

# The Associations of Trajectory of Sleep Duration and Inflammation with Hypertension: A Longitudinal Study in China

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**Background:** Existing evidence suggested that sleep duration may be involved in hypertension; however, the conclusions were still controversial. This study aimed to examine the association of longitudinal trajectory of sleep duration with hypertension and to explore the role of the inflammation in such associations.

**Methods:** A total of 3178 subjects over 30 years of age without hypertension were enrolled in 2004, and they were followed until 2009. Self-reported sleep duration was recorded, and inflammation was measured by highly sensitive C reactive protein (hs-CRP). Log-binomial regression models were applied to examine the association of sleep duration trajectory and inflammation with the risk of hypertension. The mediating effect of elevated hs-CRP was examined by the bootstrap and the process software.

**Results:** The prevalence of persistent short ( $\leq 7$  hours/day), normal (8–9 hours/day), and long ( $> 9$  hours/day) sleep duration over 5 years were 9.1%, 37.7%, and 2.3%, respectively. The incidence of hypertension was 26.6% during the follow-up period. Compared with those who persistently slept 8–9 hours/day from baseline to follow-up, those who persistently slept  $\leq 7$  hours/day, persistently slept  $\geq 10$  hours/day, and those whose sleep duration changed have higher risks of hypertension by 1.375-fold (95% CI: 1.121, 1.686), 1.557-fold (95% CI: 1.171, 2.069) and 1.299-fold (95% CI: 1.135, 1.487), respectively. In addition, persistently slept  $\leq 7$  hours/day was found to be associated with higher risk of inflammation (RR: 1.285, 95% CI: 1.008, 1.638). The mediation analysis did not find significant mediating effect of elevated CRP on the association between sleep duration trajectory and hypertension.

**Conclusion:** Experiencing both a short or long sleep duration, especially for a long time, could lead to higher risk of hypertension. Persistent exposure to short sleep duration was also associated with inflammation. However, the higher risk of hypertension caused by persistent short sleep duration does not seem to be directly mediated through inflammation.

**Keywords:** sleep duration, trajectory, inflammation, hypertension, longitudinal study

## Introduction

During the past two decades, the prevalence of hypertension has been increasing all over the world.<sup>1</sup> Due to its great contribution to human morbidity and mortality, hypertension is now a worldwide public health concern. A growing body of studies suggested that sleep duration may be associated with a higher risk of hypertension.<sup>2–4</sup> However, most existing evidence was mainly based on cross-sectional studies;<sup>5–7</sup> the longitudinal data were limited and controversial.<sup>8,9</sup> A longitudinal study in China indicated that compared with participants who slept 8 hours/day, those who slept  $\leq 7$  hours/day were associated with higher risk of

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hypertension;<sup>8</sup> however, another longitudinal study conducted in Finland found both short (<7 hours/night) and long ( $\geq 9$  hours/night) sleep duration were not associated with the incidence of hypertension, compared with those who slept 7–8 hours/night.<sup>9</sup> Considering sleep is a modifiable behavioral factor, further evidence is warranted on the association between sleep duration and hypertension.

The mechanism between sleep duration and hypertension remains unclear, and the emerging evidence points to the systemic inflammation. Chronic and mild inflammation has been demonstrated to be an important risk factor for the development of metabolic diseases.<sup>10,11</sup> C-reactive protein (CRP), as a marker of systemic inflammation, was found to be associated with a higher risk of hypertension.<sup>12–14</sup> An experimental study demonstrated that both total and partial sleep deprivation, even for only one night, could result in elevated CRP.<sup>15</sup> However, epidemiological surveys provided mixed findings.<sup>16,17</sup> A national longitudinal study in the US with 6 year follow-up found sleep duration  $\leq 6$  hours/night was associated with elevated CRP ( $\geq 3$ mg/dL).<sup>16</sup> But data from the UK found that compared with those who slept 7–8 hours, sleep duration  $\leq 5$ , 5–6, 6–7 and  $>8$  hours was not associated with CRP through a 4-year follow-up.<sup>17</sup> Therefore, the role of inflammation in the association between sleep and hypertension is far from clear. To our knowledge, till now there was no population-based study yet to explore the role of inflammation in the association between sleep duration and hypertension.

