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Short Sleep Duration Is Associated with Insulin Resistance Independent of Adiposity in Chinese Adult Twins

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Abstract

Objective—To investigate the association between sleep duration and insulin resistance in rural Chinese adults and examine whether any such associations are independent of adiposity.

Methods—This is a cross-sectional analysis of 854 men and 640 women aged 20 to 70 years from the Anqing Twin Cohort. The following measures were obtained for each subject: Body mass index (BMI) and percentage of trunk fat (%TF), fasting plasma glucose, homeostatic model assessment of insulin resistance index (HOMA-IR), self-reported sleep duration, and measures of snoring and sleep disturbance from the Pittsburgh Sleep Quality Indices (PSQI) questionnaire

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modified for a Chinese population. Multivariate linear regressions were applied to examine the association of sleep duration with HOMA-IR, with and without adjustment for adiposity variables, along with other relevant covariates.

Results—In this sample of relatively lean rural Chinese adults, short sleep duration was associated with HOMA-IR in women but not in men. In women, short (≤ 7 hrs/night) sleep duration was associated with a higher HOMA-IR ($p=0.003$) compared with normal sleep duration (>7 to ≤ 8 hrs/night) after adjustment for all the covariates except adiposity. Further adjustment for BMI or %TF attenuated the sleep-HOMA-IR association, but the association remained significant upon adjustment for BMI ($p=0.013$); and upon adjustment for %TF ($p=0.026$). Long sleep duration (>8 hrs/night) was not significantly associated with HOMA-IR.

Conclusion—In this rural Chinese cohort, short sleep duration is independently associated with increased insulin resistance among women only, even after adjusting for adiposity and other potential confounders.

Keywords

sleep duration; insulin resistance; adiposity; gender; rural; adults

INTRODUCTION

The prevalence of obesity and type 2 diabetes is increasing worldwide[1]. The causes may include health-related aspects of urbanization, westernization and economic growth. In particular, shorter habitual sleep time may be on the causal pathway[2, 3]. Sleep curtailment has accelerated over the past few decades and has become highly prevalent globally. For example, the average sleep duration for American adults has declined from 8.5 hrs/night to <7 hrs/night over the last 40 years[4]. This downward trend in sleep duration parallels the rising prevalence of obesity and type 2 diabetes.

Asians, including Chinese, have a high prevalence of type 2 diabetes despite a relatively low body mass index (BMI). Although other risk factors, such as abdominal obesity, pancreatic beta cell function and under-nutrition in early life, may help to explain this paradox[5], sleep curtailment also may be a contributing factor.

Cumulative evidence from epidemiologic studies has indicated that sleep curtailment may be involved in the increased prevalence of obesity and type 2 diabetes. A number of studies have examined the cross-sectional association between short sleep duration and markers of diabetes or glucose control[6-9] and some prospective studies have identified a longitudinal association between short sleep duration and subsequent weight gain and/or risk for type 2 diabetes[10-12]. However, most of the epidemiological studies on sleep and obesity/type 2 diabetes have been conducted in developed countries with high incidences of obesity; few have explored these relationships in developing countries such as China, and even less in relatively lean, rural populations. It is uncertain whether the findings in predominantly overweight populations can be generalized to lean populations. Furthermore, the inter-relationships between sleep duration, adiposity, and insulin resistance remain to be elucidated. Experimental data support the hypothesis that acute sleep curtailment may contribute to the development of insulin resistance and type 2 diabetes[13, 14]. But data are lacking on insulin resistance in relation to “chronic partial sleep deprivation”, which is common in populations worldwide in both genders.

The aims of this study were to investigate the association between sleep duration and insulin resistance in a relatively lean rural Chinese population, and examine the extent to which any

such associations are independent of adiposity. This information is necessary to clarify any causal relationship between short sleep time and type 2 diabetes.

