Interaction of sleep quality and sleep duration on impaired fasting glucose: A population-based cross-sectional survey in China

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Interaction of sleep quality and sleep duration on impaired fasting glucose: A population-based cross-sectional survey in China

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Abstract

Objectives: To explore the interactions of sleep quality and sleep duration and their effects on impaired fasting glucose in Chinese adults.

Design: Cross-sectional survey.

Setting: Community-based investigation in Xuzhou, China.

Participants: 15,145 Chinese men and women aged 18−75 years old who fulfilled the inclusion criteria.

Primary and secondary outcome measures: The Pittsburgh Sleep Quality Index was used to produce sleep quality categories of good, common and poor. Fasting blood glucose levels were assessed for impaired fasting glucose. Sleep duration was measured by average hours of sleep per night, with categories of <6 h, 6−8 h, and >8 h. The products of sleep and family history of diabetes, obesity and age were added to the logistic regression model to evaluate the addictive interaction and relative excess risk of interaction (RERI) on impaired fasting glucose. The attributable proportion (AP) of the interaction and the synergy index (S) were applied to evaluate the additive interaction of two factors. Bootstrap measures were used to calculate 95% confidence intervals (CI) of RERI, AP and S.

Results: After adjusting for sex, smoking, drinking and amount of exercise, RERI, AP and S values (and their 95% CI) were 1.69 (0.31−3.76), 0.42 (0.15−0.61) and 2.85 (2.14−3.92) for the interaction between poor sleep quality and short sleep duration, and 0.78 (0.12−1.43), 0.61 (0.26−0.87) and −65 (−0.94 to −0.27) for the interaction between good sleep quality and long sleep duration.

Conclusions: The results suggest that there are additive interactions between poor sleep quality and short sleep duration.

ARTICLE SUMMARY

Article focus

- To describe the combined effects of sleep duration and sleep quality for impaired fasting glucose in people in Xuzhou, China.

Key messages

- There exist additive interactions between sleep quality and sleep duration on impaired fasting glucose.
- A strength of the study is the large sample.
- Limitations of the study the cross-sectional design.

Introduction

Prediabetes has a prevalence of 15.5% and affects an estimated 148.2 million Chinese adults.[1] Prediabetes, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is the most important risk factor for type 2 diabetes. The average annual incidence of diabetes in a cohort of patients with IFG is 11% over a six-year period without intervention.[2] Older age, a family history of diabetes, being overweight, obesity, central obesity, increased heart rate, elevated systolic blood pressure, elevated serum triglyceride levels, high income, history of hypertension, history of coronary heart disease, history of drinking, eating pickled foods, and low educational level are significantly associated with an increased risk of prediabetes.[1,3] Increasingly, studies have shown that prediabetes is associated with poor sleep quantity and quality.[3,4] A cross-sectional study has suggested that, compared with those sleeping 7−8 h per night, individuals aged <60 years who slept 5 h or less had an increased odds ratio (OR) for IGT (OR: 1.37, 95% confidence interval [CI]: 1.13−1.67).[4] The Western New York Health Study including 1455 participants showed that sleep duration of less than 6 h was associated with increased prevalence of IFG, compared with those sleeping 6−8 h per night, after adjustment for confounders, over six years of follow up.[5] Spiegel et al. have demonstrated that experimental restriction of sleep to <4 h per night for six nights resulted in an impaired glucose tolerance (IGT) in young healthy adults.[6]

Our previous results suggest that poor quality of sleep and sleep duration <6 h per night are independent risk factors for type 2 diabetes, even after adjusting for a large number of possible confounders.[7,8] Our previous study also confirmed that relatively healthy individuals with poor sleep quality and sleeping times of 6 h or less had a higher risk of IFG, even after adjusting for a large number of confounding factors.[3]

Although these risk factors play a role in the development of type 2 diabetes, the disease is the result of the interaction of genetic and environmental factors. There is little understanding of multivariate explanations of IFG in relatively healthy individuals. To our knowledge, there are no studies on the interaction of sleep quality and sleep duration on IFG in relatively healthy individuals. The primary aim of this cross-sectional study was to examine the combined effects of sleep quality and sleep duration on IFG in relatively healthy individuals in a Chinese primary-care setting. A secondary aim was to assess the associations of sleep quality and IFG, and of sleep duration and IFG.

Methods

The study was a continuation of our previous work.[9] The investigation was conducted from March to November 2012 with a sample size of 15,145 volunteers (7557 men and 7588 women) aged 18 to 75 years. All volunteers received a health check and completed a structured questionnaire covering demographic information, medical history, medication

history, sleep assessment, and smoking, alcohol drinking and exercise habits. All volunteers underwent 12-h overnight fasting and blood sampling for basic fasting plasma glucose (FPG). After blood sampling, each volunteer completed the Pittsburgh Sleep Quality Index (PSQI).[10] We excluded volunteers who were pregnant, had received antihypertensive medication, or were suffering from any cardiovascular disease, stroke, neuropathy, psychosis, depression, chronic obstructive pulmonary disease, obstructive sleep apnea, diabetes, ache, or any other disease. Those who had missing information on sleep duration or sleep quality were also excluded. Trained physicians and public health workers conducted face-to-face interviews using a standardized questionnaire to collect socio-demographic, lifestyle and health-related information.

The study protocol was approved by the Xuzhou Center for Disease Control and Prevention. All participants provided written informed consent.

Key measurements

The FPG was determined by morning blood samples obtained by venipuncture after an overnight fast of at least 12h, and extracted plasma was stored at −70°C for later glucose determination by the hexokinase method. According to the current WHO definition of IFG[10].

The PSQI is a validated self-rated questionnaire that assesses sleep quality over a one-month time interval.[11] Nineteen items generate seven component scores that reflect sleep problems in the areas of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction. The sum of the scores for these seven components produces a global sleep quality score within a range of 0−21 points. A global PSQI score >5 has a diagnostic sensitivity of 89.6% and specificity of 86.5% in differentiating poor from good sleepers. The Chinese version of the PSQI, used with permission from the original PSQI authors, has an overall reliability coefficient of 0.82−0.83 and acceptable test–retest reliability, with a coefficient of 0.77−0.85.[12] Sleep quantity was categorized as <6, 6−8, and >8 h per night.

Covariates

Age, gender, current employment status, level of education, cigarette smoking, alcohol intake, physical activity, family history of diseases including diabetes, hypertension, heart disease, and cancer were assessed using a standardized questionnaire. Employment status was categorized as manual, non-manual, unemployed, and retired. Education was categorized into below high school, high school, or above high school education. Lifestyle variables included cigarette smoking, alcohol drinking and physical activity level. Cigarette smoking was defined as having smoked at least 100 cigarettes in a lifetime. Information was obtained on the amount and type of alcohol that was consumed during the previous year, and alcohol drinking was defined as the consumption of at least 30 g of alcohol per week for one year or

more. Regular leisure-time physical activity was defined as participating in moderate or vigorous activity for no less than 30 minutes per day at least three days a week. Each volunteer's body height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were measured. Body mass index (BMI; in kg/m^2) was calculated. BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5−24.0 kg/m^2) and overweight/obese (>24.0 kg/m^2).[13]

Statistical analysis

Statistical analysis was performed on a computer, using the statistical analysis program SPSS 13.0 (SPSS, Chicago, IL, USA). Mean differences of continuous variables between groups were tested using analysis of variance (ANOVA). The chi-squared test was used to calculate the difference in proportions between groups. Logistic regression analysis was performed to estimate the probability of having IFG and 95% CI for each risk factor category stratified by sleep quality and sleep duration, adjusting for age, residential areas, occupation, education and income levels, leisure-time physical activity, smoking status, drinking status and hypertension status. The observed prevalences of IFG were plotted and stratified by sleep quality and sleep duration.

Biological interactions should be based on the sum of the scale rather than multiplying the scale.[14, 15] Therefore, we used three measures to estimate biological interactions of poor sleep quality and short sleep duration: relative excess risk owing to interaction (RERI), the attributable proportion (AP) owing to interaction, and the synergy index (S). The RERI is the excess risk attributed to interaction relative to the risk without exposure to poor sleep quality and short sleep duration. AP refers to the attributable proportion of disease caused by interaction in subjects with exposure to both variables. S is the excess risk from exposure to both variables when there is a biological interaction relative to the risk from exposure to both variables without interaction. In the absence of additive interactions, RERI and AP are equal to 0.[16] In the current study, RERI > 0, AP > 0 and S > 0 indicate statistical significance. A p value < 0.05 (two-tailed) was considered statistically significant.

Results

General characteristics of participants

15,145 adults (7557 men and 7588 women) with complete data were included in our analysis. The average age was 47.6 ± 15.1 years. Among them, 634 had IFG; the remainder had normal glucose tolerance (NGT). The characteristics of the study population are presented in Table 1. The proportion of volunteers with poor sleep quality was 26.0%, the proportion with sleep duration <6 h was 12.5%, the proportion with sleep duration >8 h was 12.3%. The 6.7% prevalence of IFG in volunteers with poor sleep quality was higher than that in volunteers

with good sleep quality ($\chi^2 = 85.98$, $p < 0.001$). Individuals with sleep duration <6 h had a higher IFG prevalence compared with individuals with sleep duration 6−8 h, (7.3 *vs* 3.3%; $\chi^2 = 72.20$, $p < 0.001$). Individuals with sleep duration >8 h also had also had higher prevalence of IFG (6.2 *vs* 3.3%; $\chi^2 = 37.78$, $p < 0.001$).

Comparison of PSQI scores between the volunteers with IFG and NGT

Volunteers with IFG had significantly higher global PSQI scores than those with NGT. For all PSQI items except sleep duration, there were significant differences ($p < 0.05$) in PSQI scores between the two groups (Table 2).

Biological interaction of sleep quality and sleep duration on the prevalence of IFG

We used a combined effects method to assess interaction, with the *p* value of the interaction term indicating statistical significance of addictive interactions. Individuals with poor sleep quality or short sleep duration had significantly increased risk of IFG compared with those with good sleep quality and sleep duration 6−8 h (OR: 2.48; 95% CI: 2.12−3.03； OR: 2.79; 95% CI: 2.19−3.58; respectively. all $P<0.001$), after adjusting for confounders. Table 3 shows the results from the multiple logistic regression models. The prevalence of IFG was greatest in those with poor sleep quality and short sleep duration (OR: 6.37; 95% CI: 4.66−8.67; $p < 0.001$), after adjusting for confounders. In addition, individuals with long sleep duration had a significantly increased risk of IFG compared with those who had good sleep quality and sleep duration of 6−8 h (OR: 2.37; 95% CI: 1.89−2.96; $p < 0.001$), after adjusting for confounders. The prevalence of IFG was also greater in those with good sleep quality with long sleep duration (OR: 3.17; 95% CI: 2.29−4.41; $p < 0.001$), compared with those with 6−8 h sleep duration, after adjusting for confounders.

Sensitivity analysis

There was a strong additive interaction between poor sleep quality and short sleep duration (RERI: 1.69; 95% CI: 0.31–3.76.), with 42% of occurring IFG attributed to the interaction between poor sleep quality and short sleep duration (Table 3). There was also interaction between good sleep quality and long sleep duration (RERI: 0.78; 95% CI: 0.12–1.43), with 61% of occurring IFG attributed to the interaction between good sleep quality and long sleep duration (Table 4).

Discussion

The two main findings of this study were, firstly, that there is combined interaction of poor sleep quality and short sleep duration on the prevalence of IFG. Secondly, that total PSQI scores of volunteers with IFG were higher than those of volunteers with NGT. We also

found that poor sleep quality and short or long sleep duration increased risk for IFG in a Chinese population, independent of potential confounders such as age, obesity, family history of diabetes, alcohol consumption, smoking, physical activity, and other diseases.

Numerous epidemiologic studies have demonstrated associations between short or long sleep duration and sleep disturbances and diabetes.[17-23]. However, few articles focused on IFG, and the results of these are inconsistent. [5, 24] Rafalson et al.[5] reported the OR of IFG among short sleepers was 3.0 (95% CI: 1.05–8.59) compared with mid-range sleepers with multivariate conditional logistic regression after adjustment for several diabetes risk factors. Hung et al.[24] reported no association between IFG and poor sleepers. Our findings are consistent with the report by Rafalson et al.

The global PSQI scores in volunteers with IFG were higher than those in volunteers with NGT, which was consistent with the Hung et al. report.[24] However, there was no difference in sleep duration scores between the volunteers with IFG and the volunteers with NGT. This could be attributed to the fact that 18.3% (116/634) of the volunteers with IFG were long sleepers, while short sleepers with IFG only accounted for 22.9% (145/634).

Short sleep duration increases appetite. After four nights of 4.5 h in bed, compared with after four nights of 8.5 h in bed, caloric intake, especially of carbohydrate-rich nutrients, increased by 14% in young normal-weight men and women.[25, 26] Middle-aged obese volunteers submitted to four to five nights of restriction of their habitual sleep schedule by 2–3 h/night ate 15% more calories than those whose habitual sleep schedule was extended by the same amount.[27] In volunteers with sleep debt, glucose tolerance, glucose effectiveness and insulin sensitivity are decreased, and beta-cell function is reduced.[6,26,28,29] Sleep loss also results in decreased anorexigenic leptin levels,[30-32] especially in volunteers with chronic sleep restriction.[33] Observational epidemiologic studies have also shown reduced leptin levels, after controlling for BMI or adiposity, in habitual short sleepers.[33, 34] Conversely, leptin deficiency disrupts sleep architecture and impairs sleep consolidation.[35] Taken together, these data suggest that sleep loss is likely to have a profound impact on IFG.

Poor sleep quality, independent of sleep duration, impairs glucose regulation in healthy young adults.[36, 37] After three nights of slow-wave sleep suppression, insulin sensitivity is decreased by ~25%, reaching the level reported in older adults and in populations at high risk of diabetes.[38] The decrease in insulin sensitivity is not compensated for by an increase in insulin release. Consequently, the disposition index is ~20% lower. Consistent with an increased diabetes risk, glucose tolerance is reduced by ~23% reaching the range typical of older adults with impaired glucose tolerance.[37] Sleep fragmentation also increases sympathetic activity, which in turn leads to disorders of glucose metabolism.[39]

Taken together, short sleep duration, increased caloric intake, poor sleep quality, decreased leptin levels, decreased insulin sensitivity and increased sympathetic activity affect each other, creating a vicious circle, which elevates the risk of IFG.

