GeroScience (2021) 43:137–158
https://doi.org/10.1007/s11357-020-00312-y

REVIEW

Effects of sleep deprivation on endothelial function in adult humans: a systematic review

Brady J. Holmer · Stephanie S. Lapierre · Danielle E. Jake-Schoffman · Demetra D. Christou

Received: 26 October 2020 / Accepted: 6 December 2020 / Published online: 9 February 2021

Abstract Sleep deprivation is highly prevalent and is associated with increased cardiovascular disease (CVD) morbidity and mortality. Age-related alterations in sleep and chronobiology may exaggerate CVD susceptibility in older individuals. The mechanisms responsible for the association between sleep deprivation and CVD are not fully understood, but endothelial dysfunction may play a central role. Our objective was to conduct a systematic literature review to evaluate the evidence on the effects of sleep deprivation on endothelial function (EF). This review adhered to the PRISMA guidelines and was pre-registered with PROSPERO (#CRD42020192485, 07/24/2020). We searched PubMed, Web of Science, Embase, and Cochrane Library for articles published through May 1, 2020. Eligibility criteria included publication in English and use of well-established EF methodologies in adult humans. Two investigators independently performed the literature search, study selection, data extraction, risk-of-bias assessment, and qualitative data synthesis. Out of 3571 articles identified, 24 articles were included in the systematic review. Main findings include the following: (1) shorter sleep duration is associated with lower macrovascular EF; (2) not sleeping 7–9 h/night is linked with impaired microvascular EF; (3) sleep restriction impairs micro- and macrovascular EF; (4) acute total sleep deprivation impairs micro- and macrovascular EF but data on macrovascular EF are less consistent; and (5) shift work impairs macrovascular EF. In conclusion, sleep deprivation impairs EF, which may explain the link between insufficient sleep and CVD. Future investigations should fully elucidate the underlying mechanisms and develop strategies to combat the adverse endothelial effects of sleep deprivation across the lifespan.

Keywords Sleep deprivation · Endothelial function · Cardiovascular aging · Chronobiology

Introduction

Sleep deprivation is one of the top modifiable risk factors to human health. The American Heart Association and CDC advocate that adults receive at least 7 h of sleep each night to promote optimal health and reduce the risk for disease [1, 2]. In agreement with this, the National Sleep Foundation recommends that adults obtain 7–9 h of sleep per night [3], yet nearly 50% fail to meet this recommendation [4]. Sleep deprivation is also an important issue in the elderly, over half of whom report sleep complaints including a diminished ability to

B. J. Holmer · S. S. Lapierre · D. D. Christou (✉)
Department of Applied Physiology and Kinesiology, College of Health and Human Performance, University of Florida, 1864 Stadium Road, Gainesville, FL 32611-8205, USA
e-mail: ddchristou@ufl.edu

D. E. Jake-Schoffman
Department of Health Education and Behavior, College of Health and Human Performance, University of Florida, 1864 Stadium Road, Gainesville, FL 32611-8205, USA

achieve sufficient sleep duration and quality [5], which is likely secondary to the effects of age-related chronobiological disruption [6–8]. The consequences of insufficient sleep are far from benign. Indeed, there is compelling evidence that reduced sleep duration and poor sleep quality both dramatically increase the morbidity and mortality associated with cardiovascular disease (CVD) [2, 9–12], the leading cause of death in the USA [13]. Importantly, aging, a recognized CVD risk factor [14], may act in concert with insufficient sleep to accelerate cardiovascular aging and increase CVD risk. Promoting successful cardiovascular aging may start with extending the same consideration to sleep as has been given to other traditional CVD risk factors (e.g., hypertension, dyslipidemia, obesity, and physical inactivity) [15].

That sleep is ubiquitous among all organisms implies that it is indispensable [16]. Adequate sleep at the appropriate biological time is also critical for homeostatic maintenance. Endogenous chronobiological rhythms evolved to synchronize physiological processes with environmental and behavioral stimuli (e.g., day and night, feeding and fasting, activity and rest) [17]. The human cardiovascular system is not exempt from chronobiological influence. Circadian clocks are present in cardiac, smooth muscle, and endothelial cells, regulating processes such as heart rate, blood pressure, and endothelial function [18], all of which exhibit diurnal fluctuations. Unfortunately, modern lifestyles encourage living out of sync with our circadian biology [19], which leads to chronobiological disruption and is likely the cause of many preventable diseases including CVD [20].

The burden of chronobiological disruption and sleep deprivation on CVD risk may be exacerbated in the aging population which is expected to grow dramatically in the coming decades [21]. Aging is independently associated with chronobiological disruptions and alterations in sleep duration and quality that ultimately predispose older individuals to sleep deprivation [22]. Even though aging is associated with a reduced amount and quality of sleep, there is no evidence to conclude that the *need* for sleep decreases with age [22]. As such, the dysfunctional circadian rhythms in older individuals may impair sleep and exacerbate their predisposition to CVD by negatively impacting cardiovascular health. Given that sleep is largely a voluntary behavior, raising awareness about the interaction of sleep and health may support prioritizing healthy sleep behaviors to promote optimal cardiovascular health across the lifespan [2].

Humans experience insufficient sleep in a variety of ways, all of which likely have acute negative physiological effects and when experienced chronically, predispose to disease. Chronic sleep restriction occurs when an individual receives less sleep than their optimal sleep duration for days, weeks, months, or even years, and is likely the most prevalent form of sleep deprivation. Humans also experience insufficient sleep due to shift work which affects more than 15% of the workforce [23]. Shift workers frequently experience sleep restriction concomitant with abnormal sleep schedules that are often out of line with human biological rhythms [24–26]. Finally, extended wakefulness of 24 h or more, termed total sleep deprivation (TSD), can have dramatic physiological effects, although this form of sleep insufficiency is perhaps less prevalent, as the majority of individuals do not routinely stay awake for 24 h or more at a time. Regardless of how sleep deprivation is experienced, the resulting chronodisruption may impair cardiovascular function and increase the risk for CVD.

Identifying the mechanisms underlying the role of insufficient sleep in the pathogenesis of CVD could facilitate the development of therapeutic strategies to attenuate the adverse effects of sleep deprivation on human cardiovascular health. While various cardiometabolic risk factors have been proposed [2], a compelling but understudied mechanism by which sleep deprivation may be associated with CVD is endothelial dysfunction. Endothelial dysfunction is the initiating event in the development of atherosclerosis, detectable before clinical manifestations of CVD [27], and therefore an ideal target for investigating the early effects of sleep deprivation on cardiovascular health. Furthermore, endothelial function measured in coronary and peripheral arteries predicts future CVD events (i.e., myocardial infarction and stroke) and death [28–30]. Endothelial dysfunction is a hallmark of cardiovascular aging, even in the absence of other CVD risk factors [31]. Importantly, age-related impairments in micro- and macrovascular endothelial function contribute to increased susceptibility to CVD in the elderly (reviewed in Ghebre et al. [32]). Therefore, elucidating the role of sleep in preserving endothelial function may be paramount to successful vascular aging.

Sleep deprivation may accelerate the development of age-associated endothelial dysfunction and through this mechanism contribute to the pathogenesis and progression of CVD. Reviewing the evidence on how sleep deprivation impacts endothelial function may offer a

lens into how sleep and chronobiological disruptions throughout life may negatively impact the trajectory of cardiovascular aging. This could aid in the development of recommendations for healthy lifestyle behaviors for successful aging. It could also stimulate the design of experimental studies to define the mechanisms by which sleep deprivation affects vascular aging. Therefore, we aimed to conduct a systematic review of the literature to evaluate the observational and experimental evidence on the effects of sleep deprivation on endothelial function. We also sought to discuss the potential underlying mechanisms and construct a conceptual model linking sleep deprivation to CVD.

Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [33] and adhered to the PRISMA standards and checklist. The protocol for this systematic review was pre-registered online through the PROSPERO International Prospective Register of Systematic Reviews (registration #CRD42020192485) and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=192485.

Eligibility criteria

We sought to provide a comprehensive synthesis of the current state of knowledge; therefore, we did not restrict our systematic review to specific study designs. Articles were included if they (1) were full-length peer-reviewed primary research articles (i.e., no reviews, dissertations, or conference abstracts were considered); (2) focused on adult humans; and (3) assessed micro- or macrovascular endothelial function using well-established methodologies. Articles were excluded if they (1) focused exclusively on animal models due to confounders associated with experimental sleep deprivation (e.g., stress) which may limit their relevance to humans; (2) included individuals younger than 18 years of age due to potential developmental differences in sleep and cardiovascular physiology; and (3) focused on sleep disorders because these conditions are associated with other comorbidities that could confound the association between sleep and endothelial function.

