

# BMJ Open Sleep duration and apolipoprotein B in metabolically healthy and unhealthy overweight/obese phenotypes: a cross-sectional study in Chinese adults

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## ABSTRACT

**Objectives** Short sleep duration is independently associated with an increased risk of developing cardiovascular disease; however, the association has not yet been examined in obese populations. We assessed the associations between sleep duration, metabolic phenotype and apolipoprotein variables in a nationally representative Chinese population with overweight/obesity.

**Study design** Cross-sectional study.

**Settings** The study conducted in nine provinces of China that vary substantially in geography and economic development.

**Patients** Data were obtained from 4149 adults with overweight/obesity aged 18 to 94 years from the 2009 China Health and Nutrition Survey. Sleep duration was categorised as  $\leq 6$ , 7–8 or  $\geq 9$  hour. Phenotypes were determined based on body mass index and metabolic health status and categorised as metabolically healthy overweight/obesity (MHOO) and metabolically unhealthy overweight/obesity (MUOO).

**Main outcome measure** The outcome variables were elevated apolipoproteins.

**Results** Compared with MHOO phenotype, MUOO phenotypes were more likely to report shorter sleep duration (12.2%vs9%). In the MUOO group, the multivariate-adjusted OR (95% CI) for elevated apolipoprotein B (apoB) was 1.66 (1.23 to 2.23) for those with  $\leq 6$  hours of sleep and 1.12 (0.86 to 1.45) for those with  $\geq 9$  hours of sleep, using 7–8 hours of sleep as a reference. Similar results were obtained in the subgroup of subjects who were  $\geq 45$  or  $< 45$  years old, but shorter sleep duration was more strongly associated with elevated apoB in those  $< 45$  years ( $p$  interaction=0.023). However, no association was observed in the MHOO phenotype.

**Conclusions** The high prevalence of short sleep duration and its strong association with elevated apoB in adults who are metabolically unhealthy overweight/obese suggest an increased risk of cardiovascular disease in this population. The differences in sleep sufficiency among obese phenotypes may account for the disparities in their cardiovascular outcomes.

## INTRODUCTION

Nutrition transitions and economic changes have led to a considerable increase in the prevalence of obesity worldwide, affecting up

## Strengths and limitations of this study

- The sample size was large and the data are from a geographically diverse household-based cohort in which people are observed in their natural environment.
- The strict and standardised protocols of the cohort regarding the collection of data from questionnaires, anthropometric measures and blood samples was used.
- Sensitivity analyses were used to validate the findings.
- The cross-sectional design does not allow for establishing any causal relationships.
- There may be residual confounding effects, such as using self-reported smoking status and alcohol consumption.

to 600 million people in 2016.<sup>1</sup> Because of the increased risk for cardiometabolic diseases such as hypertension, dyslipidaemia, diabetes and cardiovascular disease (CVD) in obese individuals, it is not surprising that obesity has become a public health concern.<sup>2,3</sup> Interestingly, a proportion of obese individuals express a metabolically healthy obese (MHO) phenotype characterised by relatively low visceral fat, smaller adipocyte size and a more favourable inflammatory profile compared with their metabolically abnormal counterparts.<sup>4,5</sup> Individuals with metabolically abnormal obesity (MAO) seem to be more susceptible to insulin resistance, impaired glucose tolerance, atherogenic lipid profiles and hypertension, which are considered to be associated with an increased risk for CVD among patients with obesity. However, observations of the cardiometabolic outcomes associated with the MHO phenotype are conflicting. Most studies have reported that individuals with MHO phenotype have a lower risk for developing cardiometabolic abnormalities,<sup>6,7</sup> while others have observed a comparable risk of CVD and mortality in

metabolically healthy and unhealthy overweight/obese phenotypes.<sup>8 9</sup>

The potential difference in implications of different body size phenotypes for cardiometabolic disease risk may be due to lifestyle factors. Sleep deprivation is widely known to be associated with an increased risk for metabolic diseases,<sup>10 11</sup> CVD and mortality<sup>12 13</sup>; it predisposes individuals to energy metabolism disturbance, inflammation and dysregulation of neuroendocrine functions, which may contribute to the underlying mechanism of the association between obesity and metabolic characteristics.<sup>14</sup> Since sleep duration is a modifiable behavioural factor, it is important to understand the potential differences in associations between sleep duration and MHO and MAO phenotypes. Previous studies have evaluated whether sleep duration or sleep quality differ according to MHO and MAO phenotypes.<sup>15 16</sup> However, most of the observations were cross-sectional, had conflicting results or lacked consensus on the definitions of short and long sleep durations.