Despite the absence of the synergistic effect of good-quality sleep with long sleep duration, a strong association of IFG with long sleep duration in individuals was observed, suggesting an independent effect of long sleep duration.

This study had several potential limitations. Firstly, because of the cross-sectional design, we could not determine a causal relationship between sleep quality, sleep duration and IFG. Secondly, we were not able to control for some important and well-known risk factors of diabetes, for example, snoring.[40]. Thirdly, we did not measure poor diet, which is causally related to type 2 diabetes and may also influence sleep patterns.[41,42]

There are several notable strengths of this study. Participants were randomly selected from the general population of Xuzhou. In addition, the sample was large. Many confounding risk factors were adjusted for.

In summary, volunteers who experience short sleep durations are six times more likely to develop IFG than those whose average sleep was 6−8 h a night with good sleep quality. The joint effect of short sleep duration and poor sleep quality was positive.

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Conflict of Interest Statement

None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. The researchers were independent from funders. The study funders had no influence on the study design, data collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Contributors Steering Committee: PL (principal investigator), PC (principal investigator), PC and LZ. Operating Committee: LZ,PZ, GC, NZ, TL and CQ.

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Table 1 Baseline characteristics of the study population (N = 15,145)

Reported variable	All	IFG		
		No	Yes	*P*
n	**15145**	**14,511**	**634**	
Age(years)	**47.6±15.1**	**47.4±14.7**	**52.2±16.2**	**8.012**
⩾45 years	**8362**	**7928**	**434**	**0.000**
Sex(% man)	**49.9**	**50.0**	**49.8**	**0.938**
Rural (%)	**72.4**	**72.4**	**72.9**	**0.795**
Manual	**10833**	**10359**	**474**	**0.023**
Non-manual	**1045**	**1016**	**29**	
Unemployed	**677**	**658**	**19**	
retired	**2590**	**2478**	**112**	
Marred (living with partners)(%)	**88.5**	**88.6**	**86.3**	**0.073**
Below high school	**11899**	**11400**	**499**	**0.986**
high school	**1760**	**1686**	**74**	
Above high school	**1486**	**1425**	**61**	
smoker	**3514**	**3367**	**174**	0.014
alcohol use	**2872**	**2752**	**120**	0.981
Regular exercise	**2559**	**2452**	**107**	0.989
Family history of diabetes	**483**	**362**	**121**	0.000
BMI, mean(SD)	**23.9±4.7**	**23.8±5.8**	**25.2±4.1**	＜0. 001
Central obesity	**4613**	**4219**	**394**	0.000
Hypertension	**3060**	**2901**	**159**	0.002
Sleep duration(hour)				
≤6	**1984**	**1839**	**145**	0.000
6-8	**11292**	**10919**	**373**	
≥8	**1869**	**1753**	**116**	
Sleep quality				
Good	**11209**	**10840**	**369**	0.000
Poor	**3936**	**3671**	**265**	

Table 2 Comparison of Pittsburgh Sleep Quality Index scores between individuals with impaired fasting glucose and controls ($\bar{x} \pm sd$)

Items	IFG		*Z* value	*P*
	No	Yes		
Subjective sleep quality	0.45±0.60	0.47±0.62	-3.240	<0.05
Sleep latency	0.79±0.62	0.90±0.62	-7.430	<0.05
Sleep duration	0.34±0.54	0.35±0.57	-0.634	0.526
Sleep efficiency	0.54±0.84	0.59±0.88	-2.377	<0.05
Sleep disturbance	0.49±0.58	0.54±0.58	-3.590	<0.05
Use of hypnotic	0.05±0.28	0.06±0.30	-3.627	<0.05
Daytime dysfunction	0.16±0.49	0.20±0.54	-3.272	<0.05
Global PSQI scores	2.81±2.27	3.09±2.34	-5.655	<0.05

Table 3 Odds ratios for the association between sleep quality and impaired fasting glucose by sleep duration among participants

Sleep quality versus sleep duration	Sleep quality	IFG	No IFG	OR (95%CI)	P
Sleep duration 6-8h	Good	246	8743	1	
	Poor	127	2176	1.98（1.76-2.52）	<0.001
Sleep duration＜6h	Good	53	1329	1.38（1.12-1.61）	<0.001
	Poor	92	510	6.37（4.66-8.67）	<0.001
Sleep duration＞8h	Good	70	768	3.17 （2.29-4.41）	<0.001
	Poor	46	985	1.59（1.08-2.29）	<0.001

Adjusted for age, sex, education, employment, BMI, family history of diabetes, smoking status, alcohol consumption and physical activity.

Table 4 Measures for estimation of the biological interaction between sleep quality and sleep duration for the prevalence of impaired fasting glucose in participants

Measures of biological interaction	Estimate (95% CI)
Poor sleep quality versus sleep duration ＜6h	
RERI	**1.69(0.31－3.76)**
AP	**0.42(0.15－0.61)**
S	**2.85(2.14－3.92)**
Good sleep quality versus sleep duration ＞ 8h	
RERI	0.78(0.12－1.43)
AP	0.61(0.26－0.87)
S	-0.65(-0.94－-0.27)

Reference group is good sleep quality with 6-8 sleep duration.

Adjusted for age, sex, education, occupation, BMI, family history of diabetes, smoking status, alcohol consumption, and hypertension.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page3
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 3
Methods			
Study design	4	Present key elements of study design early in the paper	Page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 3-4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Page 4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 4-5
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 5
		(*b*) Describe any methods used to examine subgroups and interactions	Page 5
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Page 5
		(*e*) Describe any sensitivity analyses	Page 5

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 6
		(b) Give reasons for non-participation at each stage	Page 6
		(c) Consider use of a flow diagram	Figur1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table1
		(b) Indicate number of participants with missing data for each variable of interest	Table2
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Page6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Page6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table3-5
		(*b*) Report category boundaries when continuous variables were categorized	Page7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page10
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Interaction of sleep quality and sleep duration on impaired fasting glucose: A population-based cross-sectional survey in China

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Interaction of sleep quality and sleep duration on impaired fasting glucose: A population-based cross-sectional survey in China

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Abstract

Objectives: To explore the interactions of sleep quality and sleep duration and their effects on impaired fasting glucose in Chinese adults.

Design: Cross-sectional survey.

Setting: Community-based investigation in Xuzhou, China.

Participants: 15,145 Chinese men and women aged 18−75 years old who fulfilled the inclusion criteria.

Primary and secondary outcome measures: The Pittsburgh Sleep Quality Index was used to produce sleep quality categories of good, common and poor. Fasting blood glucose levels were assessed for impaired fasting glucose. Sleep duration was measured by average hours of sleep per night, with categories of <6 h, 6−8 h, and >8 h. The products of sleep and family history of diabetes, obesity and age were added to the logistic regression model to evaluate the addictive interaction and relative excess risk of interaction (RERI) on impaired fasting glucose. The attributable proportion (AP) of the interaction and the synergy index (S) were applied to evaluate the additive interaction of two factors. Bootstrap measures were used to calculate 95% confidence intervals (CI) of RERI, AP and S.

Results: The prevalence of IFG was greatest in those with poor sleep quality and short sleep duration (OR: 6.37; 95% CI: 4.66−8.67; $p < 0.001$) compared with those who had good sleep quality and 6−8 h sleep duration, after adjusting for confounders. After adjusting for potential confounders, RERI, AP and S values (and their 95% CI) were 1.69 (0.31−3.76), 0.42 (0.15−0.61) and 2.85 (2.14−3.92) for the interaction between poor sleep quality and short sleep duration, and 0.78 (0.12−1.43), 0.61 (0.26−0.87) and −65 (−0.94 to −0.27) for the interaction between good sleep quality and long sleep duration.

Conclusions: The results suggest that there are additive interactions between poor sleep quality and short sleep duration.

ARTICLE SUMMARY

Article focus

- To describe the combined effects of sleep duration and sleep quality for impaired fasting glucose in people in Xuzhou, China.

Key messages

- There exist additive interactions between sleep quality and sleep duration on impaired fasting glucose.
- A strength of the study is the large sample.
- Limitations of the study the cross-sectional design.

Introduction

Prediabetes has a prevalence of 15.5% and affects an estimated 148.2 million Chinese adults.[1] Prediabetes, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is the most important risk factor for type 2 diabetes. The average annual incidence of diabetes in a cohort of patients with IFG is 11% over a six-year period without intervention.[2] Older age, a family history of diabetes, being overweight, obesity, central obesity, increased heart rate, elevated systolic blood pressure, elevated serum triglyceride levels, high income, history of hypertension, history of coronary heart disease, history of drinking, eating pickled foods, and low educational level are significantly associated with an increased risk of prediabetes.[1,3] Increasingly, studies have shown that prediabetes is associated with poor sleep quantity and quality.[3,4] A cross-sectional study has suggested that, compared with those sleeping 7−8 h per night, individuals aged <60 years who slept 5 h or less had an increased odds ratio (OR) for IGT (OR: 1.37, 95% confidence interval [CI]: 1.13−1.67).[4] The Western New York Health Study including 1455 participants showed that sleep duration of less than 6 h was associated with increased prevalence of IFG, compared with those sleeping 6−8 h per night, after adjustment for confounders, over six years of follow up.[5] Spiegel et al. have demonstrated that experimental restriction of sleep to <4 h per night for six nights resulted in an impaired glucose tolerance (IGT) in young healthy adults.[6]

Our previous results suggest that poor quality of sleep and sleep duration <6 h per night are independent risk factors for type 2 diabetes, even after adjusting for a large number of possible confounders.[7,8] Our previous study also confirmed that relatively healthy individuals with poor sleep quality and sleeping times of 6 h or less had a higher risk of IFG, even after adjusting for a large number of confounding factors.[3]

Although these risk factors play a role in the development of type 2 diabetes, the disease is the result of the interaction of genetic and environmental factors. There is little understanding of multivariate explanations of IFG in relatively healthy individuals. To our knowledge, there are no studies on the interaction of sleep quality and sleep duration on IFG in relatively healthy individuals. The primary aim of this cross-sectional study was to examine the combined effects of sleep quality and sleep duration on IFG in relatively healthy individuals in a Chinese primary-care setting. A secondary aim was to assess the associations of sleep quality and IFG, and of sleep duration and IFG.

Methods

The study was a continuation of our previous work.[9] The investigation was conducted from March to November 2012 with a sample size of 15,145 volunteers (7557 men and 7588 women) aged 18 to 75 years. Briefly, the sampling was selected with probability proportional

to size from all of the eleven regions in Xuzhou city. In the first stage, 5 subdistricts/townships in urban/rural areas were selected from each region. In the second stage, 5 communities/ villages were selected from each subdistricts/townships. In the final stage, one person who was at least 18 years old and lived in the current residence for at least 5 years was selected from each household using a Kish selection table. A total of 16500 people were selected assuming an estimation prevalence of diabetes of 5.5% with 90% power and α=0.05 and allowing for a drop-out of 10%. All volunteers received a health check and completed a structured questionnaire covering demographic information, medical history, medication history, sleep assessment, and smoking, alcohol drinking and exercise habits. All volunteers underwent 12-h overnight fasting and blood sampling for basic fasting plasma glucose (FPG). After blood sampling, each volunteer completed the Pittsburgh Sleep Quality Index (PSQI).[10] We excluded volunteers who were pregnant, had received antihypertensive medication, or were suffering from any cardiovascular disease, stroke, neuropathy, psychosis, depression, chronic obstructive pulmonary disease, obstructive sleep apnea, diabetes, ache, or any other disease. Those who had missing information on sleep duration or sleep quality were also excluded. Trained physicians and public health workers conducted face-to-face interviews using a standardized questionnaire to collect socio-demographic, lifestyle and health-related information.

The study protocol was approved by the Xuzhou Center for Disease Control and Prevention. All participants provided written informed consent.

Key measurements

The FPG was determined by morning blood samples obtained by venipuncture after an overnight fast of at least 12h, and extracted plasma was stored at −70°C for later glucose determination by the hexokinase method. According to the current WHO definition of IFG[11].

The PSQI is a validated self-rated questionnaire that assesses sleep quality over a one-month time interval.[10] Nineteen items generate seven component scores that reflect sleep problems in the areas of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction. The sum of the scores for these seven components produces a global sleep quality score within a range of 0−21 points. A global PSQI score >5 has a diagnostic sensitivity of 89.6% and specificity of 86.5% in differentiating poor from good sleepers. The Chinese version of the PSQI, used with

permission from the original PSQI authors, has an overall reliability coefficient of 0.82−0.83 and acceptable test–retest reliability, with a coefficient of 0.77−0.85.[12] Accordingly, in this study design, a PSQI score ≤5 was also conventionally defined as 'good sleep quality', , and a PSQI score ＞ 5 was defined as 'poor sleep quality'

Self-reported sleep measures of chronic sleep. Two variables were used to evaluate degree of "chronic sleep restriction" by estimating average nightly sleep duration: (i) "usual sleep" (from questionnaires) and (ii) "average nightly sleep" (from sleep diaries).Sleep quantity was categorized as <6, 6−8, and >8 h per night accordance with our previous study.[3,7,8]

Covariates

Age, gender, current employment status, level of education, cigarette smoking, alcohol intake, physical activity, family history of diseases including diabetes, hypertension, heart disease, and cancer were assessed using a standardized questionnaire. Employment status was categorized as manual, non-manual, unemployed, and retired. Education was categorized into below high school, high school, or above high school education. Lifestyle variables included cigarette smoking, alcohol drinking and physical activity level. Cigarette smoking was defined as having smoked at least 100 cigarettes in a lifetime. Information was obtained on the amount and type of alcohol that was consumed during the previous year, and alcohol drinking was defined as the consumption of at least 30 g of alcohol per week for one year or more. Regular leisure-time physical activity was defined as participating in moderate or vigorous activity for no less than 30 minutes per day at least three days a week. Each volunteer's body height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were measured. Body mass index (BMI; in kg/m^2) was calculated. BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5−24.0 kg/m^2) and overweight/obese (>24.0 kg/m^2).[13]

Statistical analysis

Statistical analysis was performed on a computer, using the statistical analysis program SPSS 13.0 (SPSS, Chicago, IL, USA). Mean differences of continuous variables between groups were tested using analysis of variance (ANOVA). The chi-squared test was used to calculate the difference in proportions between groups. Logistic regression analysis was performed to estimate the probability of having IFG and 95% CI for each risk factor category stratified by sleep quality and sleep duration, adjusting for age, residential areas, occupation, education and income levels, leisure-time physical activity, smoking status, drinking status and hypertension status. The observed prevalences of IFG were plotted and stratified by sleep quality and sleep duration.

