased generation of circulating immune cells[194]. A study of white blood cell counts in a large cross-sectional analysis reported that sleep duration relates to higher all-cause mortality[195]. Investigating monocyte subsets in individuals with OSA shows elevated circulating CD16^{+} monocytes, increased programmed cell death ligand 1 expression and heightened formation of monocyte–T cell complexes[196], observations that normalize after initiation of CPAP[197]. These studies support the idea that more than a week of chronic insufficient sleep expands hematopoiesis and immune cell generation leading to circulating leukocytosis, an important ASCVD risk factor in humans[198]. Finally, there are important associations between sleep, aging and the immune system. For example, sleep abundance declines in the elderly which may influence the rate of ‘inflammaging’ in ASCVD (Box 4).

Sleep-related modulation of endothelial cell function

In addition to its effects on immune cell production and biology, sleep impacts endothelial cell inflammation. Circulating levels of soluble adhesion molecules, such as intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) or E-selectin, are increased following short-term sleep deprivation in humans[199]. OSA also associates with complement system activation and higher levels of C3a leading to vascular endothelial cell inflammation and dysfunction[200,201]. Moreover, OSA increases microRNAs miR-92a and miR-630, which are implicated in endothelial inflammation[202]. T cells in individuals with OSA have expanded cytotoxicity and specifically target vascular endothelial cells, parameters that CPAP improves[203], while VCAM-1 (but not ICAM-1) abundance is independently associated with higher incidence of coronary artery disease in individuals with moderate-to-severe OSA[204]. Exposing human coronary artery endothelial cells to serum retrieved from individuals with OSA results in chemoattractant activity and augmented *VCAM1*, *ICAM1* and *IL8* mRNA expression, whereas these effects are less

potent with serum retrieved individuals with OSA treated with CPAP[205,206]. Mechanistic studies suggest endothelial dysfunction in individuals with OSA may involve sterol regulatory element binding protein 2, miR-210 and mitochondrial alterations[207].

Proper vasodynamics are important to vascular health. Moderate sleep restriction for 8 days lowers flow-mediated brachial artery vasodilation[208], while short nightly sleep duration associates with nitric oxide-dependent vasodilator dysfunction[209]. In line with this, individuals sleeping 6 h or fewer show increased occurrence of pathological vascular inflammation, while carotid wall thickness positively associates with sleep fragmentation[210]. In mice, sleep fragmentation induces vascular endothelial dysfunction and instigates morphological changes in vessels, changes that include the emergence of elastic fiber disruptions and elevated markers of senescence[211]. In accordance, a recent report demonstrated that circulating exosomes from mice undergoing persistent sleep fragmentation promote endothelial cell injury and exacerbate atherosclerosis through exosomal miR-182–5p-dependent upregulation of endothelial NF-κB and NLRP3 signaling[169]. Fluctuations in clock genes may also contribute to endothelial dysfunction upon sleep loss, as overexpression of a circadian regulator, cryptochrome 1, in vascular endothelial cells mitigates pro-inflammatory cytokines, adhesion factors and NF-κB activity caused by sleep deprivation[212]. Taken together, these findings show that sleep additionally benefits ASCVD by preserving endothelial cell function.

Conclusion

Healthy sleep is essential for cardiovascular health. A growing body of data from humans and animal models causally connect poor sleep and increased ASCVD and have begun to uncover the underlying mechanisms. While further work is needed to better understand this association, the autonomic nervous, metabolic and immune systems clearly link sleep to ASCVD. Sleep is a body-wide phenomenon; therefore, insufficient or poor-quality sleep elevates ASCVID risk by dysregulating intercommunication among multiple systems. Furthermore, the relationship between sleep and CVD is bidirectional as emerging data suggest cardiovascular complications perpetuate underlying sleep disturbances[213,214].

