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# Sleep Duration and Cardiovascular Disease Risk: Epidemiologic and Experimental Evidence

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## Synopsis

Inadequate sleep has become increasingly pervasive, and the impact on health and quality of life remains to be fully understood. The cardiovascular consequences alone appear to be substantial and significant. This brief review summarizes epidemiologic evidence regarding the association between extremes of sleep duration and the prevalence and incidence of cardiovascular diseases. The adverse effects of experimental sleep loss on physiological functions are discussed, along with those cardiovascular risk factors that may underlie the association with increased morbidity and mortality. Current data support the concept that inadequate sleep duration confers heightened cardiovascular risk. Thus implementation of preventative strategies may be needed to reduce the potential disease burden associated with this widespread high-risk behavior.

### Keywords

sleep duration; cardiovascular disease; sleep deprivation; hypertension; coronary heart disease; stroke

## Introduction

According to outcome-based recommendations issued recently by the National Sleep Foundation, the appropriate sleep duration for adults lies between 7 to 9 hours per night[1]. Notably, only 48% of the US adult population reports a habitual sleep time falling within that range[2], while 26% average 6 to 7 hours of sleep/night, and 20% sleep less than 6 hours/night.

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The time allotted to sleep has gradually declined over the past decades, with similar trends observed in multiple Western countries[3]. A growing proportion of individuals are curtailing their sleep in response to increasing demands and lifestyle changes, such as prolonged working hours, increased environmental lighting, and introduction of new communication technologies, which enable living “around the clock”.

Nevertheless, changes in sleep habits are not without consequences. Deviations from optimal sleep duration may pose a substantial threat to health, with the detrimental effects of abnormal sleep on physical and psychological well-being only beginning to be unraveled. In this review, available data on the relation between abnormal sleep duration and risk of prevalent and incident cardiovascular disease, the leading cause of morbidity and mortality, will be presented. The putative physiologic mechanisms underlying the observed associations and potential confounders will also be discussed.

## Epidemiologic evidence

### Hypertension

Hypertension is widespread affecting approximately one-third of the adult population in the US, and is a prominent risk factor for other cardiovascular and cerebrovascular diseases[4]. Epidemiologic evidence indicates that the relationship between customary sleep duration and risk of hypertension is better described as a curvilinear phenomenon, with both extremes of the sleep length distribution independently associated with enhanced likelihood of prevalent hypertension in the general population[5–7].

A U-shaped relationship between self-reported sleep length and hypertension has been documented in a large (N=71,455) national representative sample (National Health Interview Survey, NHIS)[6], with both ends of the tail exhibiting larger age-standardized prevalences of hypertension (<6 hours/night: 32.4%; ≥10 hours/night: 32.5%) compared to the referent category (8 hours/night, 23.2%). Similarly, the lowest risk of hypertension in the Sleep Heart Health Study [7] was observed in those subjects sleeping 7 to 7.9 hours/night, while a progressive increase was seen when moving away from this reference. The greater hazard conferred by both short and long sleep withstood multivariable adjustments for lifestyle, clinical and sleep-related covariates (adjusted OR=1.66, 95% CI=1.35–2.04 for <6 hours/night; OR=1.30, 1.04–1.62 for ≥9 hours/night). Large population studies have replicated this pattern[5,8].

While both ends of sleep duration have been cross-sectionally related to hypertension, the prospective contribution of long sleep is less compelling. As concluded by a recent meta-analysis[9], current longitudinal data mainly support a role of short sleep as independent marker of incident hypertension.

Indeed, it has been estimated that individuals sleeping less than 6 hours/night are 20–32% more likely to develop hypertension compared to those sleeping 7–8[8,10]. Gangwisch[10] studied the incidence of hypertension over a 8 to 10 year time span using the first National Health and Nutrition Examination Survey (NHANES I) dataset. In the pooled cohort comprising 4810 participants, fully-adjusted probability of high blood pressure (BP) was

more elevated in those sleeping ≤5 hours/night (adjusted HR=1.32, 1.02–1.71) than in normal sleepers (7–8 hours/night). Nevertheless, age-stratified analysis revealed that those who were 32 to 59 years old and reported habitual sleep ≤5 hours were 60% more likely to develop hypertension than peers sleeping 7–8 hours. Conversely, sleep duration was unrelated to outcomes in the older age strata (60–86 years). Several cohort studies have subsequently replicated these null findings in the geriatric population[8,11,12].

Women have been found to be more susceptible to the pressor effects of abnormal sleep. Estimates for both prevalent and incident hypertension derived from the Whitehall II study[13] were higher in middle-aged women who were sleeping ≤5 hours/night compared to those sleeping 7 hours, but not in men. Sex-specific associations have been confirmed and further detailed in a transversal examination of the Western New York Health Study[14], where a sub-analysis of the female sample classified by menopausal status unveiled significantly higher odds only in premenopausal women.