Additionally, it is unclear how sleep duration may differentially influence the cardiometabolic consequences of these phenotypes. CVD has recently become the leading cause of morbidity and mortality in obesity; additionally, deaths attributable to CVD may be partly explained by sleep debt. An association between sleep duration and CVD risk has been reported in the general population<sup>17 18</sup>; however, the association in different obese phenotypes is still unknown. Low apolipoprotein (apo)A1 levels and elevated apoB levels and apoB/A1 ratio have been reported to be independently associated with an increased CVD risk.<sup>19</sup> A large body of prospective studies have provided evidence that these apolipoprotein variables are superior to conventional cardiovascular risk factors in predicting cardiovascular events.<sup>20 21</sup> This study aimed to address the hypotheses that sleep duration has a differential impact on cardiovascular risk in subjects who are metabolically healthy and unhealthy overweight/obese. Therefore, using data from the China Health and Nutrition Survey (CHNS) 2009, we explored the relationship between sleep duration and apolipoprotein profile according to overweight/obese phenotypes.

## MATERIALS AND METHODS

### The CHNS

CHNS is an ongoing longitudinal survey to collect health and nutrition data at the individual, household and community levels. Information collected for each family individual included clinical and sociodemographic characteristics, lifestyle factors, anthropometrics, dietary habits and indicators of health status. The study was conducted from 1989 to 2011 with nine rounds of surveys beginning in eight provinces. A ninth province (Heilongjiang) was added in 1997, and three autonomous cities, Beijing, Shanghai and Chongqing, were added in 2011. The survey used a multistage, random cluster progress to draw samples in the provinces. Counties in the nine

provinces were stratified based on income levels (low, middle and high) and a weighted sampling scheme was used to randomly select four counties in each province. Additionally, two cities including the provincial capital and a lower income city were selected. By 2011, the survey provinces covered 47% of the Chinese population (according to the 2010 census). The details of the design and data collection for the CHNS have been described elsewhere.<sup>22</sup> The survey was approved by the Institutional Review Committees of the University of North Carolina at Chapel Hill and the National Institute of Nutrition and Food Safety, China Centres for Disease Control and Prevention. All participants provided written informed consent.

### Study participants

Only the 2009 CHNS data were analysed for the purpose of this study because the 2009 survey collected fasting blood samples for the first time. The sample size of the study was estimated based on parameters, such as confidence level ( $1-\alpha$ ), power of test ( $\beta$ ) and tolerance ( $\delta$ ). In the study, the confidence level was 0.95 ( $1-\alpha$ ), and the tolerance was 0.3. According to the literature,<sup>22</sup> the response rate was 90%, and the pass rate of the questionnaire was predicted to be 70%. Participants were eligible for enrolment if they were 18 years old or older, not pregnant and overweight/obese and had available biomarker data ( $n=4372$ ). Among them, participants were excluded for the following reasons: missing data on sleep duration ( $n=47$ ) or metabolic components ( $n=62$ ) and a history of myocardial infarction and stroke ( $n=114$ ). A total of 4149 participants (1952 men and 2197 women) between the ages of 18 and 94 years were included in the final analysis.

### Data collection and clinical assessments

A self-administered questionnaire was completed for each individual to collect sociodemographic information including age, smoking status, alcohol consumption, medical history of diabetes, hypertension, myocardial infarction or stroke and use of medications for diabetes, hypertension and dyslipidaemia. Smoking status was categorised as never, former or current smoker. Alcohol drinking status in the previous year was evaluated and categorised as either 'ever' or 'never.'

The body weight of the participants was measured to the nearest 0.1 kg, and height was measured to the nearest 0.1 cm in subjects in light clothing and without shoes. Body mass index (BMI) was calculated as body weight divided by the square of the height ( $\text{kg}/\text{m}^2$ ). Overweight/obesity was defined as a  $\text{BMI} \geq 23 \text{ kg}/\text{m}^2$  based on the WHO criteria for Asia.<sup>23</sup> The waist circumference (WC) of each subject was measured at the midpoint between the lowest rib and the top of the iliac crest. Trained staff obtained blood pressures for each individual after 5 min of seated rest using a mercury sphygmomanometer. The right arm was selected. Patients were required not to wear tight cloth; avoid the following activities 1 hour before blood pressure: intense sports or exercise, eating,

drinking (except water), especially drinks with caffeine; expose under very high/very low temperature; take medicine which may affect blood pressure; etc. Measures were collected in triplicate, and the average of the three readings was used in the analyses.