While epidemiological studies clearly associate insufficient or poor sleep with increased risk for ASCVD, causal evidence remains limited. Thorough and expanded assessments of specific sleep interventions, in humans and mice, are needed to demonstrate the direct influence of sleep on ASCVD and its molecular and cellular drivers. Most of the data summarized here illustrate the impact of inadequate sleep and sleep disorders on ASCVD. However, we cannot assume that reversing sleep deficiencies will translate to favorable ASCVD outcomes in clinical populations without rigorous empirical evidence. Indeed, as outlined in this Review, reversal of OSA symptoms with CPAP has generated mix results on ASCVD risk. Behavior-change therapy to increase sleep represents a feasible intervention[110], with low implementation burden and cost, that might meaningfully lower ASCVD risk. Additionally, personalized treatment of sleep disorders may also have ASCVD benefit. However, there is a critical need to test behavioral sleep intervention programs, explore new pharmacological and device-based options and refine treatment plans. Future studies in clinical populations will need to causally demonstrate that improving sleep

among short or poor sleepers mitigates ASCVD and its underlying autonomic, metabolic and inflammatory drivers. Such data would not only uncover novel biological connections between sleep and ASCVD but also influence public health policy, lifestyle guidelines and clinical management.

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BOX 1

Animal models in experimental sleep studies

Mice and rats are the most widely used animals in biomedical research. There is extensive understanding of their physiology, genetics and behavior with numerous genetically manipulated strains available. Technologies and reagents have been developed for their specific use and the animals reproduce rapidly, expediting experimental results and knowledge. However, their use in experimental sleep science and extrapolation of data to human sleep biology faces unique hurdles. Zeitgebers (ZTs), external rhythmic cues including light and food, entrain circadian biological rhythms of all animals. Unlike humans, rodents are nocturnal as approximately 80% of their sleep occurs during the light (inactive, ZT0-ZT12 in experimental laboratory settings) phase and 20% during the dark (active, ZT12-ZT24) phase. Rodent sleep is more fragmented compared to humans and they cycle through sleep stages more rapidly. Even in well-controlled settings, rodent sleep is highly sensitive to diverse genetic and environmental factors. Nonetheless, animal studies enable causal mechanistic investigations that uncover biological details at a scale that is not achievable in humans.

Multiple methods of experimental rodent sleep manipulation have been developed. The most common approaches are by physical or tactile sleep disruption with a rotating wheel or platform, an automated sweep bar or gentle handling. Such interventions have the advantage of compromising sleep in any animal model or strain, can be incorporated with additional experimental interventions and have more subtle and nuanced impact on stress responses. Chronic mild physical sleep fragmentation with a sweep bar does not cause overt systemic stress or result in circadian and molecular clock changes[11,12], allowing researchers to distinguish between the effects of sleep and circadian rhythm. Physical models of frequent sleep disruption, such as rotating or shaking platform or forced locomotion, may stimulate systemic stress responses depending on the setting[215–217]. Pharmacological and genetic interventions offer organ-specific and tissue-specific manipulation of sleep-mediating genes and pathways[218–221]; however, influences on circadian timing and developmental effects must be carefully considered. Optogenetic and chemogenetic tools allow for the most sophisticated and precise manipulation of sleep-licensing neural circuits with rapid and precise spatiotemporal control over specific neuronal structures and populations[222,223]. Finally, intermittent hypoxia recapitulates sleep apnea where hypoxic episodes cause awakenings[224,225].

Experimental sleep manipulation in rodents has enabled profound insights into the links between sleep and atherosclerosis. Animal models allow unfettered access and manipulation of relevant cells, tissues and organs enabling the discovery of complex and intertwining biological pathways including the autonomic nervous, metabolic and immune systems. Insights gained from rodent models of experimental sleep manipulations are robust and rigorous and have led to new mechanistic discoveries advancing our knowledge on the role of sleep in cardiovascular health.

