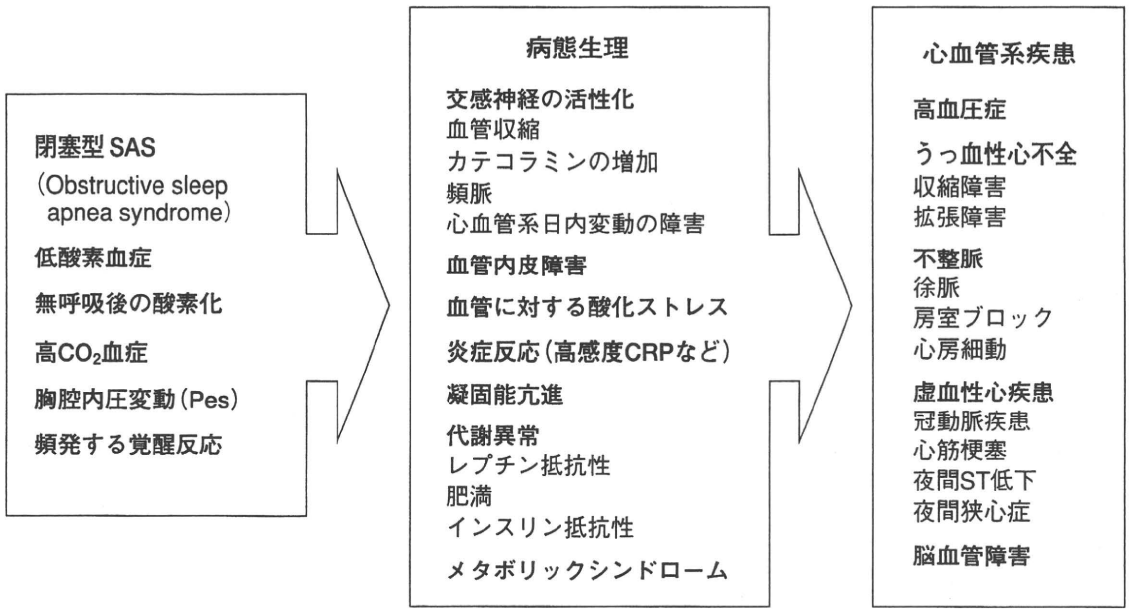

図4　SASの病態生理が心血管系に及ぼす影響(文献[19]より引用し改変)

が認められたと報告されている。欧米人に比し肥満の程度が軽い日本人においても，SAS患者の約半数にMetSが認められたと報告されている[21]。

しかし，近年の研究では，SAS自体が肥満とは独立してMetS発症に関与することが明らかにされており，疫学的研究では前述したSHHSからの報告[22]で，2000例以上を対象にして，AHIと空腹時血糖と糖負荷2時間後血糖値を検討したところ，軽症SAS(5≦AHI<15)，中等症SAS(AHI≧15)群では非SAS群に比し，耐糖能異常のオッズ比がおのおの1.27, 1.46と有意に高かったと報告されている。ヨーロッパからの報告[23]でも，494例のSAS群と101例のイビキ群(非SAS)を比較すると，2型糖尿病はSAS群で30.1%，イビキ群で13.9%，耐糖能異常はSAS群で20%，イビキ群で13.9%と有意にSAS群で糖代謝異常の頻度が高いとされている。

185例のSASと85例の非SASを比較検討した香港からの報告[24]でも，SAS群はインスリン抵抗性になりやすく，HOMA indexが高値をとりやすいとされている。さらに，年齢，肥満度，喫煙歴を一致させたSAS群(AHI>15)と非SAS群(AHI<5)とで，インスリン抵抗性を検討した報告でも，SAS群では有意にインスリン抵抗性が高いことが報告されており[25]，SAS自体が肥満とは独立して糖代謝異常の要因であることが明らかとなった。

近年，SASだけでなく，単独の睡眠障害，すなわち睡眠不足や頻回の中途覚醒，断眠などにより耐糖能異常などの代謝障害がもたらされることが明らかになっている。Spiegelら[26]は，一般健常人を対象に断眠実験を行い，断眠により糖のクリアランスが低下し耐糖能異常が生ずることを初めて明らかにした。その後の研究で，睡眠の障害は，代謝機能を障害し耐糖能障害を惹起し，Metsの形成に大きな役割を果たしていると考えられている。

SAS患者は，睡眠中に頻回に出現する上気道閉塞によって中途覚醒を余儀なくされ，必然的に睡眠が障害される。それに加え，無呼吸のためガス交換が障害され，間歇的な低酸素状態を呈する。この間歇的な低酸素血症が耐糖能を障害することは動物実験でも明らかにされており[27]，臨床的にもSHHSで，低酸素の程度と耐糖能異常とが有意に関連することが認められている。

すなわち，SASという病態は，睡眠障害と間歇的低酸素という耐糖能異常をもたらす2大要因を持っていることになり，Metsをもっとも形成しやすい病態といえるであろう。