Differential vulnerability to abnormal sleep length has also been reported across ethnicities. Event rates for hypertension were higher in Black subjects from the NHIS who were sleeping <6 hours/night or >8 hours/night, compared to their White counterparts[15]. These data are in line with findings from the Coronary Artery Risk Development in Young Adults (CARDIA) study[16], where objective sleep duration, as quantified from actigraphy, related to greater surges in BP in African-Americans.

The moderating effect of demographic variables on the link between sleep duration and hypertension interestingly parallels the increased prevalence of this condition in women after 65 years old and in the African-American population[4].

When BP is treated as continuous variable, again a U-shaped relation with sleep hours can be described, although more robust for systolic values[12,17]. Abnormal sleep duration is also associated with altered diurnal BP rhythmicity. Both excess sleep and curtailed sleep have been linked with attenuated nocturnal dipping in BP[17,18], which is a sensitive prognostic marker for cardiovascular disease[19].

## Coronary heart disease

Coronary heart disease (CHD), which comprises a spectrum of acute and chronic manifestations, remains the major cause of death worldwide[20], with rising prevalence[4]. Abnormal sleep duration has been identified as a risk factor for CHD on the basis of epidemiologic studies, which show a cross-sectional relation consistent with a U-shaped curve[21–24]. Weighted prevalence of total CHD was higher in respondents of the Behavioral Risk Factor Surveillance System (BRFSS) survey reporting either ≤6 hours/night (11.1%, 95% CI: 10.1–12.1) or ≥10 hours/night (14.8%, 12.0–17.6) than in the reference group sleeping 7 to 9 hours (7.9%, 7.3–8.5)[22]. When the clinical presentations of CHD are considered separately, a heterogeneous pattern of risk emerges. Both sleep lengths of 6 or less hours/night and 9 or more hours/night were associated with heightened odds for history of myocardial infarction in a Finnish population[23] and in the NHIS cohort[24], but only short sleepers has a significant adjusted prevalence of myocardial infarction using the 2007–2008

NHANES dataset[21]. Findings are discrepant for angina, although this condition seems more closely related to short sleep duration[23,24].

Similarly to prevalence, incidence of fatal and non-fatal CHD events is greater with habitual sleep duration above or below 7 to 8 hours, as indicated by pooled relative disease risk of 1.48 (1.22–1.80) for short sleepers and 1.38 (1.15–1.66) for long sleepers[25]. This trend is in line with data on all-cause mortality[26], which depict a curvilinear relationship between time asleep and death estimates, with best life expectancy achieved by those reporting sleeping habitually 7–8 hours/night.

In a longitudinal study comprising 71,617 female participants enrolled in the Nurses' Health Study[27], multivariate-adjusted relative risks of coronary heart disease at 10-year follow-up were 1.39-fold higher in women reporting ≤5 hours/night and 1.37-fold higher in those sleeping ≥9 hours compared to those sleeping 8 hours/night. A similar pattern has been described for CHD deaths in a community-based Chinese cohort[28], while likelihood of future fatal and non-fatal CHD was better predicted by the short sleep category in the Framingham Offspring Cohort[29]. Compared to 7–8 hours/night, self-reported sleep of ≤5 hours or ≥10 hours induced, respectively, a 25% and a 43% age- and race-adjusted raised risk for CHD in a large national cohort of postmenopausal women[30]. However, the estimates were markedly attenuated when controlling for behavioral, socioeconomic and clinical covariates and fell out of statistical significance. Comparable results were noted in a prospective investigation on a Dutch cohort[31]. Disparities in CHD risk have been evident in age- and sex-stratified analyses, although with divergent results[32–35].

In addition to established coronary disease, sleep length has been examined in relationship with early indices of subclinical atherosclerotic disease, and findings are compatible with normal sleep duration being protective against later cardiovascular events.

Ultrasonographic measurement of carotid intima-media thickness (IMT) is often adopted as a non-invasive indicator of atherogenic vascular damage[36]. Data from the Study of Health in Pomerania[37] depict a J-shaped association between habitual hours of sleep and carotid wall thickening, with the lowest carotid IMT values detected in subjects sleeping 7–8 hours. A monotonic relation was instead observed in the CARDIA study[38], where actigraphy-derived sleep duration predicted carotid IMT in middle-aged men, but not in women, with each additional hour of sleep associated with 0.026 mm decrease in IMT. A longitudinal examination sampling 495 individuals from the same cohort[39] confirmed the contribution of curtailed sleep to incident coronary risk. Using CT-assessed coronary artery calcification as an early predictor of CHD[40], and accounting for conventional risk factors, risk of calcification at 5 year follow up declined progressively as sleep time lengthened.

## Cerebrovascular disease

Cerebrovascular disease is among the leading causes of long-term disability[41] and responsible of 16.4% of cardiovascular deaths[4]. As outlined recently in a meta-analysis by Ge and Guo[42], enhanced cross-sectional and prospective vulnerability to cerebrovascular events is associated with both ends of the sleep duration distribution. Pooled ORs (95% CI) for prevalent stroke were 1.71 (1.39–2.02) for short sleep duration and 2.12 (1.51–2.73) for

long sleep duration. The corresponding pooled HRs for incident stroke were 1.13 (1.02–1.25) and 1.40 (1.16–1.64). The concept of a U-shaped relation is corroborated by results from large population-based studies including the BRFSS survey[22] and the NHIS[24]. There are also data reflecting a more robust association of stroke with excessive sleep[35,43,44].