Biological interactions should be based on the sum of the scale rather than multiplying the scale.[14,15] Therefore, we used three measures to estimate biological interactions of poor

sleep quality and short sleep duration: relative excess risk owing to interaction (RERI), the attributable proportion (AP) owing to interaction, and the synergy index (S). The RERI is the excess risk attributed to interaction relative to the risk without exposure to poor sleep quality and short sleep duration. AP refers to the attributable proportion of disease caused by interaction in subjects with exposure to both variables. S is the excess risk from exposure to both variables when there is a biological interaction relative to the risk from exposure to both variables without interaction. In the absence of additive interactions, RERI and AP are equal to 0.[16] In the current study, RERI > 0, AP > 0 and S > 0 indicate statistical significance. A p value < 0.05 (two-tailed) was considered statistically significant.

Results

General characteristics of participants

The response rate was 91.3%. Of the16584 initial participants, 125 did not respond to the sleep items or blood glucose, 1314 did not meet our study criteria, 15,145 adults (7557 men and 7588 women) with complete data were included in our analysis. The average sleep duration per night was 7.16 ±1.06h. The average age was 47.6 ± 15.1 years. Among them, 634 had IFG; the remainder had normal glucose tolerance (NGT). The characteristics of the study population are presented in Table 1. The proportion of volunteers with poor sleep quality was 26.0%, the proportion with sleep duration <6 h was 12.5%, the proportion with sleep duration >8 h was 12.3%. The 6.7% prevalence of IFG in volunteers with poor sleep quality was higher than that in volunteers with good sleep quality ($\chi^2 = 85.98$, $p < 0.001$). Individuals with sleep duration <6 h had a higher IFG prevalence compared with individuals with sleep duration 6−8 h, (7.3 *vs* 3.3%; $\chi^2 = 72.20$, $p < 0.001$). Individuals with sleep duration >8 h also had also had higher prevalence of IFG (6.2 *vs* 3.3%; $\chi^2 = 37.78$, $p < 0.001$).

Comparison of PSQI scores between the volunteers with IFG and NGT

Volunteers with IFG had significantly higher global PSQI scores than those with NGT. For all PSQI items except sleep duration, there were significant differences ($p < 0.05$) in PSQI scores between the two groups (Table 2) even after adjusted age.

The association of sleep time and quality with IFG

Individuals with short sleep duration or long sleep duration had significantly increased risk of IFG compared with those with good sleep quality and sleep duration 6−8 h (OR:2.16 ; 95% CI: 1.33−3.47； OR: 1.89; 95% CI: 1.50−2.34; respectively. all $P<0.001$), after adjusting for confounders (See table 3). Individuals with poor sleep quality had significantly increased risk of IFG compared with those with good sleep quality (OR:1.98; 95% CI: 1.69−2.21; $P<0.001$), after adjusting for confounders (See table 3).

Biological interaction of sleep quality and sleep duration on the prevalence of IFG

We used a combined effects method to assess interaction, with the *p* value of the interaction term indicating statistical significance of addictive interactions. Individuals with poor sleep quality or short sleep duration had significantly increased risk of IFG compared with those with good sleep quality and sleep duration 6−8 h (OR: 2.48; 95% CI: 2.12−3.03； OR: 2.79; 95% CI: 2.19−3.58; respectively. all *P*<0.001), after adjusting for confounders. Table 4 shows the results from the multiple logistic regression models. The prevalence of IFG was greatest in those with poor sleep quality and short sleep duration (OR: 6.37; 95% CI: 4.66−8.67; $p < 0.001$), after adjusting for confounders. In addition, individuals with long sleep duration had a significantly increased risk of IFG compared with those who had good sleep quality and sleep duration of 6−8 h (OR: 2.37; 95% CI: 1.89−2.96; $p < 0.001$), after adjusting for confounders. The prevalence of IFG was also greater in those with good sleep quality with long sleep duration (OR: 3.17; 95% CI: 2.29−4.41; $p < 0.001$), compared with those with 6−8 h sleep duration, after adjusting for confounders.

Sensitivity analysis

There was a strong additive interaction between poor sleep quality and short sleep duration (RERI: 1.69; 95% CI: 0.31–3.76.), with 42% of occurring IFG attributed to the interaction between poor sleep quality and short sleep duration (Table 5). There was also interaction between good sleep quality and long sleep duration (RERI: 0.78; 95% CI: 0.12–1.43), with 61% of occurring IFG attributed to the interaction between good sleep quality and long sleep duration (Table 5).

Discussion

The two main findings of this study were, firstly, that there is combined interaction of poor sleep quality and short sleep duration on the prevalence of IFG. Secondly, that total PSQI scores of volunteers with IFG were higher than those of volunteers with NGT. We also found that poor sleep quality and short or long sleep duration increased risk for IFG in a Chinese population, independent of potential confounders such as age, obesity, family history of diabetes, alcohol consumption, smoking, physical activity, and other diseases.

Numerous epidemiologic studies have demonstrated associations between short or long sleep duration and sleep disturbances and diabetes.[17-23]. However, few articles focused on IFG, and the results of these are inconsistent. [5, 24] Rafalson et al.[5] reported the OR of IFG among short sleepers was 3.0 (95% CI: 1.05–8.59) compared with mid-range sleepers with multivariate conditional logistic regression after adjustment for several diabetes risk factors. Hung et al.[24] reported no association between IFG and poor sleepers. Our findings are consistent with the report by Rafalson et al.

The global PSQI scores in volunteers with IFG were higher than those in volunteers with

NGT, which was consistent with the Hung et al. report.[24] However, there was no difference in sleep duration scores between the volunteers with IFG and the volunteers with NGT. This could be attributed to the fact that 18.3% (116/634) of the volunteers with IFG were long sleepers, while short sleepers with IFG only accounted for 22.9% (145/634).

Short sleep duration increases appetite. After four nights of 4.5 h in bed, compared with after four nights of 8.5 h in bed, caloric intake, especially of carbohydrate-rich nutrients, increased by 14% in young normal-weight men and women.[25, 26] Middle-aged obese volunteers submitted to four to five nights of restriction of their habitual sleep schedule by 2–3 h/night ate 15% more calories than those whose habitual sleep schedule was extended by the same amount.[27] In volunteers with sleep debt, glucose tolerance, glucose effectiveness and insulin sensitivity are decreased, and beta-cell function is reduced.[6,26,28,29] Sleep loss also results in decreased anorexigenic leptin levels,[30-32] especially in volunteers with chronic sleep restriction.[33] Observational epidemiologic studies have also shown reduced leptin levels, after controlling for BMI or adiposity, in habitual short sleepers.[33, 34] Conversely, leptin deficiency disrupts sleep architecture and impairs sleep consolidation.[35] Taken together, these data suggest that sleep loss is likely to have a profound impact on IFG.

Poor sleep quality, independent of sleep duration, impairs glucose regulation in healthy young adults.[36, 37] After three nights of slow-wave sleep suppression, insulin sensitivity is decreased by ~25%, reaching the level reported in older adults and in populations at high risk of diabetes.[38] The decrease in insulin sensitivity is not compensated for by an increase in insulin release. Consequently, the disposition index is ~20% lower. Consistent with an increased diabetes risk, glucose tolerance is reduced by ~23% reaching the range typical of older adults with impaired glucose tolerance.[37] Sleep fragmentation also increases sympathetic activity, which in turn leads to disorders of glucose metabolism.[39]

Taken together, short sleep duration, increased caloric intake, poor sleep quality, decreased leptin levels, decreased insulin sensitivity and increased sympathetic activity affect each other, creating a vicious circle, which elevates the risk of IFG.

Despite the absence of the synergistic effect of good-quality sleep with long sleep duration, a strong association of IFG with long sleep duration in individuals was observed, suggesting an independent effect of long sleep duration.

This study had several potential limitations. Firstly, because of the cross-sectional design, we could not determine a causal relationship between sleep quality, sleep duration and IFG. Secondly, we were not able to control for some important and well-known risk factors of diabetes, for example, snoring.[40]. Thirdly, we did not measure poor diet, which is causally related to type 2 diabetes and may also influence sleep patterns.[41,42]

There are several notable strengths of this study. Participants were randomly selected from the general population of Xuzhou. In addition, the sample was large. Many confounding risk factors were adjusted for.

In summary, volunteers who experience short sleep durations are six times more likely to develop IFG than those whose average sleep was 6−8 h a night with good sleep quality. The joint effect of short sleep duration and poor sleep quality was positive.

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Conflict of Interest Statement

None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. The researchers were independent from funders. The study funders had no influence on the study design, data collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Contributors Steering Committee: PL (principal investigator), PC (principal investigator), PC and LZ. Operating Committee: LZ,PZ, GC, NZ, TL and CQ.

Data Sharing Statement

Our material is original, has not been published except in abstract form, and is not being considered for publication elsewhere, including publicly accessible websites or e-print servers, no part of the research presented has been funded by tobacco industry sources, and all authors have read the manuscript and approve its submission.

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Table 1 Baseline characteristics of the study population (N = 15,145)

Reported variable	*All*	*IFG*		
		No	Yes	*P*
	15145	14,511(95.81%)	634(4.19%)	
Age(years)	47.6±15.1	47.4±14.7	52.2±16.2	8.012
≥45 years	8362	7928(94.81%)	434(5.19%)	0.000
Sex(% man)	49.9	50.0	49.8	0.938
Rural (%)	72.4	72.4	72.9	0.795
Manual	10833	10359(95.62%)	474(4.38%)	0.023
Non-manual	1045	1016(97.22%)	29(2.78%)	
Unemployed	677	658(97.19%)	19(2.81%)	
retired	2590	2478(95.68%)	112(4.32%)	
Marred (living with partners)(%)	88.5	88.6	86.3	0.073
Below high school	11899	11400(95.81%)	499(4.19%)	0.986
high school	1760	1686(95.80%)	74(4.20%)	
Above high school	1486	1425(95.90%)	61(4.10%)	
smoker	3541	3367(95.09%)	174(4.91%)	0.014
alcohol use	2872	2752(95.82%)	120(4.18%)	0.981
Regular exercise	2559	2452(95.82%)	107(4.18%)	0.989
Family history of diabetes	483	362(74.95%)	121(25.05%)	0.000
BMI, mean(SD)	23.9±4.7	23.8±5.8	25.2±4.1	＜0.001
Central obesity	4613	4219(91.46%)	394(8.54%)	0.000
Hypertension	3060	2901(94.80%)	159(5.20%)	0.002
Sleep duration(hour)				
≤6	1984	1839(92.70%)	145(7.30%)	0.000
6-8	11292	10919(96.70%)	373(3.30%)	
≥8	1869	1753(93.80%)	116(6.20%)	
Sleep quality				
Good	11209	10840(96.71%)	369(3.29%)	0.000
Poor	3936	3671(93.27%)	265(6.73%)	

Table 2 Comparison of Pittsburgh Sleep Quality Index scores between individuals with impaired fasting glucose and controls ($\bar{x}$ ± sd)

Items	*IFG*		*F value*	*P*
	No	Yes		
Subjective sleep quality	0.415±0.013	0.463±0. 03	31.823	0.000
Sleep latency	0.742±0.004	0.800±0.016	27.446	0.000
Sleep duration	0.152±0.002	0.159±0.001	0.503	0.478
Sleep efficiency	0.444±0.003	0. 321±0.001	29.452	0.000
Sleep disturbance	0.591±0. 003	0.658±0.012	28.259	0.000
Use of hypnotic	0.051±0.002	0.065±0.007	16.651	0.000
Daytime dysfunction	0.147±0.011	0.170±0.002	9.725	0.000
Global PSQI scores	2.302±0.009	2.495±0. 041	20.957	0.000

Using analysis of covariance, Covariates for age =47.26 years old

Table 3 Odds ratios for the association between sleep quality, sleep duration and impaired fasting glucose among participants

Variables		IFG	No IFG	OR (95%CI)	P
Sleep quality	Good	369	10840	1	
	Poor	265	3671	1.21(1.09-1.34）	0.000
Sleep duration	6-8h	373	10919	1	
	＜6h	145	1839	2.16 (1.33-3.47)	0.000
	＞8h	116	1753	1.89 (1.50-2.34)	0.000

Adjusted for age, sex, education, employment, BMI, family history of diabetes, smoking status, alcohol consumption and physical activity.

Table 4 Odds ratios for the association between sleep quality and impaired fasting glucose by sleep duration among participants

Sleep duration	*Sleep quality*	*IFG*	*No IFG*	*OR (95%CI)*	*P*
6-8h	Good	246	8743	1	
	Poor	127	2176	1.98（1.76-2.52）	<0.001
＜6h	Good	53	1329	1.38（1.12-1.61）	<0.001
	Poor	92	510	6.37（4.66-8.67）	<0.001
＞8h	Good	70	768	3.17 （2.29-4.41）	<0.001
	Poor	46	985	1.59（1.08-2.29）	<0.001

Adjusted for age, sex, education, employment, BMI, family history of diabetes, smoking status, alcohol consumption and physical activity.

Table 5 Measures for estimation of the biological interaction between sleep quality and sleep duration for the prevalence of impaired fasting glucose in participants

Measures of biological interaction	Estimate (95% CI)
Poor sleep quality versus sleep duration ＜6h	
RERI	1.69(0.31－3.76)
AP	0.42(0.15－0.61)
S	2.85(2.14－3.92)
Good sleep quality versus sleep duration ＞ 8h	
RERI	0.78(0.12－1.43)
AP	0.61(0.26－0.87)
S	-0.65(-0.94－-0.27)

Reference group is good sleep quality with 6-8 sleep duration.

Adjusted for age, sex, education, occupation, BMI, family history of diabetes, smoking status, alcohol consumption, and hypertension.