SUBJECTS and METHODS

Study Population and Procedures

This report included men and women aged 20 to 70 years old who participated in an ongoing NIH-funded research study of metabolic syndrome in a large population-based twin cohort in Anqing, Anhui province in China. A baseline study was carried out in eight rural counties of the Anqing from 1998 to 2000; follow-up data, including those used in the current analysis, were collected from 2005 to 2006. The sleep questionnaires were only administrated at the follow-up study. As such, we can only perform cross-sectional analysis.

Participants were invited to a central office and stayed overnight to complete an interview-based questionnaire, including the modified Pittsburgh Sleep Quality Indices (PSQI), as well as participate in a fasting blood chemical examination, physical examination and dual-energy X-ray absorptiometry (DEXA) scans. Physical examinations were conducted by physicians trained specifically for the study. Individuals who had missing data on the DEXA scan (n=22), fasting plasma glucose and insulin (n=134), had been diagnosed with diabetes prior to the follow-up (n=8), or did not answer the questions on snoring or sleep disturbance (n=17) were excluded from the analyses. This yielded a final sample size of 1494 subjects. The study protocol was approved by the Institutional Review Board of Children's Memorial Hospital and the Institute of Biomedicine, Anhui Medical University in Hefei, China. All participants gave written consent prior to enrolling in the study.

Anthropometric Measurements

Height and weight were measured using standard protocols, without shoes and outerwear. Height was measured to the nearest 0.1 cm on a portable stadiometer, and weight to the nearest 0.1 kg. Body mass index (BMI) was calculated as $\text{weight(kg)}/\text{height squared(m}^2\text{)}$. Waist circumference (WC) was measured to the nearest 0.1 cm at the horizontal circumference midway between the lowest rib margin and the iliac crest. A standard whole-body scan was performed by DEXA[15] to determine trunk fat (TF). %TF was calculated as $[(\text{total TF}/\text{body weight}) \times 100]$.

Physical Activity

Physical activity was assessed using a short version of the International Physical Activity Questionnaire (IPAQ-Short) (<http://www.ipaq.ki.se>). Participants were asked about three types of physical activity (vigorous, moderate and walking) across four physical activity domains (i.e., leisure time, occupational or school, domestic, and transport) using the "last 7 days" as the reference period. Utilizing both the total amount of activity and the number of activity days/sessions per week, the IPAQ generated a categorical indicator (low, moderate, and high) of regular physical activity.

Smoking and Alcohol Use

Smoking refers to smoking one or more cigarettes every day for more than one year, or smoking more than 18 packs of cigarettes in a lifetime. Alcohol use refers to drinking one glass twice or more per week for more than one year.

Sleep Quality and Quantity

Data on sleep duration, snoring and sleep disturbance were derived from the Chinese version of the PSQI. The validity and reliability of the PSQI have been demonstrated[16, 17]. The

Chinese version of the PSQI contains all 19 self-rated questions from the original PSQI, as well as additional questions on snoring and other behavioral problems. The measure of self-reported sleep duration was taken from the PSQI based on response to the question: "During the past month, how many hours of actual sleep did you get at night (This may be different than the number of hours you spent in bed)?" Respondents only could report in half hour increments. Subjects reporting loud and disturbing snoring more than three times/week were considered "habitual snorers." Sleep disturbance was defined according to the score for that component on the PSQI, ranging from 0 to 3. Subjects' scores >2 were considered to have a sleep disturbance.

Insulin Resistance Assessment

Blood samples were obtained after at least 10 hours of fasting. Plasma glucose was measured by modified hexokinase enzymatic method (Hitachi 7020 Automatic Analyzer, Japan). Standard quality control procedures were performed each day using standard samples that came with the reagents (CV<8%). Serum insulin was measured by electrochemiluminescence (ECL) on an Elecsys 2010 system (Roche, Switzerland). Duplicate analyses also were conducted daily using samples collected from study participants (CV<10%, mean=3%). HOMA was used as a marker of IR (insulin resistance): $HOMA-IR = FPI (\mu U/mL) \times FPG (mmol/L) / 22.5$, with higher values suggestive of low insulin sensitivity.