An early prospective investigation on how sleep pattern affects the likelihood of stroke was conducted using the NHANES I study population[43], which comprised 7,844 participants followed for 10 years. This analysis revealed that the independent relative risk of ischemic or hemorrhagic stroke was 1.5 times higher in individuals reporting >8 hours/night than in those who were sleeping 6–8 hours.

Chen et al[44] prospectively examined a cohort of 93,175 postmenopausal women and found both self-reported short (≤6 hours/night) and long sleep (≥9 hours/night) to be significant predictors of ischemic stroke (including fatal and non-fatal events) at 7.5 year follow-up in the age- and race-adjusted analysis. While curtailed sleep was no longer an independent determinant in multivariate models including socioeconomic, lifestyle, psychiatric and medical covariates (HR: 1.14, 0.97–1.33), long sleep retained its predictive strength (HR: 1.70, 1.32–2.21). In addition, an association with short sleep was unmasked when the analysis was restricted to women without cardiovascular disease at baseline. Conversely, in a 4-year examination of a population of Japanese elderly hypertensives who underwent brain scans for detection of silent cerebral infarcts[45], insufficient sleep predicted future stroke only in those with brain lesions at study entry.

Similarly to cardiovascular disorders, the impact of extreme sleep lengths on cerebrovascular disease risk appears to be modified by demographic characteristics. Among the 154,599 participants of the 2006–2011 NHIS study[46], age standardized-prevalences of stroke were 2.78%, 1.99% and 5.21% in respondents reporting sleeping ≤6, 7–8 and ≥9 hours/night, respectively. Risk of stroke remained more elevated in short and long sleepers in the pooled sample compared to the reference (7–8 hours/night) after controlling for pertinent covariates. Nonetheless, further stratification by age and gender revealed that the association with short sleep persisted in young women (18–44 years) while the association with long sleep was maintained in both male and female older adults (≥65 years). Notably however, the increased crude hazard for incident stroke symptoms found in US employed individuals aged ≥45 years sleeping <6 hours/night[47] was abolished in adjusted models.

## Putative biological mechanisms and moderators

Observational findings from epidemiologic investigations are supplemented by experimental, laboratory-based evidence, which provide mechanistic insights into the biological substrate underlying the heightened cardiovascular risk associated with inadequate sleep.

A causative link between sleep deficiency and aberrant cardiovascular function is supported by multiple studies which applied models of short-term, total sleep deprivation. Along with these traditional protocols, extended sleep restriction paradigms have been more recently implemented to better simulate the chronic, partial sleep loss commonly experienced in everyday life.

Acute surges in systolic and diastolic BP occur following 24–88 hours of sustained wakefulness[48–53]. In the absence of sizable increases in diurnal resting BP[54–56], healthy individuals exposed to prolonged partial sleep curtailment exhibit elevations in nocturnal BP along with dampened nocturnal dipping[57] and an amplified morning surge[58].

A sympathoexcitatory effect of sleep loss has been proposed to account for the rise in BP. Research on hemodynamics and neural circulatory control largely supports the enhanced release of plasma and urinary norepinephrine after sustained sleep restriction[54,59] but not in response to acute sleep loss[49,50,60]. While results on heart rate are mixed, being either unaffected[48,49,54,55] or accelerated[50–52] after sleep loss, muscle sympathetic nerve activity has been consistently found to be inhibited[48,49,60]. An altered arterial baroreflex functioning in terms of resetting towards a higher BP level has thus been postulated, substantiated by findings of a rightward and downward shift in the operating point following sleep restriction[48,60]. Results on baroreflex sensitivity are less clear, showing an increase,[61] decrease,[62] or no change[48]. On the contrary, enhanced cardiac sympathetic drive as estimated from heart rate variability, a non-invasive index of cardiac autonomic modulation predictive of adverse events[63], has been more consistently documented after total sleep loss[50,62] and after 5 days of sleep truncation[54].

Electrocardiographic abnormalities in cardiac conduction and repolarization resembling a proarrhythmogenic profile have also been detected after acute experimental sleep deprivation[64,65].

In addition, sleep debt provokes early deterioration of vascular structure and function that may promote cardiovascular risk. Exposure to one night of sleep deprivation increases arterial stiffness as estimated by brachial-ankle pulse-wave velocity[53]. Interestingly, these experimental data are in contrast with those gathered from population studies, which linked greater arterial stiffness to long sleep duration in men[66,67]. Impaired endothelial function reflects poor vascular health and is thought to be a precursor of atherosclerosis[68]. Individuals undergoing experimental sleep curtailment exhibit reduced endothelium-dependent vasodilation, indicated by diminished acetylcoline -induced cutaneous[50,55] and venous vasodilation[54] and decreased brachial flow-mediated vasodilation[69]. Sleep loss also damages the coronary microcirculation[70]. The concomitant enhanced release of cellular adhesion molecules and selectins from activated endothelial cells[50,71] further supports the concept of systemic endothelial dysfunction promoted by sleep deprivation. Findings of abbreviated prothrombin and thrombin times,[72] consistent with development of a pro-thrombotic state, have also been reported.