Interaction of sleep quality and sleep duration on impaired fasting glucose: A population-based cross-sectional survey in China

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Abstract

Objectives: To explore the interactions of sleep quality and sleep duration and their effects on impaired fasting glucose in Chinese adults.

Design: Cross-sectional survey.

Setting: Community-based investigation in Xuzhou, China.

Participants: 15,145 Chinese men and women aged 18−75 years old who fulfilled the inclusion criteria.

Primary and secondary outcome measures: The Pittsburgh Sleep Quality Index was used to produce sleep quality categories of good, common and poor. Fasting blood glucose levels were assessed for impaired fasting glucose. Sleep duration was measured by average hours of sleep per night, with categories of <6 h, 6−8 h, and >8 h. The products of sleep and family history of diabetes, obesity and age were added to the logistic regression model to evaluate the addictive interaction and relative excess risk of interaction (RERI) on impaired fasting glucose. The attributable proportion (AP) of the interaction and the synergy index (S) were applied to evaluate the additive interaction of two factors. Bootstrap measures were used to calculate 95% confidence intervals (CI) of RERI, AP and S.

Results: The prevalence of IFG was greatest in those with poor sleep quality and short sleep duration (OR: 6.37; 95% CI: 4.66−8.67; $p < 0.001$) compared with those who had good sleep quality and 6−8 h sleep duration, after adjusting for confounders. After adjusting for potential confounders, RERI, AP and S values (and their 95% CI) were 1.69 (0.31−3.76), 0.42 (0.15−0.61) and 2.85 (2.14−3.92) for the interaction between poor sleep quality and short sleep duration, and 0.78 (0.12−1.43), 0.61 (0.26−0.87) and −65 (−0.94 to −0.27) for the interaction between good sleep quality and long sleep duration.

Conclusions: The results suggest that there are additive interactions between poor sleep quality and short sleep duration.

ARTICLE SUMMARY

Article focus

- To describe the combined effects of sleep duration and sleep quality for impaired fasting glucose in people in Xuzhou, China.

Key messages

- There exist additive interactions between sleep quality and sleep duration on impaired fasting glucose.
- A strength of the study is the large sample.
- Limitations of the study the cross-sectional design.

Introduction

Prediabetes has a prevalence of 15.5% and affects an estimated 148.2 million Chinese adults.[1] Prediabetes, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is the most important risk factor for type 2 diabetes. The average annual incidence of diabetes in a cohort of patients with IFG is 11% over a six-year period without intervention.[2] Older age, a family history of diabetes, being overweight, obesity, central obesity, increased heart rate, elevated systolic blood pressure, elevated serum triglyceride levels, high income, history of hypertension, history of coronary heart disease, history of drinking, eating pickled foods, and low educational level are significantly associated with an increased risk of prediabetes.[1,3] Increasingly, studies have shown that prediabetes is associated with poor sleep quantity and quality.[3,4] A cross-sectional study has suggested that, compared with those sleeping 7−8 h per night, individuals aged <60 years who slept 5 h or less had an increased odds ratio (OR) for IGT (OR: 1.37, 95% confidence interval [CI]: 1.13−1.67).[4] The Western New York Health Study including 1455 participants showed that sleep duration of less than 6 h was associated with increased prevalence of IFG, compared with those sleeping 6−8 h per night, after adjustment for confounders, over six years of follow up.[5] Spiegel et al. have demonstrated that experimental restriction of sleep to <4 h per night for six nights resulted in an impaired glucose tolerance (IGT) in young healthy adults.[6]

Our previous results suggest that poor quality of sleep and sleep duration <6 h per night are independent risk factors for type 2 diabetes, even after adjusting for a large number of possible confounders.[7,8] Our previous study also confirmed that relatively healthy individuals with poor sleep quality and sleeping times of 6 h or less had a higher risk of IFG, even after adjusting for a large number of confounding factors.[3]

Although these risk factors play a role in the development of type 2 diabetes, the disease is the result of the interaction of genetic and environmental factors. There is little understanding of multivariate explanations of IFG in relatively healthy individuals. To our knowledge, there are no studies on the interaction of sleep quality and sleep duration on IFG in relatively healthy individuals. The primary aim of this cross-sectional study was to examine the combined effects of sleep quality and sleep duration on IFG in relatively healthy individuals in a Chinese primary-care setting. A secondary aim was to assess the associations of sleep quality and IFG, and of sleep duration and IFG.

Methods

The study was a continuation of our previous work.[9] The investigation was conducted from March to November 2012 with a sample size of 15,145 volunteers (7557 men and 7588 women) aged 18 to 75 years. Briefly, the sampling was selected with probability proportional

to size from all of the eleven regions in Xuzhou city. In the first stage, 5 subdistricts/townships in urban/rural areas were selected from each region. In the second stage, 5 communities/ villages were selected from each subdistricts/townships. In the final stage, one person who was at least 18 years old and lived in the current residence for at least 5 years was selected from each household using a Kish selection table. A total of 16500 people were selected assuming an estimation prevalence of diabetes of 5.5% with 90% power and α=0.05 and allowing for a drop-out of 10%. All volunteers received a health check and completed a structured questionnaire covering demographic information, medical history, medication history, sleep assessment, and smoking, alcohol drinking and exercise habits. All volunteers underwent 12-h overnight fasting and blood sampling for basic fasting plasma glucose (FPG). After blood sampling, each volunteer completed the Pittsburgh Sleep Quality Index (PSQI).[10] We excluded volunteers who were pregnant, had received antihypertensive medication, or were suffering from any cardiovascular disease, stroke, neuropathy, psychosis, depression, chronic obstructive pulmonary disease, obstructive sleep apnea, diabetes, ache, or any other disease. Those who had missing information on sleep duration or sleep quality were also excluded. Trained physicians and public health workers conducted face-to-face interviews using a standardized questionnaire to collect socio-demographic, lifestyle and health-related information.

The study protocol was approved by the Xuzhou Center for Disease Control and Prevention. All participants provided written informed consent.

Key measurements

The FPG was determined by morning blood samples obtained by venipuncture after an overnight fast of at least 12h, and extracted plasma was stored at −70°C for later glucose determination by the hexokinase method. According to the current WHO definition of IFG[11].

The PSQI is a validated self-rated questionnaire that assesses sleep quality over a one-month time interval.[10] Nineteen items generate seven component scores that reflect sleep problems in the areas of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction. The sum of the scores for these seven components produces a global sleep quality score within a range of 0−21 points. A global PSQI score >5 has a diagnostic sensitivity of 89.6% and specificity of 86.5% in differentiating poor from good sleepers. The Chinese version of the PSQI, used with

permission from the original PSQI authors, has an overall reliability coefficient of 0.82−0.83 and acceptable test–retest reliability, with a coefficient of 0.77−0.85.[12] Accordingly, in this study design, a PSQI score ≤5 was also conventionally defined as 'good sleep quality', , and a PSQI score ＞ 5 was defined as 'poor sleep quality'

Self-reported sleep measures of chronic sleep. Two variables were used to evaluate degree of "chronic sleep restriction" by estimating average nightly sleep duration: (i) "usual sleep" (from questionnaires) and (ii) "average nightly sleep" (from sleep diaries).Sleep quantity was categorized as <6, 6−8, and >8 h per night accordance with our previous study.[3,7,8]

Covariates

Age, gender, current employment status, level of education, cigarette smoking, alcohol intake, physical activity, family history of diseases including diabetes, hypertension, heart disease, and cancer were assessed using a standardized questionnaire. Employment status was categorized as manual, non-manual, unemployed, and retired. Education was categorized into below high school, high school, or above high school education. Lifestyle variables included cigarette smoking, alcohol drinking and physical activity level. Cigarette smoking was defined as having smoked at least 100 cigarettes in a lifetime. Information was obtained on the amount and type of alcohol that was consumed during the previous year, and alcohol drinking was defined as the consumption of at least 30 g of alcohol per week for one year or more. Regular leisure-time physical activity was defined as participating in moderate or vigorous activity for no less than 30 minutes per day at least three days a week. Each volunteer's body height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were measured. Body mass index (BMI; in kg/m^2) was calculated. BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5−24.0 kg/m^2) and overweight/obese (>24.0 kg/m^2).[13]

Statistical analysis

Statistical analysis was performed on a computer, using the statistical analysis program SPSS 13.0 (SPSS, Chicago, IL, USA). Mean differences of continuous variables between groups were tested using analysis of variance (ANOVA). The chi-squared test was used to calculate the difference in proportions between groups. Logistic regression analysis was performed to estimate the probability of having IFG and 95% CI for each risk factor category stratified by sleep quality and sleep duration, adjusting for age, residential areas, occupation, education and income levels, leisure-time physical activity, smoking status, drinking status and hypertension status. The observed prevalences of IFG were plotted and stratified by sleep quality and sleep duration.

Biological interactions should be based on the sum of the scale rather than multiplying the scale.[14,15] Therefore, we used three measures to estimate biological interactions of poor

sleep quality and short sleep duration: relative excess risk owing to interaction (RERI), the attributable proportion (AP) owing to interaction, and the synergy index (S). The RERI is the excess risk attributed to interaction relative to the risk without exposure to poor sleep quality and short sleep duration. AP refers to the attributable proportion of disease caused by interaction in subjects with exposure to both variables. S is the excess risk from exposure to both variables when there is a biological interaction relative to the risk from exposure to both variables without interaction. In the absence of additive interactions, RERI and AP are equal to 0.[16] In the current study, RERI > 0, AP > 0 and S > 0 indicate statistical significance. A p value < 0.05 (two-tailed) was considered statistically significant.

Results

General characteristics of participants

The response rate was 91.3%. Of the16584 initial participants, 125 did not respond to the sleep items or blood glucose, 1314 did not meet our study criteria, 15,145 adults (7557 men and 7588 women) with complete data were included in our analysis. The average sleep duration per night was 7.16 ±1.06h. The average age was 47.6 ± 15.1 years. Among them, 634 had IFG; the remainder had normal glucose tolerance (NGT). The characteristics of the study population are presented in Table 1. The proportion of volunteers with poor sleep quality was 26.0%, the proportion with sleep duration <6 h was 12.5%, the proportion with sleep duration >8 h was 12.3%. The 6.7% prevalence of IFG in volunteers with poor sleep quality was higher than that in volunteers with good sleep quality ($\chi^2 = 85.98$, $p < 0.001$). Individuals with sleep duration <6 h had a higher IFG prevalence compared with individuals with sleep duration 6−8 h, (7.3 *vs* 3.3%; $\chi^2 = 72.20$, $p < 0.001$). Individuals with sleep duration >8 h also had also had higher prevalence of IFG (6.2 *vs* 3.3%; $\chi^2 = 37.78$, $p < 0.001$).

Comparison of PSQI scores between the volunteers with IFG and NGT

Volunteers with IFG had significantly higher global PSQI scores than those with NGT. For all PSQI items except sleep duration, there were significant differences ($p < 0.05$) in PSQI scores between the two groups (Table 2) even after adjusted age.

The association of sleep time and quality with IFG

Individuals with short sleep duration or long sleep duration had significantly increased risk of IFG compared with those with good sleep quality and sleep duration 6−8 h (OR:2.16 ; 95% CI: 1.33−3.47； OR: 1.89; 95% CI: 1.50−2.34; respectively. all $P<0.001$), after adjusting for confounders (See table 3). Individuals with poor sleep quality had significantly increased risk of IFG compared with those with good sleep quality (OR:1.98; 95% CI: 1.69−2.21; $P<0.001$), after adjusting for confounders (See table 3).

Biological interaction of sleep quality and sleep duration on the prevalence of IFG

We used a combined effects method to assess interaction, with the *p* value of the interaction term indicating statistical significance of addictive interactions. Individuals with poor sleep quality or short sleep duration had significantly increased risk of IFG compared with those with good sleep quality and sleep duration 6−8 h (OR: 2.48; 95% CI: 2.12−3.03； OR: 2.79; 95% CI: 2.19−3.58; respectively. all *P*<0.001), after adjusting for confounders. Table 4 shows the results from the multiple logistic regression models. The prevalence of IFG was greatest in those with poor sleep quality and short sleep duration (OR: 6.37; 95% CI: 4.66−8.67; $p <$ 0.001), after adjusting for confounders. In addition, individuals with long sleep duration had a significantly increased risk of IFG compared with those who had good sleep quality and sleep duration of 6−8 h (OR: 2.37; 95% CI: 1.89−2.96; $p < 0.001$), after adjusting for confounders. The prevalence of IFG was also greater in those with good sleep quality with long sleep duration (OR: 3.17; 95% CI: 2.29−4.41; $p < 0.001$), compared with those with 6−8 h sleep duration, after adjusting for confounders.

Sensitivity analysis

There was a strong additive interaction between poor sleep quality and short sleep duration (RERI: 1.69; 95% CI: 0.31–3.76.), with 42% of occurring IFG attributed to the interaction between poor sleep quality and short sleep duration (Table 5). There was also interaction between good sleep quality and long sleep duration (RERI: 0.78; 95% CI: 0.12–1.43), with 61% of occurring IFG attributed to the interaction between good sleep quality and long sleep duration (Table 5).

Discussion

The two main findings of this study were, firstly, that there is combined interaction of poor sleep quality and short sleep duration on the prevalence of IFG. Secondly, that total PSQI scores of volunteers with IFG were higher than those of volunteers with NGT. We also found that poor sleep quality and short or long sleep duration increased risk for IFG in a Chinese population, independent of potential confounders such as age, obesity, family history of diabetes, alcohol consumption, smoking, physical activity, and other diseases.

Numerous epidemiologic studies have demonstrated associations between short or long sleep duration and sleep disturbances and diabetes.[17-23]. However, few articles focused on IFG, and the results of these are inconsistent. [5, 24] Rafalson et al.[5] reported the OR of IFG among short sleepers was 3.0 (95% CI: 1.05–8.59) compared with mid-range sleepers with multivariate conditional logistic regression after adjustment for several diabetes risk factors. Hung et al.[24] reported no association between IFG and poor sleepers. Our findings are consistent with the report by Rafalson et al.

The global PSQI scores in volunteers with IFG were higher than those in volunteers with

NGT, which was consistent with the Hung et al. report.[24] However, there was no difference in sleep duration scores between the volunteers with IFG and the volunteers with NGT. This could be attributed to the fact that 18.3% (116/634) of the volunteers with IFG were long sleepers, while short sleepers with IFG only accounted for 22.9% (145/634).