Sleep is a dynamic process throughout an individual's lifespan, which was affected by environmental, physical, and psychological factors.<sup>18</sup> Recent evidence suggested that changes in sleep duration or persistent short or long sleep duration over time were associated with higher risk of adverse outcomes,<sup>19–21</sup> which indicated that the trajectory of sleep may be a better predictor of health risk than a single measurement.

In the present study, we particularly focus on the trajectory of sleep duration, to examine its association with hypertension by a 5-year follow-up, which could provide stronger evidence for us to understand the role of sleep duration in the development of hypertension; meanwhile, the potential effect of CRP on the association between sleep duration and hypertension would be specifically explored based on population-based study.

## Methods

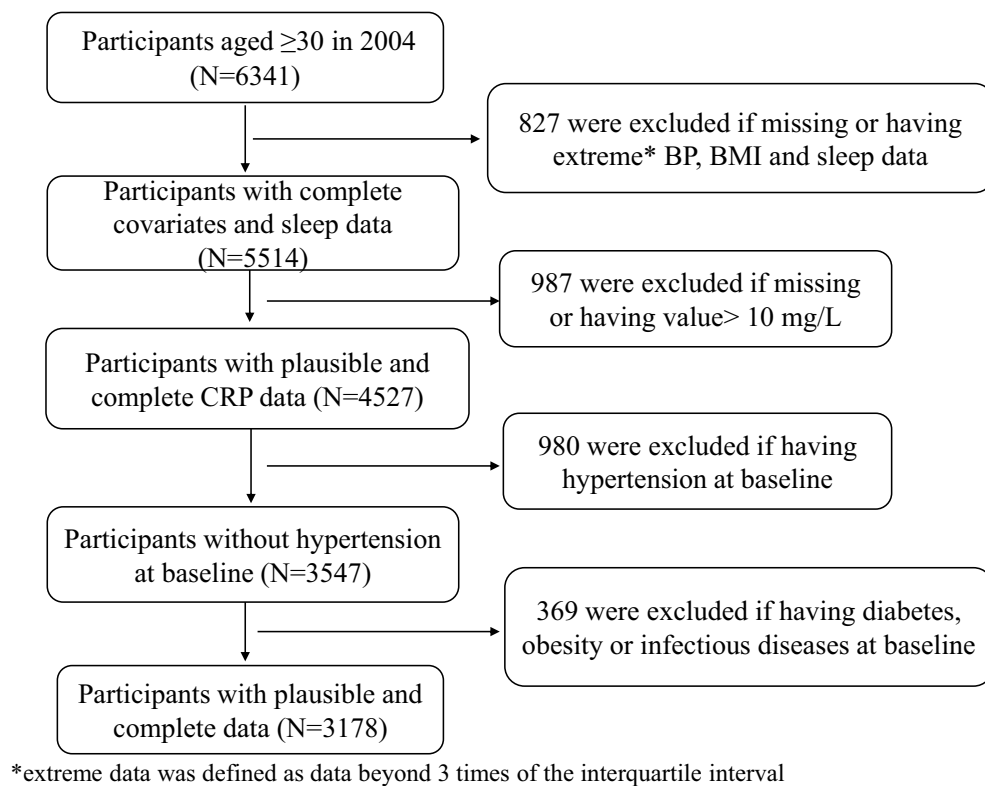
### Study Design and Participants

The present study was derived from China Health and Nutrition Survey (CHNS), a nationally ongoing survey based on household since 1989, covering 9 provinces in national wide. The survey was followed every two to four years and the investigation content included personal basic characteristics, lifestyles, family information, physical examination, and clinical detection. Sleep duration data was collected since 2004. The available clinical detection data were only in 2009. Further detailed information can be obtained at <http://www.cpc.unc.edu/projects/china>. The CHNS has been approved by the institutional review committees of the National Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention, the University of North Carolina at Chapel Hill, and the China-Japan Friendship Hospital, Ministry of Health. All the participants signed informed consent forms at the survey enrollment.

