












Long sleep duration and cardiovascular disease: Associations with arterial stiffness and blood pressure variability

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Abstract

Although short and long sleep duration are both risk factors of cardiovascular disease (CVD), the recent meta-analyses have been shown that long sleep duration was closely associated with CVD mortality. While the specific mechanism underlying the association between long sleep duration and CVD remains unclear, long sleep duration was shown to be associated with arterial stiffness and blood pressure variability (BPV) in many Asian populations. This review article will focus on the pathophysiology of long sleep duration, arterial stiffness, BPV and their effects on CVD. To set the stage for this review, we first summarize the current insights for the relationship between long sleep duration and CVD in relation to arterial stiffness and BPV.

These authors contributed equally to this work.

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1 | INTRODUCTION

While sleep duration has been shown to be associated with mortality,^{1,2} it was demonstrated that short and long sleep duration are both risk factors of cardiovascular disease (CVD).²⁻⁴ Specifically, recent meta-analyses have reported that long sleep duration was associated with cardiovascular mortality.^{3,4} However, the specific mechanisms underlying the association between the sleep components and CVD remain unclear. Arterial stiffness⁵ and blood pressure variability (BPV)⁶ were suggested to be mediators linking long sleep duration and CVD. From these standpoints, this review article will focus on the physiology of long sleep duration, arterial stiffness, BPV and their effects on CVD. To set the stage for this review, we first summarize the current insights for the relationship between long sleep duration and CVD in relation to arterial stiffness and BPV.

2 | EFFECTS OF SLEEP DURATION ON HYPERTENSION, CORONARY ARTERY DISEASE, AND MORTALITY

2.1 | Sleep duration and hypertension

Over the past decade, average sleep duration in the United States has been steadily declining,⁷ while the prevalence of hypertension (HT) has been increasing.⁸ In the First National Health and Nutrition Examination Survey (NHANES),⁹ the analyses over 8 to 10 yrs on 4810 subjects aged 25 to 74 yrs were performed to determine the relationship between sleep duration and incidence of HT. Sleep duration less than 5 hr per night was significantly associated with an increased risk of HT in the subjects aged 32 to 59 yrs. A significant association between short sleep duration and an increased risk of HT was suggested to be observed specifically in the middle-aged subjects.⁹

2.2 | Sleep duration and acute coronary syndrome

In the Alameda County Study¹ and the Finnish study,¹⁰ the men who slept less than 6 hr as well as those who slept above 9 hours were shown to have a greater risk of coronary heart disease (CHD) compared with those who slept for 7-8 hr

In the Nurses' Health Study,¹¹ a relationship between self-reported sleep duration and the incidence of CHD was investigated in 71 617 women aged 45 to 65 yrs. During 10 years of the follow-up period, coronary events were documented in 934 women. Age-adjusted relative risks (RRs) of CHD for individuals reporting 5 or fewer, 6, and 7 hr of sleep were 1.82, 1.30, and 1.06, respectively, while the age-adjusted RR for 9 or more hours of sleep was 1.57 compared with 8 hr of daily sleep.¹¹

Short or long sleep duration was a significantly increased risk for CHD. The U-shaped relationship was suggested between sleep duration and CHD incidence.

2.3 | Sleep duration and mortality

In the Alameda County Study,¹ the mortality risk associated with different sleeping patterns was investigated based on data from a 9-year mortality follow-up of 6928 adults. The mortality rates of ischemic heart disease, cancer, stroke, and all causes combined were lowest for individuals sleeping 7 or 8 hr per night. While men sleeping 6 hr or less, or 9 hr or more, had 1.7 times of total age-adjusted mortality compared with men sleeping 7 or 8 hr per night, the comparable RR in women was 1.6. In the American Cancer Society,² men sleeping less than 4 hr had 2.8 times of the mortality during 6 years of follow-up period compared with men sleeping 7.0 to 7.9 hr while the ratio for women was 1.48. Men and women sleeping 10 hr or more had about 1.8 times the mortality compared with those sleeping 7.0 to 7.9 hr. The relationship between sleep duration and mortality was U shaped.