BOX 2

Interplay between sleep and the autonomic system in modulating inflammation

Chronic activation of the SNS mediates inflammatory responses in CVD through various neurotransmitters, including norepinephrine, ATP, neuropeptide Y and nitric oxide[226]. This sympathetic control can be direct, through pro-inflammatory cytokine production and increased adhesion to endothelial cells, or indirect, by regulating leukocyte distribution, production or recruitment. However, causal mechanistic data connecting sleep-mediated SNS activity and inflammatory CVD remain limited. In mice, frequent sleep fragmentation (every 30 s) elevates systemic corticosterone[217] and SNS abrogation attenuates inflammation in multiple models of CVD[227]. Acute and chronic sleep fragmentation expand cytokine production in cardiovascular tissue and elevate systemic norepinephrine. Chemical sympathectomy blunts these responses and sleep recovery normalizes inflammation but not norepinephrine levels[228]. Sleep fragmentation-induced expression of inflammatory cytokines in heart and spleen is abated by blockade of alpha-adrenergic or beta-adrenergic receptors[229]. These findings suggest pharmacological manipulation of autonomic responses can reduce inflammation resulting from sleep disruption. In humans, increased sympathetic activation has been observed due to sleep fragmentation in the setting of OSA-related respiratory events[68]. Increased pulse rate response to OSA events represents a noninvasive measure of these sympathetic surges and is associated with worse CVD outcomes[95]. Stabilization of breathing and sleep fragmentation through OSA treatment among individuals with an elevated pulse rate response results in lower rates of major adverse CVD events[96].

The PNS has a key role in the regulation of inflammation via the ‘cholinergic anti-inflammatory pathway’ that is mediated via the vagus nerve and its major neurotransmitter, ACh[230]. The vagus nerve collects information on the inflammatory status of multiple organs via its sensory fibers and conveys signals back to the brain; a process known as the inflammatory reflex. Importantly, vagus nerve stimulation can modulate local inflammation by ACh-mediated suppression of cytokine production by macrophages[231]. Accordingly, manipulation of the inflammatory reflex shows promising therapeutic potential in many inflammatory diseases, including ASCVD[232].

In the heart, ACh mediates anti-inflammatory effects[233] through systemic and local attenuation of inflammation and decreased leukocyte infiltrates. Whether sleep affects the vagus inflammatory reflex is poorly understood. In mice, vagal afferents affect sleep via TNF[234] and, in a rat model, vagal nerve stimulation attenuated insufficient sleep-induced pro-inflammatory cytokine levels in the blood[235]. The spleen is a key organ in orchestrating the vagus nerve control over inflammation, where activated catecholaminergic fibers release norepinephrine, which promotes ACh production by local β_2-adrenergic receptor-expressing cells, including B cells and T cells[236]. Using a lipopolysaccharide (LPS)-induced sepsis model, a recent study described a microbiota–vagus nerve–spleen axis in modulating systemic inflammation upon sleep deprivation[237]. Further studies are warranted to understand whether persistent sleep manipulation

influences cholinergic anti-inflammatory pathways by suppressing vagal tone and local ACh production.

BOX 3

Sleep recovery and the resolution of inflammation

Can sleep recovery revert the effects of chronic suboptimal sleep on hematopoiesis? In mice, the number and proliferation of bone marrow hematopoietic progenitors remains raised after 4 weeks of sleep recovery following 16 weeks of sleep fragmentation[11]. However, a longer sleep recovery opportunity (10 weeks) normalizes hematopoiesis. These findings indicate that sleep persistently impacts the hematopoietic system. Indeed, sleep fragmentation exerts long-lasting effects on HSPCs by restructuring their epigenome[11]. Accordingly, a secondary immunological challenge after sleep fragmentation and recovery results in immunological recall responses that lead to an exaggerated, myeloid-biased inflammatory burst and worse outcomes[11]. Similarly, in human experimental sleep manipulation studies, 3 to 5 days of sleep restriction increases circulating blood monocytes and neutrophils[187,188], while subsequent recovery sleep lowers monocytes and lymphocytes, but not neutrophils[188]. The effects of prolonged repetitive patterns of sleep loss and recovery have also been investigated in the context of inflammation. Healthy individuals exposed to three sleep disturbance/recovery cycles —each consisting of three nights of various sleep interruptions (including delayed sleep onset, frequent awakenings and advanced sleep offset times) followed by one night of recovery sleep—showed an increase in plasma IL-6 levels[238]. Men, but not women, displayed increased circulating numbers of $CD8^+$ T cells and monocytosis, and the latter remained elevated even after recovery sleep[238]. Similar sex-specific effects of repetitive sleep loss with intermittent recovery were reported with regards to plasma IL-8 levels and progressively increased vasodilatory changes of small vessels[239]. In a slightly different experimental setting, a repetitive five-night sleep restriction/two-night recovery protocol induced increased IL-6 expression by monocytes, which remained heightened following recovery[240]. While these sleep intervention studies were not perceived as stressful by the participants, a dysregulated rhythm of serum cortisol and altered glucocorticoid sensitivity in monocytes was reported, indicating a compromised interplay between stress and the immune system that may contribute to the inflammatory sequelae. Moreover, prolonged sleep interruption may affect the resolution of inflammation, which is in part mediated by specialized pro-resolving mediators that are dysregulated in CVD[241]. Indeed, plasma levels of a prominent class of specialized pro-resolving mediators, called resolvins, were decreased following repeated exposure to sleep loss and remained low after a recovery sleep period[242]. Taken together, these findings suggest that recovery or ‘catch-up’ sleep might be insufficient in restoring inflammatory alterations arising from prolonged sleep disruption.