### Sleep duration assessment

Sleep duration of all adults was assessed from self-reported questionnaires that asked about the number of hours of sleep obtained in a 24-hour period. For sleep assessment, individuals were asked, 'How many hours each day do you usually sleep, including daytime and nighttime?'. Short sleep duration was defined as  $\leq 6$  hours/day, optimal sleep as 7 and 8 hours/day, and long sleep as  $\geq 9$  hours/day. Self-reported has been shown to correlated highly with objective measures (Pearson's correlation coefficients, range 0.84–0.95).<sup>24</sup>

### Biochemical assessment

Fasting (8–12 hours overnight) blood samples were obtained from each participant and were separated immediately and frozen at  $-86^{\circ}\text{C}$  for subsequent laboratory analysis. Serum glucose was measured by the GOD-PAP method using a Hitachi 7600 analyzer (Randox Laboratories, UK). Serum insulin was measured using radioimmunoassay (North Institute of Bio-Tech, China). Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR) defined as follows: fasting plasma glucose (FPG, mmol/L)  $\times$  fasting blood insulin ( $\mu\text{U}/\text{mL}$ )/22.5. Serum apoA1 and apoB levels were determined by the immunoturbidimetric method (Randox Laboratories, UK). Serum apoA1 and apoB levels were determined by the immunoturbidimetric method (Randox Laboratories, UK). Decreased apoA1 levels were defined as  $<15$ th percentile (0.85 g/L), elevated apoB were defined as  $\geq 85$ th percentile (1.3 g/L) and elevated apoB/apoA1 ratio was defined as  $\geq 85$ th percentile.<sup>25</sup> Low-density and high-density lipoprotein cholesterol (LDL-C and HDL-C, respectively) were measured by the enzymatic method (Kyowa, Japan). Serum triglyceride (TG) concentration and total cholesterol (TC) were measured by the GPO-PAP method and CHOD-PAP method (Kyowa, Japan), respectively. All lipid measurements were performed on the Hitachi 7600 automated analyzer (Hitachi, Tokyo, Japan). Serum high-sensitivity C-reactive protein (hs-CRP) concentrations were measured using the immunoturbidimetric assay (Denka Seiken, Japan).

### Definitions of body size phenotypes

Individuals were classified as metabolically at-risk if they met two or more metabolic abnormalities according to the criteria for the diagnosis of metabolic syndrome recommended by the Adult Treatment Panel (ATP) III of the National Cholesterol Education Programme.<sup>26</sup> These metabolic components were defined as follows: (1) TG concentration  $\geq 150$  mg/dL; (2) HDL-C levels  $< 40$  mg/dL for men and  $< 50$  mg/dL for women; (3) systolic/diastolic

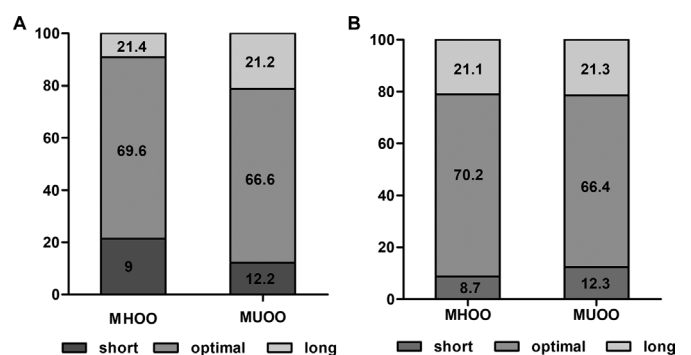
blood pressure (SBP/DBP)  $\geq 130/85$  mm Hg or antihypertensive medication use; and (4) FPG  $\geq 100$  mg/dL or anti-diabetes medication use. Individuals with one or none of the abnormal components were classified as metabolically healthy. The following two body size phenotypes were classified based on consideration of both BMI values and the metabolic status: metabolically healthy overweight/obesity (MHOO) (BMI  $\geq 23$  kg/m<sup>2</sup> and  $< 2$  metabolic syndrome components) and metabolically unhealthy overweight/obesity (MUOO) (BMI  $\geq 23$  kg/m<sup>2</sup> and  $\geq 2$  metabolic syndrome components).

### Patients involvement

No patients were involved in the development of research question, the outcome measures, the design or implementation of the study. There are no plans about dissemination of the results.

### Statistical analysis

Statistical analyses were performed using SPSS software (V.19; SPSS, Chicago, Illinois, USA).  $P < 0.05$  was considered statistically significant. Continuous variables were expressed as the means and SEs, and categorical data were expressed as percentages. Differences in continuous variables between groups were analysed using general linear models, while the differences in categorical variables were analysed using the  $\chi^2$  test or Fisher's exact test. A Bonferroni post hoc analysis was used for multiple comparisons when necessary. Univariate and multiple logistic regression models were used to determine the independent associations between sleep duration ( $\leq 6$  hours/day, 7–8 hours/day,  $\geq 9$  hours/day) and the variables of apoA1, apoB and the apoB/A1 ratio using the optimal sleep duration of 7–8 hours/day as the reference category. Multiple logistic regression analysis was performed with low apoA1 levels, high apoB levels and high apoB/apoA1 ratios as the dependent variable. The potential confounders entered into the model was based on its significance in univariate analysis ( $p < 0.15$ ) and clinical implication. Models were initially adjusted for age and sex, and were additionally adjusted for potential



**Figure 1** The proportion of sleep duration among the two overweight/obese phenotypes according to the Adult Treatment Panel (ATP) III definition (A) or a previously used definition (B). MHOO, metabolically healthy overweight/obese; MUOO, metabolically unhealthy overweight/obese.