This review evaluated diverse lines of evidence based on observational and experimental studies. Observational studies compared endothelial function in adults who receive short vs. normal sleep duration or assessed the association of sleep duration with endothelial function. Experimental studies manipulated sleep duration and compared endothelial function following normal sleep and sleep deprivation. Sleep deprivation models included (1) TSD, where participants were deprived of sleep for 24 h or more; (2) prolonged sleep restriction, where nightly sleep was limited to a fraction of the participants' habitual sleep duration for several days to weeks; and (3) shift work, where participants worked an overnight or extended shift of 24 h or more.

Primary outcome

The primary outcome of this systematic review was micro- and macrovascular endothelial function including assessments of blood vessels in the coronary circulation, periphery, or skin using vasodilation or blood flow responses to physiological or pharmacological stimuli.

Information sources

Studies were identified by two investigators (BJH and SSL) from independent computerized literature searches of the following databases: PubMed, Web of Science, Embase, and Cochrane Register of Controlled Trials. Each database was searched using a customized search string to optimize results. Searches were restricted to (1) human studies and (2) studies published in the English language. Additional articles were identified by scanning the references of identified articles. All searches were conducted between the earliest available search date for each database and the last search date of May 1, 2020.

Search strategy

The search strategy used for this systematic review is provided below. The following customized search string and limits were used: (sleep deprivation OR sleep restriction OR insufficient sleep OR sleep curtailment OR short sleep duration OR sleep loss) AND (brachial artery flow-mediated dilation OR brachial artery flow-mediated vasodilation OR brachial artery OR vasodilation OR vascular reactivity OR microvascular function OR vascular function OR endothelial function OR FMD OR vascular health OR microvascular OR vascular tone

OR arterial stiffness OR pulse wave velocity OR PWV OR hemodynamics OR wave reflection OR augmentation index OR vascular stiffness OR aortic stiffness). Filters: Humans, English.

Study selection

Search results from each database were downloaded and imported into EndNote X9 to identify and remove duplicates. Two review team members (BJH and SSL) independently screened the titles and abstracts of all records to identify additional duplicates. After removal of duplicate articles, BJH and SSL reviewed the title and abstract of each record to determine its potential for inclusion based on the participants, intervention, comparison, outcomes, and study (PICOS) types. Relevant articles were downloaded as full-text and further screened to determine eligibility based on our specific inclusion and exclusion criteria. Any discrepancies between the two reviewers were reconciled through discussion and consultation with a third review team member (DDC) was sought if a consensus could not be reached. Included and excluded records were tracked within EndNote, and reasons for exclusion were documented in a Microsoft Excel spreadsheet.

Data collection and data items

Data collection and extraction were performed independently by BJH and SSL, while a third review team member (DDC) was available for mediation. Extracted data were inputted into a pre-formatted Microsoft Excel spreadsheet using open-text responses. If data were missing or clarifications were needed, the study's corresponding author was contacted with a request to obtain unreported data or additional details. Following data extraction, review team members discussed and reconciled any discrepancies. The following variables were extracted from each study: authors, publication year, participant characteristics (average age, # of males/females), study design, sample size, method used for evaluating/manipulating sleep and assessing endothelial function, and key results.

Data synthesis

Data on study selection and inclusion are presented quantitatively in the text and in a flow diagram (Fig. 1) and include number of articles identified at each stage, number of articles included/excluded, and reasons for exclusion. Study characteristics are summarized in text and presented in Tables 1 and 2. Outcome data were organized by study design consisting of observational and experimental studies and within each study design, data were summarized based on sleep deprivation model. Data were then qualitatively synthesized to examine similarities and differences in key findings. When findings conflicted, subject characteristics and other methodological aspects were closely examined as potential explanatory factors. There was no plan to conduct a meta-analysis due to the diverse methodologies used to implement sleep deprivation and assess sleep and endothelial function. The mechanisms responsible for the adverse effects of sleep deprivation on endothelial function were investigated only in some of the studies included in this systematic review. Although not a formal objective of our review, mechanistic data are discussed in the text and incorporated in a conceptual model linking sleep deprivation to CVD.

Risk of bias

Risk of bias was assessed independently by BJH and SSL and any discrepancies between reviewers were resolved through discussion. Risk of bias was conducted for each study at the outcome level for the effect of assignment to intervention. For observational and non-randomized experimental studies, the risk of bias was assessed using the Risk of Bias in Non-Randomized Studies—of Interventions (ROBINS-I) [58] that focuses on 7 domains which include bias arising from (1) confounding; (2) selection of participants; (3) classification of interventions; (4) deviations from intended interventions; (5) missing outcome data; (6) measurement of outcome; and (7) selection of the reported result. For randomized experimental studies, the risk of bias was assessed using the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB 2) [59] that focuses on 5 domains which include bias arising from (1) randomization process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of outcome; and (5) selection of the reported result. Determination of risk of bias was aided using the Cochrane Risk of Bias Tools [58, 59]. Risk of bias for each domain and overall risk of bias across all domains for each study were graphically presented using the Risk-of-bias VISualization (robvis) software [60]. Additionally, risk of bias for each domain were graphically

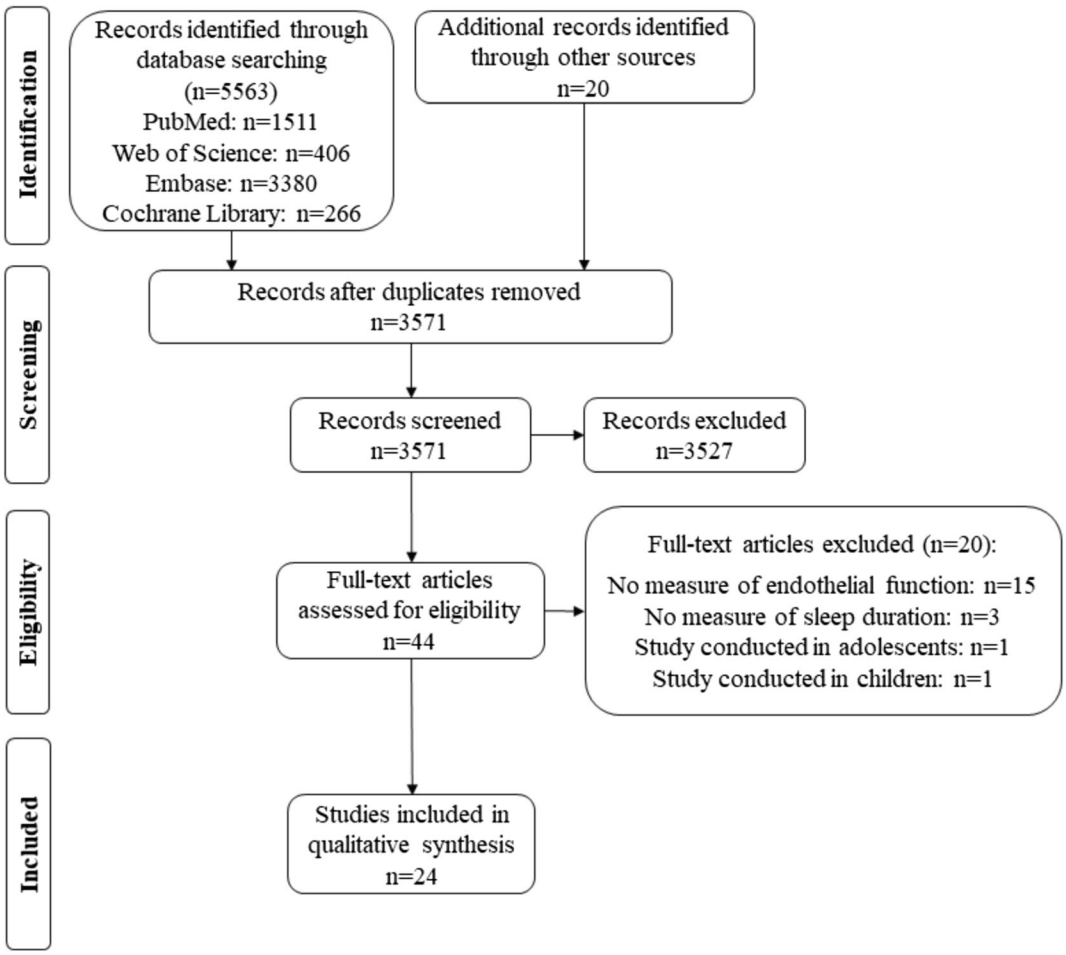

Fig. 1 Flow chart summarizes the results of the screening process and final article selection

presented across all observational/non-randomized experimental studies and across all randomized experimental studies using the same software.