BOX 4

Sleep's influence on 'inflamm-aging' in ASCVD

As we age, consolidated nightly sleep decreases, incidence of sleep disorders increases, our immune system shifts toward a more inflammatory and myeloid-dominant profile, and our risk for ASCVD rises dramatically. These changes raise the hypothesis that age-related alterations in sleep compromise immunological function and thus contribute to ASCVD. In older adults, the hematopoietic system becomes less heterogeneous and a myeloid bias emerges. In murine clonal tracking experiments, chronic sleep disruption expedites hematopoietic neutral drift, thereby accelerating the decline of hematopoietic heterogeneity and skewing the system toward a myeloid fate[11]. Clonal hematopoiesis, a premalignant expansion of often deleterious hematopoietic stem cell clones, results from somatic mutations common in epigenetic modifiers, such as Tet2 or Dmnt3a, and increased risk of CVD twofold[243]. Murine data suggest poor-quality sleep expedites mutant HSPC clonal expansion[244]. In mixed chimeric mice, sleep fragmentation accelerates the proliferation and expansion of Tet2-mutant HSPC clones, leading to more frequent mutant myeloid cells in the blood. In support of the hypothesis that healthy sleep restricts HSPC epigenetic dysregulation and promotes diversity, human data demonstrate that sleep duration and fragmentation in adolescents correlate with leukocyte DNA methylation patterns and epigenetic age[245]. Symptoms of insomnia, including restlessness, difficulties falling asleep and frequent wake bouts, associate with increased epigenetic aging, as determined by DNA methylation levels, and immune senescence, including elevated counts of late differentiated T cells[246,247]. Additionally, individuals with severe OSA have shorter leukocyte telomers, and among these individuals, higher arousal index is associated with leukocyte telomere attrition over the prior decade[248]. Using PSG and sleep electroencephalography, estimations of 'brain age' can by derived that incorporate sleep fragmentation and changes in sleep architecture; greater age estimations associate with increased all-cause mortality and CVD[32]. Altogether, these observations support the hypothesis that poor-quality sleep contributes to systemic and cellular immunological aging and thus increased risk of age-related inflammatory diseases like ASCVD.