In the present analysis, we targeted the middle-aged and elderly participants who took part in both surveys of 2004 and 2009. Totally, 6341 participants aged  $\geq 30$  years in 2004 were followed until 2009. Among them, 827 were excluded due to the missing or extreme data on sleep duration, blood pressure (BP), body mass index (BMI) (the extreme data was defined as beyond three times of the interquartile interval); 987 were excluded because of the missing data on CRP or the value of CRP  $>10$ mg/L, which was defined as acute inflammation.<sup>22</sup> Besides, 980 participants who have hypertension at baseline were excluded. Moreover, because of the unavailability of CRP at 2004, 369 participants who have diabetes, obesity or infectious diseases were further excluded to control the possible influence of baseline inflammation. Finally, a total of 3178 participants qualified the inclusion criteria of this study (Figure 1).

### Measurements of Sleep Duration and CRP

Sleep duration was measured through the question “How many hours do you usually sleep each day, including daytime and nighttime in the last year?”. Sleep duration was categorized into three groups:  $\leq 7$ , 8–9 and  $\geq 10$  hours/day, therefore, the trajectory of sleep duration from 2004 to 2009 were categorized into:  $\leq 7$  hours/day  $\rightarrow \leq 7$  hours/day as persistent short sleep duration;  $\geq 10$  hours/day  $\rightarrow \geq 10$  hours/day as persistent long sleep duration; 8–9 hours/



**Figure 1** Sampling flowchart and participants enrollment.

day→8–9 hours/day as persistent normal sleep duration; considering the limited sample size, the others, covering sleep duration either decreased or increased, were defined as changed pattern over time.

For each participant, a fasting blood sample was drawn from the antecubital vein. The plasma and serum samples centrifuged from whole blood were frozen and stored, and then were transported to a national lab in Beijing. Highly sensitive C reactive protein (hs-CRP) was detected using the immunoturbidimetric method (Hitachi 7600 automated analyzer, Hitachi, Tokyo, Japan). Values >2 mg/L (elevated hs-CRP) were considered inflammation due to its association with high risk of future cardiovascular events<sup>23</sup> and which has been recommended by previous study.<sup>23</sup>

## Definition of Hypertension

Hypertension was defined as a self-report of diagnosis by a physician via the question “Has a doctor ever told you that you suffer from high blood pressure?”. As for those subjects who did not answer this question or answered “no” or “unknown”, their BP values were examined by trained examiners, mercury sphygmomanometers with appropriate-sized cuffs were applied. Measurements were taken in triplicate after at least a 10-min rest, and the three

readings were averaged as the BP values, and hypertension was diagnosed as average systolic BP (SBP)/diastolic BP (DBP)≥140/90 mmHg.

## Covariates

BMI was calculated as weight in kilograms divided by height in meters squared. Education was categorized into low (less than high school), medium (from high school to technical school), and high (higher than university) level. Smoke (yes or no) was based on the question “Ever smoked cigarettes?” and a smoker was defined as smoked continuously or cumulatively for 6 months or more. Drank alcohol (yes or no) was based on the question “Drank alcohol last year?”. Physical activity (PA)/day was based on transportation and leisure activities, and expressed as metabolic equivalent of task (MET) by using a Compendium of Physical Activities.<sup>24</sup> Sedentary time was estimated based on major screen exposure (watching television, video compact disc, video games, surfing internet, joining chat rooms, and playing computer games) and other sedentary activities. The following covariates were included, which have been demonstrated in published literature to be associated with hypertension:<sup>25</sup> age, BMI, gender (male vs female), education (low, medium, high),

family income per capita (tertiles), smoke (yes vs no), drank alcohol (yes vs no), PA (tertiles), sedentary time (tertiles). Models for each outcome accounted for the same covariates to maintain consistency.

## Statistical Analysis

The sample characteristics between 2004 and 2009 were compared, Student's test, Kruskal–Wallis test, and chi-square tests being applied where appropriate. The distributions of elevated hs-CRP and hypertension were analyzed based on sleep duration groups, and the difference was estimated by chi-square tests.