Results

Study selection

Detailed information regarding study identification, screening, eligibility, exclusion from and inclusion in the review is presented in the flow diagram (Fig. 1). The initial literature search produced 5563 articles which after removal of duplicates yielded 3571 articles. After an initial screening, 3527 articles were excluded based on title and abstract and 44 articles were assessed for eligibility based on full-text using our inclusion and exclusion criteria. Following full-text screening, a total of 20 articles [61–80] were excluded for the following reasons: no measure of endothelial function ($n = 15$), no measure of sleep duration ($n = 3$), and inclusion of children or adolescents ($n = 2$). In total, 24 articles were included in this systematic review. Excluded articles and reasons for exclusion can be found in Supplementary table 1 in the Online Supplementary Material.

Study characteristics

Our search resulted in 7 observational [34–40] (Table 1) and 17 experimental [41–57] (Table 2) studies involving a total of 1598 participants (51.3% female) ranging from 20 to 60 years of age. Eleven studies (45.8%) enrolled both males and females, 11 (45.8%) enrolled only males, and 2 (8.3%) enrolled only females. Study characteristics are presented in Tables 1 and 2.

Table 1 Main characteristics of observational studies included in the systematic review

Study	Study design	Participants (age in years)	Sample size	Sleep duration assessment	Endothelial function assessment	Results
Bonsen 2015 [34]	Cross-sectional	Healthy adults (42)	259 (116M/143F)	Self-reported SSD: <7 h/night NSD: ≥7 h/night	Capillary recruitment to reactive hyperemia	↓ Capillary function in women with SSD (β=−11.17, P=0.04) but not in men (β=−0.79, P=0.81)
Bain 2017 [35]	Cross-sectional	Sedentary men SSD: 55±2 NSD: 58±2	30 (15 SSD/15 NSD)	Self-reported SSD: <7 h/night NSD: ≥7 h/night	FBF in response to ACh	↓ Vasodilation to ACh in SSD: FBF: (SSD: 11.7±1 vs. NSD: 14.5± 0.5 ml/100 ml tissue/min, P<0.05) FBF_{auc}: (SSD: 53±6 vs. NSD: 74±6 ml/100 ml tissue/min, P<0.05)
Weil 2013 [36]	Cross-sectional	Sedentary men SSD: 50±2 NSD: 50±3	30 (15 SSD/15 NSD)	Self-reported SSD: 6.1±0.2 h/night NSD: 7.6±0.2 h/night	FBF in response to BK	No group diff. in FBF response (SSD: 16.1±0.8 vs. NSD: 14.9±0.9, ml/100 ml tissue/min, P≥0.05)
Weil 2010 [37]	Cross-sectional	Sedentary adults (57±1)	80 (50 NSD [32M/18F]/30 SSD [17M/13F])	Self-reported SSD: 6.1±0.1 h/night NSD: 7.6±0.1 h/night	FBF response to BQ-123	~3-fold ↑ dilation to BQ-123 infusion in SSD (P<0.05, means not reported)
Hall 2017 [38]	Prospective	Adults SSD: 61.5±8.4 NSD: 56.8±10.3	141 (94 in SSD [39M/55F]/47 in NSD [10M/37F])	Sleep monitored using polysomnography SSD: <7 h/night NSD: ≥7 h/night	Brachial artery FMD	No group diff. in FMD: (SSD: 6.1±4.7% vs. NSD: 7.3±4.2%, P>0.05) ↓Sleep duration associated with ↓ FMD (β=0.171, P=0.04)
Aggarwal 2018 [39]	Cross-sectional	Women (31±9)	26	Sleep monitored using actigraphy over 14 days (7.62±0.45 h)	Brachial artery FMD	No association of sleep duration with FMD (r and P values not reported)
Behl 2014 [40]	Cross-sectional	Healthy adults (48±11)	684 (219 M/465F)	Self-reported	Brachial artery FMD	No association of sleep duration with FMD (P=0.07, r value not provided)

ACh acetylcholine, *BK* bradykinin, *BQ-123* selective ET-A receptor antagonist, *F* females, *FBF* forearm blood flow, FBF_{auc} forearm blood flow area under the curve, *FMD* flow-mediated dilation, *M* males, *NSD* normal sleep duration, *SSD* short sleep duration

Table 2 Main characteristics of experimental studies included in the systematic review

Study	Study design	Participants (age in years)	Sample size	Sleep deprivation model	Endothelial function assessment	Results
Total sleep deprivation						
Grassi 2016 [41]	Randomized crossover	Healthy adults (25.3±3.6)	32 (16M/16F)	Supervised TSD SD: 24-h TSD NS: FS	Brachial artery FMD	FMD ↓ after TSD (SD: 5.52±0.53% vs. NS: 6.53±0.63%, P=0.02)
Wehrens 2012 [42]	Non-randomized crossover	Men Shift workers (35.7±7.2) Non-shift workers (32.5±6.2)	25 (11 shift/14 non-shift workers)	Supervised TSD Polysomnography SD: 30.5-h TSD NS: 7.5–8 h	Brachial artery FMD	No change in FMD after TSD (means and P value not reported)
Sauvet 2009 [43]	Non-randomized crossover	Healthy men (29.1±3.3)	12	Supervised TSD Polysomnography SD: 40-h TSD NS: FS	CVC in response to ACh	CVC_{peak} and CVC_{auc} to ACh ↓ after 29 h TSD: CVC_{peak} (SD: 283±163 vs. NS: 454±158 PU/mmHg, P=0.03); CVC_{auc} (SD: 8.1±2.2 vs. NS: 16.7±6.5 PU/mmHg, P=0.02)
Sauvet 2017 [44]	Non-randomized crossover	Healthy men (27.3±5.4)	16	Supervised TSD Polysomnography SD: 40-h TSD NS: 8 h	CVC in response to ACh/insulin/heat	CVC_{peak} after TSD in response to ACh/insulin/heat ↓: ACh (SD: 67.2±8.2 vs. NS: 106.5±7.5 PU/mmHg, P=0.001); insulin (SD: 19.7±3.2 vs. NS: 35.8±5.1 PU/mmHg, P=0.001); heat (SD: 115.5±11.0 vs. NS: 131.7±9.6 PU/mmHg, P=0.004)
Sauvet 2012 [45]	Randomized crossover	Healthy men (30.6±2.1)	10	Supervised TSD Polysomnography SD: 29-h TSD NS: FS	CVC in response to CWI	No change in baseline CVC after TSD (SD: 0.6±0.2 vs. NS: 0.8±0.2, P=0.9). CVC during CWI lower after TSD: CVC (SD: 30.0±40.2 vs. NS: 143.6±78 PU/mmHg, P=0.04), CVC_{max} (SD: 240±133.7 vs. NS: 385.9±169.7 PU/mmHg, P=0.04), CVC_{auc} (SD: 225.3±123.9 vs. NS: 995.0±181.6 PU/mmHg, P=0.04)
Yang 2012 [46]	Randomized crossover	Healthy adults (22±1)	28 (14M/14F)	Supervised TSD SD: 24- h TSD NS: FS	FBF and FVC in response to reactive hyperemia	No change in FBF or FVC to reactive hyperemia after TSD: FBF: (Δ67±12% vs. Δ83±13%, P=0.2); FVC: (Δ47±8% vs. Δ59±11%, P=0.25)

Table 2 (continued)