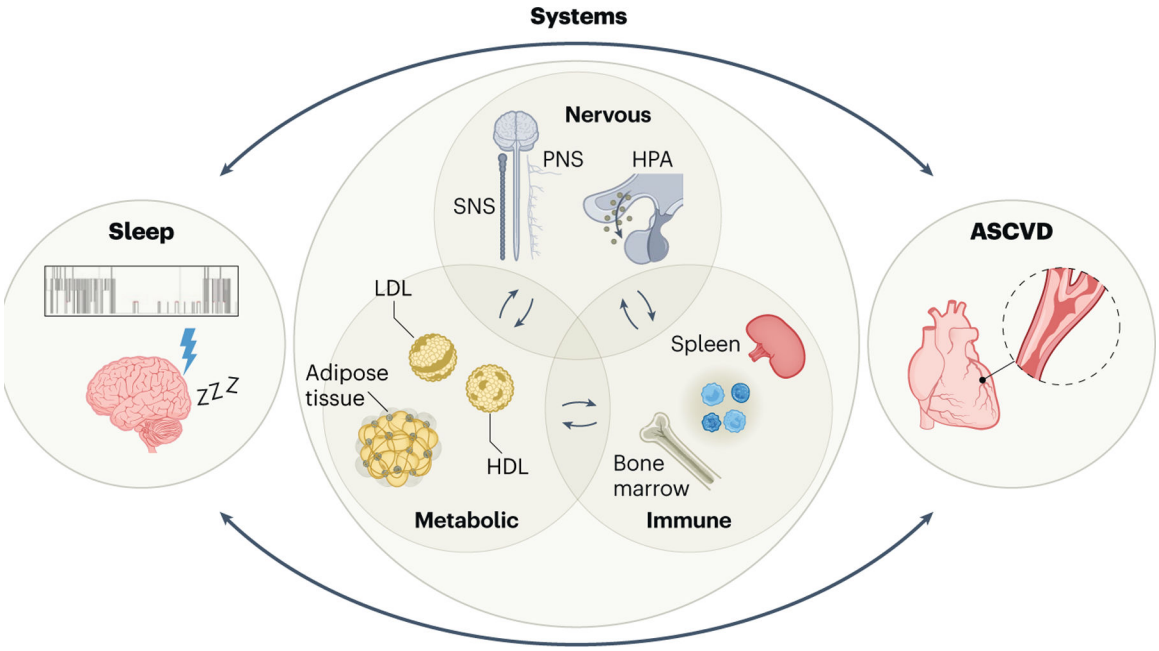

Fig. 1 |. Sleep and atherosclerotic cardiovascular disease are connected through the integration of the nervous, immune and metabolic systems.

Sleep calibrates ASCVD by modulating multiple core body systems. Interference of adequate sleep including sleep duration, quality and timing adversely affects the function of the nervous, metabolic and immune systems, which predisposes to ASCVD and its complications, including myocardial infarction and stroke. Emerging studies suggest these connections between ASCVD and sleep are bidirectional and peripheral metabolic, nervous and immune imbalance alter sleep.