Short sleep duration increases appetite. After four nights of 4.5 h in bed, compared with after four nights of 8.5 h in bed, caloric intake, especially of carbohydrate-rich nutrients, increased by 14% in young normal-weight men and women.[25, 26] Middle-aged obese volunteers submitted to four to five nights of restriction of their habitual sleep schedule by 2–3 h/night ate 15% more calories than those whose habitual sleep schedule was extended by the same amount.[27] In volunteers with sleep debt, glucose tolerance, glucose effectiveness and insulin sensitivity are decreased, and beta-cell function is reduced.[6,26,28,29] Sleep loss also results in decreased anorexigenic leptin levels,[30-32] especially in volunteers with chronic sleep restriction.[33] Observational epidemiologic studies have also shown reduced leptin levels, after controlling for BMI or adiposity, in habitual short sleepers.[33, 34] Conversely, leptin deficiency disrupts sleep architecture and impairs sleep consolidation.[35] Taken together, these data suggest that sleep loss is likely to have a profound impact on IFG.

Poor sleep quality, independent of sleep duration, impairs glucose regulation in healthy young adults.[36, 37] After three nights of slow-wave sleep suppression, insulin sensitivity is decreased by ~25%, reaching the level reported in older adults and in populations at high risk of diabetes.[38] The decrease in insulin sensitivity is not compensated for by an increase in insulin release. Consequently, the disposition index is ~20% lower. Consistent with an increased diabetes risk, glucose tolerance is reduced by ~23% reaching the range typical of older adults with impaired glucose tolerance.[37] Sleep fragmentation also increases sympathetic activity, which in turn leads to disorders of glucose metabolism.[39]

Taken together, short sleep duration, increased caloric intake, poor sleep quality, decreased leptin levels, decreased insulin sensitivity and increased sympathetic activity affect each other, creating a vicious circle, which elevates the risk of IFG.

Despite the absence of the synergistic effect of good-quality sleep with long sleep duration, a strong association of IFG with long sleep duration in individuals was observed, suggesting an independent effect of long sleep duration.

This study had several potential limitations. Firstly, because of the cross-sectional design, we could not determine a causal relationship between sleep quality, sleep duration and IFG. Secondly, we were not able to control for some important and well-known risk factors of diabetes, for example, snoring.[40]. Thirdly, we did not measure poor diet, which is causally related to type 2 diabetes and may also influence sleep patterns.[41,42]

There are several notable strengths of this study. Participants were randomly selected from the general population of Xuzhou. In addition, the sample was large. Many confounding risk factors were adjusted for.

In summary, volunteers who experience short sleep durations are six times more likely to develop IFG than those whose average sleep was 6−8 h a night with good sleep quality. The joint effect of short sleep duration and poor sleep quality was positive.

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Conflict of Interest Statement

None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. The researchers were independent from funders. The study funders had no influence on the study design, data collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Contributors Steering Committee: PL (principal investigator), PC (principal investigator), PC and LZ. Operating Committee: LZ,PZ, GC, NZ, TL and CQ.

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Table 1 Baseline characteristics of the study population (N = 15,145)

Reported variable	*All*	*IFG*		
		No	Yes	*P*
	15145	14,511(95.81%)	634(4.19%)	
Age(years)	47.6±15.1	47.4±14.7	52.2±16.2	8.012
≥45 years	8362	7928(94.81%)	434(5.19%)	0.000
Sex(% man)	49.9	50.0	49.8	0.938
Rural (%)	72.4	72.4	72.9	0.795
Manual	10833	10359(95.62%)	474(4.38%)	0.023
Non-manual	1045	1016(97.22%)	29(2.78%)	
Unemployed	677	658(97.19%)	19(2.81%)	
retired	2590	2478(95.68%)	112(4.32%)	
Marred (living with partners)(%)	88.5	88.6	86.3	0.073
Below high school	11899	11400(95.81%)	499(4.19%)	0.986
high school	1760	1686(95.80%)	74(4.20%)	
Above high school	1486	1425(95.90%)	61(4.10%)	
smoker	3541	3367(95.09%)	174(4.91%)	0.014
alcohol use	2872	2752(95.82%)	120(4.18%)	0.981
Regular exercise	2559	2452(95.82%)	107(4.18%)	0.989
Family history of diabetes	483	362(74.95%)	121(25.05%)	0.000
BMI, mean(SD)	23.9±4.7	23.8±5.8	25.2±4.1	＜0.001
Central obesity	4613	4219(91.46%)	394(8.54%)	0.000
Hypertension	3060	2901(94.80%)	159(5.20%)	0.002
Sleep duration(hour)				
≤6	1984	1839(92.70%)	145(7.30%)	0.000
6-8	11292	10919(96.70%)	373(3.30%)	
≥8	1869	1753(93.80%)	116(6.20%)	
Sleep quality				
Good	11209	10840(96.71%)	369(3.29%)	0.000
Poor	3936	3671(93.27%)	265(6.73%)	

Table 2 Comparison of Pittsburgh Sleep Quality Index scores between individuals with impaired fasting glucose and controls ($\bar{x} \pm sd$)

Items	*IFG*		*F value*	*P*
	No	Yes		
Subjective sleep quality	0.415±0.013	0.463±0. 03	31.823	0.000
Sleep latency	0.742±0.004	0.800±0.016	27.446	0.000
Sleep duration	0.152±0.002	0.159±0.001	0.503	0.478
Sleep efficiency	0.444±0.003	0. 321±0.001	29.452	0.000
Sleep disturbance	0.591±0. 003	0.658±0.012	28.259	0.000
Use of hypnotic	0.051±0.002	0.065±0.007	16.651	0.000
Daytime dysfunction	0.147±0.011	0.170±0.002	9.725	0.000
Global PSQI scores	2.302±0.009	2.495±0. 041	20.957	0.000

Using analysis of covariance, Covariates for age =47.26 years old

Table 3 Odds ratios for the association between sleep quality, sleep duration and impaired fasting glucose among participants

Variables		IFG	No IFG	OR (95%CI)	P
Sleep quality	Good	369	10840	1	
	Poor	265	3671	1.21(1.09-1.34）	0.000
Sleep duration	6-8h	373	10919	1	
	＜6h	145	1839	2.16 (1.33-3.47)	0.000
	＞8h	116	1753	1.89 (1.50-2.34)	0.000

Adjusted for age, sex, education, employment, BMI, family history of diabetes, smoking status, alcohol consumption and physical activity.

Table 4 Odds ratios for the association between sleep quality and impaired fasting glucose by sleep duration among participants

Sleep duration	*Sleep quality*	*IFG*	*No IFG*	*OR (95%CI)*	*P*
6-8h	Good	246	8743	1	
	Poor	127	2176	1.98（1.76-2.52）	<0.001
＜6h	Good	53	1329	1.38（1.12-1.61）	<0.001
	Poor	92	510	6.37（4.66-8.67）	<0.001
＞8h	Good	70	768	3.17 （2.29-4.41）	<0.001
	Poor	46	985	1.59（1.08-2.29）	<0.001

Adjusted for age, sex, education, employment, BMI, family history of diabetes, smoking status, alcohol consumption and physical activity.

Table 5 Measures for estimation of the biological interaction between sleep quality and sleep duration for the prevalence of impaired fasting glucose in participants

Measures of biological interaction	Estimate (95% CI)
Poor sleep quality versus sleep duration ＜6h	
RERI	1.69(0.31－3.76)
AP	0.42(0.15－0.61)
S	2.85(2.14－3.92)
Good sleep quality versus sleep duration ＞ 8h	
RERI	0.78(0.12－1.43)
AP	0.61(0.26－0.87)
S	-0.65(-0.94－-0.27)

Reference group is good sleep quality with 6-8 sleep duration.

Adjusted for age, sex, education, occupation, BMI, family history of diabetes, smoking status, alcohol consumption, and hypertension.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page3
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 3
Methods			
Study design	4	Present key elements of study design early in the paper	Page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 3-4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Page 4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 4-5
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 5
		(*b*) Describe any methods used to examine subgroups and interactions	Page 5
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Page 5
		(*e*) Describe any sensitivity analyses	Page 5

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 6
		(b) Give reasons for non-participation at each stage	Page 6
		(c) Consider use of a flow diagram	Figur1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table1
		(b) Indicate number of participants with missing data for each variable of interest	Table2
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Page6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Page6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table3-5
		(*b*) Report category boundaries when continuous variables were categorized	Page7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page10
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Interaction of sleep quality and sleep duration on impaired fasting glucose: A population-based cross-sectional survey in China

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Interaction of sleep quality and sleep duration on impaired fasting glucose: A population-based cross-sectional survey in China

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Key words: Interaction; Sleep quality; Sleep duration; Impaired fasting glucose

Word count: 2543

Abstract

Objectives: To explore the interactions of sleep quality and sleep duration and their effects on impaired fasting glucose in Chinese adults.

Design: Cross-sectional survey.

Setting: Community-based investigation in Xuzhou, China.

Participants: 15,145 Chinese men and women aged 18−75 years old who fulfilled the inclusion criteria.

Primary and secondary outcome measures: The Pittsburgh Sleep Quality Index was used to produce sleep quality categories of good, common and poor. Fasting blood glucose levels were assessed for impaired fasting glucose. Sleep duration was measured by average hours of sleep per night, with categories of <6 h, 6−8 h, and >8 h. The products of sleep and family history of diabetes, obesity and age were added to the logistic regression model to evaluate the addictive interaction and relative excess risk of interaction (RERI) on impaired fasting glucose. The attributable proportion (AP) of the interaction and the synergy index (S) were applied to evaluate the additive interaction of two factors. Bootstrap measures were used to calculate 95% confidence intervals (CI) of RERI, AP and S.

Results: The prevalence of IFG was greatest in those with poor sleep quality and short sleep duration (OR: 6.37; 95% CI: 4.66−8.67; $p < 0.001$) compared with those who had good sleep quality and 6−8 h sleep duration, after adjusting for confounders. After adjusting for potential confounders, RERI, AP and S values (and their 95% CI) were 1.69 (0.31−3.76), 0.42 (0.15−0.61) and 2.85 (2.14−3.92) for the interaction between poor sleep quality and short sleep duration, and 0.78 (0.12−1.43), 0.61 (0.26−0.87) and −65 (−0.94 to −0.27) for the interaction between good sleep quality and long sleep duration.

Conclusions: The results suggest that there are additive interactions between poor sleep quality and short sleep duration.

ARTICLE SUMMARY

Article focus

- To describe the combined effects of sleep duration and sleep quality for impaired fasting glucose in people in Xuzhou, China.

Key messages

- There exist additive interactions between sleep quality and sleep duration on impaired fasting glucose.
- A strength of the study is the large sample.
- Limitations of the study the cross-sectional design.

Introduction

Prediabetes has a prevalence of 15.5% and affects an estimated 148.2 million Chinese adults.[1] Prediabetes, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is the most important risk factor for type 2 diabetes. The average annual incidence of diabetes in a cohort of patients with IFG is 11% over a six-year period without intervention.[2] Older age, a family history of diabetes, being overweight, obesity, central obesity, increased heart rate, elevated systolic blood pressure, elevated serum triglyceride levels, high income, history of hypertension, history of coronary heart disease, history of drinking, eating pickled foods, and low educational level are significantly associated with an increased risk of prediabetes.[1,3] Increasingly, studies have shown that prediabetes is associated with poor sleep quantity and quality.[3,4] A cross-sectional study has suggested that, compared with those sleeping 7−8 h per night, individuals aged <60 years who slept 5 h or less had an increased odds ratio (OR) for IGT (OR: 1.37, 95% confidence interval [CI]: 1.13−1.67).[4] The Western New York Health Study including 1455 participants showed that sleep duration of less than 6 h was associated with increased prevalence of IFG, compared with those sleeping 6−8 h per night, after adjustment for confounders, over six years of follow up.[5] Spiegel et al. have demonstrated that experimental restriction of sleep to <4 h per night for six nights resulted in an impaired glucose tolerance (IGT) in young healthy adults.[6]

Our previous results suggest that poor quality of sleep and sleep duration <6 h per night are independent risk factors for type 2 diabetes, even after adjusting for a large number of possible confounders.[7,8] Our previous study also confirmed that relatively healthy individuals with poor sleep quality and sleeping times of 6 h or less had a higher risk of IFG, even after adjusting for a large number of confounding factors.[3]

Although these risk factors play a role in the development of type 2 diabetes, the disease is the result of the interaction of genetic and environmental factors. There is little understanding of multivariate explanations of IFG in relatively healthy individuals. To our knowledge, there are no studies on the interaction of sleep quality and sleep duration on IFG in relatively healthy individuals. The primary aim of this cross-sectional study was to examine the combined effects of sleep quality and sleep duration on IFG in relatively healthy individuals in a Chinese primary-care setting. A secondary aim was to assess the associations of sleep quality and IFG, and of sleep duration and IFG.

Methods

The study was a continuation of our previous work.[9] The investigation was conducted from March to November 2012 with a sample size of 15,145 volunteers (7557 men and 7588 women) aged 18 to 75 years. Briefly, the sampling was selected with probability proportional

to size from all of the eleven regions in Xuzhou city. In the first stage, 5 subdistricts/townships in urban/rural areas were selected from each region. In the second stage, 5 communities/ villages were selected from each subdistricts/townships. In the final stage, one person who was at least 18 years old and lived in the current residence for at least 5 years was selected from each household using a Kish selection table. A total of 16500 people were selected assuming an estimation prevalence of diabetes of 5.5% with 90% power and α=0.05 and allowing for a drop-out of 10%. All volunteers received a health check and completed a structured questionnaire covering demographic information, medical history, medication history, sleep assessment, and smoking, alcohol drinking and exercise habits. All volunteers underwent 12-h overnight fasting and blood sampling for basic fasting plasma glucose (FPG). After blood sampling, each volunteer completed the Pittsburgh Sleep Quality Index (PSQI).[10] We excluded volunteers who were pregnant, had received antihypertensive medication, or were suffering from any cardiovascular disease, stroke, neuropathy, psychosis, depression, chronic obstructive pulmonary disease, obstructive sleep apnea, diabetes, ache, or any other disease. Those who had missing information on sleep duration or sleep quality were also excluded. Trained physicians and public health workers conducted face-to-face interviews using a standardized questionnaire to collect socio-demographic, lifestyle and health-related information.