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Research report

Self-help behaviors for sleep and depression: A Japanese nationwide general population survey

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ABSTRACT

Objective: The aim of this study was to examine the relationship between self-help behaviors for sleep (SHBS) and depression among the general adult population in Japan.
Methods: The survey was conducted in June 2000 using self-administered questionnaires for subjects living in 300 communities randomly selected throughout Japan. A total of 24,686 responses were analyzed from individuals aged 20 years or older. The Center for Epidemiologic Studies Depression Scale was used to assess the prevalence of depression with two cut-off points: 16 and 25. Details of 6 types of SHBS were asked, based on given examples of actual behavior and frequency.
Results: After adjusting for sociodemographic variables, sleep problems and other SHBS, multiple logistic regression analyses revealed that "snacking on food and/or beverages" was independently associated with an increased odds ratio for depression, whereas "maintaining lifestyle regularity" was independently associated with a decreased odds ratio for depression. "Drinking alcoholic beverages," "having a bath," and "reading books or listening to music" were associated with an increased odds ratio for depression in crude analyses, but the significance of the association disappeared after adjusting for sociodemographic variables, sleep problems and other SHBS.
Limitation: Complex constructs are being correlated.
Conclusions: These results suggest that individual SHBS are differentially associated with depression, thus providing important clues for establishing sleep hygiene for treatment and prevention of depression.

1. Introduction

Sleep disturbance is common among individuals suffering from depression, and it has been reported that 50–90% of patients with depression suffer from insomnia (Tsuno et al., 2005). Conversely, previous epidemiological studies have documented that 14–20% of individuals with insomnia were diagnosed as having depression (Ford and Kamerow, 1989; Mellinger et al., 1985). Recent findings in the field of sleep and depression research have indicated that insomnia is not only a symptom of, but also a risk factor for depression (Brabbins et al., 1993; Chang et al., 1997; Foley et al., 1999; Livingston et al., 1993; Paffenbarger et al., 1994).

It has been well demonstrated that antidepressant treatments significantly improve insomnia in depressive patients, even when no interventions are employed to treat insomnia (Benca, 2000). Recently, it has been reported that co-administration of hypnotics in addition to antidepressants leads to significantly greater improvement of insomnia and depressive symptoms in patients suffering from both (Fava et al., 2006; Londborg et al., 2000). A non-controlled study has

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suggested that cognitive-behavioral therapy (CBT) for insomnia is effective for ameliorating not only insomnia but also symptoms of depression (Taylor et al., 2007). A more recent randomized controlled study comparing antidepressant therapy with and without CBT for insomnia documented that additional CBT for insomnia improved depressive symptoms more effectively than drug therapy alone (Manber et al., 2008). The results obtained from these studies indicate that attempted interventions to improve insomnia in patients with depression may ameliorate coexisting depressive symptoms.

Most of those who experience insomnia, before visiting physicians, seem to cope by adopting self-help behaviors for sleep (SHBS) (Morin, 2004). Previous studies have reported that such SHBS include intake of alcohol or natural products, reading books, listening to music, mental relaxation techniques, and over-the-counter sleep medications (Ancoli-Israel and Roth, 1999; Morin et al., 2006). Some SHBS may allow individuals to cope successfully with insomnia, whereas others may not. Since insomnia is reported to be one of the earliest symptoms of depression (Jackson et al., 2003; Perlis et al., 1997), it is possible to consider that patients with depression might attempt SHBS in the early stage of the disorder. Moreover, SHBS in patients with insomnia might influence the risk of developing depression, given that attempted interventions to improve insomnia have been reported to influence depression with respect to hypnotic medication therapy and CBT for insomnia, in addition to treatment of depression (Fava et al., 2006; Londborg et al., 2000; Manber et al., 2008; Taylor et al., 2007). However, there has been virtually no information about the relationships between depression and SHBS.

In the present study we investigated the associations between SHBS and depression using a cross-sectional approach, based on epidemiologic data for a large sample of the general population of Japan. Our findings provide the first documented evidence that some SHBS have a positive or negative association with depression, providing important data for establishing sleep hygiene for the treatment and prevention of depression.

2. Methods

2.1. Selection of subjects

The present study was part of a national survey (Active Survey of Health and Welfare) conducted by the Ministry of Health, Labor and Welfare of Japan in June 2000. The Active Survey of Health and Welfare was conducted in 1996, 1997, 1999 and 2000 to provide the information required for establishing governmental health and welfare policies. To ensure that the survey sample was representative of the general population, study participants were selected from residents aged 12 years or over living in 300 target areas. These areas were selected randomly, through stratified sampling, from 881,851 areas included in the national census (2000). Part-time investigators paid by the public health center in each area delivered self-administered questionnaires to the subjects and collected the completed questionnaires a few days later. Oral informed consent to participate was obtained from the subjects, whose privacy was protected in accordance with Declaration of Helsinki guidelines.