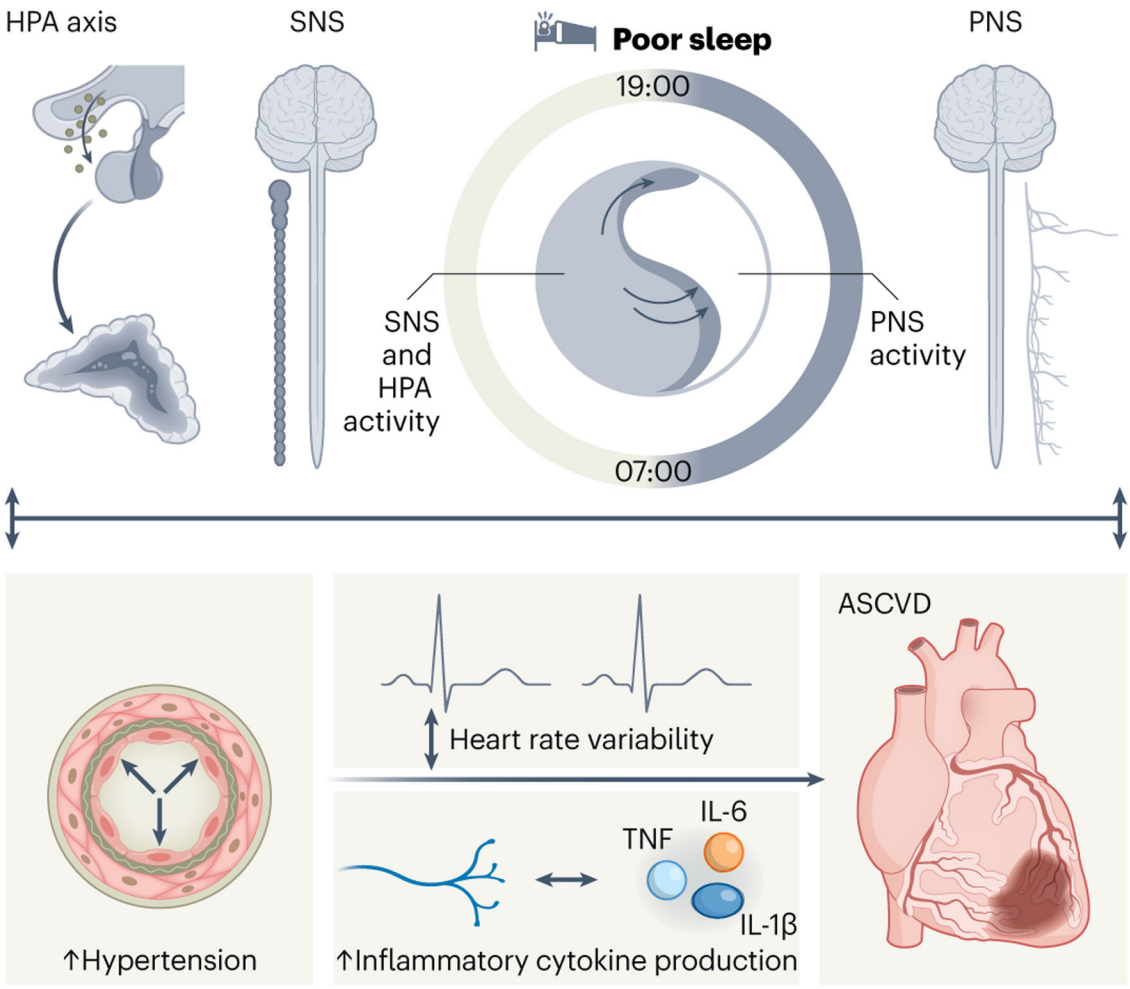

Fig. 2 |. Sleep and autonomic nervous balance.

Sleep exerts a modulatory effect on the activity of the autonomic nervous system. Persistent sleep disturbances lead to elevated SNS and HPA activity during sleep and wakefulness and modulate the tone of the PNS. Consequently, desynchronization of the HPA axis compromises heart electrophysiology leading to extremities in heart rate variability, while aberrant SNS and PNS activation triggers nocturnal non-dipping of blood pressure (BP) and daytime HTN. In addition, sleep manipulates SNS/PNS equilibrium instigating adverse immune responses in the heart including accentuated inflammatory cytokine production. Altogether, sleep deficiencies promote heart rate alterations, HTN and inflammation via compromising the autonomic nervous system, thus exacerbating ASCVD.