The study protocol was approved by the Xuzhou Center for Disease Control and Prevention. All participants provided written informed consent.

Key measurements

The FPG was determined by morning blood samples obtained by venipuncture after an overnight fast of at least 12h, and extracted plasma was stored at −70°C for later glucose determination by the hexokinase method. According to the current WHO definition of IFG[11].

The PSQI is a validated self-rated questionnaire that assesses sleep quality over a one-month time interval.[10] Nineteen items generate seven component scores that reflect sleep problems in the areas of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction. The sum of the scores for these seven components produces a global sleep quality score within a range of 0−21 points. A global PSQI score >5 has a diagnostic sensitivity of 89.6% and specificity of 86.5% in differentiating poor from good sleepers. The Chinese version of the PSQI, used with

permission from the original PSQI authors, has an overall reliability coefficient of 0.82−0.83 and acceptable test–retest reliability, with a coefficient of 0.77−0.85.[12] Accordingly, in this study design, a PSQI score ≤5 was also conventionally defined as 'good sleep quality', and a PSQI score ＞ 5 was defined as 'poor sleep quality'

Self-reported sleep measures of chronic sleep. Two variables were used to evaluate degree of "chronic sleep restriction" by estimating average nightly sleep duration: (i) "usual sleep" (from questionnaires) and (ii) "average nightly sleep" (from sleep diaries).Sleep quantity was categorized as <6, 6−8, and >8 h per night accordance with our previous study.[3,7,8]

Covariates

Age, gender, current employment status, level of education, cigarette smoking, alcohol intake, physical activity, family history of diseases including diabetes, hypertension, heart disease, and cancer were assessed using a standardized questionnaire. Employment status was categorized as manual, non-manual, unemployed, and retired. Education was categorized into below high school, high school, or above high school education. Lifestyle variables included cigarette smoking, alcohol drinking and physical activity level. Cigarette smoking was defined as having smoked at least 100 cigarettes in a lifetime. Information was obtained on the amount and type of alcohol that was consumed during the previous year, and alcohol drinking was defined as the consumption of at least 30 g of alcohol per week for one year or more. Regular leisure-time physical activity was defined as participating in moderate or vigorous activity for no less than 30 minutes per day at least three days a week. Each volunteer's body height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were measured. Body mass index (BMI; in kg/m^2) was calculated. BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5−24.0 kg/m^2) and overweight/obese (>24.0 kg/m^2).[13]

Statistical analysis

Statistical analysis was performed on a computer, using the statistical analysis program SPSS 13.0 (SPSS, Chicago, IL, USA). Mean differences of continuous variables between groups were tested using analysis of variance (ANOVA). The chi-squared test was used to calculate the difference in proportions between groups. Logistic regression analysis was performed to estimate the probability of having IFG and 95% CI for each risk factor category stratified by sleep quality and sleep duration, adjusting for age, residential areas, occupation, education and income levels, leisure-time physical activity, smoking status, drinking status and hypertension status. The observed prevalences of IFG were plotted and stratified by sleep quality and sleep duration.

Biological interactions should be based on the sum of the scale rather than multiplying the scale.[14,15] Therefore, we used three measures to estimate biological interactions of poor

sleep quality and short sleep duration: relative excess risk owing to interaction (RERI), the attributable proportion (AP) owing to interaction, and the synergy index (S). The RERI is the excess risk attributed to interaction relative to the risk without exposure to poor sleep quality and short sleep duration. AP refers to the attributable proportion of disease caused by interaction in subjects with exposure to both variables. S is the excess risk from exposure to both variables when there is a biological interaction relative to the risk from exposure to both variables without interaction. In the absence of additive interactions, RERI and AP are equal to 0.[16] In the current study, RERI > 0, AP > 0 and S > 0 indicate statistical significance. A p value < 0.05 (two-tailed) was considered statistically significant.

Results

General characteristics of participants

The response rate was 91.3%. Of the16584 initial participants, 125 did not respond to the sleep items or blood glucose, 1314 did not meet our study criteria, 15,145 adults (7557 men and 7588 women) with complete data were included in our analysis. The average sleep duration per night was 7.16 ±1.06h. The average age was 47.6 ± 15.1 years. Among them, 634 had IFG; the remainder had normal glucose tolerance (NGT). The characteristics of the study population are presented in Table 1. The characteristics between individuals with poor sleep quality and sleep duration ＜6h and controls are presented in Table 2. The proportion of volunteers with poor sleep quality was 26.0%, the proportion with sleep duration <6 h was 12.5%, the proportion with sleep duration >8 h was 12.3%. The 6.7% prevalence of IFG in volunteers with poor sleep quality was higher than that in volunteers with good sleep quality (χ^2 = 85.98, p < 0.001). Individuals with sleep duration <6 h had a higher IFG prevalence compared with individuals with sleep duration 6−8 h, (7.3 *vs* 3.3%; χ^2 = 72.20, p < 0.001). Individuals with sleep duration >8 h also had also had higher prevalence of IFG (6.2 *vs* 3.3%; χ^2= 37.78, p < 0.001).

Comparison of PSQI scores between the volunteers with IFG and NGT

Volunteers with IFG had significantly higher global PSQI scores than those with NGT. For all PSQI items except sleep duration, there were significant differences (p < 0.05) in PSQI scores between the two groups (Table 3) even after adjusted age.

The association of sleep time and quality with IFG

Individuals with short sleep duration or long sleep duration had significantly increased risk of IFG compared with those with good sleep quality and sleep duration 6−8 h (OR:2.16 ; 95% CI: 1.33−3.47； OR: 1.89; 95% CI: 1.50−2.34; respectively. all P<0.001), after adjusting for confounders (See table 3). Individuals with poor sleep quality had significantly increased risk of IFG compared with those with good sleep quality (OR:1.98; 95% CI: 1.69−2.21; P<0.001),

after adjusting for confounders (See table 4).

Biological interaction of sleep quality and sleep duration on the prevalence of IFG

We used a combined effects method to assess interaction, with the *p* value of the interaction term indicating statistical significance of addictive interactions. Individuals with poor sleep quality or short sleep duration had significantly increased risk of IFG compared with those with good sleep quality and sleep duration 6−8 h (OR: 2.48; 95% CI: 2.12−3.03； OR: 2.79; 95% CI: 2.19−3.58; respectively. all $P<0.001$), after adjusting for confounders. Table 5 shows the results from the multiple logistic regression models. The prevalence of IFG was greatest in those with poor sleep quality and short sleep duration (OR: 6.37; 95% CI: 4.66−8.67; $p < 0.001$), after adjusting for confounders. In addition, individuals with long sleep duration had a significantly increased risk of IFG compared with those who had good sleep quality and sleep duration of 6−8 h (OR: 2.37; 95% CI: 1.89−2.96; $p < 0.001$), after adjusting for confounders. The prevalence of IFG was also greater in those with good sleep quality with long sleep duration (OR: 3.17; 95% CI: 2.29−4.41; $p < 0.001$), compared with those with 6−8 h sleep duration, after adjusting for confounders.

Sensitivity analysis

There was a strong additive interaction between poor sleep quality and short sleep duration (RERI: 1.69; 95% CI: 0.31–3.76.), with 42% of occurring IFG attributed to the interaction between poor sleep quality and short sleep duration (Table 5). There was also interaction between good sleep quality and long sleep duration (RERI: 0.78; 95% CI: 0.12–1.43), with 61% of occurring IFG attributed to the interaction between good sleep quality and long sleep duration (Table 6).

Discussion

The two main findings of this study were, firstly, that there is combined interaction of poor sleep quality and short sleep duration on the prevalence of IFG. Secondly, that total PSQI scores of volunteers with IFG were higher than those of volunteers with NGT. We also found that poor sleep quality and short or long sleep duration increased risk for IFG in a Chinese population, independent of potential confounders such as age, obesity, family history of diabetes, alcohol consumption, smoking, physical activity, and other diseases.

Numerous epidemiologic studies have demonstrated associations between short or long sleep duration and sleep disturbances and diabetes.[17-23]. However, few articles focused on IFG, and the results of these are inconsistent. [5, 24] Rafalson et al.[5] reported the OR of IFG among short sleepers was 3.0 (95% CI: 1.05–8.59) compared with mid-range sleepers with multivariate conditional logistic regression after adjustment for several diabetes risk factors. Hung et al.[24] reported no association between IFG and poor sleepers. Our findings are

consistent with the report by Rafalson et al.

The global PSQI scores in volunteers with IFG were higher than those in volunteers with NGT, which was consistent with the Hung et al. report.[24] However, there was no difference in sleep duration scores between the volunteers with IFG and the volunteers with NGT. This could be attributed to the fact that 18.3% (116/634) of the volunteers with IFG were long sleepers, while short sleepers with IFG only accounted for 22.9% (145/634).

Short sleep duration increases appetite. After four nights of 4.5 h in bed, compared with after four nights of 8.5 h in bed, caloric intake, especially of carbohydrate-rich nutrients, increased by 14% in young normal-weight men and women.[25, 26] Middle-aged obese volunteers submitted to four to five nights of restriction of their habitual sleep schedule by 2–3 h/night ate 15% more calories than those whose habitual sleep schedule was extended by the same amount.[27] In volunteers with sleep debt, glucose tolerance, glucose effectiveness and insulin sensitivity are decreased, and beta-cell function is reduced.[6,26,28,29] Sleep loss also results in decreased anorexigenic leptin levels,[30-32] especially in volunteers with chronic sleep restriction.[33] Observational epidemiologic studies have also shown reduced leptin levels, after controlling for BMI or adiposity, in habitual short sleepers.[33, 34] Conversely, leptin deficiency disrupts sleep architecture and impairs sleep consolidation.[35] Taken together, these data suggest that sleep loss is likely to have a profound impact on IFG.

Poor sleep quality, independent of sleep duration, impairs glucose regulation in healthy young adults.[36, 37] After three nights of slow-wave sleep suppression, insulin sensitivity is decreased by ~25%, reaching the level reported in older adults and in populations at high risk of diabetes.[38] The decrease in insulin sensitivity is not compensated for by an increase in insulin release. Consequently, the disposition index is ~20% lower. Consistent with an increased diabetes risk, glucose tolerance is reduced by ~23% reaching the range typical of older adults with impaired glucose tolerance.[37] Sleep fragmentation also increases sympathetic activity, which in turn leads to disorders of glucose metabolism.[39]

Taken together, short sleep duration, increased caloric intake, poor sleep quality, decreased leptin levels, decreased insulin sensitivity and increased sympathetic activity affect each other, creating a vicious circle, which elevates the risk of IFG.

Despite the absence of the synergistic effect of good-quality sleep with long sleep duration, a strong association of IFG with long sleep duration in individuals was observed, suggesting an independent effect of long sleep duration.

This study had several potential limitations. Firstly, because of the cross-sectional design, we could not determine a causal relationship between sleep quality, sleep duration and IFG. Secondly, we were not able to control for some important and well-known risk factors of diabetes, for example, snoring.[40]. Thirdly, we did not measure poor diet, which is causally related to type 2 diabetes and may also influence sleep patterns.[41,42]

There are several notable strengths of this study. Participants were randomly selected

from the general population of Xuzhou. In addition, the sample was large. Many confounding risk factors were adjusted for.

In summary, volunteers who experience short sleep durations are six times more likely to develop IFG than those whose average sleep was 6−8 h a night with good sleep quality. The joint effect of short sleep duration and poor sleep quality was positive.

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Conflict of Interest Statement

None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. The researchers were independent from funders. The study funders had no influence on the study design, data collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Data Sharing Statement

Our material is original, has not been published except in abstract form, and is not being considered for publication elsewhere, including publicly accessible websites or e-print servers, no part of the research presented has been funded by tobacco industry sources, and all authors have read the manuscript and approve its submission.

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Table 1 Baseline characteristics of the study population (N = 15,145)

Reported variable	*All*	*IFG*		
		No	Yes	*P*
	15145	14,511(95.81%)	634(4.19%)	
Age(years)	47.6±15.1	47.4±14.7	52.2±16.2	8.012
≥45 years	8362	7928(94.81%)	434(5.19%)	0.000
Sex(% man)	49.9	50.0	49.8	0.938
Rural (%)	72.4	72.4	72.9	0.795
Manual	10833	10359(95.62%)	474(4.38%)	0.023
Non-manual	1045	1016(97.22%)	29(2.78%)	
Unemployed	677	658(97.19%)	19(2.81%)	
retired	2590	2478(95.68%)	112(4.32%)	
Marred (living with partners)(%)	88.5	88.6	86.3	0.073
Below high school	11899	11400(95.81%)	499(4.19%)	0.986
high school	1760	1686(95.80%)	74(4.20%)	
Above high school	1486	1425(95.90%)	61(4.10%)	
smoker	3541	3367(95.09%)	174(4.91%)	0.014
alcohol use	2872	2752(95.82%)	120(4.18%)	0.981
Regular exercise	2559	2452(95.82%)	107(4.18%)	0.989
Family history of diabetes	483	362(74.95%)	121(25.05%)	0.000
BMI, mean(SD)	23.9±4.7	23.8±5.8	25.2±4.1	＜0.001
Central obesity	4613	4219(91.46%)	394(8.54%)	0.000
Hypertension	3060	2901(94.80%)	159(5.20%)	0.002
Sleep duration(hour)				
≤6	1984	1839(92.70%)	145(7.30%)	0.000
6-8	11292	10919(96.70%)	373(3.30%)	
≥8	1869	1753(93.80%)	116(6.20%)	
Sleep quality				
Good	11209	10840(96.71%)	369(3.29%)	0.000
Poor	3936	3671(93.27%)	265(6.73%)	

Table 2.Comparison of characteristics between individuals with poor sleep quality and sleep duration ＜6h and controls