2.2. Procedures

The self-administered questionnaire consisted of 44 items, including: (1) sociodemographic information such as age, gender, and size of the community, (2) general health status, (3) physical and psychological complaints, (4) information on mental stress, (5) sleep habits and sleep problems, and (6) the Japanese version of the Center for Epidemiologic Studies Depression Scale (CES-D) (Shima et al., 1985).

The CES-D, which is a 20-item inventory designed specifically to assess symptoms of depression in the general population, was used to screen for current depressive states during the period of one week leading up to the survey (Radloff, 1977). This questionnaire is adequately reliable and valid for use in a general population. The CES-D yields an item score (range: 0–3) and a sum of the 20-item scores (range: 0–60). Higher scores indicate increasing severity of depressive symptoms. Although this scale is designed to screen, but not diagnose, major depressive disorder, a score of 16 or higher is highly suggestive of symptoms of depression. In addition, a severe cut-off point has been assumed in several studies (Cho et al., 1998; Madianos et al., 1988; Nagase et al., 2009). We set a score of 25 or higher to define CES-D-25 depression as described previously (Kaneita et al., 2006), because the cut-off point of 16 demonstrated that nearly 30% of the Japanese adult population had depression, indicating an over-estimation of prevalence in comparison with Western countries (20% or less) (Barnes et al., 1988; Eaton and Kessler, 1981; Hsu and Marshall, 1987).

The following six questions about SHBS during the previous month were embedded in the questionnaire:

1. Do you drink alcoholic beverages? (None/Once or twice per month/Once or twice per week/Three times or more per week)
2. Do you snack on food and/or beverages? (Yes/No)
3. Do you take light exercise? (Yes/No)
4. Do you take a bath? (Yes/No)
5. Do you read a book or listen to music? (Yes/No)
6. Do you try to maintain lifestyle regularity? (Yes/No)

One of the four options ("None," "Once or twice per month," "Once or twice per week," or "Three times or more per week") was to be selected regarding use of alcohol. In the statistical analysis, these four optional categories were regrouped, if required, into two categories: the former two categories and the latter two (i.e., "Once or more per week" and "Less than once per week").

With regard to sleep duration, we asked the question, "What was your average sleep duration per night?" Participants who answered "less than 6 h" were categorized as having "short sleep duration".

For subjective sleep insufficiency, participants were asked to respond to the question, "Have you had sufficiently restful sleep?" by selecting one of the following four options: "Sufficient," "Fairly sufficient," "Rather insufficient," and "Completely insufficient". Those who selected the latter two options were categorized as having "subjective insufficient sleep".

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For hypnotic medications, participants were asked to respond to the question, "Did you take medicine, such as a hypnotic, during the previous month?" by selecting one of the following four options: "None/Once or twice per month/Once or twice per week/Three times or more per week." Because, in 2000, no over-the-counter hypnotic drug was available in Japan, those who selected the latter three options were categorized as using "taking hypnotic medication".

2.3. Statistical analysis

For statistical analysis, the CES-D scores were first calculated. To examine the association between sleep and CES-D scores, we calculated the CES-D scores based on responses to the remaining 19 questions after excluding one sleep question from the CES-D questionnaire. In addition, because some subjects may have omitted 5 or fewer answers on the CES-D questionnaire, we adjusted for CES-D scores using the following formula, to correct them as a conventional scale of 0 to 60: "CES-D score" = "sum of 19 item sores" × "20/19" × "19/number of answered questions." The prevalence of depression was calculated using two different cut-off points; 16 or higher (CES-D-16 depression) and 25 or higher (CES-D-25 depression). The effects of age and gender on the prevalence of depression were examined by χ^2 test. The mean value and standard deviation (S.D.) of the CES-D scores were calculated according to age and gender. The presence of SHBS was examined by age and gender. The associations of individual SHBS with CES-D-16 depression and that with CES-D-25 depression were examined. Multiple logistic regression analyses were utilized to examine the associations between depression and SHBS. In these analyses, CES-D-16 depression and CES-D-25 depression were separately taken as a response variable, and the following parameters were used as covariates: age group, size of community, short sleep duration, subjective sleep insufficiency, insomnia (difficulty initiating sleep, difficulty maintaining sleep, early morning awakening), and taking hypnotic medication. Odds ratios were calculated from both the crude analysis and the multiple logistic regression analysis with 95% confidence intervals. All analyses were performed using SPSS 16.0 for Windows.

3. Results

Questionnaires were returned by 32,729 subjects. As the Ministry of Health, Labor, and Welfare did not publish the number of residents contacted in the target areas, it was not possible to calculate the response rate for the present survey. The collection rates of similar investigations carried out 3 and 4 years earlier were 87.1% and 89.6%, respectively, and since the present survey was performed using similar methods, the response rate was estimated to be similar (Kaneita et al., 2006). Data from the following respondents were excluded from the analyses: (i) those who submitted blank answer forms (n = 707); (ii) those under 20 years of age, because the study was aimed at adults (n = 3086); (iii) those who did not respond to the questions on gender or age (n = 222); and (iv) those who neglected to answer six or more questions on the CES-D questionnaire (n = 4028). Finally, data from 24,686 adults were analyzed.