In addition to direct effects on cardiac and vascular regulation, sleep deficiency has been showed to adversely impact numerous physiological functions that are implicated in increased cardiovascular risk. There is substantial evidence that sleep loss impairs glucose homeostasis and insulin sensitivity[59,73–75]. Compared to 10 hours/night, one week of sleep restriction at 5 hours/night elicited a 20% decrease in insulin sensitivity[73]. Exposure to sleep truncation generated a positive energy balance leading ultimately to weight gain[76–79]. Current research indicates that the increase in body weight achieved with sleep restriction in the setting of ad libitum access to food is primarily driven by overeating, as results on

energy expenditure are inconsistent. Likewise, the underlying molecular pathways accompanying excess food intake show discrepant responses in energy balance regulatory hormones such as leptin and ghrelin[76,77]. On the other hand, compelling epidemiologic data confirm the link between inadequate sleep and metabolic disorders such as obesity and type 2 diabetes[80,81], both major precursors of cardiovascular disease. Additional manifestations of endocrine derangements triggered by experimental sleep curtailment comprise reduced testosterone in men[48,55] and upregulation of the hypothalamic-pituitary-adrenal axis[82,83]. Enhanced secretion of inflammatory cytokines such as C-reactive protein and interleukin-6 occurs in response to acute or cumulative sleep loss[50,51,84,85], reflecting stimulation of pro-inflammatory pathways. Immune functions are also compromised under sleep debt conditions[56,72].

An almost inevitable companion of sleep deprivation is circadian disruption, as demonstrated by distortion of diurnal rhythmicity of metabolic, cardiovascular, and immunologic function during experimental sleep manipulation[57–59,82,84]. Given that a 24-hour pattern of oscillation has been described in most physiological processes[86], it is not surprising that circadian misalignment may severely compromise health status. In this regard, hazards of shift work, in which circadian misalignment is often combined with chronic sleep debt, have been become increasingly apparent[87].

It is noteworthy that experimental evidence corroborating harmful cardiovascular effects of excessive sleep duration is lacking, which contributes to making any causal association between long sleep and cardiovascular disease more elusive. Controversy has indeed been raised as to whether prolonged sleep duration is truly an independent risk predictor. It has been argued that excessive sleep duration may be simply an epiphenomenon of poor health, being secondary to undiagnosed illnesses or subclinical conditions. Cross-sectional data indeed support poor perceived health in long sleepers[14,88]. In addition, prolonged sleep is often reported in conjunction with a constellation of accepted cardiovascular risk factors such as older age[24,29,34], low socioeconomic status[30,34], depressive mood[7,12,24,30], hypnotic usage[34], prevalent sleep disorders[7], metabolic syndrome components[22,24,34], and high-risk behaviors such as smoking[6,24], excess alcohol consumption[6], and low physical activity[6,24,32]. However, consistent with a U-shaped relationship, these potential confounders are also prevalent in those who report insufficient sleep[6,12,24,29,30,32,34], and therefore could similarly bias the link between short sleep and cardiovascular risk.

In agreement with this hypothesis, as mentioned above, a number of studies have unmasked modifier effects exerted by gender, age and ethnicity. Poor self-rated health[88], insomnia[30,89], sleep apnea[90], and use of hypnotics/tranquilizers[91] have been found to moderate the association between sleep duration and cardiovascular outcomes.

Nevertheless, it should be noted that in numerous large cohort studies, sleep duration retained its predictive role after maximal adjustment[7,22,24], although controlling for potential confounders and mediators generally attenuated the estimates. These findings still favor a pathogenic contribution of inadequate sleep to cardiovascular vulnerability.

It is important to acknowledge that while sleep duration is a relatively crude measure of a complex entity such as sleep, other more refined indices of sleep quality and quantity such as sleep efficiency, sleep fragmentation, or slow wave sleep, have been found to be significant predictors of cardiovascular risk, independent of sleep length[16,92]. Nevertheless, as these measures cannot be derived from questionnaires, but require technical instrumentations such as polysomnography or actigraphy, their suitability for epidemiologic research is limited.

## Conclusions

Observational and experimental data converge to indicate that inadequate sleep duration poses a substantial hazard for cardiovascular morbidity and mortality. Sleep deficiency seems to induce adverse, sustained, and systemic alterations which conceivably act in concert to ultimately predispose to cardiovascular disease. The concomitant occurrence of conventional risk factors in individuals exposed to chronic sleep debt is likely to further amplify the risk of poor outcomes. Conversely, while long sleepers exhibit a similar pattern of predominant risk factors, the putative pathophysiological pathways leading to overt disease are still largely unknown. More mechanistic research is warranted to address this gap.