**Table 1** Characteristics of participants in the MHOO and MUOO phenotypes according to the sleep duration categories

Characteristics	MHOO			MUOO			P value	P(MHOO vs MAOO)
	5 to 6	7 to 8	9 to 10	5 to 6	7 to 8	9 to 10		
	n=174	n=1345	n=413	n=271	n=1477	n=469		
Age, years	56.2±1.1	48.6±0.4	48±0.7	58.3±0.8	53±0.3	56±0.6	<0.001	<0.001
Men, %	44.8	45.6	47.5	42.8	48.9	48.4	0.763	0.181
Smoking status, %				0.057				0.392
Never	66.7	72.4	71.7	69.3	67.9	68		
Former	3.4	4.1	1.7	5.6	3.5	4.7		
Currently	29.9	23.5	26.6	25.2	28.6	27.3		
Alcohol consumption, %								
Diabetes, %	1.1	0.6	0.7	11.4	6.3	8.1	0.481	0.009
Hypertension, %	16.2	6.5	8.2	39.1	22.4	30.6	<0.001	<0.005
BMI, kg/m <sup>2</sup>	25.6±0.2	25.5±0.1	25.3±0.1	26.3±0.2	26.5±0.1	26.4±0.1	0.08	0.431
WC, cm	88.2±0.6	86.9±0.2	86.3±0.4	90.5±0.5	90.6±0.2	90.9±0.4	0.025	0.83
SBP, mm Hg	127±1.5	122±0.4	121±0.9	138±1.1	134±0.5	136±0.9	<0.001	0.004
DBP, mm Hg	81±0.8	80±0.3	79±0.5	87±0.7	87±0.3	86±0.5	0.064	0.303
FPG, mg/dL	92.8±1.6	89.9±0.4	89.5±0.7	111.1±2.1	111.2±1	109±1.6	0.033	0.494
HOMA-IR	3.6±0.6	2.8±0.1	3.0±0.2	4.8±0.3	5.9±0.3	5.8±0.5	0.012	0.223
Uric acid, mg/dL	5.0±0.1	4.9±0.04	4.9±0.07	6.1±0.1	5.9±0.1	5.9±0.1	0.738	0.593
hs-CRP, mg/dL	2.24±0.31	2.12±0.13	2.34±0.21	3.03±0.23	3.2±0.17	3.34±0.32	0.69	0.816
TC, mg/dL	195.1±2.7	187.9±1.0	186.9±1.7	206.5±2.5	199.5±1.1	197.8±2	0.025	0.017
TGs, mg/dL	109.1±4.1	110±1.7	108.6±2.6	239.2±9.9	237.7±4.6	227.6±7.9	0.912	0.52
HDL-C, mg/dL	59.8±1.1	57.2±0.4	56.3±0.8	48.1±0.8	47.6±0.6	47.2±0.6	0.053	0.86
LDL-C, mg/dL	126.3±2.5	120.1±0.9	119.6±1.6	125.9±2.5	119.3±1.1	119.8±2.2	0.054	0.067
ApoA1, g/L	1.2±0.02	1.16±0.01	1.14±0.01	1.15±0.02	1.09±0.01	1.08±0.01	0.299	0.093
ApoB, g/L	0.97±0.02	0.91±0.01	0.89±0.01	1.1±0.02	1.02±0.01	1.01±0.01	<0.001	<0.001
ApoB/A1	0.86±0.02	0.83±0.01	0.81±0.01	1.01±0.02	1±0.01	0.99±0.02	0.093	0.734

Data are presented as the mean±SE or proportion (%±SE). P values represent the difference across sleep duration categories. P (MHOO vs MUOO) represents the difference in the overall value for each variable between MHOO and MUOO individuals.

ApoB, apolipoprotein B; ApoB/A1, apolipoprotein B/apolipoprotein A1; BMI, body mass index; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MHOO, metabolically healthy overweight/obese; MUOO, metabolically unhealthy overweight/obese; SBP/DBP, systolic/diastolic blood pressure; TC, total cholesterol; WC, waist circumference.