Although the percentages of both men and women aged 70 years or older were slightly less than those revealed by the census, the percentages of other age groups were similar (Table 1).

The prevalence of CES-D-16 depression and that of CES-D-25 depression, together with the mean value and S.D. of the CES-D scores sorted by gender and age groups, are shown in Table 2. Both CES-D-16 depression and CES-D-25 depression were more prevalent in women than in men ($\chi^2 = 52.61$, $df = 1$, $p < 0.01$ for CES-D-16 depression and $\chi^2 = 28.59$, $df = 1$, $p < 0.01$ for CES-D-25 depression). By age groups, both CES-D-16 depression and CES-D-25 depression were most frequent in those aged 70 years or older ($\chi^2 = 118.7$, $df = 5$, $p < 0.01$ for CES-D-16 depression and $\chi^2 = 171.2$, $df = 5$, $p < 0.01$ for CES-D-25 depression).

The prevalence of SHBS by gender and age group is shown in Table 3. The overall prevalence of SHBS differed significantly between men and women ($p < 0.01$). Male dominance was apparent for "drinking alcoholic beverages" (48.3% vs. 18.3%) and "snacking on food and/or beverages" (36.1% vs. 27.9%), whereas female dominance was apparent for "exercising" (29.4% vs. 26.2%), "having a bath" (64.4% vs. 59.0%), "reading books or listening to music" (49.4% vs. 43.4%) and "maintaining lifestyle regularity" (58.6% vs. 49.0%).

All types of SHBS differed significantly among age groups ($p < 0.01$). "Reading books or listening to music" was prevalent in the younger group (20–39 years), "drinking alcoholic beverages" and "snacking on food and/or beverages" were prevalent in the middle-aged group (40–59 years), and other types of SHBS were prevalent in the old-age group (60 years and over) for both men and women.

Table 4 shows the association between individual SHBS and depression. "Drinking alcoholic beverages," "snacking on food and/or beverages," "having a bath" and "reading books or listening to music" were associated with an increased odds ratio for CES-D-16 depression after adjustment for sociodemographic variables, sleep problems and other SHBS. "Maintaining lifestyle regularity" was associated with a decreased odds ratio for CES-D-16 depression after adjustment for sociodemographic variables, sleep problems and other SHBS. "Exercising" was associated with an increased odds ratio for CES-D-16 depression in the crude analysis, but not in the multivariate model after adjustment for sociodemographic variables, sleep problems and other SHBS.

Table 1
Percentages of study participants and the general population classified according to gender and age groups.

Age (year)	Present study (2000)		Census (2000)	
	Male	Female	Male	Female
20–29	18%	18%	19%	17%
30–39	18%	18%	18%	16%
40–49	19%	18%	17%	16%
50–59	21%	20%	20%	19%
60–69	15%	14%	15%	15%
70+	9%	12%	12%	17%
Total	100%	100%	100%	100%
n	11,752	12,934	48,669 (thousands)	52,067 (thousands)

Due to rounding, the percentages may not equal 100%.

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Table 2
Prevalence of Depression and Mean Center for Epidemiologic Studies Depression Scale (CES-D) score by gender and age group.

	CES-D-16 Depression			CES-D-25 Depression			Mean + S.D.
Age group (year)	Total (%)	Male (%)	Female (%)	Total (%)	Male (%)	Female (%)	CES-D Score
20–29	30.0	28.6	31.3	10.1	8.9	11.2	13.4 ± 8.4
30–39	26.3	23.2	29.2	7.7	6.2	9.1	12.5 ± 8.0
40–49	27.9	26.7	29.1	8.9	8.2	9.5	13.1 ± 8.1
50–59	26.6	24.4	28.7	7.6	6.6	8.7	12.9 ± 7.5
60–69	24.8	23.5	26.0	7.5	8.1	7.0	12.8 ± 7.7
70–	36.0	32.3	38.6	15.7	14.1	16.7	15.0 ± 9.2
Total	28.1	25.9	30.1	9.1	8.1	10.1	13.2 ± 8.1

CES-D-16 Depression was defined from the CES-D score using a cut-off point of 16 or higher.
CES-D-25 Depression was defined from the CES-D score using a cut-off point of 25 or higher.

"Snacking on food and/or beverages" was associated with an increased odds ratio for CES-D-25 depression after adjustment for sociodemographic variables, sleep problems and other SHBS (OR = 1.37, 95% CI = 1.20–1.58). "Maintaining lifestyle regularity" was associated with a decreased odds ratio for CES-D-25 depression after adjustment for sociodemographic variables, sleep problems and other SHBS (OR = 0.70, 95% CI = 0.61–0.80). "Drinking alcoholic beverages," "having a bath," and "reading books or listening to music" were associated with an increased odds ratio for CES-D-25 depression in the crude analysis, but only "drinking alcoholic beverages" remained significant after adjusting for sociodemographic variables and sleep problems. However, these associations disappeared in the multivariate model after adjustment for sociodemographic variables, sleep problems and other SHBS.