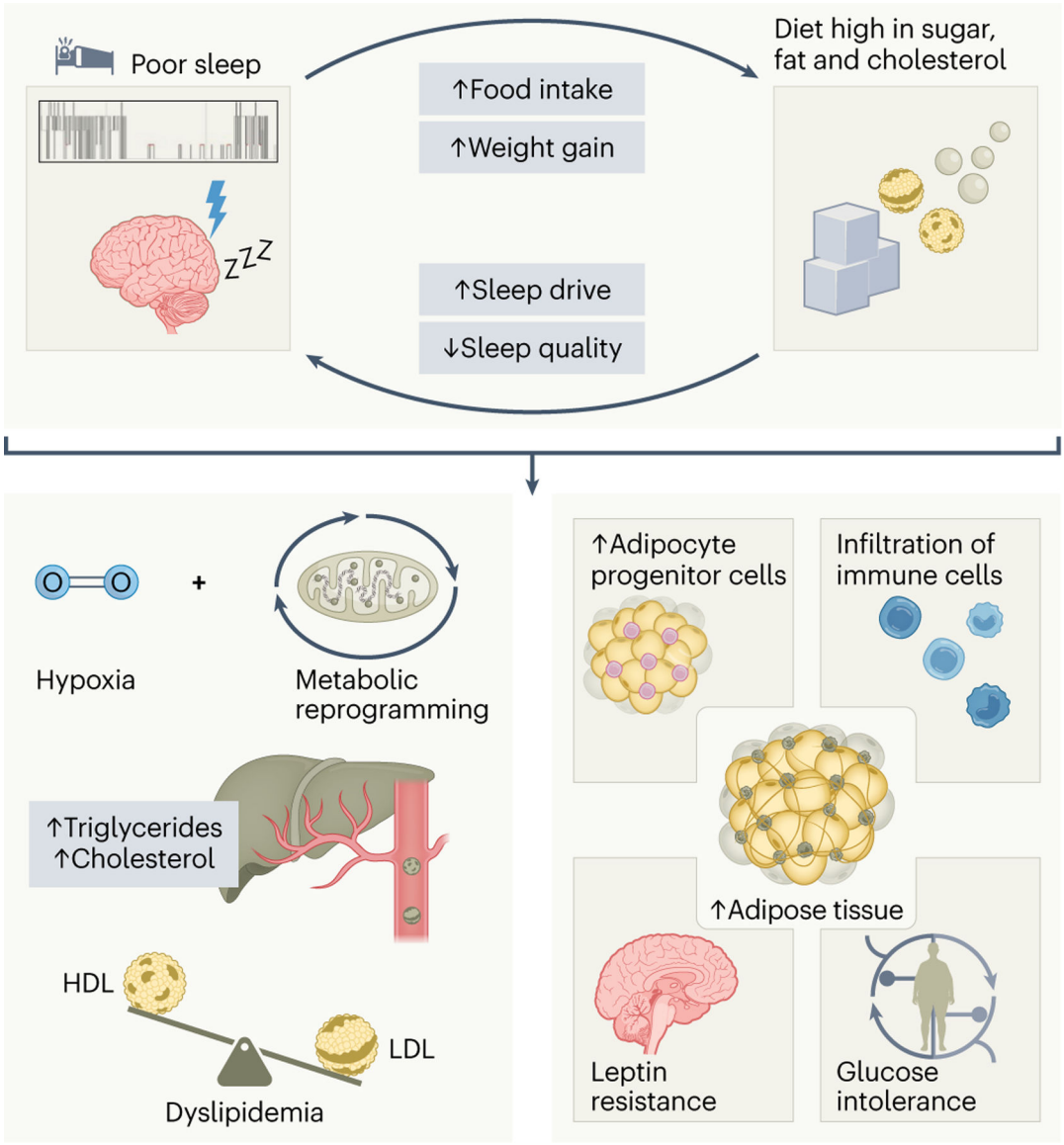

Fig. 3 |. Sleep and the metabolic system.

Sleep and the metabolic system share a bidirectional relationship. While sleep disturbances promote food intake and can cause subsequent weight gain, excess consumption of a sugar-rich and cholesterol-rich diet increases sleep drive with curtailed sleep quality. On the one hand, insufficient or irregular sleep can fuel metabolic syndrome by affecting hepatic triglyceride and cholesterol output via the modulation of hypoxia-dependent metabolic genes in the liver. Consequently, persistent sleep disruption may result in an atherogenic lipid profile with heightened LDL-c and triglyceride and lower HDL-c levels. On the other hand, suboptimal sleep hygiene propagates fat mass accumulation, adipocyte progenitor cell production and adipose tissue inflammation. Prolonged metabolic reprogramming of the adipose tissue contributes to leptin resistance as well as glucose intolerance and insulin resistance, thereby predisposing to cardiometabolic complications.