**Table 2** ORs and 95% CIs of decreased apoA1, elevated apoB and elevated apoB/A1 ratio according to the sleep duration categories in the MHO and MUO phenotypes\*

	MHO			MUO		
	5 to 6	7 to 8	9 to 10	5 to 6	7 to 8	9 to 10
<b>ApoA1</b>						
Model 1	1.01 (0.58–1.77)	–	0.84 (0.55 to 1.27)	0.69 (0.48 to 0.99)	–	1 (0.77 to 1.3)
Model 2	1.19 (0.67–2.11)	–	0.81 (0.53 to 1.23)	0.8 (0.55 to 1.15)	–	1.07 (0.82 to 1.4)
Model 3	1.22 (0.69–2.18)	–	0.81 (0.53 to 1.24)	0.79 (0.54 to 1.15)	–	1.04 (0.79 to 1.35)
<b>ApoB</b>						
Model 1	1.08 (0.65–1.8)	–	0.97 (0.67 to 1.4)	1.85 (1.38 to 2.47)	–	1.18 (0.91 to 1.53)
Model 2	0.94 (0.56–1.57)	–	0.98 (0.68 to 1.41)	1.66 (1.23 to 2.23)	–	1.1 (0.85 to 1.43)
Model 3	0.91 (0.54–1.53)	–	1.02 (0.7 to 1.47)	1.66 (1.23 to 2.23)	–	1.12 (0.86 to 1.45)
<b>ApoB/A1</b>						
Model 1	1.58 (0.97–2.57)	–	1.04 (0.7 to 1.54)	1.13 (0.83 to 1.53)	–	0.94 (0.73 to 1.21)
Model 2	1.55 (0.94–2.54)	–	1.02 (0.69 to 1.52)	1.09 (0.8 to 1.48)	–	0.91 (0.7 to 1.17)
Model 3	1.5 (0.91–2.46)	–	1.07 (0.72 to 1.59)	1.08 (0.79 to 1.47)	–	0.91 (0.7 to 1.18)

Data are presented as the OR (95% CI). Model 1 represents a crude model. Model 2 shows the results after adjusting for age and gender. Model 3 further adjusted for smoking habits, alcohol consumption and body mass index.

\*Compared with the reference category of 7 to 8 hours of sleep. Metabolic health was defined according to the Adult Treatment Panel (ATP) III. ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; MHO, metabolically healthy overweight/obese; MUO, metabolically unhealthy overweight/obese.

confounding factors, including smoking habits, alcohol consumption and BMI.

To evaluate potential differential associations of sleep duration by age (<45 vs ≥45 years), sex (male vs female), smoking status (current vs ever/never smoker), alcohol consumption (yes vs no) and medical history of chronic disease (presence vs absence), including diabetes mellitus and hypertension, stratified analyses and interaction tests were performed using logistic regression analysis with elevated apoB as the outcome of interest. ORs with 95% CIs from logistic regression models were used to assess the associations between sleep duration and apoB level and were shown by forest plots. In sensitivity analyses, we examined the relationship between sleep duration and elevated apoB levels using alternative definitions for metabolic health status used in prior literature.<sup>27</sup> Metabolically healthy was defined as having one or none of the following metabolic parameters (SBP/DBP ≥130/85 mm Hg or antihypertensive medication use; TG levels ≥150 mg/L; FPG levels ≥100 mg/dL or antidiabetes medication use; HDL-C levels <40 mg/dL in men or <50 mg/dL in women; HOMA-IR >90th percentile; and hs-CRP >90th percentile).