4. Discussion

This report represents one of the first attempts to investigate the association between SHBS and depression among the general adult population in Japan.

"Maintaining lifestyle regularity" was independently associated with a decreased odds ratio for CES-D-25 depression after adjustment for sociodemographic variables, sleep problems and other SHBS. Possible preventive effects of a regular lifestyle and possible risks of an irregular lifestyle on mental health have been documented in previous studies in clinical or community settings (Hayakawa et al., 2005; Regestein and Monk, 1995; Scott et al., 1997; Shen et al., 2008). Those studies indicated that shift work was a risk factor for mood disorders via the influences of an irregular lifestyle and psychological stress due to a shift work schedule. In their epidemiological survey, Scott et al. identified a high prevalence of major depressive disorder during or after shift work, and found that the longer an individual was engaged in shift work, there was a higher lifetime risk of depression. Shen and co-workers investigated 414 college students and found that lifestyle irregularity prospectively predicted the survival time to affective episodes during a 33-month study period. Depression was reported to be a prevalent comorbid condition with chronic lifestyle deterioration due to intrinsic circadian rhythm sleep disorders. Regestein et al. studied 33 sleep disorder clinic outpatients with delayed sleep phase syndrome and found that 25 (76%) of them were, or had been, depressed. Hayakawa et al. investigated 55 patients diagnosed as having non-24-hour sleep-wake syndrome and found that 34% of them without a history of mood disorders developed major depressive disorder after the onset of non-24-hour sleep-wake syndrome. These previous studies clearly demonstrated that an irregular lifestyle may have caused depression, and indicated that the likely pathophysiological mechanism was related to disruption of circadian rhythms, as has been proposed for classical circadian rhythm theories of mood disorders (Kripke, 1983; Wehr and Goodwin, 1981; Wehr et al., 1979).

In line with the above assumption, maintenance of lifestyle regularity may be considered to have a beneficial effect for patients with mood disorders (Ehlers et al., 1988; Frank et al., 1997; Frank et al., 1999; Leibenluft and Suppes, 1999). However, there has been no clear epidemiological evidence to confirm the favorable effect of such interventions. In the present cross-sectional study, we found, for the first time, a decreased odds ratio between depression and

Table 3
Prevalence of self-help behaviors for sleep by gender and age group.

	Male					Female					
	Total (%)	20–39 y (%)	40–59 y (%)	>60 y (%)	Sig. 1	Total (%)	20–39 y (%)	40–59 y (%)	>60 y (%)	Sig. 1	Sig. 2
Drinking alcoholic beverages	48.3	37.0	59.6	47.9	$\chi2 = 373.44$ *	18.3	16.8	23.5	11.5	$\chi2 = 123.98$ *	$\chi2 = 1848.08$ *
Snacks and/or beverages	36.1	36.1	40.0	27.4	$\chi2 = 62.82$ *	27.9	29.0	30.4	20.7	$\chi2 = 56.41$ *	$\chi2 = 127.85$ *
Exercising	26.2	23.6	27.3	30.3	$\chi2 = 25.04$ *	29.4	26.1	32.7	30.6	$\chi2 = 38.90$ *	$\chi2 = 21.77$ *
Taking a bath	59.0	50.4	64.2	68.1	$\chi2 = 191.03$ *	64.4	56.3	72.1	66.7	$\chi2 = 204.99$ *	$\chi2 = 52.75$ *
Reading a book or listening to music	43.4	48.8	38.9	39.5	$\chi2 = 74.70$ *	49.4	51.9	50.0	42.7	$\chi2 = 41.66$ *	$\chi2 = 60.65$ *
Maintaining lifestyle regularity	49.0	36.9	54.2	65.7	$\chi2 = 394.93$ *	58.6	49.8	63.6	67.8	$\chi2 = 224.92$ *	$\chi2 = 160.15$ *

Sig, significance.
Sig 1: $\chi2$ test, 2 (each SHBS-Yes or No; Drinking alcoholic beverages, Snacks and/or beverages, Exercising, Taking a bath, Reading a book or listening to music, Maintaining lifestyle regularity) × 3 (age groups; 20–39. 40–59, 61+).
Sig 2: $\chi2$ test, 2 (each SHBS-Yes or No; Drinking alcoholic beverages, Snacks and/or beverages, Exercising, Taking a bath, Reading a book or listening to music, Maintaining lifestyle regularity) × 2 (gender effect; male, female).
* $p<.01$.

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Table 4
Association between self-help behaviors for sleep and depression.