Given the pervasive and escalating prevalence of inadequate sleep and mostly sleep deficiency, the potential future burden on public health cannot be ignored. As sleep curtailment is largely voluntary and therefore modifiable, the cardiovascular complications may be preventable and plausibly reversible. Preventative strategies should therefore be undertaken to raise awareness of the possible deleterious sequelae in the general population, paralleled by interventional studies aimed at clarifying whether adherence to optimal sleep durations may improve cardiovascular risk profiles.

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## References

1. Hirshkowitz M, Whiton K, Albert SM, et al. National Sleep Foundation’s sleep time duration recommendations: methodology and results summary. Sleep Health. 2015; 1(1):40–43.
2. National Sleep Foundation. Sleep in America: bedroom poll 2012.
3. Bin YS, Marshall NS, Glozier N. Secular trends in adult sleep duration: a systematic review. Sleep Med Rev. 2012; 16(3):223–30. [PubMed: 22075214]
4. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics-2013 update: a report from the American Heart Association. Circulation. 2013; 127(1):E6–E245. [PubMed: 23239837]
5. Merikanto I, Lahti T, Puolijoki H, et al. Associations of chronotype and sleep with cardiovascular diseases and type 2 diabetes. Chronobiol Int. 2013; 30(4):470–77. [PubMed: 23281716]
6. Fang J, Wheaton AG, Keenan NL, et al. Association of sleep duration and hypertension among US adults varies by age and sex. Am J Hypertens. 2012; 25(3):335–41. [PubMed: 22052075]
7. Gottlieb DJ, Redline S, Nieto FJ, et al. Association of usual sleep duration with hypertension: the Sleep Heart Health Study. Sleep. 2006; 29(8):1009–14. [PubMed: 16944668]

8. Gangwisch JE, Feskanich D, Malaspina D, et al. Sleep duration and risk for hypertension in women: results from the Nurses Health Study. Am J Hypertens. 2013; 26(7):903–11. [PubMed: 23564028]
9. Guo XF, Zheng LQ, Wang J, et al. Epidemiological evidence for the link between sleep duration and high blood pressure: a systematic review and meta-analysis. Sleep Med. 2013; 14(4):324–32. [PubMed: 23394772]
10. Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Short sleep duration as a risk factor for hypertension - analyses of the first National Health and Nutrition Examination Survey. Hypertension. 2006; 47(5):833–39. [PubMed: 16585410]
11. van den Berg JF, Tulen JH, Neven AK, et al. Sleep duration and hypertension are not associated in the elderly. Hypertension. 2007; 50(3):585–9. [PubMed: 17635854]
12. Kim J, Jo I. Age-dependent association between sleep duration and hypertension in the adult Korean population. Am J Hypertens. 2010; 23(12):1286–91. [PubMed: 20706198]
13. Cappuccio FP, Stranges S, Kandala NB, et al. Gender-specific associations of short sleep duration with prevalent and incident hypertension: the Whitehall II Study. Hypertension. 2007; 50(4):693–700. [PubMed: 17785629]
14. Stranges S, Dorn JM, Cappuccio FP, et al. A population-based study of reduced sleep duration and hypertension: the strongest association may be in premenopausal women. J Hypertens. 2010; 28(5):896–902. [PubMed: 20040890]
15. Pandey A, Williams N, Donat M, et al. Linking sleep to hypertension: greater risk for blacks. Int J Hypertens. 2013; 2013:436502. [PubMed: 23710339]
16. Knutson KL, Van Cauter E, Rathouz PJ, et al. Association between sleep and blood pressure in midlife. The CARDIA Sleep Study. Arch Intern Med. 2009; 169(11):1055–61. [PubMed: 19506175]
17. Ramos AR, Jin ZZ, Rundek T, et al. Relation between long sleep and left ventricular mass (from a multiethnic elderly cohort). Am J Cardiol. 2013; 112(4):599–603. [PubMed: 23711813]
18. Friedman O, Shukla Y, Logan AG. Relationship between self-reported sleep duration and changes in circadian blood pressure. Am J Hypertens. 2009; 22(11):1205–11. [PubMed: 19745817]
19. Yano Y, Kario K. Nocturnal blood pressure and cardiovascular disease: a review of recent advances. Hypertens Res. 2012; 35(7):695–701. [PubMed: 22378470]
20. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380(9859):2095–128. [PubMed: 23245604]
21. Aggarwal S, Loomba RS, Arora RR, et al. Associations between sleep duration and prevalence of cardiovascular events. Clin Cardiol. 2013; 36(11):671–76. [PubMed: 24122853]
22. Liu Y, Wheaton AG, Chapman DP, et al. Sleep duration and chronic diseases among US adults age 45 years and older: evidence from the 2010 Behavioral Risk Factor Surveillance System. Sleep. 2013; 36(10):1421–27. [PubMed: 24082301]
23. Partinen M, Putkonen PT, Kaprio J, et al. Sleep disorders in relation to coronary heart disease. Acta Med Scand Suppl. 1982; 660:69–83. [PubMed: 6982602]
24. Sabanayagam C, Shankar A. Sleep duration and cardiovascular disease: results from the National Health Interview Survey. Sleep. 2010; 33(8):1037–42. [PubMed: 20815184]
25. Cappuccio FP, Cooper D, D'Elia L, et al. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Eur Heart J. 2011; 32(12):1484–92. [PubMed: 21300732]
26. Cappuccio FP, D'Elia L, Strazzullo P, et al. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. Sleep. 2010; 33(5):585–92. [PubMed: 20469800]
27. Ayas NT, White DP, Manson JE, et al. A prospective study of sleep duration and coronary heart disease in women. Arch Intern Med. 2003; 163(2):205–9. [PubMed: 12546611]
28. Shankar A, Koh WP, Yuan JM, et al. Sleep duration and coronary heart disease mortality among Chinese adults in Singapore: a population-based cohort study. Am J Epidemiol. 2008; 168(12): 1367–73. [PubMed: 18952563]
29. Liu J, Yuen J, Kang S. Sleep duration, C-reactive protein and risk of incident coronary heart disease - results from the Framingham Offspring Study. Nutr Metab Cardiovas. 2014; 24(6):600–05.