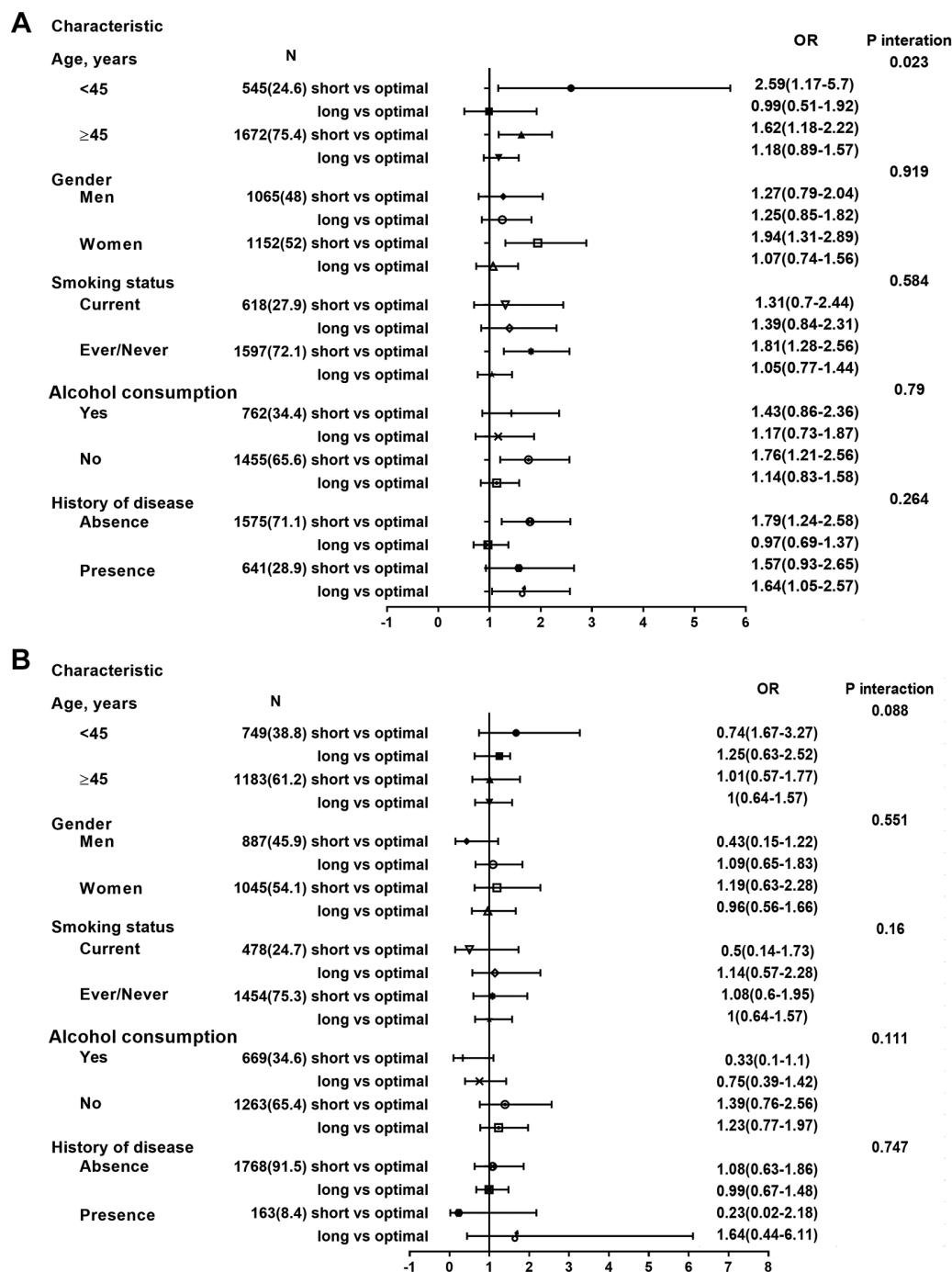
## RESULTS

MHO phenotype was observed in 46.6% (n=1932) of adults who are overweight/obese. The prevalence of short sleep duration was higher (12.2% vs 9%, p=0.003) and long sleep duration was lower (66.6% vs 69.6%, p=0.003) in the MUO group compared with the MHO group (figure 1A).

Both MHO and MUO phenotypes with short sleep duration tended to be older, and more likely to have hypertension and diabetes, higher SBP, higher TC and higher apoB (table 1). Additionally, MHO phenotypes with short sleep duration were more likely to have a higher WC, FPG and HOMA-IR. Compared with MUO phenotype, MHO phenotype tended to be younger and non-smokers and to have a more favourable metabolic profile (table 1).

Compared with the prevalence in the MHO group, a higher prevalence of individuals with decreased apoA1 (8.3% vs 18.9%, p<0.001), elevated apoB (10.2% vs 20.4%, p<0.001) and elevated apoB/A1 ratio (8.9% vs 22.2%, p<0.001) was observed in the MUO group. Of all adults with overweight/obesity, we observed a significant association only between short sleep duration and elevated apoB after adjusting for potential confounders (OR 1.46, 95% CI 1.14 to 1.88) (see online supplementary file 1).

The ORs and 95% CIs reflecting lower apoA1, higher apoB and higher apoB/apoA1 by sleep duration in MHO and MUO phenotypes are shown in table 2. In MUO phenotype, the ORs for higher apoB levels with short sleep and long sleep compared with optimal sleep were 1.66 (95% CI 1.23 to 2.23) and 1.12 (95% CI 0.86 to 1.45), respectively (p for trend=0.102), after adjusting for potential confounders. However, no significant associations were observed for sleep duration and apoA1 levels and the apoB:apoA1 ratio in the MUO phenotype. Additionally, there was no association between sleep duration and apolipoprotein variables in the MHO phenotype.



**Figure 2** Subgroup analyses of the association between sleep duration and apolipoprotein B in metabolically unhealthy overweight/obese (A) and metabolically healthy overweight/obese (B) phenotypes. Models are adjusted for age, sex and rural/urban sited, smoking habits, alcohol consumption, educational levels and body mass index, except for the stratifying factor. Presence of disease represents having diabetes mellitus and hypertension.

In stratified analyses for abnormal apoB levels in the MUOO phenotype, the positive association between short sleep and elevated apoB was stronger for individuals younger than 45 years ( $P$  interaction=0.023) (figure 2a). The association for short sleep duration tended to be stronger among female participants, non-smokers, non-drinkers and those without chronic disease including diabetes mellitus and hypertension; however, these interaction terms were not significant

(figure 2A). Similar findings were observed in the MHOO phenotype but did not meet statistical significance (figure 2B).