Study	Study design	Participants (age in years)	Sample size	Sleep deprivation model	Endothelial function assessment	Results
Sleep restriction						
Sekine 2010 [47]	Randomized crossover	Healthy men (29±6)	26	Self- reported SR SD: 3.7±0.9 h NS: 7.1±0.2 h	CFVR to ATP	CFVR to ATP ↓ after SR (SD: 3.3±0.6 vs. NS: 4.2±0.9, $P<0.001$)
Calvin 2014 [48]	Randomized parallel-group	Healthy adults (SD: 24.1±4.5; NS: 25.1±5.0)	16: 8 NS (5M/3F) 8 SD (5M/3F)	Supervised SR Polysomnography SD: 5.1±0.4 h/8 nights NS: 6.8±0.8 h/8 nights	Brachial artery FMD	FMD ↓ after SR but not NS: SD: 8.6±4.6% to 5.2±3.4%, $P=0.01$ NS: 6.7±2.9% to 5.0±3.0%, $P=0.1$ Between group difference: −4.4%, $P=0.003$
Takase 2004 [49]	Non-randomized crossover	Healthy men (21.7±1.1)	30	Self-reported SR SD: <80% sleep/4 weeks NS: habitual sleep/1 week	Brachial artery FMD	FMD ↓ after SR (SD: 3.7±2.3% vs. NS: 7.4±3.0%, $P<0.05$)
Dettoni 2012 [50]	Randomized crossover	Healthy men (31±2)	13	Monitored SR Actigraphy SD: 4.5±0.3 h/5 nights NS: 8±0.5 h/5 nights	Endothelium-dependent venodilation to ACh	Dilation to ACh ↓ after SR ($P<0.001$, means not reported)
Sauvet 2015 [51]	Non-randomized crossover	Healthy men (29.3±5.2)	12	Supervised SR and polysomnography SD: 3.68±0.18 h/6 nights NS: 7±0.3 h/1 night	CVC in response to MCh/cathode current/heat	CVC_{peak} to MCh and heat ↓ after SR day 6; ($P<0.05$, means not reported) CVC to cathode current did not change after SR ($P>0.05$, means not reported)
Shift work						
Garcia-Fernandez 2002 [52]	Randomized crossover	Healthy medical residents (27–35)	15 (9M/6F)	Unmonitored SW SD: 24-h shift NS: regular shift/FS	Brachial artery FMD	FMD ↓ after SW (SD: 3.4±2.8% vs. NS: 11.3±7.0%, $P<0.001$)
Zheng 2006 [53]	Randomized crossover	Healthy medical residents (29)	22 (15M/7F)	Unmonitored SW Self-reported SD: 30-h shift NS: 6-h shift	Brachial artery FMD	FMD ↓ after SW (SD: 3.2% vs. NS: 7.9%, $P<0.001$)
Tarzia 2011 [54]	Randomized crossover	Healthy medical trainees (27.3±1)	20 (9M/11F)	Unmonitored SW Self-reported SD: night shift NS: FS	Brachial artery FMD	FMD ↓after SW (SD: 8.0±1.4% vs. NS: 8.6±1.7%, $P=0.025$)

Table 2 (continued)

Study	Study design	Participants (age in years)	Sample size	Sleep deprivation model	Endothelial function assessment	Results
Shimada 2011 [55]	Non-randomized crossover	Healthy male medical staff (32±7)	19	Unmonitored SW Self-reported SD: night shift NS: FS	Brachial artery FMD	FMD ↓ after SW (SD: 10.4±1.8% vs. NS: 12.5±1.7% $P<0.001$)
Kim 2011 [56]	Non-randomized crossover	Healthy female nurses (30.1±4.1)	22	Unmonitored SW SD: 3 night shifts NS: regular workday/FS	Brachial artery FMD	FMD ↓ after SW (SD: 7.6±2.4% vs. NS: 13.3±3.5%, $P<0.001$)
Amir 2004 [57]	Non-randomized crossover	Healthy physicians (35±4)	30 (23M/7F)	Unmonitored SW Self-reported SD: 24-h shift NS: regular workday/FS	Brachial artery FMD	FMD ↓ after SW (SD: 6.7±4.8% vs. NS: 10.5±4.5%, $P<0.0001$)

ACh acetylcholine, *ATP* adenosine triphosphate, *CFVR* coronary flow velocity reserve, *CVC* cutaneous vascular conductance, CVC_{auc} cutaneous vascular conductance area under the curve, CVC_{max} maximal cutaneous vascular conductance, CVC_{peak} peak cutaneous vascular conductance, *CWI* cold-water immersion, *FBF* forearm blood flow, *F* female, *FMD* flow-mediated dilation, *FS* full night of sleep, *FVC* forearm vascular conductance, *M* male, *MCh* methacholine, *NS* normal sleep, *PU* perfusion units, *SD* sleep deprivation, *SR* sleep restriction, *SW* shift work, *TSD* total sleep deprivation

Observational studies

General characteristics Seven observational studies were included which enrolled a total of 1250 participants (58% female) ranging from 20 to 60 years of age. Methodologies to assess endothelial function differed widely across studies and included macrovascular function using brachial artery flow-mediated dilation (FMD) [38–40] and microvascular function using forearm blood flow (FBF) response to acetylcholine (ACh), bradykinin (BK), or a selective endothelin 1 (ET-1) receptor A antagonist (BQ-123) [35–37], and capillary recruitment response to reactive hyperemia [34]. Methodologies to assess sleep duration also varied widely with the majority of studies using self-reported methods based on validated sleep questionnaires (Stanford Physical Activity Questionnaire, Pittsburgh Sleep Quality Index, and Epworth Sleepiness Scale) [34–37, 40] while 2 studies used objective sleep tracking (actigraphy or overnight polysomnography) [38, 39]. Observational studies assessed the cross-sectional [39, 40] or prospective [38] association of habitual sleep duration with endothelial function, or compared endothelial function in individuals with short vs. normal habitual sleep duration [34–38].

Sleep duration and endothelial function Three studies examined the association of sleep duration with macrovascular endothelial function assessed by brachial artery FMD. In a cohort of men and women, shorter sleep duration assessed by polysomnography was prospectively associated with reduced FMD ~ 18 years later [38], though not after adjusting for known CVD risk factors. However, in another study in men and women, there was no significant association between self-reported sleep duration and FMD [40]. Similarly, in a study in women, no association was observed between actigraphy-assessed sleep duration and FMD [39]. No studies examined the association of sleep duration with microvascular endothelial function. Collectively, these studies show that sleep duration is directly associated with macrovascular endothelial function, but this association is not consistently observed and the association with microvascular endothelial function remains unexplored.

Four studies examined differences in microvascular function between adults with short and normal self-reported sleep duration. In adults who did not receive

the recommended amount of sleep (≥ 7 h), vasodilation to ACh was reduced by 20% [35]. Additionally, adults who did not receive the recommended 7 h of sleep/night had a ~ 3-fold greater dilator response to infusion of an ET-1 receptor A antagonist [37]. One study also found that women with short sleep duration (< 7 h) had impaired capillary recruitment in response to reactive hyperemia, while the results in men were not significant [34]. Lastly, no differences were found in forearm blood flow responses to BK between adults with short (< 7 h) and normal sleep duration [36]. No studies have compared macrovascular endothelial function between short and normal sleepers. Collectively, these studies consistently demonstrate that adults who do not meet the recommended amount of sleep have reduced microvascular endothelial function, but whether they also have reduced macrovascular endothelial function remains unknown.

Experimental studies

General characteristics Seventeen experimental studies were included, which enrolled a total of 348 participants (26% female) ranging from 20 to 40 years of age. Endothelial function was assessed using coronary artery flow velocity reserve response to adenosine triphosphate [47], brachial artery FMD [41, 42, 48–50, 52–57], FBF and forearm vascular conductance (FVC) response to reactive hyperemia [46], venodilation to ACh [50], and cutaneous vascular conductance (CVC) to ACh, MCh, insulin, heat, cold, and/or cathode current [43–45, 51]. Methods used to manipulate sleep duration included TSD lasting 24–40 h [41–46], sleep restriction lasting 1–8 nights [47, 48, 50, 51] or 4 weeks [49], and shift work involving overnight [54–56] and extended shifts of 24–30 h [52, 53, 57].

Effects of TSD on endothelial function Two studies examined the effect of supervised TSD on macrovascular endothelial function assessed by brachial artery FMD. Compared to 7–8 h of sleep, FMD was attenuated following 24 h of TSD in men and women [41] but remained unchanged after 30.5 h of TSD in men [42]. Four studies investigated the effects of TSD on microvascular function, with 3 studies reporting impaired microvascular function after TSD compared to 7–8 h of sleep. CVC to ACh, insulin, and heat was reduced after 40 h of TSD in men [44]. Similarly, CVC to ACh was reduced after 29 h of TSD in men [43]. CVC in response to cold-water immersion was impaired after 29 h of TSD in men, although no impairments were found prior to cold-water immersion [45]. One study found that FBF and FVC in response to reactive hyperemia did not change after 24 h of TSD in men and women [46]. Collectively these studies indicate that macrovascular and skin but not forearm microvascular endothelial function may be impaired in response to acute TSD.