2.4 | Sleep duration and cardiovascular disease in the meta-analysis

In the recent meta-analyses including 474 684 from 15 studies,³ 3 340 684 participants from 74 studies,⁴ 816 995 individuals from 19 studies,¹² and 5 134 036 participants from 137 prospective cohort studies,¹³ longer duration of sleep was closely associated with adverse cardiovascular outcomes (Table 1). While short sleep duration was associated with a significantly increased risk of developing³ or dying of CHD,^{3,12} there was no significant difference in all-cause mortality for periods of self-reported sleep duration of 7 hr or less.⁴

In the meta-analysis including 1 598 628 individuals from 29 cohorts with a median follow-up duration of 10.5 yrs,¹⁴ difficulties falling asleep and non-restorative sleep were associated with an increased risk of all-cause mortality and CVD mortality. Convincing associations between difficulty falling asleep and all-cause mortality were restricted to the mid to older-aged population. Insomnia disorder, difficulty maintaining sleep, and early morning awakening were not associated with all-cause and CVD mortality.¹⁴

Although there were several differences among the reports of meta-analysis in the inclusion criteria and in the duration for the literature searching periods, in the recent meta-analyses, longer duration of sleep was closely associated with adverse cardiovascular outcomes compared with shorter sleep durations.

2.5 | Sleep duration based on actigraphy and the risk of cardiovascular disease

Evidence suggests that short and long sleep durations are potential lifestyle factors associated with CVD. Research on sleep duration and CVD risk is limited by the use of self-reported sleep measures. Recently, in the Objective Physical Activity and Cardiovascular Health Study,¹⁵ cross-sectional analysis included 3367 older women (mean age 78.9 years; 53.3% White) who wore ActiGraph GT3X + accelerometers on the hip for 24 hours/7 days. A 10-year

TABLE 1 Summary of meta-analysis for the relationship between sleep duration and cerebro-cardiovascular disease

Author/Year/ID	Numbers of included studies	Subjects	Follow-up period	Number of events	Results
Cappuccio et al, 2011 (ref.3)	15 studies (24 cohort samples)	474 684 males and females	6.9 to 25 years	16 067 events (4169 for CHD, 3478 for stroke, and 8420 for total CVD)	Short duration of sleep was associated with a greater risk of developing or dying of CHD (RR 1.48, 95% CI 1.22-1.80, $p < .0001$), stroke (1.15, 1.00-1.31, $p = .047$), but not total CVD (1.03, 0.93-1.15, $p = .52$). Long duration of sleep was also associated with a greater risk of CHD (1.38, 1.15-1.66, $p = .0005$), stroke (1.65, 1.45-1.87, $p < .0001$), and total CVD (1.41, 1.19-1.68, $p < .0001$) with no evidence of publication bias ($p = .92$, $p = .96$, and $p = .79$, respectively).
Kwok et al, 2015 (ref.4)	74 studies	3 340 684 participants	61.7 months to 30 years	242 240 deaths	Self-reported duration of sleep > 8 hours was associated with a moderate increased risk of all-cause mortality, with RR, 1.14 (1.05-1.25) for 9 hours, RR, 1.30 (1.19-1.42) for 10 hours, and RR, 1.47 (1.33-1.64) for 11 hours. No significant difference was identified for periods of self-reported sleep < 7 hours, whereas similar patterns were observed for stroke and cardiovascular disease mortality.
Jike et al, 2015 (ref.15)	137 prospective cohort studies	5 134 036 participants	1 to 34 years	...	Long sleep was significantly associated with mortality (RR, 1.39; 95% CI, 1.31-1.47), incident diabetes mellitus (1.26, 1.11-1.43), CVD (1.25, 1.14-1.37), stroke (1.46, 1.26-1.69), CHD (1.24, 1.13-1.37), and obesity (1.08, 1.02-1.15). Long sleep was not significantly related to incident hypertension (1.01, 0.95-1.07). Meta-regression analyses found statistically significant linear associations between longer sleep duration and increased mortality and incident CVD.
Krittananwong et al, 2019 (ref.14)	19 studies (31 cohorts)	816 995 individuals	2 to 24.2 years	42 870 cardiovascular disease mortality cases	In pooled analyses, both short (RR 1.19; 95% CI 1.13 to 1.26, $p < .001$, $I^2 = 30.7$, P heterogeneity = 0.034), and long (RR 1.37; 95% CI 1.23 to 1.52, $p < .001$, $I^2 = 79.75$, P heterogeneity < 0.001) sleep durations were associated with a greater risk of CVD mortality.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; RR, risk ratio.