	CES-D-16 depression								CES-D-25 depression							
	Crude			Adjusted [a]			Adjusted [b]		Crude			Adjusted [a]			Adjusted [b]	
	OR	95%CI		OR	95%CI		OR	95%CI	OR	95%CI		OR	95%CI		OR	95%CI
Drinking alcoholic beverages																
No	1.00			1.00			1.00		1.00			1.00			1.00	
Yes	1.22	1.14–1.31	**	1.25	1.14–1.36	**	1.10	1.00–1.21	* 1.13	1.02–1.26	*	1.16	1.01–1.33	**	1.05	0.90–1.22
Snacks and/or beverages																
No	1.00			1.00			1.00		1.00			1.00			1.00	
Yes	1.67	1.55–1.79	**	1.56	1.44–1.69	**	1.44	1.31–1.57	** 1.54	1.38–1.72	**	1.41	1.24–1.59	**	1.37	1.20–1.58 **
Exercising																
No	1.00			1.00			1.00		1.00			1.00			1.00	
Yes	1.10	1.02–1.19	*	1.07	0.98–1.16		0.94	0.86–1.04	1.10	0.98–1.24		1.05	0.92–1.21		1.03	0.88–1.19
Taking a bath																
No	1.00			1.00			1.00		1.00			1.00			1.00	
Yes	1.33	1.24–1.43	**	1.34	1.24–1.45	**	1.28	1.17–1.40	** 1.16	1.04–1.30	*	1.12	0.99–1.27		1.08	0.94–1.24
Reading a book or listening to music																
No	1.00			1.00			1.00		1.00			1.00			1.00	
Yes	1.33	1.24–1.42	**	1.22	1.13–1.32	**	1.15	1.05–1.25	** 1.24	1.12–1.39	**	1.11	0.98–1.25		1.10	0.96–1.26
Maintaining lifestyle regularity																
No	1.00			1.00			1.00		1.00			1.00			1.00	
Yes	0.79	0.74–0.84	**	0.82	0.76–0.88	**	0.70	0.64–0.76	** 0.74	0.66–0.82	**	0.77	0.68–0.87	**	0.70	0.61–0.80 **

OR, adjusted odds ratio; CI, confidence interval.
[a] Adjusted for age group, sex, size of community, short sleep duration, subjective sleep insufficiency, insomnia (difficulty initiating sleep, difficulty maintaining sleep, early morning awakening), and taking hypnotic medication.
[b] Adjusted for age group, sex, size of community, short sleep duration, subjective sleep insufficiency, insomnia (difficulty initiating sleep, difficulty maintaining sleep, early morning awakening), taking hypnotic medication, and other SHBS.
* $p<.05$.
** $p<.01$.

relationship was not determined because of the limitation of the cross-sectional approach. From a clinical viewpoint, there may be several different interpretations regarding the association between lifestyle regularity and depression. One interpretation can be drawn from the hypothesized etiological roles of circadian rhythm disturbances on mood disorders (Kripke, 1983; Wehr and Goodwin, 1981; Wehr et al., 1979); subjects who had maintained lifestyle regularity were freer from depression risk than those who had not. In this survey, a considerable number of the sampled subjects had attempted to maintain lifestyle regularity to achieve sufficient sleep, but this might have been beneficial to their mental health independently of sleep states. Another possible interpretation can be derived in terms of depressive symptomatology; only subjects who did not suffer from depression were able to maintain lifestyle regularity because the hypoactive tendency attributable to psychomotor retardation, or the hyperactive tendency attributable to psychomotor agitation, together with severe insomnia in depressive patients, would have been likely to disturb lifestyle regularity (Monk et al., 1991; Szuba et al., 1992).

A prospective study is warranted to examine the causal relationship between maintenance of lifestyle regularity for obtaining enough sleep, and depression. Given the fact that maintaining a regular lifestyle to obtain sufficient sleep decreases the risk for depression, this SHBS may be included in clinical assessments for interventions aimed at prevention and treatment of depression.

"Snacking on food and/or beverages" to obtain enough sleep, which was found in 31.8% (male 36.1%, female 27.9%) of the adult general population in the present study, was depression. It has been well documented that hunger at bedtime disturbs the ability to fall asleep, finally leading to snacking before going to bed (Vanitallie, 2006). By contrast, eating an excessive amount of food before the bedtime is assumed to activate neural activities associated with digestion for several hours, and to disturb sleep quality thereafter. Likewise, most non-pharmacological interventions for insomnia, such as stimulus control therapy or sleep hygiene education, have indicated the potentially unfavorable effect of snacking on sleep (Morin, 2000). Since disturbed sleep naturally leads to an uncomfortable feeling or bad mood the following morning (American Psychiatric Association, 2000; American Academy of Sleep Medicine, 2005), it is possible to assume that snacking before bedtime may disturb mood by aggravating sleep quality. However, in the present study, the positive association between bedtime snacking and depression remained significant after adjustment for sociodemographic variables, sleep problems and other SHBS, indicating that this association was unlikely to be mediated by parameters of insomnia or sleep insufficiency. One possible interpretation can be made with respect to sleep apnea syndrome, which we did not use as a confounding factor in the present multivariate model. Many reports have indicated that chronic poor sleep quality due to obstructive sleep apnea, which is aggravated and sometimes caused by night-time eating and obesity, is frequently associated with depressive mood (Froese et al., 2008; Nabi et al., 2006; Ohayon, 2003; Peppard et al., 2006). It may also be possible to postulate that obesity associated with night-time eating may pose a risk for depression, since some epidemiological studies have

