Joint Effect of Alcohol and Usual Sleep Duration on the Risk of Dysglycemia

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Study Objectives: Sleep duration and alcohol use influence metabolic function. However, limited information exists regarding a combined effect of alcohol and sleep duration on glucose metabolism. The aim of this study was to assess the potential interaction effect of alcohol and inappropriate sleep duration on dysglycemia epidemiologically.

Design: Cross-sectional and observational retrospective study

Setting: A medical health checkup program in a general hospital

Participants: 2933 apparently healthy Japanese individuals, aged 46 to 60 years

Intervention: N/A

Measurements and Results: We examined the relationships between usual sleep duration and dysglycemia, and furthermore assessed the combined effects of alcohol consumption and sleep time on glucose dysmetabolism. A U-shaped relationship between sleep duration and the prevalence of hyperglycemia (fasting plasma glucose level ≥110 mg/dL) was observed when sleep duration was treated as a continuous variables and centered at 7.0 h (quadratic term P = 0.024). In a multivariate quadratic regression model, there was a significant interaction effect between sleep duration and alcohol consumption category (nondrinkers, light-moderate drinkers [ethanol comsumption ≤210 g/wk], and heavy drinkers [ethanol consumption of >210 g/wk]) on fasting plasma glucose levels, with shorter or longer sleep duration being more diabetogenic in individuals who consumed more alcohol (P interaction = 0.018).

Furthermore, we found a similar interaction effect of sleep duration and alcohol consumption on the incidence of hyperglycemia during the past 5 years (P interaction = 0.039).

Conclusion: Alcohol interacts with reduced sleep duration to increase the risk of dysglycemia.

Keywords: Sleep duration, alcohol, glucose metabolism, interaction

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INTRODUCTION

NUTRITION, EXERCISE, AND REST ARE 3 MAJOR ELEMENTS FOR THE PROMOTION OF GOOD HEALTH. SLEEP, WHICH FORMS A MAJOR PART OF REST, HAS AN important role in the prevention of "lifestyle-related diseases" such as diabetes. Epidemiologic studies have shown that habitual sleeping patterns are associated with all-cause mortality risk.[1-3] Furthermore, the relationship between sleep duration and occurrence of diabetes mellitus has been described epidemiologically by recent investigations.[4-7] In particular, sleep restriction results in insulin resistance, increased evening cortisol levels, elevated sympathovagal balance, abnormal profiles of nocturnal growth hormone secretion, and markedly decreased leptin levels.[9-14] These processes suggest inappropriate sleep duration has a potential to cause dysglycemia.

Alcohol has also been reported to have long-term effects on the body's internal clocks and on circadian-modulated behavioral, neuroendocrine, and immune functions.[15-18] Alcohol and sleep loss may therefore have a common biological mechanism of altering the body's circadian rhythm. Furthermore, alcohol appears to influence sleep quality and cause sleep disturbances including snoring, sleep apnea, and insomnia.[19-23] It is therefore possible that alcohol and sleep duration could have an interaction effect on a variety of physiological functions.

In prior epidemiologic studies on sleep-diabetes association, alcohol consumption has been considered to be one of the most critical confounders or causal intermediates of lifestyle factors, which might explain the statistical association.[4-8] However, no study assessed the potential interaction effect of alcohol consumption and sleep duration on dysglycemia.

In the present study, we examined the relationship between usual sleep duration and glucose dysmetabolism in middle-aged Japanese subjects; we also investigated the combined effect of alcohol drinking and usual sleep duration on impaired glucose regulation.

METHODS

Study Sample

The "human dry dock," is one of the most popular medical services in Japan, for the purpose of the medical health checkup promoting public health through early detection of chronic diseases and their risk factors. A standard human dry dock features anamnesis and a survey of lifestyle, a physical examination, serum and urine examination, a chest X-ray, barium gastrography, abdominal ultrasonography, and other tests. The fee is paid by participants or supported (fully or partially) by their employers or medical insurers.