Log-binomial regression was used to estimate the associations of sleep duration with elevated CRP and hypertension, as well as the association of elevated CRP with hypertension, in which the effect was expressed as relative risk (RR). In the crude model, only exposure (sleep duration or elevated CRP) was included. Then, age and gender were further adjusted in the adjusted model 1; education, family income per capita, PA, sedentary time/day, smoke, drank alcohol, and BMI were additionally adjusted in the adjusted model 2. In order to explore the role of elevated hs-CRP in the association between sleep duration and hypertension, mediation analysis was further conducted, in which elevated hs-CRP was the mediator. The mediating effect was estimated using the bootstrapping method proposed by Preacher and Hayes.<sup>26</sup>

All statistical analyses were conducted by IBM SPSS Statistics (version 24.0, IBM Corp.). Statistical tests were two-tailed and were assessed at a 5% level of significance ( $p < 0.05$ ).

## Results

### Characteristics of the Study Population

The characteristics of participants are presented in Table 1. Of 3178 participants, male was 43.0%; the mean age was 47.98 [standard deviation (SD)=11.64] years old in 2004. The mean sleep duration was slightly decreased from 8.13 (SD = 1.16) hours/day in 2004 to 7.91 (SD = 1.22) hours/day in 2009. The percentage of sleep duration  $\leq 7$  hours was increased from 24.3% to 30.6% while sleep duration  $\geq 10$  hours was decreased from 13.5% to 10.7%. The incidence of elevated CRP and hypertension in 2009 was 18.6% and 26.6%, respectively.

### The Distribution of Elevated CRP and Hypertension According to Sleep Duration

As Table 2 shows, the prevalence of elevated CRP was higher in those who slept  $\leq 7$  hours /day and  $\geq 10$  hours/day

than those who slept 8–9 hours/day, only at follow-up survey ( $p=0.024$ ). Both at baseline and follow-up survey, the incidence of hypertension was significantly higher in group of sleep duration  $\leq 7$  hours /day and sleep duration  $\geq 10$  hours/day than that in sleep duration 8–9 hours/day ( $p \leq 0.001$ ). Moreover, the incidence of hypertension was higher in subjects who have persistent short sleep (31.5%), persistent long sleep (40.3%) or changed pattern (29.1%) than in those who have persistent normal sleep duration (21.1%).

### The Association of Sleep Duration with Hypertension

As showed in Table 3, sleep duration  $\leq 7$  hours/day and  $\geq 10$  hours/day at baseline were associated with a higher risk of hypertension (RR: 1.239, 95% CI: 1.083, 1.418, RR: 1.279, 95% CI: 1.086, 1.506, respectively) in crude model. Similarly, such association was also occurred in follow-up survey (RR: 1.252, 95% CI: 1.102, 1.424; RR: 1.417, 95% CI: 1.192, 1.685, respectively). For changes in sleep duration, compared with persistently slept 8–9 hours/day, persistently slept  $\leq 7$  hours/day,  $\geq 10$  hours/day and changed pattern over the 5 years showed a 1.477-fold (95% CI: 1.201, 1.817), 1.949-fold (95% CI: 1.442, 2.634) and 1.405-fold (95% CI: 1.228, 1.609) higher risk of hypertension, respectively, in crude model. The effects were somewhat attenuated but still kept significance after adjusting for age and gender. We further adjusted lifestyles and BMI, sleep duration  $\leq 7$  hours/day and  $\geq 10$  hours/day were still associated with higher risk of hypertension (RR: 1.192, 95% CI: 1.045, 1.359, RR: 1.169, 95% CI: 0.996, 1.371, respectively) at baseline and (RR: 1.199, 95% CI: 1.059, 1.359, RR: 1.205, 95% CI: 1.019, 1.424, respectively) at follow-up survey. Similarly, persistently slept  $\leq 7$  hours/day,  $\geq 10$  hours/day and changed pattern over the 5 years were also presented 1.375-fold (95% CI: 1.121, 1.686), 1.557-fold (95% CI: 1.171, 2.069) and 1.299-fold (95% CI: 1.135, 1.487) higher risk of hypertension, respectively.

### The Association of Sleep Duration with Elevated CRP

The association between sleep duration and elevated CRP is presented in Table 4, elevated hs-CRP was not demonstrated to be associated with sleep duration at baseline. However, sleep duration  $\leq 7$  hours/day at follow-up survey increased the risk of elevated hs-CRP (RR: 1.223, 95% CI: 1.042, 1.436), so did persistent sleep duration  $\leq 7$  hours/day (RR: 1.348, 95% CI: 1.060, 1.714) in crude model.