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indicated that obesity is a risk factor for depression (Roberts et al., 2003; Johnston et al., 2004; Ohayon and Hong, 2006; Onyike et al., 2003; Ross, 1994; Simon et al., 2006). A chronobiological interpretation may be derived based on the effect of feeding schedule on circadian rhythms (Grandin et al., 2006; Monk et al., 1991). Snacking before going to bed could disturb the timing of the circadian pacemaker. Disturbance of circadian rhythms and/or their dissociation of sleep timing have been postulated to be of etiological importance in the genesis of depression (Kripke, 1983; Wehr and Goodwin, 1981; Wehr et al., 1979). It is possible to interpret that "snacking on food and/or beverages" was a consequence of depressive symptomatology. Some patients with depression show an abnormally increased appetite and weight gain, although at a frequency lower than that of appetite loss. Previous studies have documented that 28–42% of depressed outpatients show increased appetite and weight during depressive episodes (Nierenberg et al., 1998; Robertson et al., 1996; Sidney et al., 1993). Therefore, in such depressed patients, the tendency to eat at bedtime might be influenced by an abnormally increased appetite. However, this possibility is unlikely because those who provided an affirmative response to this question primarily considered "snacking on food and/or beverages" to be a method for obtaining enough sleep.

Although further longitudinal studies are needed to replicate this finding, and to explore the causal link, snacking on food and/or beverages to obtain enough sleep may be considered a risk factor for depression. Because a considerable number of people sampled in this study attempted this SHBS, it will be important in future public health activities to inform the Japanese populace that snacking on food and/or beverages in order to obtain enough sleep may pose a risk for depression.

"Drinking alcoholic beverages," "having a bath," and "reading books or listening to music" were associated with an increased odds ratio for CES-D-25 depression in crude analyses, but only "drinking alcoholic beverages" remained significant after adjustment for sociodemographic variables and sleep problems. However, the significance of all these associations disappeared after adjustment for sociodemographic variables, sleep problems and other SHBS.

In the present study, "having a bath" and "reading books or listening to music" were associated with an increased odds ratio for depression in crude analysis. However, the significance of the association disappeared after adjustment for sociodemographic variables and sleep problems, suggesting that the associations between these SHBS and depression are mediated by sleep problems. Previous cross-sectional studies have found that the prevalence of "reading and listening to music" in insomniacs is higher than in non-insomniacs (Ancoli-Israel and Roth, 1999; Morin et al., 2006). Studies on the effects of bathing on sleep reported that bathing at an appropriate temperature (approximately 40 °C) before going to bed tended to deepen nocturnal sleep (Dorsey et al., 1996; Horne and Reid, 1985; Horne and Staff, 1983) in healthy subjects and to improve sleep efficiency in insomniacs (Dorsey et al., 1996). However, no studies have examined the relationship between these SHBS and depression. The association between drinking alcoholic beverages and depression remained significant after adjustment for sociodemographic variables and sleep problems, indicating that the association of drinking alcoholic beverages at bedtime with depression was partly a direct one. A prospective study is warranted to examine the complex interactions among SHBS, sleep problems and depression.

There were some limitations to this study. First, it was a cross-sectional one, and therefore causal relationships between SHBS and symptoms of depression could not be determined. Second, depression defined in this study may have included other psychiatric disorders such as anxiety disorders. Third, respondents who neglected to answer six or more questions out of 20 in the CES-D questionnaire were excluded from the analysis, and thus a non-response bias regarding CES-D may have been generated. Fourth, a self-reported approach was adopted, and the percentage of respondents aged 70 years or older was less than that of persons aged 70 years or older in the general population as revealed by the census. It was assumed that physical difficulties of old age, such as poor eyesight, difficulty in writing, long-term physical pain and low self-recognition for health, might have made it difficult for elderly subjects to respond to the questionnaire. Further improvements, such as the introduction of an interview method, would be helpful in the future. Fifth, questions on sociodemographic factors, such as working status, size of family, education, and income, were not included in the questionnaire. These factors could possibly influence both depression and SHBS. In future studies, items on the above-mentioned points, which were not included in the present study, must be included in the questionnaires in order to improve the validity of studies on SHBS and depression. Sixth, no previous study had demonstrated the reliability of the questions for assessing self-help behavior for sleep.

This report represents one of the first to investigate the association between SHBS and depression among the general adult population. It was concluded that individual SHBS were differentially associated with depression. These results may provide important clues for establishing sleep hygiene for treatment and prevention of depression, and appear to warrant further study of this issue.

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Conflict of interest

This was not an industry supported study. Dr. Uchiyama has received research support from Astellas, Meiji Seika, Nippon Boehringer Ingelheim, Pfizer Japan, Sanofi-Aventis, Schering Plough, and Takeda Pharmaceuticals; has consulted for Pfizer Japan, Sanofi-Aventis and Takeda Pharmaceuticals. All other authors declare that they have no conflicts of interest.