Effects of sleep restriction on endothelial function Two studies investigated the effects of sleep restriction on macrovascular endothelial function assessed by brachial artery FMD. FMD was reduced after 4 weeks of sleep restriction to < 80% of habitual sleep duration in men [49] and following 8 nights of sleep restricted to ~ 5 h per night in men and women [48]. Interestingly, endothelium-independent dilation measured in response to sublingual nitroglycerin did not change after sleep restriction [48, 49], indicating that vascular smooth muscle responsiveness to nitric oxide (NO) was preserved. Three studies investigated the effects of sleep restriction on microvascular endothelial function. Microvascular function assessed by CVC to MCh and heat was reduced after 6 nights of sleep restricted to < 4 h per night in men, while CVC in response to cathode current did not change [51]. Venous endothelium-dependent dilation to ACh was also attenuated following 5 nights of sleep restricted to 4.5 h per night in men [50]. Coronary flow velocity reserve to ATP was reduced following a single night of sleep restricted to ≤ 4 h in men [47]. Collectively, these studies demonstrate that sleep restriction negatively impacts endothelial function regardless of vascular bed or sleep restriction duration.

Effects of shift work on endothelial function Six studies investigated the effects of shift work on macrovascular endothelial function using brachial artery FMD. FMD was reduced after working for a 24- [52, 57] and 30-h shift [53] and following a single night shift in medical staff [54, 55]. Similarly, FMD was reduced following 3 sequential night shifts in female nurses compared to a day with no previous night shift [56]. No studies investigated the effect of shift work on microvascular function. Collectively, these studies provide consistent evidence that macrovascular function is negatively impacted by shift work, but the effect on microvascular endothelial function remains unknown.

Risk of bias

Risk of bias for each observational and non-randomized experimental study is presented in Fig. 2. Additionally, risk of bias for each domain is presented across all observational/non-randomized experimental studies in Fig. 3. Risk of bias arising from confounding was serious in 6, moderate in 1, and low in 8 studies and resulted from inclusion of participants who were shift workers [42] or who had comorbidities [38, 57] and from not controlling important factors known to influence endothelial function (e.g., food and caffeine intake during sleep deprivation, changes in weight during sleep restriction, and standardization of menstrual cycle phase) [50, 51, 57]. Risk of bias due to selection of participants was serious in 1, moderate in 1, and low in 13 studies. Risk of bias arising from classification of interventions was serious in 5, moderate in 1, and low in 9 studies and was mainly due to intervention groups being non-explicitly defined. Risk of bias due to deviations from the intended intervention was serious in 4 and low in 11 studies and this was mainly related to the confounding effects of physical work and mental stress during shift work. However, we recognize that these are not indicative of flaws in the study designs per se, but rather that they introduce a minor bias in interpreting the results on the independent effects of sleep deprivation on endothelial function. Risk of bias due to the selection of the reported results was moderate in 2 and low in 13 studies. For all observational and non-randomized experimental studies, the risk of bias due to missing data and measurement of outcome was low. Overall, none of the observational and non-randomized experimental studies had flaws that prevented them from significantly contributing to this review.

For randomized experimental studies, risk of bias for each study is presented in Fig. 4. Additionally, risk of bias for each domain is presented across all randomized experimental studies in Fig. 5. Risk of bias arising from the randomization process was high in 6 and low in 3 studies

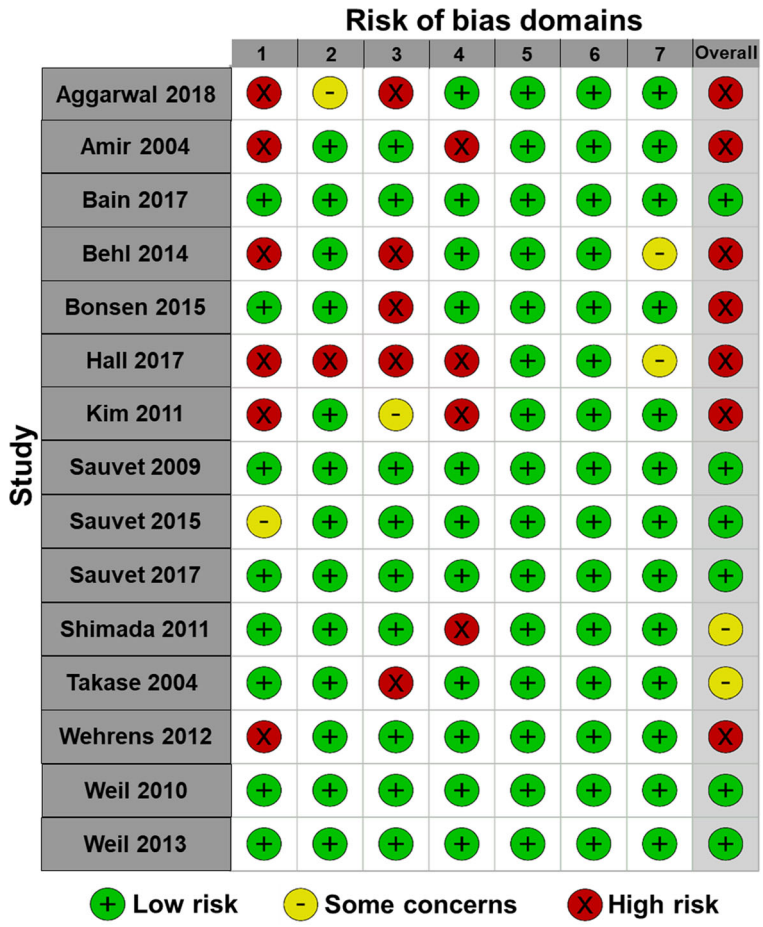

Fig. 2 Risk of bias for observational and non-randomized experimental studies. Domain 1: bias due to confounding; domain 2: bias due to selection of participants; domain 3: bias in classification of interventions; domain 4: bias due to deviations from intended interventions; domain 5: bias due to missing outcome data; domain 6: bias in measurement of outcomes; domain 7: bias in selection of the reported result

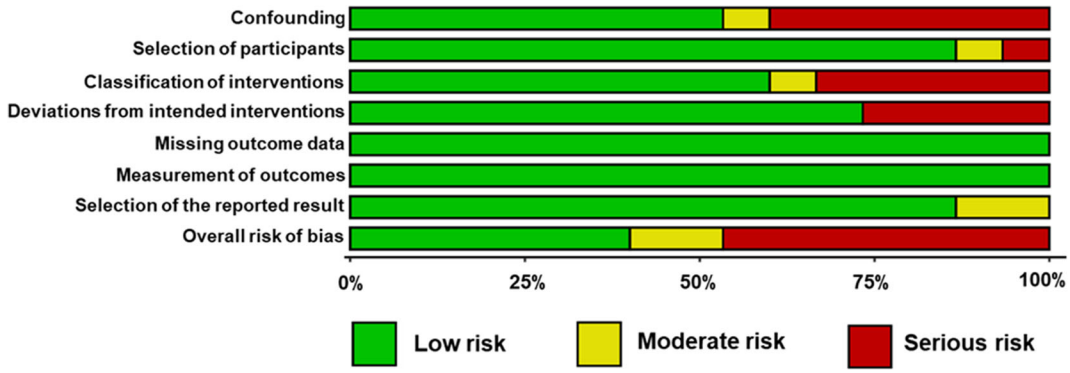

Fig. 3 Risk of bias domains across all observational/non-randomized experimental studies

and was mainly due to lack of information on the method of sequence generation and allocation concealment. We acknowledge that although this information was not reported it does not mean that the methodology was inappropriate. Risk of bias due to deviations from the intended intervention was assessed in regard to the scope of this review, which was to investigate the independent effects of sleep deprivation on endothelial function. Three studies which focused on shift work included high mental stress or physical work, in addition to sleep deprivation,