predicted probability of future CVD risk was computed using age, systolic blood pressure (BP), high-sensitivity C-reactive protein (hs-CRP), total and high-density lipoprotein cholesterol, diabetes mellitus status, smoking status, and family history of CVD based on the Reynolds Risk Score (RRS). A U-shaped relationship between sleep duration and RRS with both short and long sleep associated with higher RRS. The association remained significant after adjustments for the confounders including race/ethnicity, education, lifestyle factors, and health status indicators.¹⁵

3 | HOW LONG SHOULD WE SLEEP?—POSSIBLE PATHOPHYSIOLOGY UNDERLYING THE RELATIONSHIP BETWEEN SLEEP DURATION AND CARDIOVASCULAR DISEASE

Recent studies suggest that short sleep is a significant risk factor of developing HT and CHD compared with 7-8 hr of sleep that was suggested to be the lowest risk of CVD. In the evening of the day after sleep deprivation, sympathetic nervous system activity and BP are elevated. These increases may be associated with an increased risk of CHD.¹⁶ On the other hand, there has been still little evidence regarding the pathophysiology underlying the relationship between long sleep duration and CVD. Arterial stiffness and BPV are, therefore, gaining attention as the candidate mediators for the relationship between long sleep duration and CVD.¹⁷

3.1 | Long sleep duration and arterial stiffness

In the Japan Morning Surge-Home Blood Pressure (J-HOP) Study, among 4310 patients with ≥ 1 cardiovascular risks, the brachial-ankle PWV (baPWV) and hs-CRP levels were measured in 2304 of these patients (mean age 64.7 yrs, 49.6% males) (Table 2).⁵ In accord with the patients' sleep duration (< 6 hr, ≥ 6 to < 8 hr, and ≥ 8 hr per night), significant associations between sleep duration and the PWV were observed (1594 vs. 1644 vs. 1763 cm/s). In the multiple regression analysis adjusted for confounding factors, long sleep duration (≥ 8 hours) and log hs-CRP were significantly positively associated with PWV when sleep duration of 6-8 hr was defined as a reference. A significant interaction of long sleep duration by age for baPWV was observed. The effect of long sleep on PWV was greatest in the oldest age group.⁵ In addition, specifically for the Asian population,¹⁸⁻²² there was increasing evidence for the relationship between long sleep duration and higher PWV.

In the Multi-Ethnic Study of Atherosclerosis Sleep,²³ sleep duration was assessed by 7-day wrist actigraphy, and aortic PWV (aPWV) between ascending and descending aorta was measured based on magnetic resonance imaging. Aortic stiffness of participants with mid-range of sleep duration (6-8 hours) was compared with those of short (< 6 hr) and long sleep duration (> 8 hr). In the 908 participants (mean age 68.4 ± 9.1 yrs, 55.3% female), there was a significant linear

trend of increased aPWV across short, mid-range, and long sleep durations. Multivariable analysis showed that people with long sleep duration had significantly higher aPWV, compared with those with short sleep duration. Habitual long sleep duration as estimated by actigraphy was associated with higher aortic stiffness.²³

Although self-reporting long sleep duration was a significant indicator of increased PWV,^{5,18-22,24} the significant relationship between long sleep duration and increased aortic stiffness was observed even if sleep duration was assessed by actigraphy.²³ And, not only in the Asian populations^{5,18-22} but also in the populations from the Western countries,^{23,24} there were significant associations between long sleep duration and higher PWV. However, the association between long sleep duration and aortic stiffness might be a chicken-egg relationship because subjects with increased arterial stiffness might be less energetic and cause long duration of sleep.