The current study was designed first to cross-sectionally evaluate the interaction effect of sleep duration and alcohol consumption on dysglycemia in Japanese individuals. The study included

2393 male and 1912 female subjects, aged 46-60 years, who attended the human dry dock of the health care center at the First Red Cross Hospital in Kyoto from 2004 to 2005. In addition, we constructed a retrospective observational model. Some of the current subjects have attended the human dry dock regularly in every few years for medical check-up. Of the original subjects, those who attended the same human dry dock 5 years ago were selected (913 male and 755 female). We retrospectively analyzed the subgroup to investigate the interaction effect of sleep duration and alcohol consumption on the development of dysglycemia during the past 5 years.

Medical history and lifestyle factors were obtained from a self-administered questionnaire completed by all the subjects. These included medication use, family history of diseases, diet, physical activity, sleep, habits regarding smoking and alcohol consumption, and psychological state. When the participants had difficulty completing the questionnaire, trained nurses provided assistance. In addition, all participants underwent physical examinations, routine biochemical screening tests obtained by venipuncture after an overnight fast. All participants gave their informed consent, and the study was approved by the ethics committee of the First Red Cross Hospital. Subjects were excluded if they had a present history of cancer, liver disease, renal disease, or depression. Subjects treated with insulin or oral diabetes medications, antihypertensives, or cholesterol-lowering medications, and those carrying out rotating shift work were also excluded.

Sleep Habits Questionnaire

Habitual patterns concerning sleep (bed times, wake-up times, and symptoms of insomnia) on weekdays or workdays were recorded from answers on the questionnaire. Usual sleep duration was calculated from the responses and treated as continuous measures in hours. Subjects were categorized into 5 groups based on usual sleep duration: ≤5h, >5h-≤6h, >6h-≤7h, >7h-≤8h, 8h<. Symptoms of insomnia were questions obtained from two separate 3-category interviews which concerned the difficulty initiating sleep ("Did you have trouble falling asleep?") and the difficulty maintaining sleep ("Did you wake up during the night?"). The subjects were classified into one of two categories: "No" for those who indicated "almost never" and "Yes" for those who indicated "always" and "sometimes" in response to the questions.

Alcohol Consumption

Alcoholic beverages included beer, sake (rice wine), syouchu (traditional Japanese spirits), wine, and whiskey. For each type of beverage, alcohol consumption based on interviews of the participants was converted into grams of absolute alcohol in order to obtain an estimate of total alcohol consumption in grams per week.[24] The subjects were divided into 3 groups according to mean ethanol consumption per week: nondrinkers, light-to-moderate drinkers (≤210 g per week), or heavy drinkers (>210 g per week). This cut-off value, equivalent to 30 g per day, was chosen to separate heavy from light-to-moderate drinkers based on the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, which recommends consumption of less than 30 g of alcohol per day to decrease cardiovascular risk.[25]

Other Measures

Hypertension was defined as blood pressure values ≥130/85 mm Hg, hypercholesterolemia as a serum LDL-cholesterol level ≥140mg/dL (3.63 mmol/L) and hypertriglycemia as a serum triglyceride level ≥150 mg/dL (1.70 mmol/L). Participants were classified as active if they regularly participated in sports at least 1 h/week. Three-category interview questions were also asked concerning dietary habits ("Did you have an intake of snacks between meals?"). The subjects were classified into one of 2 categories: negative for those who indicated "sometimes" and "almost never" and positive for those who indicated "often" in response to this question. Symptoms of depression were obtained from 2 questions on a Beck Depression Inventory[26]: (1) "Did you feel so down in the dumps that nothing could cheer you up?" and (2) "Did you feel tired easily?" The subjects were classified into 2 categories: depressive for those who indicated "often" in response to either of the 2 questions and not depressive for the remainder of subjects who indicated "sometimes" and "almost never."

Classification of Hyperglycemia

Diabetes mellitus (DM) and impaired fasting glucose (IFG) were defined in accordance with the Japan Diabetes Society and World Health Organization guidelines.[27,28] DM was defined as a fasting plasma glucose (FPG) level of 126 mg/dL or more (≥7.0 mmol/L). IFG was defined as a fasting plasma glucose level of 110 mg/dL or more (≥6.1 mmol/L) in subjects not meeting the criteria for DM. Hyperglycemia was defined as a FPG level ≥110 mg/dL (DM and IFG).

Statistical Analysis

All analyses were performed using StatView software (version 5.0; SAS Institute, Cary, NC). The significance of unadjusted differences in continuous and categorical variables between sleep duration categories was assessed as appropriate using single-factor analysis of variance or contingency table analysis.