**Table 1** Sample Characteristics in 2004 and 2009

	2004	2009	p
	Mean (SD)/n (%)	Mean (SD)/n (%)	
Personal characteristics			
Energy intake (kcal/d)	2257.67 (649.36)	2158.63 (639.79)	<0.001
BMI (kg/m <sup>2</sup> )	22.44 (2.57)	22.81 (2.84)	<0.001
Gender			
Male	1366 (43.0)	—	
Female	1812 (57.0)	—	
Age (years)	47.98 (11.64)	52.95 (11.64)	<0.001
30–45	1329 (41.8)	851 (26.8)	<0.001
45–60	1316 (41.4)	1469 (46.2)	
60–75	482 (15.2)	712 (22.4)	
≥75	51 (1.6)	146 (4.6)	
Residence			
Urban	939 (29.5)	—	
Rural	2239 (70.5)	—	
Education			
Low	2538 (79.9)	—	
Medium	533 (16.8)	—	
High	105 (3.3)	—	
Income			0.439
Low	1048 (33.1)	1036 (33.4)	
Medium	1098 (34.7)	1034 (33.3)	
High	1017 (32.2)	1036 (33.4)	
Physical activities			0.970
MET/day	1.59 (7.92)	1.59 (6.59)	<0.001
Low	1673 (52.6)	1674 (52.7)	
Medium	874 (27.5)	798 (25.1)	
High	631 (19.9)	706 (22.2)	
Sedentary time (hours/day)			0.216
Low	1057 (33.3)	995 (31.3)	
Medium	1016 (31.8)	1017 (32.0)	
High	1105 (34.9)	1166 (36.7)	
Smoke			0.275
No	2163 (68.2)	2206 (69.5)	
Yes	1009 (31.8)	970 (30.5)	
Drank alcohol			0.789
No	2164 (68.2)	2178 (68.6)	
Yes	1007 (31.8)	999 (31.4)	
Sleep duration, CRP, and hypertension			
Sleep duration (hours/day)	8.13 (1.16)	7.91 (1.22)	<0.001
≤7 hours	773 (24.3)	973 (30.6)	<0.001
8–9 hours	1977 (62.2)	1866 (58.7)	
≥10 hours	428 (13.5)	339 (10.7)	
CRP (mg/L)	—	1.0 (0.0, 2.0)	

(Continued)

**Table 1** (Continued).

	2004	2009	p
	Mean (SD)/n (%)	Mean (SD)/n (%)	
Elevated CRP			
No	–	2588 (81.4)	
Yes	–	590 (18.6)	
SBP	115.34 (11.25)	122.23 (16.37)	
DBP	74.72 (7.97)	79.75 (10.79)	
Hypertension			
No	–	2334 (73.4)	
Yes	–	844 (26.6)	

**Abbreviations:** SD, standard deviation; BMI, body mass index; CRP, C-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure; MET, metabolic equivalent.

The estimated effect of sleep duration  $\leq 7$  hours/day on elevated hs-CRP was attenuated (RR: 1.182, 95% CI: 1.007, 1.388) at follow-up survey after adjusting for age and gender, as well as the effect of persistently slept  $\leq 7$  hours/day (RR: 1.283, 95% CI: 1.006, 1.635). When additionally adjusted for lifestyles and BMI, the significant effect still kept, only in persistent sleep duration  $\leq 7$  hours/day (RR: 1.285, 95% CI: 1.008, 1.638). No significant association was found between long sleep duration and elevated CRP.

## Mediation Analysis

The association of elevated CRP with hypertension was also examined, and we found that the elevated CRP was associated with higher risk of hypertension (RR: 1.204, 95% CI: 1.059, 1.368) even adjusted for multiple covariates (Table 5). Further, mediation analysis was conducted to evaluate the mediating role of elevated hs-CRP in the association between sleep trajectory and hypertension. However, the mediating effect was not found to be significant (Table S1).