3.2 | Long sleep duration and blood pressure variability

Although high average BP over a period of time is widely considered, an important risk factor for CVD,²⁵ day-by-day²⁶ and visit-to-visit systolic BPV²⁷ has also been shown to be a strong predictor of CVD independently of average BP level. Several studies have reported the relationship between long sleep duration and higher BPV.

In the Finn-home study including 1908 participants aged 41-74 years,²⁸ home BP measurements were performed for 7 consecutive days. The variability in home-measured BP was defined as the standard deviation of morning day-by-day BP. Based on self-reported sleep duration questionnaires, morning day-by-day variability of home BP was significantly higher in long sleepers.²⁸

In the 3SCO study, the 201 elderly individuals (79.9 ± 6.4 yrs) with one or more cardiovascular risks were included. Based on 12 visits during one year, visit-to-visit BPV (expressed as a coefficient of variation [CV]) and delta (defined as the difference between maximum and minimum value) BP were measured.²⁹ Long sleep duration (≥ 9 hr) had a significant positive association with delta in systolic BP. A significant interaction in a term of long sleep duration by carotid artery stiffness parameter β (an index of blood pressure-independent blood vessel elasticity) was found for delta in systolic BP.⁶

One major determinant of BPV is the sensitivity of baroreceptor function.³⁰ Vascular structural changes may reduce baroreceptor sensitivity (BRS) in hypertension. Reduced large arterial compliance appears to contribute to the depressed BRS in hypertensive individuals.³¹ Stiffening itself might enhance BP fluctuations associated with minor changes in cardiac stroke volume. Thus, BPV and arterial stiffness would affect each other. Because a significant interaction in a term of long sleep duration by carotid arterial stiffness was found for increased visit-to-visit BPV, it was suggested that arterial stiffness could augment the relationship between long sleep duration and higher visit-to-visit BPV.

TABLE 2 Summary of reports for the relationship between sleep duration and pulse wave velocity