Statistical Analyses

The Student's t-test was used to compare differences between means of continuous variables, and chi-square (X^2) tests were used to compare differences in proportions of categorical variables. Because the distribution of HOMA-IR and fasting insulin were positively skewed, natural log transformed values were used for subsequent analyses.

Generalized additive models were used to generate cubic splines to graphically depict the relationship between HOMA-IR sleep duration in both genders. Multivariate linear regression models were first applied to evaluate the effects of ≤ 6 , >6 to ≤ 7 , >8 to ≤ 9 and >9 hrs sleep duration on HOMA-IR in comparison with that of the >7 to ≤ 8 hrs sleep group (reference group). We then assessed the effects of ≤ 7 hrs sleep duration (short sleepers) or >8 hrs sleep duration (long sleepers) on HOMA-IR compared with the same reference group. Models for HOMA-IR were stratified by: gender after adjustment for age; physical activity, education, occupation, snoring and sleep disturbance for all subjects; smoking and alcohol use, just for men; and menopause, just for women. Additional models for HOMA-IR were performed with further adjustments for adiposity (BMI or %TF). Generalized estimating equations (GEE) were applied to account for the intra-twin pair correlation. Statistical significance was set at a $p < 0.05$. All analyses were performed using SAS/STAT 9.1.

RESULTS

This study includes 854 men and 640 women. Table 1 compares the characteristics of the men and women subjects. Men had higher average age, level of education, rates of smoking and alcohol consumption, as well as a higher proportion of manual occupation. Women had higher adiposity indices (BMI, %TF), fasting plasma insulin (FPI), and HOMA-IR levels. Fasting plasma glucose (FPG) levels, physical activity levels, mean sleep duration and proportion of sleep duration did not differ significantly between men and women. Men reported snoring more frequently while women were more likely to complain of sleep disturbance.

Figure 1 depicts the relationships between sleep duration and HOMA-IR by gender with adjustment for age. In women, we observed a “U” shaped relationship between sleep and HOMA-IR. While in men, HOMA-IR only varied slightly across levels of sleep duration.

Table 2 shows the results from the regression analysis of the association between sleep duration and snoring and HOMA-IR by gender. Because the strength and direction of the association was similar for the two short sleep groups (≤ 6 hrs group and >6 to ≤ 7 hrs group), they were combined to form a single short sleep group, ≤ 7 hrs (see Supplemental Table). Similarly, the two long sleep groups (>8 hrs to ≤ 9 and >9 hrs group) were combined to form a single long sleep group, >8 hrs. After adjustment for confounding variables, short sleep duration was significantly associated with a higher HOMA-IR in women only ($p=0.003$ in ≤ 7 hrs sleep group). After additionally adjusting for BMI or %TF, the observed associations were attenuated, but short sleep duration (≤ 7 hrs) remained significantly associated with HOMA-IR in women ($p=0.013$ upon adjustment for BMI; $p=0.026$ upon adjustment for %TF). No association between sleep duration and HOMA-IR was found in men. We also observed the association of snoring with a higher HOMA-IR in men ($p=0.0008$, Supplement Table 2), which, however, attenuated after adjustment for BMI or %TF.

After adjustment for BMI or %TF, there was no relationship between sleep duration and fasting glucose (data not shown).

DISCUSSION

This is the first study to examine the relationship between short sleep duration and insulin resistance in a rural Chinese population. The study demonstrated a significant and independent association between short sleep duration and insulin resistance in women but not in men. Short sleep duration was associated with a higher HOMA-IR in women prior to adjustment for adiposity. After further adjustment for adiposity indices (BMI or %TF), the sleep-HOMA-IR association was attenuated but still remained significant for women, suggesting that the effect of short sleep duration on HOMA-IR is independent of adiposity.