## Discussion

In this study, we explored the impact of sleep duration as well as its long-time trajectory on the risk of hypertension, and examined the role of inflammation in such association. Our findings revealed that for adults who persistently keep a short or long sleep duration, and those whose sleep duration has changed during the follow-up periods, the risk of hypertension has been increased. Besides, the association of persistent short sleep duration with elevated CRP was also observed. However, mediation analysis did



**Table 2** The Distribution of Elevated CRP and Hypertension According to Sleep Duration Categories

	N	Elevated CRP (n, %)	p	Hypertension (n, %)	p
<b>Participants at 2004</b>					
≤7 hours	773 (24.3)	144 (18.6)	0.834	235 (30.4)	0.001
8–9 hours	1977 (62.2)	371 (18.8)		479 (24.2)	
≥10 hours	428 (13.5)	75 (17.5)		130 (30.4)	
<b>Participants at 2009</b>					
≤7 hours	973 (30.6)	202 (20.8)	0.024	286 (29.4)	<0.001
8–9 hours	1866 (58.7)	317 (17.0)		445 (23.8)	
≥10 hours	339 (10.7)	71 (20.9)		113 (33.3)	
<b>Sleep change from 2004 to 2009</b>					
≤7 hours /day→≤7 hours	289 (9.1)	70 (24.2)	0.054	91 (31.5)	<0.001
≥10 hours→≥10 hours	72 (2.3)	16 (22.2)		29 (40.3)	
Changed pattern	1620 (50.9)	288 (17.8)		472 (29.1)	
8–9 hours→8–9 hours	1197 (37.7)	216 (18.0)		252 (21.1)	

**Table 3** The Association of Sleep Duration with Hypertension

	n (%)	Crude Model	Adjusted Model 1	Adjusted Model 2
		RR (95% CI)	RR (95% CI)	RR (95% CI)
<b>2004</b>				
≤7 hours	773 (24.3)	1.239 (1.083, 1.418)	1.178 (1.032, 1.344)	1.192 (1.045, 1.359)
8–9 hours	1977 (62.2)	Reference	Reference	Reference
≥10 hours	428 (13.5)	1.279 (1.086, 1.506)	1.179 (1.005, 1.383)	1.169 (0.996, 1.371)
<b>2009</b>				
≤7 hours	973 (30.6)	1.252 (1.102, 1.424)	1.197 (1.057, 1.356)	1.199 (1.059, 1.359)
8–9 hours	1866 (58.7)	Reference	Reference	Reference
≥10 hours	339 (10.7)	1.417 (1.192, 1.685)	1.220 (1.031, 1.443)	1.205 (1.019, 1.424)
<b>Sleep change from 2004 to 2009</b>				
≤7 hours /day→≤7 hours	289 (9.1)	1.477 (1.201, 1.817)	1.383 (1.128, 1.696)	1.375 (1.121, 1.686)
≥10 hours→≥10 hours	72 (2.3)	1.949 (1.442, 2.634)	1.580 (1.185, 2.108)	1.557 (1.171, 2.069)
Changed pattern	1620 (50.9)	1.405 (1.228, 1.609)	1.332 (1.164, 1.524)	1.299 (1.135, 1.487)
8–9 hours→8–9 hours	1197 (37.7)	Reference	Reference	Reference

**Notes:** Adjusted Model 1 adjusted age, gender. Adjusted Model 2 additionally adjusted education, family income per capita, physical activities, sedentary time per day, smoke, drank alcohol, BMI.

not find elevated CRP to be a significant mediator in the associations between persistent short sleep duration and hypertension.

Compelling evidence have demonstrated that sleep duration may be involved in the development of hypertension; however, consistent conclusion has not yet been fully achieved. Majority of studies have established the relationship between short sleep duration and subsequent higher risk of hypertension,<sup>27,28</sup> which is consistent with our findings. Meanwhile, our study also found long sleep

duration was associated with higher risk of hypertension, which was an “U-shaped” association. Similarly, another study conducted in China observed that sleep duration <7 and ≥9 hours/night were associated with high BP (SBP ≥130 and/or DBP ≥85 mmHg or diagnosed hypertension) among females;<sup>29</sup> and a study conducted in US also found that sleep duration <7 and ≥10 hours/day were associated with higher risk of hypertension,<sup>30</sup> which suggests a normal sleep duration may be essential to maintain relatively low risk of hypertension. However, the