Author/Year/ID	Subjects	Age	Gender	Measures	Results
Yoshioka et al, 2011 (ref.20)	4268 Japanese local government employees	aged 35-62 years	3410 males	Brachial-ankle PWV/Self-reported sleep duration	Results of multiple linear regression analysis after fully adjusting the model revealed that subjects with ≥ 9 h of daily sleep had significantly elevated PWV values compared with the reference group with 7 h of sleep. Stratified analyses by sex showed that there was a significant association among male subjects only.
Tsai et al, 2014 (ref.21)	3508 Taiwanese subjects from a health examination center	aged 20-87 years	3410 males	Brachial-ankle PWV/ Arterial stiffness as PWV \geq 1400 (cm/sec)/ Self-reported sleep duration	In the multivariate analysis for males, long sleepers (OR 1.75, $p = .034$) but not short sleepers (OR 0.98, $p = .92$) had a higher risk of increased arterial stiffness. However, in females, neither short nor long sleep duration was associated with increased arterial stiffness.
Kim et al, 2015 (ref.22)	18 106 Korean subjects underwent a health checkup examination	Median 45.8 years old	Male 69%	Brachial-ankle PWV/ Self-reported sleep duration	The multivariate-adjusted PWV (95% confidence interval) comparing sleep durations of ≤ 5 , 6, 8, and ≥ 9 hours with 7 hours of sleep were 6.7 (0.75-12.6), 2.9 (-1.7 to 7.4), 10.5 (4.5-16.5), and 9.6 (-0.7 to 19.8) cm/s, respectively (p for quadratic trend = .019).
Anjuo et al, 2016 (ref.26)	10 994 participants from the six major ethnic groups	Aged 18-71 years	5018 males	Duplicate PWV measurements using the Arteriograph system/ Self-reported sleep duration	Neither short (<7 h/night) nor long sleep (≥ 9 h/night) was related to PWV in all ethnic groups, except for long sleep in Dutch men which was associated with higher PWV after adjustment for potential confounders ($\beta = 0.67$, 95%CI, 0.23-1.11).
Nijima et al, 2016 (ref.5)	2304 Japanese patients with one or more risks of cardiovascular disease	Mean age 64.7 years	49.6% males	Brachial-ankle PWV/ Self-reported sleep duration	In accord with the patients' sleep duration (<6 hours, $6 \geq$ to <8 hours, and $8 \geq$ hours per night), significant associations between sleep duration and the PWV were observed (1594 vs. 1644 vs. 1763 cm/s, $p < .0001$). In the multiple regression analysis adjusted for age, body mass index, total cholesterol, HbA1c, and clinic systolic blood pressure, long sleep duration was significantly positively associated with PWV when the patients with 6- to 8-hour sleep duration were defined as a reference group.
Logan et al, 2018 (ref.25)	908 participants from white, African American, Hispanic, and Chinese adults living in six US cities	Mean age 68.4 years	55.3% female	Aortic PWV/ Sleep duration assessed by 7-day wrist actigraphy	Aortic stiffness of participants with normal sleep duration (6-8 hours) were compared with those of short (≤ 6 hours) and long sleep duration (>8 hours) adjusting for common cardiovascular risk factors and apnea-hypopnea index. There was a significant linear trend of increased aortic PWV across short ($n = 252$), normal ($n = 552$), and long sleep durations ($n = 104$) (p for trend = .008). Multivariable analysis showed that people with short sleep duration had 0.94 m/s lower aortic PWV (95% CI: -1.54, -0.35), compared with those with normal sleep duration.
Hu et al, 2020 (ref.23)	14 485 Chinese hypertensive adults	Mean age 64.4 years	40.2% male	Brachial-ankle PWV/ Arterial stiffness as PWV \geq 1800 (cm/sec)/ Self-reported sleep duration	Compared with participants with a sleep duration < 8 h per day, participants with a sleep duration ≥ 8 h per day had a significantly higher PWV level ($\beta = 13.7$ cm/s; 95% CI: 3.9, 23.5) and a nonsignificantly higher prevalence of arterial stiffness (39.7% vs. 33.0%; OR, 1.08; 95% CI: 0.99-1.19).
Liu et al, 2020 (ref.24)	17 018 Chinese participants	Aged 18 to 98 years	61.3% male	Brachial-ankle PWV/ Arterial stiffness as PWV \geq 1400 (cm/sec)/ Self-reported sleep duration	Using 7 hours of sleep as the reference group, the multivariable adjusted ORs (95% CI) for arterial stiffness were 1.00 (0.87-1.16), 1.00 (0.90-1.11), 1.0 (ref), 1.03 (0.93-1.14), and 1.48 (1.05-2.08) from the lowest to highest category of sleep duration [≤ 5.0 , 6.0, 7 (ref), 8, and ≥ 9.0 hours], respectively.

Abbreviations: CI, confidence interval; OR, odds ratio; PWV, pulse wave velocity.

3.3 | What is the pathophysiology underlying the relationship between long sleep duration and cardiovascular disease?

Arterial remodeling could moderate the impact of long sleep duration on risks of CVD. While PWV was shown to be closely linked to cerebral small vessel disease,³² long sleep duration was a significant determinant of increased PWV leading to stroke incidence in the elderly at high risk of CVD.⁵ In addition, long sleep duration was shown to be associated with sleep fragmentation^{33,34} that was suggested to increase sympathetic nervous system activity.³⁵ Thus, these factors caused by long sleep duration might lead to a stiffening effect on arterial mechanical properties in relation to cerebrocardiovascular disease.