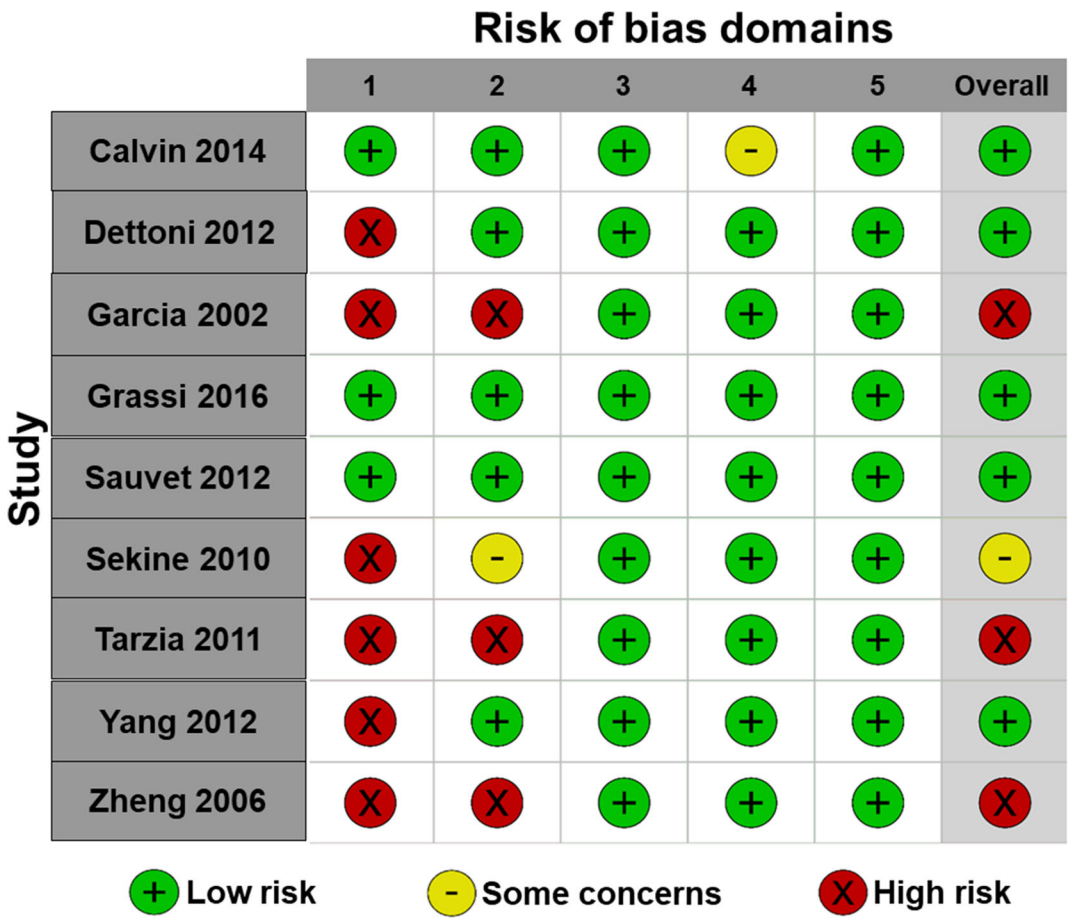

Fig. 4 Risk of bias for randomized experimental studies. Domain 1: bias arising from the randomization process; domain 2: bias due to deviations from intended intervention; domain 3: bias due to missing outcome data; domain 4: bias in measurement of the outcome; domain 5: bias in selection of the reported result

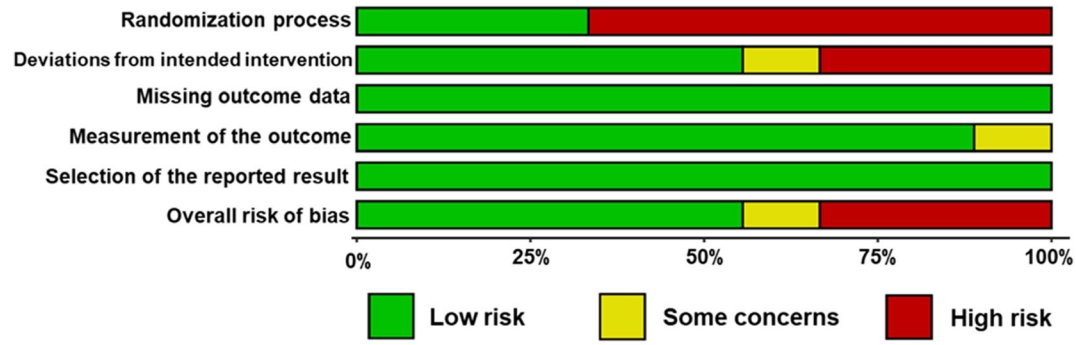

Fig. 5 Risk of bias domains across all randomized experimental studies

and were therefore deemed to have high risk of bias for this domain. In addition, 1 study raised some concerns and 5 had low risk of bias. Although deviations regarding this domain could introduce bias into the results of the current review, they were not deviations inherent to the study methods. None of the randomized experimental studies had missing outcome data and thus had low risk for this domain. All randomized experimental studies except 1 were deemed to have low risk of bias due to measurement of the outcome and bias from the awareness of outcome assessors to the intervention. When blinding of the assessor was not reported, studies were considered low risk. When blinding of participants could not occur, studies were also considered low risk because this would not have influenced the endothelial function measure. Risk of bias arising from selection of the reported results was low in all studies. Overall, none of the randomized experimental studies had flaws that prevented them from significantly contributing to this review.

Discussion

This is the first systematic review to focus on the effects of sleep deprivation on endothelial function. Our main findings include the following: (1) receiving less sleep is associated with reduced macrovascular endothelial function, but data are inconsistent and the association with microvascular endothelial function remains unexplored; (2) not meeting the sleep recommendations for adults (i.e., 7–9 h/night) is linked to impaired microvascular endothelial function, but the effect on macrovascular endothelial function remains unknown; (3) sleep restriction impairs both micro- and macrovascular endothelial function; (4) acute TSD impairs micro- and macrovascular endothelial function, but data on macrovascular endothelial function are less consistent; and (5) extended or overnight shift work impairs macrovascular endothelial function, but the effect on microvascular endothelial function remains unknown.

Observational studies

Correlational data on the association of sleep duration with macrovascular endothelial function are inconsistent and the association with microvascular endothelial function remains unexplored. This is likely due to the inclusion of a limited range of sleep duration in some studies and the challenges associated with quantifying long-term habitual sleep duration. Cross-sectional data consistently demonstrate that short sleepers have reduced microvascular endothelial function. These data complement epidemiological data showing that habitually receiving insufficient sleep is associated with greater risk for future CVD events [81] and highlight endothelial dysfunction as a potential mediator of CVD pathogenesis in short sleepers. Observational evidence provides preliminary support for insufficient sleep as a potential modifiable CVD risk factor, but well-controlled adequately powered studies are needed to provide definitive evidence. Our review supports current recommendations from leading health organizations that adults obtain between 7 and 9 h of sleep each night [82].

Experimental studies

The perils of pulling an all-nighter The negative effects of TSD on macro- and microvascular function were consistent across most experimental studies, providing strong evidence that endothelial function is directly

impacted by an acute lack of sleep. The exception to these findings is two studies which found no effect of TSD on brachial artery FMD [42] or FVC [46]. One of these studies included a group of shift workers who had reduced baseline endothelial function compared with non-shift workers, which likely influenced the impact of TSD on endothelial function [42]. The second study assessed endothelial function following TSD in combination with mental stress and a cold-pressor test; therefore, it is unknown how TSD impacted endothelial function per se [46]. Notwithstanding these two studies, the cumulative evidence supporting that a single day of acute TSD has detrimental endothelial effects is alarming.

While the TSD model may not be as generalizable to real-world settings as sleep restriction or shift work models, TSD is a well-established experimental model to understand the acute effects of insufficient sleep on physiological function in humans and animals. Even though TSD-related endothelial dysfunction is likely reversible in the near-term with adequate recovery sleep, repeated bouts of TSD-induced endothelial dysfunction could lead to the development of CVD. Indeed, endothelial dysfunction is one of the primary initiating events in the development of atherosclerosis [27]. Furthermore, endothelial function governs blood flow to the heart, brain, skeletal muscle, and skin [83], impacting quality of life, activities of daily living, and exercise tolerance. Therefore, our review underscores the importance of receiving an adequate amount of sleep for optimal function and warns of the perils of pulling an all-nighter.