**Table 4** The Association of Sleep Duration with Elevated CRP

	Crude Model	Adjusted Model 1	Adjusted Model 2
	RR (95% CI)	RR (95% CI)	RR (95% CI)
<b>2004</b>			
≤7 hours	0.998 (0.837, 1.190)	0.969 (0.812, 1.156)	0.959 (0.806, 1.141)
8–9 hours	Reference	Reference	Reference
≥10 hours	0.937 (0.746, 1.177)	0.908 (0.722, 1.142)	0.881 (0.702, 1.105)
<b>2009</b>			
≤7 hours	1.223 (1.042, 1.436)	1.182 (1.007, 1.388)	1.169 (0.996, 1.372)
8–9 hours	Reference	Reference	Reference
≥10 hours	1.220 (0.956, 1.543)	1.130 (0.892, 1.431)	1.110 (0.878, 1.402)
<b>Sleep change from 2004 to 2009</b>			
≤7 hours /day→≤7 hours	1.348 (1.060, 1.714)	1.283 (1.006, 1.635)	1.285 (1.008, 1.638)
≥10 hours→≥10 hours	1.255 (0.802, 1.965)	1.166 (0.742, 1.832)	1.201 (0.765, 1.886)
Changed pattern	1.001 (0.851, 1.177)	0.977 (0.830, 1.150)	0.965 (0.821, 1.134)
8–9 hours→8–9 hours	Reference	Reference	Reference

**Notes:** Adjusted Model 1 adjusted age, gender. Adjusted Model 2 additionally adjusted education, family income per capita, physical activities, sedentary time per day, smoke, drank alcohol, BMI.

**Table 5** The Association of hs-CRP with Hypertension

	Crude Model	Adjusted Model 1	Adjusted Model 2
hs-CRP (mg/L)	RR (95% CI)	RR (95% CI)	RR (95% CI)
≤2	Reference	Reference	Reference
>2	1.380 (1.211, 1.572)	1.235 (1.088, 1.402)	1.204 (1.059, 1.368)

**Notes:** Adjusted Model 1 adjusted age, gender. Adjusted Model 2 additionally adjusted education, family income per capita, physical activities, sedentary time per day, smoke, drank alcohol, BMI.

differences in the sample characteristics, definition of short and long sleep duration, as well as covariate controlling strategy, could result in the inconsistency of the findings.<sup>9,31</sup>

In addition, the sleep duration fluctuates day from day, contingency is inevitable when adopting one-off measurement, while the changes in sleep duration over time could provide deeper and more reliable insight on its health impact.<sup>20,21</sup> To date, the evidence on the association of sleep duration changes with the risk of hypertension was quite scarce, with only several studies focused on the topic. A study revealed that persistently slept ≤6 hours, compared with persistently slept 7 hours, increased the risk of hypertension among women in Korea through over 5 years follow-up;<sup>20</sup> another study conducted in China suggested persistently decrease of sleep duration was significantly associated with an increased risk of hypertension.<sup>32</sup> In consistent with the two findings, our results also observed that persistent short sleep duration

increased the risk of hypertension. In addition, our findings found that persistently slept ≥10 hours/day and changed pattern over time also increased the risk of hypertension. Thus, keeping normal sleep duration over time, rather than only one-off measurement, should be emphasized in further perspective studies.

A bulk of literature have reported the association of sleep duration with inflammation,<sup>33–35</sup> however, the evidence from prospective study was limited. A cohort study among participants aged 18 to 30 years in the US showed short sleep duration (<6 hours) at baseline was associated with an increased level of CRP at follow-up survey; however, the effect became non-significant after adjusting for multi-covariates.<sup>36</sup> Another prospective cohort study conducted in England did not find the relationship between sleep duration at baseline and follow-up CRP among people aged 50 years and older.<sup>17</sup> Our analysis was conducted among middle-aged and older participants in China, and we did not observe the sleep duration at baseline was