On the other hand, the significant associations of long sleep duration with age and lower physical health status were found in both the WhitehallIII Study and the Western New York Health Study.³⁶ Additionally, the relationship between long sleep duration and morbidity was suggested to be caused by lack of physical activity as an outcome or an effect of infirmity and disease.³⁶ In the study reported by Nijima et al,⁵ the long sleepers were older than those with the mid-range of sleep duration, and thus, they might have a poor level of physical activity. However, the significant relationships between long sleep duration and increased arterial stiffness were independently of age and physical activity.^{18-22,24}

Several mechanisms would explain the relationship between inflammation and arterial stiffness. There has been evidence of increased secretion of proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF- α).³⁷ The CRP activation by these factors could inhibit endothelium-dependent vasodilation and the nitric oxide synthesis. Inflammation could also adversely impact the collagen-to-elastin ratio of the vessel that was suggested to lead to arterial stiffening.^{38,39} In light of these findings, it is apparent that long sleep duration and hs-CRP might underlie the pathophysiology of increased arterial stiffness.

Although it would be suggested that short sleep duration was associated with elevated BP and arterial remodeling which may contribute to increased arterial stiffness,¹⁶ shorter sleep duration was associated with lower arterial stiffness. Among those studies which reported the sleep duration and PWV, the shortest sleep duration was defined as 5 hour or less. Because the subjects with extreme short sleep duration such as less than 4 hr were less included in those studies, this bias might be related to the lower aortic stiffness in people with shorter sleep duration.⁵

In addition, sleep duration was determined based on the self-report questionnaire in the most of the studies, while several studies were based on the actigraphy.^{15,23} Short sleep duration was defined as less than 5 hours,^{21,22} 5 hours or less,^{11,18,20} less than 6 hours,^{5,6,19,23,28} 6 hours or less,¹ or less than 7 hours,²⁴ while long sleep duration was defined as more than 8 hours,^{19,23} 8 hours or more,^{5,21} or 9 hours or more.^{1,6,11,18,20,22,24,28} Although the methods for measurement of sleep duration and the definitions of short or long sleep duration were different through the studies, short sleep

duration was defined as \leq 5-6 hours per night and long sleep duration was defined as $>$ 8-9 hours per night in most studies.³ Thus, the relationships between sleep duration and CVD would be consistent across different study populations.

4 | CONCLUSION

Short and long sleep durations have been shown to be associated with CVD or mortality. The recent literature confirms that short sleep is associated with HT and CHD. Increased sympathetic nervous system activity is considered to serve as a common pathophysiology in short sleep duration with these diseases. On the other hand, long sleep duration was associated with diabetes mellitus, obesity, CVD, and mortality. Long sleep duration was associated with increased arterial stiffness and increased BPV which serve as key risks of CVD. While the relationships of long sleep duration with higher arterial stiffness and increased BPV were reported extensively in the Asian populations that relationship would be observed in the populations in the Western population also. In addition to sleep duration, sleep quality is another important issue in relation to CVD, long sleep duration was shown to be associated with higher risk of CVD mortality in the elderly with poor sleep quality.⁴⁰ Thus, long sleep duration with concomitant poor sleep quality might be an important target for the prevention of CVD. Further prospective studies are needed to reveal the pathophysiology of long sleep duration with CVD in the viewpoint of inflammation, arterial stiffness, BPV, and sleep quality.

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AUTHOR CONTRIBUTIONS

HM, MN, and KD involved in conceptualization. HM, MN, KD, and KK involved in project administration. KD, YT, KK, YT, SS, YCC, CHC,

HMC, HVM, NV, JCT, and BWT involved in supervision. HM, MN, and KD involved in writing-original draft. HM, MN, KD, YT, KK, SS, YCC, CHC, HMC, HVM, NV, JCT, and BWT involved in writing-review and editing.

DISCLOSURE

All of the authors declare no conflict of interest.

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