Additionally, using a different definition of metabolic health, the prevalence of the MHOO phenotype was 43.6% ( $n=1807$ ). Similar results were observed in terms of sleep duration (figure 1B) and elevated apoB levels with short sleep duration in MUOO phenotype only (table 3).

**Table 3** ORs and 95% CIs of decreased apoA1, elevated apoB and elevated apoB/A1 ratio according to the sleep duration categories in the MHOO and MUOO phenotypes\*

	MHOO			MUOO		
	five to 6	seven to 8	–	5 to 6	7 to 8	9 to 10
<b>ApoA1</b>						
Model 1	0.86 (0.46 to 1.61)	–	0.8 (0.52 to 1.24)	0.74 (0.52 to 1.05)	–	1.01 (0.78 to 1.3)
Model 2	1.03 (0.54 to 1.93)	–	0.78 (0.49 to 1.2)	0.85 (0.59 to 1.21)	–	1.06 (0.82 to 1.38)
Model 3	1.05 (0.56 to 1.99)	–	0.78 (0.5 to 1.21)	0.85 (0.59 to 1.22)	–	1.04 (0.8 to 1.35)
<b>ApoB</b>						
Model 1	1.11 (0.65 to 1.9)	–	0.96 (0.65 to 1.42)	1.78 (1.33 to 2.36)	–	1.17 (0.91 to 1.5)
Model 2	0.96 (0.55 to 1.65)	–	0.97 (0.65 to 1.43)	1.6 (1.2 to 2.1)	–	1.1 (0.85 to 1.41)
Model 3	0.95 (0.55 to 1.64)	–	1.03 (0.68 to 1.49)	1.6 (1.2 to 2.14)	–	1.11 (0.86 to 1.43)
<b>ApoB/A1</b>						
Model 1	1.51 (0.9 to 2.54)	–	1.05 (0.7 to 1.57)	1.15 (0.85 to 1.54)	–	0.93 (0.73 to 1.19)
Model 2	1.48 (0.87 to 2.51)	–	1.05 (0.69 to 1.58)	1.11 (0.82 to 1.5)	–	0.91 (0.7 to 1.16)
Model 3	1.44 (0.85 to 2.46)	–	1.08 (0.72 to 1.64)	1.1 (0.81 to 1.49)	–	0.91 (0.71 to 1.17)

Data are presented as the OR (95% CI). Model 1 represents a crude model. Model 2 shows the results after adjusting for age and gender. Model 3 further adjusted for smoking habits, alcohol consumption and body mass index.

\*Compared with the reference category of 7 to 8 hours of sleep. Metabolic health was defined according to previous studies.

ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; MHOO, metabolically healthy overweight/obese; MUOO, metabolically unhealthy overweight/obese.

## DISCUSSION

In a nationally representative sample of Chinese adults who are overweight/obese, short sleep duration was associated with higher apoB levels in the MUOO phenotype, independent of potential confounders. We observed a 66% increase in the risk of higher apoB levels in individuals with short sleep duration among MUOO subjects. The association was stronger in individuals who were younger than 45 years old compared with those aged 45 years old or older. However, the adverse association between short sleep duration and elevated apoB was not observed in the MHOO phenotype. To our knowledge, apoB is an independent predictor of CVD. The present study is the first to report a differential association of sleep duration with cardiovascular risk in the MHOO and MUOO phenotypes.

Epidemiological studies have demonstrated an association between decreased sleep duration and an increased prevalence of obesity,<sup>28 29</sup> CVD<sup>30 31</sup> and mortality risk.<sup>12</sup> A meta-analysis of 15 prospective studies showed that sleep duration was associated with an increased risk of developing CVD and stroke.<sup>17</sup> In a prospective study of 10308 participants from the Whitehall II cohort, Tarani *et al*<sup>18</sup> reported that short sleep duration and sleep disturbance have a combined effect on increasing CVD risk. However, no study has explored the association between sleep duration and cardiovascular risk in the population with overweight/obesity, irrespective of their metabolic health. Our results showed that sleep loss was independently associated with elevated apoB in MUOO phenotype, and this association persisted in our sensitivity analyses. It is well established that apoB is a better predictor of premature

coronary artery disease,<sup>20</sup> fatal myocardial infarction<sup>21</sup> and coronary artery calcification in midlife<sup>32</sup> than traditional factors, including TC, TG and LDL-C. Our data appear to confirm the previous findings that short sleep duration increases the risk of incident CVD.