Reported variable	*All*	Poor sleep quality with short sleep time(＜6h)		
		Yes	**No**	***P***
	15145	602	14543	
Age(years)	47.6±15.1	47.8±15.5	47.5±15.1	0.63
Sex(man)	7557	299(3.96%)	7258(96.04%)	0.91
Rural	10965	435(3.97%)	10530(96.03%)	0.94
Manual	10833	421(3.89%)	10412(96.11%)	0.38
Non-manual	1045	44(4.21%)	1001(95.79%)	0.69
Unemployed	677	35(5.17%)	642(94.83%)	0.10
retired	2590	102(3.94%)	2488(96.06%)	0.92
Marred (living with partners)(%)	13403	535(3.99%)	12868(96.01%)	0.77
Below high school	11899	470(3.95%)	11429(96.05%)	0.76
high school	1760	70(3.98%)	1690(96.02%)	1
Above high school	1486	62(4.17%)	1424(95.83%)	0.68
smoker	3541	145(4.09%)	3396(95.91%)	0.68
alcohol use	2872	121(4.21%)	2751(98.79%)	0.48
Regular exercise	2559	92(3.60%)	2467(96.40%)	0.28
Family history of diabetes	483	20(4.14%)	463(95.86%)	0.85
BMI, mean(SD)	23.9±4.7	24.0±4.9	23.9±4.6	0.60
Central obesity	4613	186(4.03%)	4427(95.97%)	0.81
Hypertension	3060	131(4.28%)	2929(95.72%)	0.33

Table 3 Comparison of Pittsburgh Sleep Quality Index scores between individuals with impaired fasting glucose and controls ($\bar{x}$ ± sd)

Items	*IFG*		*F value*	*P*
	No	Yes		
Subjective sleep quality	0.415±0.013	0.463±0. 03	31.823	0.000
Sleep latency	0.742±0.004	0.800±0.016	27.446	0.000
Sleep duration	0.152±0.002	0.159±0.001	0.503	0.478
Sleep efficiency	0.444±0.003	0. 321±0.001	29.452	0.000
Sleep disturbance	0.591±0. 003	0.658±0.012	28.259	0.000
Use of hypnotic	0.051±0.002	0.065±0.007	16.651	0.000
Daytime dysfunction	0.147±0.011	0.170±0.002	9.725	0.000
Global PSQI scores	2.302±0.009	2.495±0. 041	20.957	0.000

Using analysis of covariance, Covariates for age =47.6 years old

Table 4 Odds ratios for the association between sleep quality, sleep duration and impaired fasting glucose among participants

Variables		IFG	No IFG	OR (95%CI)	P
Sleep quality	Good	369	10840	1	
	Poor	265	3671	1.21(1.09-1.34）	0.000
Sleep duration	6-8h	373	10919	1	
	＜6h	145	1839	2.16 (1.33-3.47)	0.000
	＞8h	116	1753	1.89 (1.50-2.34)	0.000

Adjusted for age, sex, education, employment, BMI, family history of diabetes, smoking status, alcohol consumption and physical activity.

Table 5 Odds ratios for the association between sleep quality and impaired fasting glucose by sleep duration among participants

Sleep duration	*Sleep quality*	*IFG*	*No IFG*	*OR (95%CI)*	*P*
6-8h	Good	246	8743	1	
	Poor	127	2176	1.98（1.76-2.52）	<0.001
＜6h	Good	53	1329	1.38（1.12-1.61）	<0.001
	Poor	92	510	6.37（4.66-8.67）	<0.001
＞8h	Good	70	768	3.17 （2.29-4.41）	<0.001
	Poor	46	985	1.59（1.08-2.29）	<0.001

Adjusted for age, sex, education, employment, BMI, family history of diabetes, smoking status, alcohol consumption and physical activity.

Table 6 Measures for estimation of the biological interaction between sleep quality and sleep duration for the prevalence of impaired fasting glucose in participants

Measures of biological interaction	Estimate (95% CI)
Poor sleep quality versus sleep duration ＜6h	
RERI	1.69(0.31－3.76)
AP	0.42(0.15－0.61)
S	2.85(2.14－3.92)
Good sleep quality versus sleep duration ＞ 8h	
RERI	0.78(0.12－1.43)
AP	0.61(0.26－0.87)
S	-0.65(-0.94－-0.27)

Reference group is good sleep quality with 6-8 sleep duration.

Adjusted for age, sex, education, occupation, BMI, family history of diabetes, smoking status, alcohol consumption, and hypertension.

Interaction of sleep quality and sleep duration on impaired fasting glucose: A population-based cross-sectional survey in China

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Key words: Interaction; Sleep quality; Sleep duration; Impaired fasting glucose

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Abstract

Objectives: To explore the interactions of sleep quality and sleep duration and their effects on impaired fasting glucose in Chinese adults.

Design: Cross-sectional survey.

Setting: Community-based investigation in Xuzhou, China.

Participants: 15,145 Chinese men and women aged 18−75 years old who fulfilled the inclusion criteria.

Primary and secondary outcome measures: The Pittsburgh Sleep Quality Index was used to produce sleep quality categories of good, common and poor. Fasting blood glucose levels were assessed for impaired fasting glucose. Sleep duration was measured by average hours of sleep per night, with categories of <6 h, 6−8 h, and >8 h. The products of sleep and family history of diabetes, obesity and age were added to the logistic regression model to evaluate the addictive interaction and relative excess risk of interaction (RERI) on impaired fasting glucose. The attributable proportion (AP) of the interaction and the synergy index (S) were applied to evaluate the additive interaction of two factors. Bootstrap measures were used to calculate 95% confidence intervals (CI) of RERI, AP and S.

Results: The prevalence of IFG was greatest in those with poor sleep quality and short sleep duration (OR: 6.37; 95% CI: 4.66−8.67; $p < 0.001$) compared with those who had good sleep quality and 6−8 h sleep duration, after adjusting for confounders. After adjusting for potential confounders, RERI, AP and S values (and their 95% CI) were 1.69 (0.31−3.76), 0.42 (0.15−0.61) and 2.85 (2.14−3.92) for the interaction between poor sleep quality and short sleep duration, and 0.78 (0.12−1.43), 0.61 (0.26−0.87) and −65 (−0.94 to −0.27) for the interaction between good sleep quality and long sleep duration.

Conclusions: The results suggest that there are additive interactions between poor sleep quality and short sleep duration.

ARTICLE SUMMARY

Article focus

- To describe the combined effects of sleep duration and sleep quality for impaired fasting glucose in people in Xuzhou, China.

Key messages

- There exist additive interactions between sleep quality and sleep duration on impaired fasting glucose.
- A strength of the study is the large sample.
- Limitations of the study the cross-sectional design.

Introduction

Prediabetes has a prevalence of 15.5% and affects an estimated 148.2 million Chinese adults.[1] Prediabetes, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is the most important risk factor for type 2 diabetes. The average annual incidence of diabetes in a cohort of patients with IFG is 11% over a six-year period without intervention.[2] Older age, a family history of diabetes, being overweight, obesity, central obesity, increased heart rate, elevated systolic blood pressure, elevated serum triglyceride levels, high income, history of hypertension, history of coronary heart disease, history of drinking, eating pickled foods, and low educational level are significantly associated with an increased risk of prediabetes.[1,3] Increasingly, studies have shown that prediabetes is associated with poor sleep quantity and quality.[3,4] A cross-sectional study has suggested that, compared with those sleeping 7−8 h per night, individuals aged <60 years who slept 5 h or less had an increased odds ratio (OR) for IGT (OR: 1.37, 95% confidence interval [CI]: 1.13−1.67).[4] The Western New York Health Study including 1455 participants showed that sleep duration of less than 6 h was associated with increased prevalence of IFG, compared with those sleeping 6−8 h per night, after adjustment for confounders, over six years of follow up.[5] Spiegel et al. have demonstrated that experimental restriction of sleep to <4 h per night for six nights resulted in an impaired glucose tolerance (IGT) in young healthy adults.[6]

Our previous results suggest that poor quality of sleep and sleep duration <6 h per night are independent risk factors for type 2 diabetes, even after adjusting for a large number of possible confounders.[7,8] Our previous study also confirmed that relatively healthy individuals with poor sleep quality and sleeping times of 6 h or less had a higher risk of IFG, even after adjusting for a large number of confounding factors.[3]

Although these risk factors play a role in the development of type 2 diabetes, the disease is the result of the interaction of genetic and environmental factors. There is little understanding of multivariate explanations of IFG in relatively healthy individuals. To our knowledge, there are no studies on the interaction of sleep quality and sleep duration on IFG in relatively healthy individuals. The primary aim of this cross-sectional study was to examine the combined effects of sleep quality and sleep duration on IFG in relatively healthy individuals in a Chinese primary-care setting. A secondary aim was to assess the associations of sleep quality and IFG, and of sleep duration and IFG.

Methods

The study was a continuation of our previous work.[9] The investigation was conducted from March to November 2012 with a sample size of 15,145 volunteers (7557 men and 7588 women) aged 18 to 75 years. Briefly, the sampling was selected with probability proportional

to size from all of the eleven regions in Xuzhou city. In the first stage, 5 subdistricts/townships in urban/rural areas were selected from each region. In the second stage, 5 communities/ villages were selected from each subdistricts/townships. In the final stage, one person who was at least 18 years old and lived in the current residence for at least 5 years was selected from each household using a Kish selection table. A total of 16500 people were selected assuming an estimation prevalence of diabetes of 5.5% with 90% power and α=0.05 and allowing for a drop-out of 10%. All volunteers received a health check and completed a structured questionnaire covering demographic information, medical history, medication history, sleep assessment, and smoking, alcohol drinking and exercise habits. All volunteers underwent 12-h overnight fasting and blood sampling for basic fasting plasma glucose (FPG). After blood sampling, each volunteer completed the Pittsburgh Sleep Quality Index (PSQI).[10] We excluded volunteers who were pregnant, had received antihypertensive medication, or were suffering from any cardiovascular disease, stroke, neuropathy, psychosis, depression, chronic obstructive pulmonary disease, obstructive sleep apnea, diabetes, ache, or any other disease. Those who had missing information on sleep duration or sleep quality were also excluded. Trained physicians and public health workers conducted face-to-face interviews using a standardized questionnaire to collect socio-demographic, lifestyle and health-related information.

The study protocol was approved by the Xuzhou Center for Disease Control and Prevention. All participants provided written informed consent.

Key measurements

The FPG was determined by morning blood samples obtained by venipuncture after an overnight fast of at least 12h, and extracted plasma was stored at −70°C for later glucose determination by the hexokinase method. According to the current WHO definition of IFG[11].

The PSQI is a validated self-rated questionnaire that assesses sleep quality over a one-month time interval.[10] Nineteen items generate seven component scores that reflect sleep problems in the areas of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction. The sum of the scores for these seven components produces a global sleep quality score within a range of 0−21 points. A global PSQI score >5 has a diagnostic sensitivity of 89.6% and specificity of 86.5% in differentiating poor from good sleepers. The Chinese version of the PSQI, used with

permission from the original PSQI authors, has an overall reliability coefficient of 0.82−0.83 and acceptable test–retest reliability, with a coefficient of 0.77−0.85.[12] Accordingly, in this study design, a PSQI score ≤5 was also conventionally defined as 'good sleep quality', and a PSQI score ＞ 5 was defined as 'poor sleep quality'

Self-reported sleep measures of chronic sleep. Two variables were used to evaluate degree of "chronic sleep restriction" by estimating average nightly sleep duration: (i) "usual sleep" (from questionnaires) and (ii) "average nightly sleep" (from sleep diaries).Sleep quantity was categorized as <6, 6−8, and >8 h per night accordance with our previous study.[3,7,8]

Covariates

Age, gender, current employment status, level of education, cigarette smoking, alcohol intake, physical activity, family history of diseases including diabetes, hypertension, heart disease, and cancer were assessed using a standardized questionnaire. Employment status was categorized as manual, non-manual, unemployed, and retired. Education was categorized into below high school, high school, or above high school education. Lifestyle variables included cigarette smoking, alcohol drinking and physical activity level. Cigarette smoking was defined as having smoked at least 100 cigarettes in a lifetime. Information was obtained on the amount and type of alcohol that was consumed during the previous year, and alcohol drinking was defined as the consumption of at least 30 g of alcohol per week for one year or more. Regular leisure-time physical activity was defined as participating in moderate or vigorous activity for no less than 30 minutes per day at least three days a week. Each volunteer's body height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were measured. Body mass index (BMI; in kg/m^2) was calculated. BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5−24.0 kg/m^2) and overweight/obese (>24.0 kg/m^2).[13]

Statistical analysis

Statistical analysis was performed on a computer, using the statistical analysis program SPSS 13.0 (SPSS, Chicago, IL, USA). Mean differences of continuous variables between groups were tested using analysis of variance (ANOVA). The chi-squared test was used to calculate the difference in proportions between groups. Logistic regression analysis was performed to estimate the probability of having IFG and 95% CI for each risk factor category stratified by sleep quality and sleep duration, adjusting for age, residential areas, occupation, education and income levels, leisure-time physical activity, smoking status, drinking status and hypertension status. The observed prevalences of IFG were plotted and stratified by sleep quality and sleep duration.

Biological interactions should be based on the sum of the scale rather than multiplying the scale.[14,15] Therefore, we used three measures to estimate biological interactions of poor

sleep quality and short sleep duration: relative excess risk owing to interaction (RERI), the attributable proportion (AP) owing to interaction, and the synergy index (S). The RERI is the excess risk attributed to interaction relative to the risk without exposure to poor sleep quality and short sleep duration. AP refers to the attributable proportion of disease caused by interaction in subjects with exposure to both variables. S is the excess risk from exposure to both variables when there is a biological interaction relative to the risk from exposure to both variables without interaction. In the absence of additive interactions, RERI and AP are equal to 0.[16] In the current study, RERI > 0, AP > 0 and S > 0 indicate statistical significance. A p value < 0.05 (two-tailed) was considered statistically significant.

Results

General characteristics of participants

The response rate was 91.3%. Of the16584 initial participants, 125 did not respond to the sleep items or blood glucose, 1314 did not meet our study criteria, 15,145 adults (7557 men and 7588 women) with complete data were included in our analysis. The average sleep duration per night was 7.16 ±1.06h. The average age was 47.6 ± 15.1 years. Among them, 634 had IFG; the remainder had normal glucose tolerance (NGT). The characteristics of the study population are presented in Table 1. The characteristics between individuals with poor sleep quality and sleep duration ＜6h and controls are presented in Table 2. The proportion of volunteers with poor sleep quality was 26.0%, the proportion with sleep duration <6 h was 12.5%, the proportion with sleep duration >8 h was 12.3%. The 6.7% prevalence of IFG in volunteers with poor sleep quality was higher than that in volunteers with good sleep quality (χ^2 = 85.98, p < 0.001). Individuals with sleep duration <6 h had a higher IFG prevalence compared with individuals with sleep duration 6−8 h, (7.3 *vs* 3.3%; χ^2 = 72.20, p < 0.001). Individuals with sleep duration >8 h also had also had higher prevalence of IFG (6.2 *vs* 3.3%; χ^2= 37.78, p < 0.001).