30. Sands-Lincoln M, Loucks EB, Lu B, et al. Sleep duration, insomnia, and coronary heart disease among postmenopausal women in the Women's Health Initiative. J Womens Health. 2013; 22(6): 477–86.
31. Hoevenaar-Blom MP, Spijkerman AM, Kromhout D, et al. Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: the MORGEN study. Sleep. 2011; 34(11): 1487–92. [PubMed: 22043119]
32. Meisinger C, Heier M, Lowel H, et al. Sleep duration and sleep complaints and risk of myocardial infarction in middle-aged men and women from the general population: the MONICA/KORA Augsburg cohort study. Sleep. 2007; 30(9):1121–27. [PubMed: 17910384]
33. Amagai Y, Ishikawa S, Gotoh T, et al. Sleep duration and incidence of cardiovascular events in a Japanese population: the Jichi Medical School cohort study. J Epidemiol. 2010; 20(2):106–10. [PubMed: 20009370]
34. Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Sleep duration associated with mortality in elderly, but not middle-aged, adults in a large US sample. Sleep. 2008; 31(8):1087–96. [PubMed: 18714780]
35. Kronholm E, Laatikainen T, Peltonen M, et al. Self-reported sleep duration, all-cause mortality, cardiovascular mortality and morbidity in Finland. Sleep Med. 2011; 12(3):215–21. [PubMed: 21317033]
36. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness - a systematic review and meta-analysis. Circulation. 2007; 115(4):459–67. [PubMed: 17242284]
37. Wolff B, Volzke H, Schwahn C, et al. Relation of self-reported sleep duration with carotid intima-media thickness in a general population sample. Atherosclerosis. 2008; 196(2):727–32. [PubMed: 17289054]
38. Sands MR, Lauderdale DS, Liu K, et al. Short sleep duration is associated with carotid intima-media thickness among men in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Stroke. 2012; 43(11):2858–64. [PubMed: 22935396]
39. King CR, Knutson KL, Rathouz PJ, et al. Short sleep duration and incident coronary artery calcification. JAMA. 2008; 300(24):2859–66. [PubMed: 19109114]
40. Polonsky TS, McClelland RL, Jorgensen NW, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA. 2010; 303(16):1610–16. [PubMed: 20424251]
41. Center for Disease Control and Prevention. Prevalence and most common causes of disability among adults-United States, 2005. MMWR: Morb Mortal Wkly Rep. 2009; 58:421–26. [PubMed: 19407734]
42. Ge BH, Guo XM. Short and long sleep durations are both associated with increased risk of stroke: a meta-analysis of observational studies. Int J Stroke. 2015; 10(2):177–84. [PubMed: 25366107]
43. Qureshi AI, Giles WH, Croft JB, et al. Habitual sleep patterns and risk for stroke and coronary heart disease: a 10-year follow-up from NHANES I. Neurology. 1997; 48(4):904–11. [PubMed: 9109875]
44. Chen JC, Brunner RL, Ren H, et al. Sleep duration and risk of ischemic stroke in postmenopausal women. Stroke. 2008; 39(12):3185–92. [PubMed: 18635832]
45. Eguchi K, Hoshide S, Ishikawa S, et al. Short sleep duration is an independent predictor of stroke events in elderly hypertensive patients. J Am Soc Hypertens. 2010; 4(5):255–62. [PubMed: 20940066]
46. Fang J, Wheaton AG, Ayala C. Sleep duration and history of stroke among adults from the USA. J Sleep Res. 2014; 23(5):531–7. [PubMed: 24815229]
47. Ruiter-Petrov ME, Letter AJ, Howard VJ, et al. Self-reported sleep duration in relation to incident stroke symptoms: nuances by body mass and race from the REGARDS study. J Stroke Cerebrovasc. 2014; 23(2):E123–E32.
48. Carter JR, Durocher JJ, Larson RA, et al. Sympathetic neural responses to 24-hour sleep deprivation in humans: sex differences. Am J Physiol-Heart C. 2012; 302(10):H1991–H97.
49. Kato M, Phillips BG, Sigurdsson G, et al. Effects of sleep deprivation on neural circulatory control. Hypertension. 2000; 35(5):1173–75. [PubMed: 10818083]