associated with an elevated CRP at follow-up, while a significant association was observed between persistent short sleep and elevated CRP. To date, only several studies explored the association of changes in sleep duration with inflammation. Whitehall II study was conducted on participants aged 33–55 years from multicenter in London, demonstrating that decreased sleep duration between two waves of measurements was associated with an increased level of CRP though the significance was disappeared after adjusting for confounders.<sup>37</sup> Another cohort study was performed among American participants aged 18–26 years and followed up until they were 24–32 years old, and the finding revealed that short sleep duration was associated with higher risk of elevated CRP ( $>3$  mg/L).<sup>16</sup> Such effect is biologically plausible. The existing data indicated that the hypothalamic–pituitary–adrenal axis (HPA axis) and the sympathetic nervous system (SNS) are the major effector systems involved in sleep.<sup>38</sup> Sleep deprivation could activate the HPA system to release excessive cortisol, and further induce inflammation by increasing glucocorticoid resistance of immune cells.<sup>39,40</sup> The activity of SNS could significantly increase when sleep deprivation occurs,<sup>41</sup> which was implicated in the promoted expression of an inflammatory transcriptional profile.<sup>42–44</sup>

Evidence has suggested that inflammation was implicated in hypertension,<sup>45–47</sup> which was also observed in our study. Therefore, we conducted mediation analysis to explore the mediating effect of inflammation measured by elevated CRP in the associations between sleep duration trajectory and hypertension; however, in contrast to our expectation, the mediating effect was not significant. Nevertheless, our results should be interpreted with caution, because in all observational studies, the potential assumptions of causality between each pair of factors in mediation analysis were unable to be confirmed.<sup>48</sup> More studies are needed to clarify the association between short sleep, inflammation, and hypertension.

Our study also found that persistent long sleep duration, in addition to single-point, was associated with hypertension. Similarly, previous studies also reported sleep duration increased  $\geq 2$  hours over time or persistent long sleep duration could increase the risk of diabetes<sup>21,49</sup> and stroke.<sup>50</sup> Persistent long sleep duration in this study was not associated with inflammation, which differed from persistent short sleep duration. Inflammation in this study may not interpret the effect of long sleep duration on hypertension. The mechanism of the association between

long sleep duration and hypertension was still unclear. Several possible pathways may give some explanations. Long sleep duration could reflect the existence of comorbidities, which may lead to sleep;<sup>21</sup> besides, it may indicate a sedentary lifestyle, which is related to hypertension;<sup>51</sup> further, long sleep duration was also related to other risk factors of hypertension, such as depression, low socioeconomic status.<sup>52</sup> More studies are needed to explore the possible mechanisms.

This study has several limitations. Firstly, the sample size was not large enough to categorize sleep duration trajectories into more groups, which restricted the further exploration. Secondly, sleep duration was self-reported but not objective measurements (such as actigraphy); however, it was particularly suitable in large epidemiology studies for its good feasibility and cost-effective features. Fortunately, a previous study has confirmed a moderate correlation between objective and subjective measurements.<sup>53</sup> Moreover, only information on sleep duration was collected, sleep habits or sleep disturbance (such as sleep apnea) were unavailable, which may be related to the risk of hypertension.<sup>54</sup> Thirdly, inflammation in this study was measured by CRP; however, other inflammatory markers, such as interleukin-6, tumor necrosis factor- $\alpha$ , were also related to sleep duration and hypertension,<sup>34,55</sup> further studies are needed to estimate the role of these inflammatory markers on the association between sleep duration and hypertension. Finally, our data are based on sleep duration measured at two time points 5 years apart; therefore, we could not capture the full change of sleep duration throughout the 5-year follow-up period.

## Conclusion

In this study, we found that sleep duration trajectory, including persistent short and long sleep duration, as well as changed pattern over time, could increase higher risk of hypertension. Keeping normal sleep duration over time, rather than only at one moment, should be emphasized in further perspective studies. In addition, persistent short sleep duration also increased the risk of inflammation, highlighting the significance of keeping normal sleep duration to control inflammation. However, we did not observe that CRP mediated the association of persistent short sleep duration with hypertension. Additional studies should be performed to elucidate the mediating roles of CRP and other inflammatory markers.



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## Disclosure

The authors declare that they have no conflicts of interest.

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