Short sleep duration may lead to insulin resistance by various well-described mechanisms. These include increased sympathetic activity, decreased cerebral glucose utilization, elevated evening cortisol levels, increased growth hormone secretion, and dysregulation of neuroendocrine control of appetite (increasing the risk of weight gain)[18]. These putative causal pathways have been elucidated through a series of landmark studies. Spiegel and colleagues demonstrated that short-term experimental sleep restriction in healthy, lean young adults profoundly altered key components of energy homeostasis, including glucose tolerance, food cravings, and hormones critical to appetite regulation[13, 14, 19, 20]. This study showed approximately a 40% reduction in glucose tolerance following sleep restriction. The same study also found that sleep restriction was related to abnormalities in two endocrine functions. One is elevated evening cortisol levels, which may predispose to insulin resistance; the other is an increase in sympathetic tone, which has an inhibitory effect on pancreatic function leading to reduced glucose tolerance and a possible long-term result of visceral fat accumulation[21]. Sleep restriction also appears to be accompanied by alterations in appetite control. It was observed in the Sleep Debt Study that peak and diurnal variations in leptin are reduced by 20% in response to sleep restriction[14]. Furthermore, ghrelin concentration was increased and the resultant ghrelin-to-leptin ratio increased by $>70\%$ [20]. The change in this ratio was strongly correlated to a change in hunger ratings, suggesting that the changes observed in these appetite hormones were in part responsible for the increases in appetite and hunger. Subjects developed a greater desire for calorie-dense

foods and experienced weight gain, which can further influence glucose control and the development of obesity.

In contrast, possible mechanisms for an association between long sleep duration and high diabetes risk are poorly understood. Commonly unmeasured sleep variables—other than duration—could contribute: it has been reported that obstructive sleep apnea[22] and sleep disturbance[23] are related to obesity, insulin resistance and diabetes. In our study, we included snoring (a surrogate for obstructive sleep apnea) and sleep disturbance in the regression models. Although our study discovered a significant association between longer sleep duration (>9 hrs) and higher insulin resistance in women (Supplement Table 1), the significance was attenuated after controlling adiposity variables. We even found that in men, snoring is strongly associated with a higher insulin resistance but dependent of adiposity. The well-known Finnish Diabetes Prevention Study [24] observed that the weight loss by diet-exercise intervention may ameliorate the association of long sleep time with higher risk of type 2 diabetes. All of these findings indicate that the relationship of long sleep time and obstructive sleep apnea with insulin resistance, if any, is mainly mediated by adiposity. Therefore, lifestyle intervention seems to play an extremely important role in the prevention of diabetes.

Meanwhile, previous population studies have yielded inconsistent results on gender differences in the association of sleep duration and type 2 diabetes. A multicenter study conducted in Finland[7] found short or long sleep to be related to an increased risk of type 2 diabetes in women only. Another prospective study found that short sleep duration is associated with an increased incidence of diabetes only in men[10]. However, the Sleep Heart Health Study[6] and Quebec Family Study[9] observed independent relationships between short or long sleep duration and diabetes in both genders. Although experimental data supports the hypothesis that short sleep affects insulin resistance, the Quebec Family Study[9] is the only other population-based study, apart from this one, to examine the relationship between sleep duration and insulin resistance. The Quebec study demonstrated that both short and long sleepers had a higher HOMA-IR index than “normal sleepers” in both genders without adjustment for BMI or other adiposity variables, whereas our study supports the association in women alone either before or after adjustment for adiposity.

A possible explanation for this gender-specific association is related to gender differences in fat distribution. Evidence from an Italian population study suggests that there is a more marked visceral fat redistribution in women than in men with age[25]. Our data also showed that trunk fat varied by age groups in woman but with no clear trend, whereas among the men, trunk fat declined in the older age groups (Supplemental Figure 1). Although it has been suggested that high sympathetic activity may promote visceral fat accumulation[21], gender-specific differences in fat redistribution in men may attenuate any effect of altered sympathetic activity produced by sleep deprivation. It is possible that elevated adiposity mediates the relationship between short sleep and insulin resistance in men. Of note, the alteration in body fat proportion across age in men in the present study was strikingly different from those in western populations where an approximate doubling of body fat was observed between the ages of 20 and 50 years[26] (Supplemental Figure); if so, the preponderance of lean men in our study may have limited our ability to detect the association seen in populations with higher BMI.