Comparison of PSQI scores between the volunteers with IFG and NGT

Volunteers with IFG had significantly higher global PSQI scores than those with NGT. For all PSQI items except sleep duration, there were significant differences (p < 0.05) in PSQI scores between the two groups (Table 3) even after adjusted age.

The association of sleep time and quality with IFG

Individuals with short sleep duration or long sleep duration had significantly increased risk of IFG compared with those with good sleep quality and sleep duration 6−8 h (OR:2.16 ; 95% CI: 1.33−3.47； OR: 1.89; 95% CI: 1.50−2.34; respectively. all P<0.001), after adjusting for confounders (See table 3). Individuals with poor sleep quality had significantly increased risk of IFG compared with those with good sleep quality (OR:1.98; 95% CI: 1.69−2.21; P<0.001),

after adjusting for confounders (See table 4).

Biological interaction of sleep quality and sleep duration on the prevalence of IFG

We used a combined effects method to assess interaction, with the *p* value of the interaction term indicating statistical significance of addictive interactions. Individuals with poor sleep quality or short sleep duration had significantly increased risk of IFG compared with those with good sleep quality and sleep duration 6−8 h (OR: 2.48; 95% CI: 2.12−3.03； OR: 2.79; 95% CI: 2.19−3.58; respectively. all $P<0.001$), after adjusting for confounders. Table 5 shows the results from the multiple logistic regression models. The prevalence of IFG was greatest in those with poor sleep quality and short sleep duration (OR: 6.37; 95% CI: 4.66−8.67; $p < 0.001$), after adjusting for confounders. In addition, individuals with long sleep duration had a significantly increased risk of IFG compared with those who had good sleep quality and sleep duration of 6−8 h (OR: 2.37; 95% CI: 1.89−2.96; $p < 0.001$), after adjusting for confounders. The prevalence of IFG was also greater in those with good sleep quality with long sleep duration (OR: 3.17; 95% CI: 2.29−4.41; $p < 0.001$), compared with those with 6−8 h sleep duration, after adjusting for confounders.

Sensitivity analysis

There was a strong additive interaction between poor sleep quality and short sleep duration (RERI: 1.69; 95% CI: 0.31–3.76.), with 42% of occurring IFG attributed to the interaction between poor sleep quality and short sleep duration (Table 5). There was also interaction between good sleep quality and long sleep duration (RERI: 0.78; 95% CI: 0.12–1.43), with 61% of occurring IFG attributed to the interaction between good sleep quality and long sleep duration (Table 6).

Discussion

The two main findings of this study were, firstly, that there is combined interaction of poor sleep quality and short sleep duration on the prevalence of IFG. Secondly, that total PSQI scores of volunteers with IFG were higher than those of volunteers with NGT. We also found that poor sleep quality and short or long sleep duration increased risk for IFG in a Chinese population, independent of potential confounders such as age, obesity, family history of diabetes, alcohol consumption, smoking, physical activity, and other diseases.

Numerous epidemiologic studies have demonstrated associations between short or long sleep duration and sleep disturbances and diabetes.[17-23]. However, few articles focused on IFG, and the results of these are inconsistent. [5, 24] Rafalson et al.[5] reported the OR of IFG among short sleepers was 3.0 (95% CI: 1.05–8.59) compared with mid-range sleepers with multivariate conditional logistic regression after adjustment for several diabetes risk factors. Hung et al.[24] reported no association between IFG and poor sleepers. Our findings are

consistent with the report by Rafalson et al.

The global PSQI scores in volunteers with IFG were higher than those in volunteers with NGT, which was consistent with the Hung et al. report.[24] However, there was no difference in sleep duration scores between the volunteers with IFG and the volunteers with NGT. This could be attributed to the fact that 18.3% (116/634) of the volunteers with IFG were long sleepers, while short sleepers with IFG only accounted for 22.9% (145/634).

Short sleep duration increases appetite. After four nights of 4.5 h in bed, compared with after four nights of 8.5 h in bed, caloric intake, especially of carbohydrate-rich nutrients, increased by 14% in young normal-weight men and women.[25, 26] Middle-aged obese volunteers submitted to four to five nights of restriction of their habitual sleep schedule by 2–3 h/night ate 15% more calories than those whose habitual sleep schedule was extended by the same amount.[27] In volunteers with sleep debt, glucose tolerance, glucose effectiveness and insulin sensitivity are decreased, and beta-cell function is reduced.[6,26,28,29] Sleep loss also results in decreased anorexigenic leptin levels,[30-32] especially in volunteers with chronic sleep restriction.[33] Observational epidemiologic studies have also shown reduced leptin levels, after controlling for BMI or adiposity, in habitual short sleepers.[33, 34] Conversely, leptin deficiency disrupts sleep architecture and impairs sleep consolidation.[35] Taken together, these data suggest that sleep loss is likely to have a profound impact on IFG.

Poor sleep quality, independent of sleep duration, impairs glucose regulation in healthy young adults.[36, 37] After three nights of slow-wave sleep suppression, insulin sensitivity is decreased by ~25%, reaching the level reported in older adults and in populations at high risk of diabetes.[38] The decrease in insulin sensitivity is not compensated for by an increase in insulin release. Consequently, the disposition index is ~20% lower. Consistent with an increased diabetes risk, glucose tolerance is reduced by ~23% reaching the range typical of older adults with impaired glucose tolerance.[37] Sleep fragmentation also increases sympathetic activity, which in turn leads to disorders of glucose metabolism.[39]

Taken together, short sleep duration, increased caloric intake, poor sleep quality, decreased leptin levels, decreased insulin sensitivity and increased sympathetic activity affect each other, creating a vicious circle, which elevates the risk of IFG.

Despite the absence of the synergistic effect of good-quality sleep with long sleep duration, a strong association of IFG with long sleep duration in individuals was observed, suggesting an independent effect of long sleep duration.

This study had several potential limitations. Firstly, because of the cross-sectional design, we could not determine a causal relationship between sleep quality, sleep duration and IFG. Secondly, we were not able to control for some important and well-known risk factors of diabetes, for example, snoring.[40]. Thirdly, we did not measure poor diet, which is causally related to type 2 diabetes and may also influence sleep patterns.[41,42]

There are several notable strengths of this study. Participants were randomly selected

from the general population of Xuzhou. In addition, the sample was large. Many confounding risk factors were adjusted for.

In summary, volunteers who experience short sleep durations are six times more likely to develop IFG than those whose average sleep was 6−8 h a night with good sleep quality. The joint effect of short sleep duration and poor sleep quality was positive.

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Conflict of Interest Statement

None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. The researchers were independent from funders. The study funders had no influence on the study design, data collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Contributors Steering Committee: PL (principal investigator), PC (principal investigator), PC and LZ. Operating Committee: LZ,PZ, GC, NZ, TL and CQ.

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Table 1 Baseline characteristics of the study population (N = 15,145)

Reported variable	*All*	*IFG*		
		No	Yes	*P*
	15145	14,511(95.81%)	634(4.19%)	
Age(years)	47.6±15.1	47.4±14.7	52.2±16.2	8.012
≥45 years	8362	7928(94.81%)	434(5.19%)	0.000
Sex(% man)	49.9	50.0	49.8	0.938
Rural (%)	72.4	72.4	72.9	0.795
Manual	10833	10359(95.62%)	474(4.38%)	0.023
Non-manual	1045	1016(97.22%)	29(2.78%)	
Unemployed	677	658(97.19%)	19(2.81%)	
retired	2590	2478(95.68%)	112(4.32%)	
Marred (living with partners)(%)	88.5	88.6	86.3	0.073
Below high school	11899	11400(95.81%)	499(4.19%)	0.986
high school	1760	1686(95.80%)	74(4.20%)	
Above high school	1486	1425(95.90%)	61(4.10%)	
smoker	3541	3367(95.09%)	174(4.91%)	0.014
alcohol use	2872	2752(95.82%)	120(4.18%)	0.981
Regular exercise	2559	2452(95.82%)	107(4.18%)	0.989
Family history of diabetes	483	362(74.95%)	121(25.05%)	0.000
BMI, mean(SD)	23.9±4.7	23.8±5.8	25.2±4.1	＜0.001
Central obesity	4613	4219(91.46%)	394(8.54%)	0.000
Hypertension	3060	2901(94.80%)	159(5.20%)	0.002
Sleep duration(hour)				
≤6	1984	1839(92.70%)	145(7.30%)	0.000
6-8	11292	10919(96.70%)	373(3.30%)	
≥8	1869	1753(93.80%)	116(6.20%)	
Sleep quality				
Good	11209	10840(96.71%)	369(3.29%)	0.000
Poor	3936	3671(93.27%)	265(6.73%)	

Table 2.Comparison of characteristics between individuals with poor sleep quality and sleep duration ＜6h and controls

Reported variable	*All*	Poor sleep quality with short sleep time(＜6h)		
		Yes	**No**	***P***
	15145	602	14543	
Age(years)	47.6±15.1	47.8±15.5	47.5±15.1	0.63
Sex(man)	7557	299(3.96%)	7258(96.04%)	0.91
Rural	10965	435(3.97%)	10530(96.03%)	0.94
Manual	10833	421(3.89%)	10412(96.11%)	0.38
Non-manual	1045	44(4.21%)	1001(95.79%)	0.69
Unemployed	677	35(5.17%)	642(94.83%)	0.10
retired	2590	102(3.94%)	2488(96.06%)	0.92
Marred (living with partners)(%)	13403	535(3.99%)	12868(96.01%)	0.77
Below high school	11899	470(3.95%)	11429(96.05%)	0.76
high school	1760	70(3.98%)	1690(96.02%)	1
Above high school	1486	62(4.17%)	1424(95.83%)	0.68
smoker	3541	145(4.09%)	3396(95.91%)	0.68
alcohol use	2872	121(4.21%)	2751(98.79%)	0.48
Regular exercise	2559	92(3.60%)	2467(96.40%)	0.28
Family history of diabetes	483	20(4.14%)	463(95.86%)	0.85
BMI, mean(SD)	23.9±4.7	24.0±4.9	23.9±4.6	0.60
Central obesity	4613	186(4.03%)	4427(95.97%)	0.81
Hypertension	3060	131(4.28%)	2929(95.72%)	0.33

Table 3 Comparison of Pittsburgh Sleep Quality Index scores between individuals with impaired fasting glucose and controls ($\bar{x}$ ± sd)

Items	*IFG*		*F value*	*P*
	No	Yes		
Subjective sleep quality	0.415±0.013	0.463±0. 03	31.823	0.000
Sleep latency	0.742±0.004	0.800±0.016	27.446	0.000
Sleep duration	0.152±0.002	0.159±0.001	0.503	0.478
Sleep efficiency	0.444±0.003	0. 321±0.001	29.452	0.000
Sleep disturbance	0.591±0. 003	0.658±0.012	28.259	0.000
Use of hypnotic	0.051±0.002	0.065±0.007	16.651	0.000
Daytime dysfunction	0.147±0.011	0.170±0.002	9.725	0.000
Global PSQI scores	2.302±0.009	2.495±0. 041	20.957	0.000

Using analysis of covariance, Covariates for age =47.6 years old

Table 4 Odds ratios for the association between sleep quality, sleep duration and impaired fasting glucose among participants

Variables		IFG	No IFG	OR (95%CI)	P
Sleep quality	Good	369	10840	1	
	Poor	265	3671	1.21(1.09-1.34）	0.000
Sleep duration	6-8h	373	10919	1	
	＜6h	145	1839	2.16 (1.33-3.47)	0.000
	＞8h	116	1753	1.89 (1.50-2.34)	0.000

Adjusted for age, sex, education, employment, BMI, family history of diabetes, smoking status, alcohol consumption and physical activity.

Table 5 Odds ratios for the association between sleep quality and impaired fasting glucose by sleep duration among participants

Sleep duration	*Sleep quality*	*IFG*	*No IFG*	*OR (95%CI)*	*P*
6-8h	Good	246	8743	1	
	Poor	127	2176	1.98（1.76-2.52）	<0.001
＜6h	Good	53	1329	1.38（1.12-1.61）	<0.001
	Poor	92	510	6.37（4.66-8.67）	<0.001
＞8h	Good	70	768	3.17 （2.29-4.41）	<0.001
	Poor	46	985	1.59（1.08-2.29）	<0.001

Adjusted for age, sex, education, employment, BMI, family history of diabetes, smoking status, alcohol consumption and physical activity.

Table 6 Measures for estimation of the biological interaction between sleep quality and sleep duration for the prevalence of impaired fasting glucose in participants

Measures of biological interaction	Estimate (95% CI)
Poor sleep quality versus sleep duration ＜6h	
RERI	1.69(0.31－3.76)
AP	0.42(0.15－0.61)
S	2.85(2.14－3.92)
Good sleep quality versus sleep duration ＞ 8h	
RERI	0.78(0.12－1.43)
AP	0.61(0.26－0.87)
S	-0.65(-0.94－-0.27)

Reference group is good sleep quality with 6-8 sleep duration.

Adjusted for age, sex, education, occupation, BMI, family history of diabetes, smoking status, alcohol consumption, and hypertension.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page3
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 3
Methods			
Study design	4	Present key elements of study design early in the paper	Page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 3-4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Page 4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 4-5
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 5
		(*b*) Describe any methods used to examine subgroups and interactions	Page 5
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Page 5
		(*e*) Describe any sensitivity analyses	Page 5

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 6
		(b) Give reasons for non-participation at each stage	Page 6
		(c) Consider use of a flow diagram	Figur1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table1
		(b) Indicate number of participants with missing data for each variable of interest	Table2
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Page6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Page6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table3-5
		(*b*) Report category boundaries when continuous variables were categorized	Page7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page10
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.