Restricting sleep has vascular consequences Our review demonstrates that moderately restricting sleep, equivalent to ~ 2–3 h per night, impairs endothelial function throughout the vascular tree. This includes endothelial function impairments in coronary, peripheral, and skin vasculature, which hold strong prognostic value for future CVD and CVD events [84–87]. While only one study assessed coronary endothelial function [47], the finding that a single night of < 4 h of sleep reduces coronary artery function is a cause for concern. A night of insufficient sleep could significantly elevate the risk for acute myocardial ischemia and other cardiovascular events, especially in the morning when this risk is already elevated [88]. Furthermore, peripheral endothelial dysfunction is evident in all experimental studies included in our review independent of the vascular bed or the duration or magnitude of sleep restriction.

While the effects of experimental sleep restriction are acute and likely reversible once a normal and consistent sleep pattern is resumed, findings have relevance to adults who are chronically not meeting the recommended sleep duration. As our review shows, habitually receiving less than the recommended 7 h of sleep/night is associated with micro- and macrovascular endothelial dysfunction. Therefore, experimental sleep restriction data align with observational data and provide a potential mechanism for explaining the association of short habitual sleep duration and CVD.

Working the night shift Shift work is common among > 15% of the workforce [23], with potentially wide-ranging effects on cardiovascular health. Indeed, our review finds compelling evidence that extended or overnight shift work impairs macrovascular endothelial function assessed by brachial artery FMD, a measure that is highly predictive of future CVD events [28–30, 86]. While multiple mechanisms have been proposed for the increased CVD risk in shift workers including psychosocial stress, circadian misalignment, weight gain, smoking, and increased prevalence of metabolic syndrome [25], our review identifies endothelial dysfunction as a novel potential mechanism by which long-term shift work may increase the risk for CVD. In support of this, a longer duration of shift work is associated with a lower brachial artery FMD [42, 57, 89], suggesting that acute endothelial dysfunction likely progresses along a continuum to persistent endothelial dysfunction, atherosclerosis, and CVD as the duration of shift work increases. These findings are cautionary for individuals involved in professions where extended or night shift work is common. Shift workers do not appear to adapt to chronic sleep deprivation and chronobiological disruption. Indeed, evidence supports that < 3% of night-shift workers ever experience a complete adaptation of endogenous circadian rhythms to this schedule [90]. Adequate physical activity, proper nutrition, and strategic timing of these circadian time-givers [91] may have increased importance in shift workers to mitigate the CVD risk imposed by their work schedule.

Mechanisms

The mechanisms responsible for sleep deprivation–induced impairments in endothelial function have not been fully elucidated. This section will discuss direct mechanistic evidence focusing on inflammation and

oxidative stress and autonomic nervous system dysregulation, the main areas investigated in the studies included in this systematic review. Novel potential mechanisms related to chronobiological disruption, a rapidly evolving area of research, will also be discussed.

Inflammation and oxidative stress Sleep is an important modulator of the immune system and thus, sleep deprivation may cause endothelial dysfunction in part by increasing vascular inflammation and reactive oxygen species (ROS) production [92]. Inflammation due to acute or chronic sleep deprivation could be the result of a chronically elevated sympathetic stress response and increased blood pressure. While blood pressure normally dips 10–20% during nighttime sleep, absence of dipping or elevations in blood pressure during sleep deprivation activate the endothelium, causing the release of inflammatory mediators, vascular adhesion molecules, and factors promoting coagulation that contribute to endothelial dysfunction [93]. This would also explain why chronic sleep deprivation, by preventing resolution of this inflammatory response, is associated with chronic low-grade inflammation and inflammatory diseases [93, 94].

Sleep deprivation has been shown to cause acute changes in inflammatory biomarkers including C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6). In some studies, endothelial dysfunction was accompanied by acute elevations in inflammatory biomarkers. CRP was increased after a 30-h work shift [53] and 10 days of chronic sleep restriction [95]. TNF-α was elevated following 1, 2, and 6 days of sleep restriction [51, 96, 97]. IL-6 was also increased after a 30-h work shift [53], a single night of sleep restriction [96, 97], and 24-h TSD [44]. Interestingly, 7 weeks of aerobic exercise training prior to TSD abolished the inflammatory response and preserved endothelial function after TSD [44], suggesting a causal role of inflammation in endothelial dysfunction and highlighting exercise as a promising intervention that may prevent sleep deprivation–induced endothelial dysfunction.

Acute inflammation causes endothelial dysfunction by promoting oxidative stress within the vasculature and by reducing the bioavailability of NO [98]. ROS cause endothelial damage, apoptosis, and cell proliferation and directly/indirectly reduce NO bioavailability [98]. Superoxide anions (O_2^-) rapidly react with NO and form peroxynitrite ($ONOO^-$), both of which may cause lipid, protein, and DNA damage [99]. This reaction reduces NO bioavailability while also raising ROS within the endothelium [99]. ROS further reduce NO bioavailability by causing endothelial nitric oxide synthase (eNOS) uncoupling, a process that results in the paradoxical eNOS formation of ROS, rather than NO [99]. Reduced NO bioavailability impairs endothelium-dependent vasodilatory capacity. There is some evidence based on studies included in our review that reduced NO bioavailability, perhaps a result of increased oxidative stress, may be an underlying cause of sleep deprivation–induced endothelial dysfunction. Men who reported sleeping < 7 h per night had a reduced contribution of NO to endothelium-dependent dilation compared to men sleeping > 7 h each night, suggesting that sufficient sleep is necessary for adequate NO availability/action [35]. Additionally, after working 3 consecutive night shifts, female nurses had reduced levels of NO metabolites [56], though whether this was due to altered NO production or increased degradation was not investigated.

Opposing the actions of NO is ET-1, which when bound to endothelial ET_A receptors induces vascular smooth muscle constriction. ET_A receptor binding also increases ROS production and interferes with NO production and actions [100, 101], thereby implicating ET-1 in the pathogenesis of endothelial dysfunction. One study in our review found that short sleepers had greater ET-1-mediated vasoconstrictor tone [37]. Acute sleep deprivation may also impair NO/ET-1 balance. One study found that acute TSD increased plasma ET-1 without altering levels of plasma nitrites [43], thus favoring vasoconstriction and promoting endothelial dysfunction. Therefore, low-grade inflammation, increased ROS, and their influence on the vasodilator/vasoconstrictor balance likely play a major role in endothelial dysfunction associated with acute and chronic sleep deprivation.

Autonomic nervous system dysregulation With the exception of REM sleep, parasympathetic nervous system activity is dominant during the majority of sleep duration [102]. Thus, acute sleep deprivation may induce autonomic dysregulation, characterized by a state of sympathetic nervous system (SNS) hyperactivity [102]. SNS stimulation causes augmented vascular smooth muscle tone, alters NO bioavailability and activity, elevates ROS production, and stimulates vasoconstrictor pathways, predisposing to endothelial

dysfunction [103]. Indeed, there is an inverse relationship between measures of endothelial function and sympathetic activity, and acutely raising SNS activity reduces endothelial function [103], potentially triggering the negative effects of short- and long-term sleep deprivation.

Several studies included in this systematic review reported evidence of TSD-induced SNS elevation occurring in tandem with endothelial dysfunction. SNS activity measured using heart-rate variability (HRV) was shown to increase after 32 and 40 h of TSD [43, 104], and 5 nights of partial sleep restriction [50], while other studies found no change in HRV after 24 h of TSD [42, 61]. One of these studies observed no change in HRV after TSD, but shift workers in this study had lower baseline HRV indicating higher SNS activity in these individuals [42]. Other measures known to be associated with SNS activity including epinephrine [49], norepinephrine [43, 50, 53], cortisol [47], and blood pressure [41, 43, 46, 47, 49, 52] increase in response to sleep deprivation. However, some studies found no increase in blood pressure [50, 51], catecholamines [45, 51], or muscle sympathetic nerve activity [46] after acute sleep deprivation, or found that endothelial dysfunction preceded sympathetic activation [43], suggesting that endothelial dysfunction can occur in the presence or absence of elevated SNS activity.

Chronobiological disruption Human experimental data on the effects of acute or chronic sleep deprivation on endogenous circadian clock gene expression, circadian rhythmicity, or chronobiological function are limited. As this is an emerging field of research, we believe it is worthwhile to speculate on the potential ways sleep deprivation may contribute to chronobiological disruption of endothelial function predisposing to CVD development. Acute overnight sleep deprivation has been shown to alter epigenetic and transcriptional circadian clock gene profiles in humans [105]. The presence of circadian clocks in vascular cells and time-of-day variance in vascular tone and endothelial function [106–108] likely function to anticipate external and internal stimuli. The specific time-of-day release of circulating metabolites including NO and ET-1 [109] likely helps to promote optimal vascular function. Sleep deprivation may promote endothelial dysfunction by altering circadian release profiles of NO, ET-1, and endothelial and vascular smooth muscle cell sensitivity to these vasoactive stimuli. Indeed, animal models of circadian disruption show evidence of vascular senescence, endothelial dysfunction, and loss of diurnal variation in endothelial function and blood pressure [110].