An aspect of this study that is likely to be controversial was our choice of using ≤ 7 hrs of sleep to define short sleep duration. First, we observed that typical sleep duration in our rural Chinese study population tended to be longer compared to the US population, and we believe that our cutoff better reflected the distribution of actual sleep duration in our study population. Second, the mean of sleep duration in this study was consistent with figures

reported in a previous Chinese study (7.76 hrs for residents in both urban and rural areas) [27]. This evidence further supports that a population-specific cutoff may be more appropriate. As shown in Supplemental Figure 2, the distribution of sleep duration in our population is shifted to the right of that estimated for the US population[28]. Also, as the light gray shaded area indicates, the lowest quartile of sleep duration in our study population corresponds to 7hrs or less, whereas in the US population, the dark gray shaded area, the lowest quartile corresponds to 6hrs or less. This apparent sleep duration shift to the right in our study population, relative to the US population, made 7hrs or less a comparable cut-off point for short sleep duration in our study. In and of itself, this is an intriguing point with regard to questions surrounding the physiological or cultural basis for sleep duration.

A notable strength of this study is that it involves a large, relatively lean sample of adults of both genders from a rural community in China. This lean sample (mean BMI 21.7 in men, 22.0 in women) strengthens our findings in that it is much less likely to be confounded by adiposity. Previous studies have linked sleep curtailment to type 2 diabetes and/or impaired glucose tolerance, but few, if any, have focused on the early indicators of these conditions. Because insulin resistance is causally involved in the development of type 2 diabetes and cardiovascular disease, our study examines HOMA-IR as an earlier contributor to glucose-intolerance and type 2 diabetes. If confirmed by future longitudinal and experimental studies, our findings also may have important implications with regard to the prevention of type 2 diabetes and cardiovascular disease. In this study, DEXA-scans made it possible to assess adiposity more accurately than BMI or waist circumference. Furthermore, we have assessed and adjusted for some sleep quality variables, which were known to be associated with insulin resistance and/or diabetes but have not been taken into account in most of the previous epidemiologic studies[9, 11, 12, 29]. In addition, this is a community-based sample that excludes subjects who were diagnosed with diabetes before the follow-up interview; hence it does not entail the potential influence of hypoglycemic drugs on HOMA-IR.

Some limitations of this study deserve attention. First, we assumed that one month of average sleep duration data reflected long-term sleep patterns. Self-reported sleep duration has been validated against quantitative sleep assessments[30]. The stability of self-reported sleep duration over time is not known. Second, due to our cross-sectional design, we were unable to examine possible temporal relationships between sleep duration and insulin resistance. Third, the sleep duration categories we created were not based on an individual biological need of sleep, which may have led to the misclassification of long or short sleepers as “normal”; this may in part have confounded the association we observed in the study. Fourth, our analyses were based on sleep patterns over the past month; we were not able to adjust for the acute effects of disturbed sleep. Finally, while “trunk fat” is a preferable method to evaluate central adiposity compared to waist circumference, we were unable to distinguish between visceral fat and subcutaneous fat in the abdomen. This may be an important distinction due to their differential associations with insulin resistance[31]. Future studies should carefully examine this question.

In summary, this study found that short sleep duration was associated with higher insulin resistance in a sample of relatively lean rural Chinese women independent of adiposity. However, the gender difference we observed is intriguing and suggests the need for additional studies. Meanwhile, this study primarily focused on HOMA-IR; further study of the relation of sleep disordered breathing and type 2 diabetes should also be given high priority in the future. Sleep disordered breathing has been found to be associated with diabetes in the Chinese population[32]. Given that sleep duration is potentially modifiable, our findings, once confirmed, may have important clinical and public health implications for the prevention and management of obesity and metabolic disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Smoothing plots of HOMA-IR against sleep duration adjusted for age.

Table 1

Characteristics of the study subjects aged 20-70 from the Anqing twin cohort.