Firstly, general categorical logistic regression was used to assess the relationship between usual sleep duration and the prevalence of hyperglycemia. In addition, multiple multinomial logistic regression was used to assess the relation between sleep duration and a 3-level dependent variable: 1) DM, 2) IFG, and 3) normal fasting glucose. We chose a reference category of ≥7-<8h per night, as this time is considered conventionally to be the appropriate duration of sleep,[1-2] and also because individuals reporting ≥7h-<8 h of sleep per night had the lowest mortality reported in a previous Japanese study.[3] For tests of linear trend, we treated the categories of sleep duration as continuous variable. For tests of quadratic trend, we treated sleep duration as a continuous variable in hours, which showed normal distribution, and squared the variable after centering it on 7 hours. Covariates included in the models were age and body mass index (BMI) as continuous measures, with gender, alcohol consumption category, smoking status, physical activity, dietary habits, symptoms of depression, hypertension, hypertriglycemia, hypercholesterolemia, and familial history of diabetes as categorical variables.

Secondly, we evaluated the interaction effect between usual sleep duration and alcohol consumption on dysglycemia. The relation between sleep duration and dysglycemia is U-shaped;

Table 1—Characteristics of the 2933 Study Participants

Characteristic	≤5h	>5h - ≤6h	>6h - ≤7h	>7h - ≤8h	8h<	P value †
	Hours of sleep per day*					
No. of subjects	133	554	1273	783	190	
Female sex (%)	58.6	54.5	45.3	42.9	30.5	0.0001
Age (y)	52.5 (3.9)	52.2 (3.9)	53.0 (3.9)	53.9 (4.0)	54.5 (3.9)	0.0001
Body mass index (kg/m^2)	23.1 (3.5)	22.8 (3.0)	22.7 (2.9)	22.5 (2.8)	22.8 (2.9)	0.1275
Fasting plasma glucose (mg/dl)#	101.3 (18.3)	99.0 (14..9)	100.0 (13.4)	100.3 (14.3)	105.4 (24.8)	0.0001
Hyperglycemia (DM/IFG) (%)	19.9 (11.5 /8.4)	12.2 (8.6 /3.6)	14.2 (10.6/3.6)	13.4 (9.3/4.1)	21.4(16.2/5.2)	0.0002
HbA$_{1C}$ (%)	5.41(0.58)	5.36(0.52)	5.33(0.48)	5.36(0.59)	5.44(0.93)	0.0576
Hypertension (%)	32.1	35	38.4	39.5	40.8	0.2282
Hypertriglycemia (%)	15.3	16.2	18.2	22.3	26.7	0.0001
Hypercholesterolemia (%)	29.8	27.6	27.2	27.5	29.3	0.9488
Smoking (none/past/current) (%)	58 26 16	60 20 20	53 27 20	53 24 23	42 27 31	0.0002
Alcohol consumption (g/week)	62 (9.5)	57 (4.0)	66 (2.8)	93 (8.0)	118 (7.0)	0.0001
Nondrinkers (%)	46	48	41	39	35	0.0001
Light-to-moderate drinkers (%)	44	44	50	46	41	0.0001
Heavy drinkers (%)	10	8	9	15	24	0.0001
Snack intake (positive) (%)	27	19	20	17	14	0.013
Physical activity (active) (%)	65	64	67	72	65	0.063
Psychological state (depressive) (%)	24	21	16	15	17	0.0066
Positive family history of diabetes (%)	10.7	13.5	13.5	11.8	9.9	0.4751

*Data are expressed as percentage of subjects in each group for the categorical characteristics or as mean (SD) for the continuous characteristics. Weekly alcohol consumption is expressed as mean (SE). †Statistical differences were determined by analysis of variance for continuous characteristics and by the χ^2 test for categorical characteristics. # To convert to mM/L multiply by 0.05551.

therefore, a multivariate regression model including a quadratic term for sleep duration which is centered at 7 hours was used to identify independent correlates of FPG levels, and to assess the adjusted interaction between sleep duration and alcohol consumption category on FPG levels. The alcohol consumption categories (nondrinkers, light-to-moderate drinkers, heavy drinkers) were treated as continuous variable (Nondrinker = 0, Light-to-moderate drinkers = 1, Heavy drinkers = 2). Because of a skewed distribution, logarithmic transformation (log) of FPG was applied in the analysis.