Reductions in blood pressure and shear stress during sleep, when cellular turnover is active, suppress pro-hypertrophic stimuli, thereby favoring repair mechanisms (reviewed in Rana et al. [17]). An absence of the nocturnal blood pressure dip and other regenerative functions during the night is likely to impair vascular remodeling in humans, increase vascular and endothelial inflammation and oxidative stress, and promote cell senescence, mechanisms implicated in the pathogenesis of vascular aging [111]. Furthermore, sleep deprivation and shift work require being awake at night when, according to human biology, one should be sleeping, likely causing circadian rhythm desynchrony. Being awake during the night also exposes one to time cues known as zeitgebers (e.g., light, food, and physical activity) that disrupt normal circadian rhythms [112–114]. Shift workers who suffer from chronic insufficient sleep have disrupted circadian clocks, as evidenced by a lack of complete entrainment of their circadian rhythms to the night shift [115], which may promote endothelial dysfunction.

Conceptual model on link of sleep deprivation to CVD

The current systematic review demonstrates that sleep deprivation impairs endothelial function. Chronic sleep deficiency across the lifespan may have cumulative adverse effects on endothelial function, thus accelerating vascular aging and promoting CVD development (Fig. 6). Human experimental evidence supports the role of inflammation, oxidative stress, and autonomic nervous system dysregulation in endothelial dysfunction associated with acute and chronic sleep deprivation. However, other mechanisms may be involved and should be elucidated in future investigations. Human evidence on the role of chronobiological disruption is limited but presents an exciting new direction for future studies. Long-term exposure to sleep deprivation may have devastating chronobiological consequences and provides an attractive target for the development of therapeutic strategies focusing on clock re-entrainment by optimizing timing of cues such as light, food intake, and physical activity to preserve/restore endothelial function.

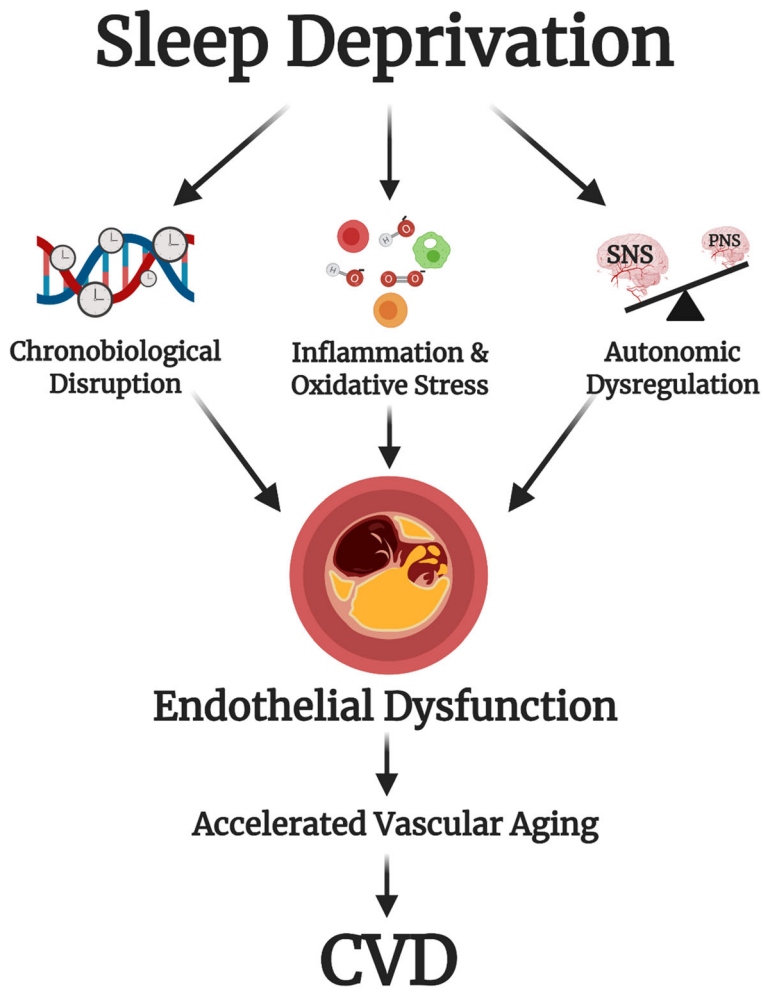

Fig. 6 Conceptual model of the link between sleep deprivation and cardiovascular disease. Sleep deprivation leads to inflammation, oxidative stress, autonomic nervous system dysregulation, and chronobiological disruption, which impair endothelial function and may lead to accelerated vascular aging and cardiovascular disease. SNS, sympathetic nervous system; PNS, parasympathetic nervous system; CVD, cardiovascular disease. Created with BioRender.com

Implications for human aging

Adequate sleep should be encouraged in individuals of all ages given that chronic sleep deficiency likely has cumulative adverse cardiovascular effects that may lead to accelerated vascular aging. The evidence summarized in this review clearly demonstrates that achieving adequate sleep should be considered indispensable to promote optimal cardiovascular health. Whether insufficient sleep impairs endothelial function to the same extent in individuals older than 60 years of age remains to be determined because all studies that were included in this review focused on individuals 20 to 60 years of age. The well-documented age-related biological changes in sleep characteristics and chronobiology including reductions in sleep duration and quality [5–8] are concerning considering the evidence from our review that even a moderate amount of sleep restriction has adverse vascular consequences. As individuals age and receive a reduced amount of sleep, this could have compounding effects on vascular aging. Therefore, healthy sleep behaviors should be encouraged in older individuals. Future research in the field of gerontology and aging chronobiology should investigate the influence of sleep deprivation on chronobiological disruption and develop interventions to reduce the negative effects of sleep deprivation on endothelial health in this population.

Limitations

It was not possible to conduct a meta-analysis on the effects of sleep deprivation on endothelial function due to the significant heterogeneity in the methods used to evaluate endothelial function. However, this has resulted in a comprehensive assessment of the effects of sleep deprivation on endothelial function across the vascular tree. We included both observational and experimental studies to

maximize the impact of our review but realize the limitations of observational data in informing conclusions about causation. Observational studies that rely on self-reported sleep duration are limited in their ability to make definitive conclusions about the association of sleep duration with endothelial function, especially given that self-reported sleep duration is only moderately correlated with objectively measured sleep duration [112, 113]. Shift work studies also have some limitations. These investigations rarely controlled for work stress, sleep time, and food and beverage consumption. Although this maximizes external validity, it limits direct comparisons with well-controlled sleep deprivation studies. Some studies in this review included women varying in menopausal status [34, 37, 38, 41, 46, 48, 52–54, 56, 57], individuals who smoked [53, 57], or who had hypertension, diabetes, major depressive disorder, and obesity [38], which could confound the association of short sleep duration with endothelial function. Limitations notwithstanding, the inclusion of observational and shift work studies greatly complements evidence of well-controlled experimental studies.

Conclusions

We present the first systematic review of the literature on the effects of sleep deprivation on endothelial function. Taken together, evidence from observational and experimental studies link sleep deprivation to endothelial dysfunction, which may be the link between insufficient sleep and CVD. Current guidelines state that adults should get between 7 and 9 h of sleep each night, and the current review supports this recommendation in the context of reducing CVD risk. Given the pervasiveness of sleep deprivation, interventions to combat its adverse effects on endothelial health are urgently needed. Getting an adequate amount of sleep should become a priority for cardiovascular health across the lifespan.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11357-020-00312-y.

Author contributions BJH and DDC conceived and designed the systematic review. BJH and SSL performed the literature search and screening, data extraction and synthesis, and risk-of-bias assessment. BJH wrote the initial draft of the manuscript. DDC, SSL, and DEJS critically revised the manuscript for intellectual content. All authors reviewed and approved the final manuscript.

Funding DDC was supported by the National Institute on Aging of the National Institutes of Health [grant AG063143].

Data availability Not applicable.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval This systematic review was based on data acquired through previously published articles.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

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