50. Sauvet F, Leftheriotis G, Gomez-Merino D, et al. Effect of acute sleep deprivation on vascular function in healthy subjects. J Appl Physiol. 2010; 108(1):68–75. [PubMed: 19910332]
51. Meier-Ewert HK, Ridker PM, Rifai N, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. J Am Coll Cardiol. 2004; 43(4):678–83. [PubMed: 14975482]
52. Lusardi P, Zoppi A, Preti P, et al. Effects of insufficient sleep on blood pressure in hypertensive patients - a 24-h study. Am J Hypertens. 1999; 12(1):63–68. [PubMed: 10075386]
53. Sunbul M, Kanar BG, Durmus E, et al. Acute sleep deprivation is associated with increased arterial stiffness in healthy young adults. Sleep Breath. 2014; 18(1):215–20. [PubMed: 23852444]
54. Dettoni JL, Consolim-Colombo FM, Drager LF, et al. Cardiovascular effects of partial sleep deprivation in healthy volunteers. J Appl Physiol. 2012; 113(2):232–36. [PubMed: 22539169]
55. Sauvet F, Drogou C, Bougard C, et al. Vascular response to 1 week of sleep restriction in healthy subjects. A metabolic response? Int J Cardiol. 2015; 190:246–55. [PubMed: 25932797]
56. van Leeuwen WMA, Lehto M, Karisola P, et al. Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP. PLoS One. 2009; 4(2)
57. Covassin N, Bukartyk J, Sahakyan K, et al. Experimental sleep restriction increases nocturnal blood pressure and attenuates blood pressure dipping in healthy individuals. J Am Coll Cardiol. 2015; 65(10_S)
58. Yang H, Haack M, Lamanna M, et al. Blunted nocturnal blood pressure dipping and exaggerated morning blood pressure surge in response to a novel repetitive sleep restriction challenge. Faseb J. 2015; 29(1 Suppl):957–58.
59. Nedeltcheva AV, Kessler L, Imperial J, et al. Exposure to recurrent sleep restriction in the setting of high caloric intake and physical inactivity results in increased insulin resistance and reduced glucose tolerance. J Clin Endocr Metab. 2009; 94(9):3242–50. [PubMed: 19567526]
60. Ogawa Y, Kanbayashi T, Saito Y, et al. Total sleep deprivation elevates blood pressure through arterial baroreflex resetting: a study with microneurographic technique. Sleep. 2003; 26(8):986–89. [PubMed: 14746379]
61. Pagani M, Pizzinelli P, Pavy-Le Traon A, et al. Hemodynamic, autonomic and baroreflex changes after one night sleep deprivation in healthy volunteers. Auton Neurosci. 2009; 145(1–2):76–80. [PubMed: 19006684]
62. Zhong X, Hilton HJ, Gates GJ, et al. Increased sympathetic and decreased parasympathetic cardiovascular modulation in normal humans with acute sleep deprivation. J Appl Physiol. 2005; 98(6):2024–32. [PubMed: 15718408]
63. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol. 2010; 141(2):122–31. [PubMed: 19910061]
64. Cakici M, Dogan A, Cetin M, et al. Negative effects of acute sleep deprivation on left ventricular functions and cardiac repolarization in healthy young adults. Pacing Clin Electrophysiol. 2015; 38(6):713–22. [PubMed: 25353305]
65. Ozer O, Ozbala B, Sari I, et al. Acute sleep deprivation is associated with increased QT dispersion in healthy young adults. Pacing Clin Electrophysiol. 2008; 31(8):979–84. [PubMed: 18684254]
66. Yoshioka E, Saijo Y, Kita T, et al. Relation between self-reported sleep duration and arterial stiffness: a cross-sectional study of middle-aged Japanese civil servants. Sleep. 2011; 34(12): 1681–86. [PubMed: 22131605]
67. Tsai TC, Wu JS, Yang YC, et al. Long sleep duration associated with a higher risk of increased arterial stiffness in males. Sleep. 2014; 37(8):1315–20. [PubMed: 25083011]
68. Verma S, Buchanan MR, Anderson TJ. Endothelial function testing as a biomarker of vascular disease. Circulation. 2003; 108(17):2054–59. [PubMed: 14581384]
69. Calvin AD, Covassin N, Kremers WK, et al. Experimental sleep restriction causes endothelial dysfunction in healthy humans. J Am Heart Assoc. 2014; 3(6):e001143. [PubMed: 25424573]
70. Sekine T, Daimon M, Hasegawa R, et al. The impact of sleep deprivation on the coronary circulation. Int J Cardiol. 2010; 144(2):266–67. [PubMed: 19203808]