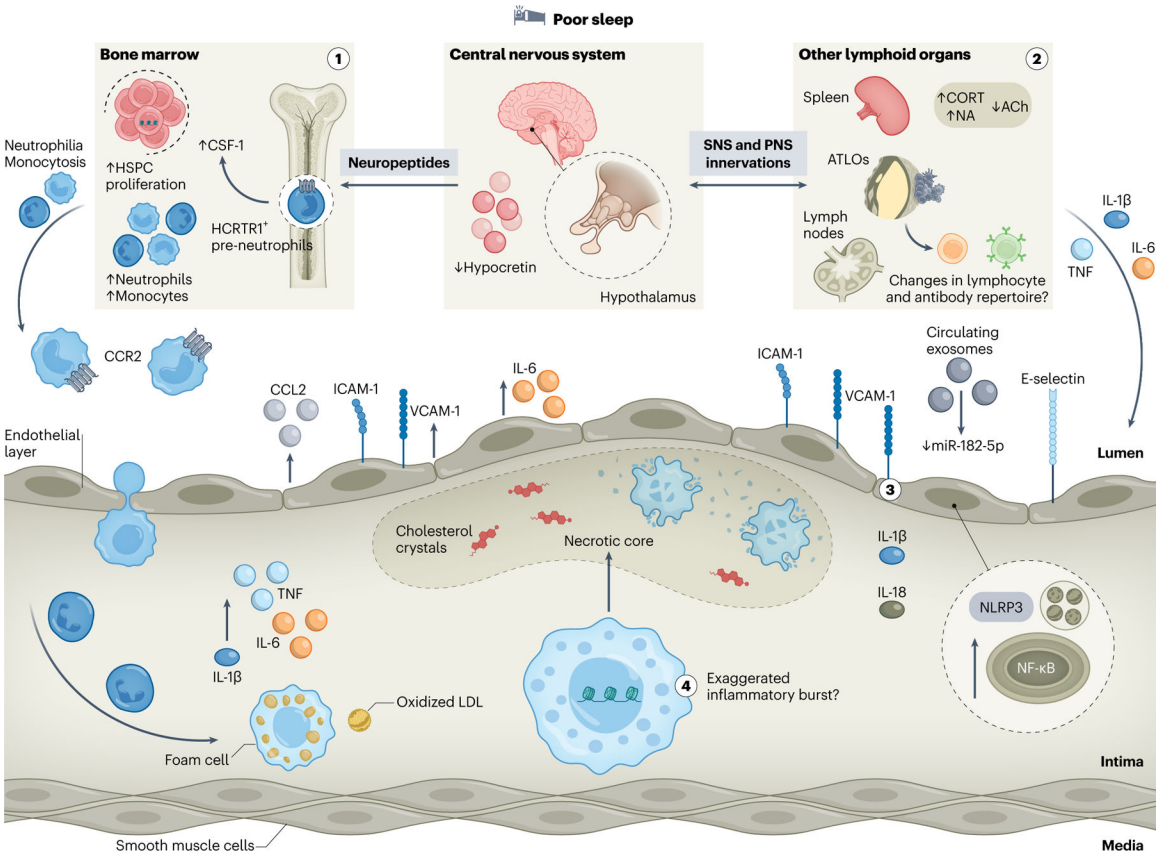

Fig. 4 |. Sleep protects from ASCVD by modulating inflammation.

The beneficial impacts of proper sleep on the immune system are manifold; thus, insufficient or poor-quality sleep exerts various adverse effects on inflammation that underlies atherosclerosis. Prolonged sleep disruption compromises neuroimmune communication axes that modulate leukocyte numbers and function via neuropeptide, SNS or PNS innervations. (1) Blunted hypocretin signaling from the lateral hypothalamus to bone marrow pre-neutrophils following sleep fragmentation heightens colony-stimulating factor-1 (CSF-1)-mediated medullary hematopoiesis and results in subsequent monocytosis and neutrophilia. Consequently, increased aortic immune cell infiltration drives exacerbated atherosclerotic lesion formation. (2) Enhanced sympathetic and compromised anti-inflammatory parasympathetic inputs to secondary lymphoid organs and neuroimmune cardiovascular interfaces at the adventitia — that is, artery tertiary lymphoid organs (ATLOs) — augment the production of pro-inflammatory cytokines including IL-6, TNF and IL-1β, further inciting an inflammatory milieu. Whether this affects local lymphocyte function and repertoire remains unknown. (3) Sleep disturbances promote endothelial cell dysfunction characterized by enhanced chemoattractant activity, including CCL2 release and increased expression of adhesion molecules, such as ICAM-1, VCAM-1 or E-selectin. Circulating exosomes promote endothelial cell injury via increased miR-182-5p-dependent NF-κB and NLRP3 signaling, thus licensing IL-1β and IL-18 production. These effects compromise endothelial cell integrity and further facilitate immune cell entry into the atheroma. (4) Persistent sleep fragmentation poses profound and lasting changes on hematopoietic stem cells via epigenetic restructuring, leading to exaggerated myeloid-biased

inflammatory bursts. Consequently, aortic macrophages derived from recruited monocytes may be strongly pro-inflammatory, defective of rate-limiting processes, such as lipid handling or efferocytosis and more prone to necrotic death, further fueling plaque growth and instability. ACh, acetylcholine; CORT, corticosterone; HCRTR1, hypocretin receptor 1; NA, noradrenaline.