Variables	Men(N=854)	Women(N=640)	P value
Mean±SD			
Age(Yr)	39.3±13.2	37.1±10.8	0.0004
BMI(kg/m2)	21.7±2.6	22.0±2.7	0.0237
WC(cm)	74.1±8.3	72.6±8.0	0.0003
FMI(kg/m2)	3.1±2.1	6.4±2.1	<0.0001
%TF	7.7±4.7	14.6±4.1	<0.0001
FPG(mmol/l)	5.4±0.9	5.4±0.8	0.653
FPI(mU/l)	4.5(2.8,7.0)*	6.2(4.5,8.8)*	<0.0001
HOMA-IR	1.0(0.7,1.7)*	1.5(1.0,2.2)*	<0.0001
Total sleep time(hour)	8.0±1.4	8.0±1.4	0.496
N(%)			
Sleep duration group			
≤6	94(11.0)	69(10.8)	0.998
6~7	150(17.6)	114(17.8)	
7~8	257(30.1)	194(30.3)	
8~9	217(25.4)	165(25.8)	
>9	136(15.9)	98(15.3)	
BMI classification			
Underweight(<18.5)	69(8.1)	42(6.6)	0.007
Normal(18.5~22.9)	566(66.3)	383(59.8)	
Overweight(23~24.9)	120(14.0)	126(19.7)	
Obese(≥25)	99(11.6)	89(13.9)	
Physical activity			
I	138(16.2)	119(18.6)	0.527
II	180(21.0)	127(19.8)	
III	398(46.6)	305(47.7)	
Unknown	138(16.2)	89(13.9)	
Smoking			
Yes	525(61.5)	25(3.9)	<0.0001
No	329(38.5)	615(96.1)	
Alcohol			
Yes	342(40.1)	18 (2.8)	<0.0001
No	512(59.9)	622 (97.2)	
Education			
Literate	786(92.0)	435(68.0)	<0.0001
Illiterate	68(8.0)	205(32.0)	
Menopause			
Yes	—	96(15.0)	
No	—	544(85.0)	

Variables	Men(N=854)	Women(N=640)	P value
Snoring	158(18.5)	44(6.9)	0.0001
Sleep disturbance	76(8.9)	98(15.3)	0.0001

T-tests were performed to compare the differences between continuous variables and Chi-square tests were performed to compare categorical variables between men and women.

BMI, body mass index. WC, waist circumference. FMI, fat mass index. %TF, percentage of trunk fat mass. FPG, fasting plasma glucose. FPI, fasting plasma insulin. HOMA-IR, homeostasis model assessment of insulin resistance.

* median (Q1,Q3) due to skewed distribution

Table 2
Association of sleep duration (SD) with insulin resistance (HOMA-IR) in adults, Anqing twin cohort, by gender.

		Men (n=854)		Women (n=640)		
SD	LSM(se)*	B(se)	p	LSM(se)*	B(se)	P
Model 1						
≤7	0.107(0.062)	-0.035(0.048)	0.475	0.579(0.065)	0.147(0.050)	0.003
7~8	0.142(0.062)	Reference		0.432(0.060)	Reference	
>8	0.159(0.058)	0.018(0.048)	0.715	0.514(0.062)	0.082(0.050)	0.104
Model 2						
≤7	0.095(0.058)	0.002(0.045)	0.956	0.552(0.053)	0.114(0.046)	0.013
7~8	0.093(0.058)	Reference		0.438(0.049)	Reference	
>8	0.116(0.055)	0.023(0.043)	0.592	0.485(0.051)	0.046(0.046)	0.312
Model 3						
≤7	0.061(0.057)	0.010(0.043)	0.814	0.531(0.056)	0.104(0.046)	0.026
7~8	0.051(0.056)	Reference		0.427(0.051)	Reference	
>8	0.103(0.054)	0.052(0.042)	0.214	0.483(0.052)	0.055(0.047)	0.242

Model 1: adjusted for age, physical activity, education, snoring and sleep disturbances (all subjects); smoking and alcohol (only for men), and menopause (only for women).

Model 2: Model 1 plus BMI.

Model 3: Model 1 plus %TF.

LSM: least squares mean adjusted for the variables detailed above.

GEE model was applied to account for intra twin pair correlation.