71. Frey DJ, Fleshner M, Wright KP. The effects of 40 hours of total sleep deprivation on inflammatory markers in healthy young adults. Brain Behav Immun. 2007; 21(8):1050–57. [PubMed: 17524614]
72. Liu H, Wang GG, Luan GH, et al. Effects of sleep and sleep deprivation on blood cell count and hemostasis parameters in healthy humans. J Thromb Thrombolys. 2009; 28(1):46–49.
73. Buxton OM, Pavlova M, Reid EW, et al. Sleep restriction for 1 week reduces insulin sensitivity in healthy men. Diabetes. 2010; 59(9):2126–33. [PubMed: 20585000]
74. Reynolds AC, Dorrian J, Liu PY, et al. Impact of five nights of sleep restriction on glucose metabolism, leptin and testosterone in young adult men. PLoS One. 2012; 7(7)
75. van Leeuwen WMA, Hublin C, Sallinen M, et al. Prolonged sleep restriction affects glucose metabolism in healthy young men. Int J Endocrinol. 2010
76. Bosy-Westphal A, Hinrichs S, Jauch-Chara K, et al. Influence of partial sleep deprivation on energy balance and insulin sensitivity in healthy women. Obes Facts. 2008; 1(5):266–73. [PubMed: 20054188]
77. Markwald RR, Melanson EL, Smith MR, et al. Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. P Natl Acad Sci USA. 2013; 110(14):5695–700.
78. Nedeltcheva AV, Kilkus JM, Imperial J, et al. Sleep curtailment is accompanied by increased intake of calories from snacks. Am J Clin Nutr. 2009; 89(1):126–33. [PubMed: 19056602]
79. Calvin AD, Carter RE, Adachi T, et al. Effects of experimental sleep restriction on caloric intake and activity energy expenditure. Chest. 2013; 144(1):79–86. [PubMed: 23392199]
80. Cappuccio FP, D'Elia L, Strazzlillo P, et al. Quantity and quality of sleep and incidence of type 2 diabetes - a systematic review and meta-analysis. Diabetes Care. 2010; 33(2):414–20. [PubMed: 19910503]
81. Cappuccio FP, Taggart FM, Kandala NB, et al. Meta-analysis of short sleep duration and obesity in children and adults. Sleep. 2008; 31(5):619–26. [PubMed: 18517032]
82. Guyon A, Balbo M, Morselli LL, et al. Adverse effects of two nights of sleep restriction on the hypothalamic-pituitary-adrenal axis in healthy men. J Clin Endocr Metab. 2014; 99(8):2861–68. [PubMed: 24823456]
83. Minkel J, Moreta M, Muto J, et al. Sleep deprivation potentiates HPA axis stress reactivity in healthy adults. Health Psychol. 2014; 33(11):1430–4. [PubMed: 24818608]
84. Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. Sleep. 2007; 30(9):1145–52. [PubMed: 17910386]
85. Vgontzas AN, Zoumakis E, Bixler EO, et al. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. J Clin Endocr Metab. 2004; 89(5):2119–26. [PubMed: 15126529]
86. Hastings MH, Reddy AB, Maywood ES. A clockwork web: circadian timing in brain and periphery, in health and disease. Nat Rev Neurosci. 2003; 4(8):649–61. [PubMed: 12894240]
87. Esquirol Y, Perret B, Ruidavets JB, et al. Shift work and cardiovascular risk factors: new knowledge from the past decade. Arch Cardiovasc Dis. 2011; 104(12):636–68. [PubMed: 22152516]
88. Kakizaki M, Kuriyama S, Nakaya N, et al. Long sleep duration and cause-specific mortality according to physical function and self-rated health: the Ohsaki Cohort Study. J Sleep Res. 2013; 22(2):209–16. [PubMed: 23005259]
89. Vgontzas AN, Liao DP, Bixler EO, et al. Insomnia with objective short sleep duration is associated with a high risk for hypertension. Sleep. 2009; 32(4):491–97. [PubMed: 19413143]
90. Priou P, Le Vaillant M, Meslier N, et al. Cumulative association of obstructive sleep apnea severity and short sleep duration with the risk for hypertension. PLoS One. 2014; 9(12):e115666. [PubMed: 25531468]
91. Garde AH, Hansen AM, Holtermann A, et al. Sleep duration and ischemic heart disease and all-cause mortality: prospective cohort study on effects of tranquilizers/hypnotics and perceived stress. Scand J Work Environ Health. 2013; 39(6):550–8. [PubMed: 23804297]
92. Fung MM, Peters K, Redline S, et al. Decreased slow wave sleep increases risk of developing hypertension in elderly men. Hypertension. 2011; 58(4):596–603. [PubMed: 21876072]

**Key points**

- Inadequate sleep has become increasingly pervasive, and its impact on health and quality of life remains to be fully understood.
- Both extremes of sleep duration have been associated with increased prevalence and incidence of cardiovascular diseases including hypertension, coronary heart disease, and stroke.
- Aberrations in physiological functions induced by abnormal sleep may explain this association, along with enhanced prevalence of established cardiovascular risk factors.