Thirdly, we investigated the relationships between usual alcohol consumption and insomnia. The prevalence of difficulty initiating or maintaining sleep was calculated for each group categorized by alcohol consumption. Statistical associations were assessed by logistic regression analysis.

Lastly, we analyzed the subgroup of the original subjects who were normoglycemic 5 years ago in order to investigate the effect of sleep duration on the incidence of hyperglycemia during the past 5 years. We also tested a potential interaction effect of alcohol consumption and sleep duration on the incidence of hyperglycemia during that period. Covariates included in the models were age, gender, hypertension, hypercholesterolemia, hypertriglycemia, and BMI, all of which were obtained from data recorded on the subgroup in 1999 to 2000. These analyses were performed with multivariate logistic regression.

A probability value <0.05 was considered to indicate statistical significance.

RESULTS

Of the 4305 participants, 15 subjects were excluded for missing data. Other subjects excluded were 331 subjects with a present treatment history of liver disease, renal disease, or depression;

127 subjects treated with insulin or oral diabetes medications; 445 subjects taking antihypertensive medications; 171 subjects receiving cholesterol-lowering therapy, and 223 subjects working rotating shifts. No subjects had a diagnosis of alcoholism. The final cross-sectional analysis, therefore, comprised 2933 participants (1582 males and 1351 females). In these subjects, mean age was 53.2 ± 8.5 y (range; 46-60 y), mean BMI was 22.7 ± 2.9 kg/m^2 and mean usual sleep time was 6.9 ± 1.0 hours. The majority of subjects reported sleeping 6 to 8 h, although 4.5% reported sleeping ≤5 h per night and 6.5% reported sleeping for >8 h per night (Table 1). The subjects who were short sleepers were significantly younger, more likely to be female and obese, and reported consuming snacks more frequently. Subjects who were long sleepers had a significantly increased prevalence of hypertriglycemia and consumed significantly more alcohol. Those subjects with a sleep duration of >7h-≤8h were more likely to be physically active.

We examined the relationship between usual sleep duration and hyperglycemia (either DM or IFG) (Table 2). Compared with those subjects reporting >7 h to ≤8 h of sleep per night, subjects reporting ≤5 h and >8 h had higher adjusted ORs for hyperglycemia of 1.98 (95% CI, 1.33-3.33) and 1.45 (95% CI, 1.02-2.06), respectively. Furthermore, a U-shaped relationship was shown when sleep duration was treated as a continuous variable and centered in 7.0 h (P = 0.024 for quadratic term). The results of the multinomial analysis indicated that sleep duration had similar U-shaped relationships with both DM and IFG. Subjects reporting ≤5 h and >8 h had higher adjusted ORs for DM of 2.84 (95% CI, 1.33-3.33) and 1.16 (95% CI, 0.53-1.99), respectively, and for IFG of 1.58 (95% CI, 0.81-3.07) and 1.59 (95% CI 1.06-2.39), respectively.

Recently, the American Diabtes Association lowered the fasting glucose threshold value for IFG from 110 to 100 mg/dL.[29]

Table 2—Data for Hyperglycemia (Diabetes Mellitus and Impaired Fasting Glucose) by Reported Usual Sleep Time in 2933 Subjects

Adjusted odds ratio (95% CI) for Hyperglycemia (either DM or IFG) relative to normal fasting glucose

	Model 1			Model 2	
Sleep duration	**Hyperglycemia**	**†P value**		**Hyperglycemia**	**†P value**
≤5h	2.34 (1.38~3.97)			1.98 (1.13~3.33)	
>5h-≤6h	1.11 (0.76~1.62)			1.01(0.69~1.48)	
>6h-≤7h	1.16 (0.85~1.59)	0.94		1.09 (0. 80~1.49)	0.52
>7h-≤8h	1			1	
8h<	1.53 (1.07~2.19)			1.45 (1.02~2.06)	
Sleep duration (h^2)^a	1.07 (1.01~1.13)	(0.022)		1.07 (1.01~1.13)	(0.024)

Adjusted odds ratio (95% CI) for DM or IFG relative to normal fasting glucose, from multinomial logistic regression models