The underlying mechanisms of the adverse effect of short sleep duration on the abnormal functions in MUOO phenotype are largely unclarified. It is known that MUOO phenotype is at high risk of an adverse inflammatory profile, hormonal/metabolic disturbances and excess visceral fat.<sup>33 34</sup> Insufficient sleep-associated metabolic hormones alteration and chronic inflammation may be implicated in the underlying mechanism. Sleep deprivation can significantly affect energy expenditure, weight regulation and inflammatory cytokine levels,<sup>35 36</sup> which may contribute to the pathogenesis of abnormal apo levels. Sleep loss is also associated with metabolic hormonal alterations, including reduced leptin concentration levels and increased serum ghrelin levels, which can considerably influence lipid metabolism.<sup>35</sup> Additionally, sleep restriction increases the expression of genes related to immune function, including those for interleukin-8 production and nuclear factor kappa-light-chain-enhancer of activated B cells signalling, which could result in chronic, low-level inflammation.<sup>37</sup> Furthermore, sleep loss was significantly associated with elevated CRP,<sup>38</sup> an atherogenic dyslipidaemia profile,<sup>39 40</sup> and insulin resistance,<sup>41</sup> which are also involved in the pathogenesis of CVD. These observations suggest that sleep deprivation may increase the risk of abnormal apo variables, thereby increasing the risk of abnormal metabolic indices and CVD, or that sleep loss mediates the effect on excess

CVD risk through abnormal apo variables and metabolic indices in the MUOO phenotype.

Interestingly, the deleterious effect of short sleep duration on cardiovascular risk was more pronounced in those aged 18–44 years in MUOO phenotype. Since adults aged 18–44 years are less likely to report a prevalence of cardiometabolic risk factors,<sup>42</sup> the increased CVD risk can be mainly attributed to short sleep duration. In addition, those individuals were more likely to work long hours, work in shifts and use electronics, such as cell phones, televisions or computers, all of which can lead to decreased sleep duration.<sup>43</sup> Among those aged 45 y or older, short sleep duration accounted for only 62% of the increase in CVD risk, suggesting the synergistic effects of an unfavourable cardiometabolic profile and potentially unhealthy lifestyles. Therefore, more evidence is necessary from prospective studies assessing the effects of short sleep duration on CVD risk in MUOO phenotype while considering disparities by age.

We found no association between short sleep duration and elevated apoB in MHO phenotype. This finding may suggest that sleep loss alone may not be adequate to increase the cardiovascular risk of those already at lower risk for CVD. It is important to consider that these individuals with MHO phenotype have favourable metabolic profiles and are, on average, younger than those with MUOO phenotype, less likely to report current smoking and less likely to have hypertension and diabetes. Moreover, the relatively low prevalence of abnormal apoB levels in adults with MHO phenotype may have limited the investigation of the risk of CVD. In fact, in the univariate analyses, short sleepers had higher FBS, higher insulin resistance, higher SBP and higher apoB levels, though these associations were no longer statistically significant after adjusting for multiple confounders. Previous studies have demonstrated that subjects with MHO phenotype are at increased risk of adverse long-term outcomes. The prospective cohort North West Adelaide Health Study reported that MHO was an unstable state and that individuals with MHO had an increased risk of developing diabetes during the 5–10-year follow-up period.<sup>43</sup> Another prospective population-based study of 3052 Spanish individuals demonstrated that a subset of individuals with MHO progressed from MHO to MUOO over time.<sup>44</sup> These data suggested that management of metabolic risk factors should also be recommended to MHO. The longitudinal effect of short sleep on CVD risk in the MHO phenotype is not well described or understood and requires further investigation.

The strengths of our study include the large sample size and that the data are from a geographically diverse household-based cohort in which people are observed in their natural environment. The strict and standardised protocols of the cohort regarding the collection of data from questionnaires, anthropometric measures and blood samples should also be acknowledged. Moreover, we used sensitivity analyses to validate the findings. Nevertheless, there are several limitations to our study that should be

considered. First, the cross-sectional design does not allow for establishing any causal relationships. Long-term prospective cohort studies are needed. Second, our findings are based on self-reported sleep duration. However, self-reported sleep duration has been validated by polysomnography or actigraphy in previous studies and has been shown to be as accurate as these objective measures.<sup>24</sup> Additionally, the questionnaires in the present study were not validated, and some variables were self-reported which could cause systematic bias. Thus, in every round, the project teams supervised and conducted quality inspections to make appropriate adjustments to some questions. Finally, although we adjusted for multiple potential confounders, there may be residual confounding effects, such as using self-reported smoking status, alcohol consumption and sleep apnoea. Note that sleep apnoea was reported to be associated with multiple cardiometabolic diseases, which may mediate the association of sleep duration and apolipoprotein variables.

In conclusion, based on a nationally representative Chinese adult population, our results suggest that short sleep duration is associated with a higher risk of CVD exclusively in the MUOO phenotype. Sleep improvement may be particularly beneficial both for overweight and obesity with metabolic abnormalities. The lack of an adverse association between sleep duration and CVD risk in MHO phenotype may suggest that future prospective cohort studies are needed.

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**Data sharing statement** The data sets used for this study are available on request from the China Health and Nutrition Survey database ([www.cpc.unc.edu/projects/china/](http://www.cpc.unc.edu/projects/china/)).

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