	Model 1			Model 2		
Sleep duration	**DM**	**IFG**	**†P value**	**DM**	**IFG**	**†P value**
≤5h	3.90(1.73-8.79)	1.86(0.97-3.56)		2.84(1.44-7.51)	1.58(0.81-3.07)	
>5h – ≤6h	1.16(0.61-2.24)	1.12(0.72-1.74)		1.03(0.53-1.99)	1.02 (0.66 -1.59)	
>6h – ≤7h	1.02(0.59-1.77)	1.22(0.85-1.75)	0.24	0.94(0.55-1.63)	1.14 (0.80 -1.64)	0.21
>7h – ≤8h	1	1		1	1	
8h<	1.24(0.67-2.31)	1.68(1.11-2.52)		1.16(0.53 -1.99)	1.59(1.06-2.39)	
Sleep duration (h^2)^a	1.09(1.00-1.19)	1.06(1.00~1.13)	(0.053)	1.09(0.99-1.19)	1.06(0.99-1.13)	(0.068)

Abbreviations: DM, diabetes mellitus; IFG, impaired fasting glucose.
Model 1 was adjusted for age, sex, smoking status, alcohol consumption, hypertension, hypercholesterolemia, hypertriglycemia, physical activity, snack intake, depression and insomnia; Model 2, adjusted for all variables in model 1 plus BMI.
^{a}Quadratic term for sleep duration in hours which is centered at 7 hours.
P values are expressed as tests of linear (quadratic) trend.

Table 3—Determinants of Fasting Plasma Glucose Levels as Evaluated by Multiple Regression Analysis

Parameter	β	P value†
Female sex	-0.19	<0.0001
Age (yr)	0.11	<0.0001
Body mass index (kg/m^2)	0.19	<0.0001
Hypertension	0.116	<0.0001
Hypertriglycemia	0.093	<0.0001
Sleep duration(h^2)^a	-0.032	(0.186)
Alcohol^b	0.008	0.704
*Sleep duration(h^2)^a×alcohol^b	0.062	0.018

R^2 = 0.19
^{a}Quadratic term for sleep duration in hours which is centered at seven hours
^{b}alcohol consumption category as a continuous variable
*Interaction term between sleep duration(h^2)^a and alcohol^b.
†P values are expressed as tests of linear (quadratic) trend.

When the new ADA criteria was used, a similar U-shaped association of sleep duration with odds of hyperglycemia was found but failed to reach statistical significance: adjusted ORs for subjects reporting ≤5h and >8h were 1.49 (95% CI, 0.98-2.26) and 1.23 (95% CI, 0.93-1.62) (P = 0.15 for quadratic term).

To analyze the interaction effect of sleep duration and alcohol consumption category on FPG levels, we then performed multivariate quadratic regression analysis. The model was adjusted for all covariates, as mentioned above. In addition, interaction term "sleep duration(h^2)×alcohol" were entered into the model. Factors independently associated with FPG levels are shown in Table 3 with their respective regression coefficients and adjusted probability values. There was a significant interaction between sleep duration and alcohol consumption category. The quadratic (U-shaped) association between sleep duration and FPG levels was found to be steeper for individuals who consumed more alcohol (β = 0.062, P interaction = 0.018). On the other hand, not a U –shaped, but rather a nonsignificant inverted- U association was observed between sleep and FPG levels (β = -0.032, P = 0.18). Furthermore, no association was found between alcohol consumption and FPG levels (β = 0.008, P = 0.7). These results indicated that dysglycemia associated with inappropriate sleep duration and alcohol consumption was related primarily to their combined effect rather than separate effects.

Our data showed light-to-moderate drinkers and heavy drinkers had higher odd ratios for difficulty maintaining sleep than nondrinkers (Table 4). Adjustment for age and sex did not reduce the observed associations of drinking habits with difficulty maintaining sleep. On the other hand, the prevalence of difficulty initiating sleep was not statistically different according to drinking habits.

We performed a final analysis to assess the combined effect of alcohol and sleep duration on incident hyperglycemia during the past 5 years. Of the 1668 subjects who attended the same human dry dock 5 years ago, 131 had hyperglycemia then. Thus, the final sample for this analysis comprised 1537 participants (Table 5a, 5b). Short sleepers and long sleepers had multivariate ORs for incident hyperglycemia of 2.36 (95% confidence interval 0.94 ~5.93) and 1.52 (0.83~2.78), respectively. A U-shaped relationship was suggested when sleep duration was treated as continuous measure in hours; a quadratic term approached significance (P = 0.09 for trend). Furthermore, we found a similar interaction effect of sleep duration and alcohol consumption on the incident hyperglycemia during the past 5 years (P interaction = 0.039).

Table 4—Relationship Between Alcohol Consumption and Difficulty Initiating and Maintaining Sleep

| | | Difficulty initiating sleep | |
| | | Crude | Adjusted[a] |
	%	OR (95%CI)	OR (95%CI)
Nondrinkers	30.4	1	1
Light-to-moderate drinkers	28.5	0.91(0.77-1.08)	0.97(0.81-1.16)
Heavy drinkers	28.5	0.91(0.72-1.19)	1.03(0.78-1.37)
		Difficulty maintaining sleep	
		Crude	Adjusted[a]
	%	OR (95%CI)	OR (95%CI)
Nondrinkers	50.4	1	1
Light-to-moderate drinkers	53.4	1.13(0.97-1.32)	1.19(1.01-1.40)
Heavy drinkers	57.9	1.35(1.06-1.72)	1.36 (1.05-1.77)

Data are expressed as prevalence (%)of difficulty initiating or maintaining sleep in 1582 males and 1351 females grouped according to alcohol consumption and as odds ratios (95% confidence intervals) for difficulty initiating or maintaining sleep, calculated by categorical logistic regression models using nondrinkers as the reference.
[a]adjusted for age and sex.

Table 5—a. Data for incident hyperglycemia (diabetes mellitus or impaired fasting glucose)by reported usual sleep duration in the subgroup (n=1537) who did not have a diagnosis of hyperglycemia 5 years ago

Sleep duration	OR(95% CI)	P value
≤5h	2. 36 (0.94~5.93)	
>5h-≤6h	0.98 (0. 51~1.89)	
>6h-≤7h	1.05 (0. 61~1.80)	0.52
>7h-≤8h	1	
8h<	1. 52 (0. 83~2.78)	
Sleep duration(h^2)[a]	1.07 (0.99 ~1.17)	(0.09)

b. Multivariable model predicting incident hyperglycemia

Parameter	OR(95% CI)	P value†
Female sex	0.56(0.34-0.90)	0.038
BMI (kg/m^2)	1.15(1.07-1.23)	<0.0001
Hypertriglycemia	1.77 (1.16-2.70)	0.003
Smoker	1.85(1.11-3.08)	0.0083
Sleep duration(h^2)[a]	0.92(0.77-1.11)	(0.36)
Alcohol[b]	1.13(0.82-1.57)	0.45
*Sleep duration(h^2)[a]×alcohol[b]	1.15(1.00-1.31)	0.039

Data are expressed as odds ratios (95% confidence intervals) for the incidence of hyperglycemia (DM and IFG) relative to normal glucose, calculated by categorical logistic regression model based on backward selection algorithm. BMI, serum fasting blood sugar, cholesterol, and triglyceride were measured from 1999-2000.
[a]Quadratic term for sleep duration in hours which is centered at 7 hours
[b]Alcohol consumption categories as a continuous variable.
*Interaction term between sleep duration (h^2)[a] and alcohol[b].
†P values are expressed as tests of linear (quadratic) trend.

DISCUSSION

The present study in Japanese middle-aged subjects demonstrated a U- shaped relationship between sleep duration and glucose dysmetabolism. The relationships we observed between sleep time and dysglycemia were almost identical to those reported in other epidemiologic studies.[4-6] However, to our knowledge, this is the first epidemiological study evaluating the interaction effect of alcohol and inappropriate sleep duration on metabolic function. We demonstrated a combined effect of alcohol drinking and usual sleep time on glucose dysmetabolism. According to our cross-sectional and retrospective analyses, drinkers with both extremes at sleep duration were at the highest risk of developing dysglycemia.

There are a number of biological mechanisms by which short sleep duration may lead to glucose dysmetabolism. Several physiological studies have demonstrated that sleep restriction causes elevation in evening cortisol level, increased sympathetic nervous activity and suppressed secretion of leptin.[9-14] It is postulated that these changes may induce body weight gain and glucose intolerance.[30] Unlike short sleep, there are no compelling hypotheses regarding the mechanism for the association between long sleep and disease. Prior studies suggest sociodemographic status, depression, chronic medical diseases, lifestyle, and social isolation are the most likely to have a strong effect on the long sleep-mortality association.[3,31] We were unable to identify the variables that could produce the greatest alterations in the long sleep-dysglycemia association in our models, except that the long sleepers were older, more likely to be male, consumed significantly more alcohol, and had an increased prevalence of hypertriglycemia. In the current study, lifestyle and psychological state might be underreported. Otherwise, this association might be due to another unmeasured confounding variable.

There are a number of explanations to account for the joint effect of alcohol use and usual sleep time on glucose dysmetabolism. Firstly, it has been reported that excessive alcohol consumption increases the risk of type 2 diabetes.[32,33] Therefore, short and long sleepers could have some unrecognized confounding factors that increase the susceptibility to the diabetogenic effects of alcohol. Secondly, alcohol appears to affect sleep quality and exacerbate sleep disturbances such as snoring, sleep apnea, and insomnia, all of which are recognized as risk factors of impaired glucose regulation.[34-36] In fact, our data showed heavy drinkers have a higher frequency of difficulty maintaining sleep compared with nondrinkers and light-to-moderate drinkers (Table 4). As a consequence, disturbed sleep quality induced by alcohol consumption may exacerbate glucose dysmetabolism resulting from inappropriate sleep duration. Lastly, sleep and alcohol have a common chronobiological effect of altering circadian rhythmicity. As shown in preliminary studies, altered endogenous circadian rhythms contribute partially to the causal link between sleep deprivation, shift work, and glucose intolerance.[37,38] Alcohol has also been reported to act directly on the central pacemaker located in the suprachiasmatic nuclei in the brain that controls circadian clock function, thereby affecting a variety of physiological processes governed by the body's internal clock.[15-18] Taken together, these findings suggest alcohol and sleep duration have an interaction effect on glucose dysmetabolism by disrupting circadian rhythms.

When interpreting our data it is important to also consider ethnic characteristics regarding life style and genetic background. Japanese use alcohol in order to improve sleep more than other populations.[39] In addition, more than 90% of Japanese people

have the *2-allele of alcohol dehydrogenase-2 (ADH2*2), with nearly half also having the *2-allele of aldehyde dehydrogenase-2 (ALDH2*2). These alleles account for rapid accumulation of acetaldehyde in the blood and various uncomfortable symptoms after alcohol consumption.[40] These unique genetic polymorphisms in ethanol-metabolizing enzymes in Japanese people could therefore also influence sleep quality.[41]

Although we considered a broad set of potential confounding variables, some limitations of this study deserve attention. Usual sleep habits and other potential risk factors including usual alcohol consumption, psychological state, daily activity, and diet were self-reported by the participants, and therefore reliability cannot be confirmed. Sleep disturbance could also have been misclassified as we did not inquire about snoring or the actions taken to manage insomnia, nor did we estimate disordered breathing sleep electronically. We also did not perform a glucose loading test to assess glucose intolerance. If the subjects were given a 75 g oral glucose tolerance test for the purpose of diagnosing glucose intolerance, normal glucose tolerance in this study would have been reclassified as glucose intolerance by postprandial hyperglycemia. Furthermore, the cross-sectional nature of our study did not permit determination of causality. Large prospective trials and interventional studies are therefore needed to better assess the combined effect of alcohol and sleep loss on glucose regulation.

In conclusion, our data indicated alcohol has a joint effect with usual sleep duration on glucose metabolism. The present study provides information that should contribute to the primary prevention of lifestyle-related diseases as well as improving sleep hygiene.

ABBREVIATIONS

BMI: body mass index
DM: diabetes mellitus
IFG: impaired fasting glucose
OR: odds ratio
CI: confidence interval
FPG: fasting plasma glucose
HbA_{1C}: glycated hemoglobin A1c
ADH2*2: *2-allele of alcohol dehydrogenase-2
ALDH2*2: *2-allele of aldehyde dehydrogenase-2

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