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(18603012, 2006–2007). The authors report no other financial affiliation or relationship relevant to the subject of the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.jad.2010.09.019.

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ORIGINAL ARTICLE

Obstructive sleep apnoea is associated with risk factors comprising the metabolic syndrome

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ABSTRACT

Background and objective: **Several features of OSA syndrome suggest that it is a manifestation of the metabolic syndrome (MS). In this study, we investigated the prevalence of the MS among male Japanese patients with OSA, as well as the relationship between OSA in non-obese patients and components of the MS other than obesity (hypertension, dyslipidaemia and glucose intolerance).**

Methods: **The study included 416 Japanese men who were diagnosed as having OSA by polysomnography. Among these, 101 non-obese patients were selected and the severity of OSA, as well as the prevalence of hypertension, dyslipidaemia and glucose intolerance, was assessed.**

Results: **The MS was associated with OSA in 218/416 patients (52.4%). A significant increase in the prevalence of the MS was associated with increased severity of OSA, as categorized according to AHI. In the non-obese patients with OSA (mean age 57.6 years, BMI 22.7 kg/m^2, AHI 34.3 events/h), hypertension, dyslipidaemia and glucose intolerance were identified in 70 (69.3%), 43 (42.6%) and 20 patients (19.8%), respectively. At least two of these factors were identified in 40 patients (39.6%). Non-obese patients with severe OSA had a significantly higher prevalence of two or more of these factors (33/59 patients, 55.9%).**

Conclusions: **Although Asians are generally less obese than Caucasians, the prevalence of the MS was high among Japanese patients with OSA, and even among non-obese patients, OSA was associated with risk factors for the MS.**

Key words: hypoxaemia, insulin resistance, metabolic syndrome, obesity, obstructive sleep apnoea.

SUMMARY AT A GLANCE

The prevalence of the metabolic syndrome (MS), as well as the relationship between OSA in non-obese patients and components of the MS, was assessed in Japanese patients with OSA. Early identification of metabolic risk factors, including hypertension, dyslipidaemia and glucose intolerance, may be beneficial in the clinical management of OSA, especially in non-obese patients.

INTRODUCTION

OSA syndrome is a common condition that affects 4% of middle-aged men and 2% of middle-aged women, as reported by the Wisconsin Sleep Cohort Study.[1] OSA can influence survival if it leads to the progression of arteriosclerosis and cardiovascular disease.[2] One of the classical risk factors for OSA is obesity.[3] The metabolic syndrome (MS) is caused by the accumulation of visceral fat and an increase in insulin resistance.[4] It has been suggested that adipose tissue is the most important endocrine organ in the human body, as it secretes numerous cytokines and hormones. An increase in the amount of visceral fat may lead to abnormalities in the levels of various cytokines/adipocytokines that are related to the progression of arteriosclerosis, and such changes may also constitute the molecular basis of the MS.

OSA is most common in middle-aged men, especially those with lifestyle-related diseases, such as obesity, hypertension, hyperlipidaemia and diabetes. It is now recognized that OSA is closely related to the MS. Thus, OSA is associated with the accumulation of visceral fat, which is an essential requirement for diagnosis of the MS, and OSA may also be related to other metabolic abnormalities that comprise the diagnostic criteria for the MS. The lifestyles of Asian people have become more westernized, although they are still generally less obese than Westerners. It is

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unclear whether OSA is related to components of the MS other than obesity, and whether OSA promotes progression of the MS.

In the present study, the prevalence of the MS among male Japanese patients with OSA was investigated. In addition, the relationship between OSA in non-obese patients and three components of the MS (high blood pressure, dyslipidaemia and glucose intolerance) was assessed, in order to examine the possibility that the pathogenesis of OSA is related to that of the MS.

METHODS

Subjects

The study included 416 Japanese men who presented to Nihon University Itabashi Hospital between April 2007 and March 2008, with a history of snoring, and witnessed episodes of apnoea during sleep or daytime sleepiness, and who were diagnosed as having OSA by polysomnography (PSG) (Alice 4, Respironics Inc., Pittsburgh, PA, USA). None of the patients had other respiratory problems such as COPD or heart failure. The study was approved by the Research Ethics Committee of Nihon University Itabashi Hospital and informed consent was obtained from all patients.

Subjects were questioned about their sleep, past medical history and use of medications. Body measurements, physical examination, CXR and electrocardiography were performed. Lung function was assessed (CHESTAC 8800 spirometer, Chest MI Inc., Tokyo, Japan), and an arterial blood sample for measurement of PaO_2 and $PaCO_2$ was collected with the subject in the supine position. OSA was diagnosed if the patient had relevant symptoms, such as daytime sleepiness, and an AHI of >5/h on PSG.[5]

Polysomnography included recording of the electroencephalogram at C_3/M_2 and C_4/M_1, the right and left electrooculograms, the submental and bilateral anterior tibialis electromyograms, the ECG and changes in body position. Respiration was monitored with a nasal pressure transducer, thermocouples at the nose and mouth, and thoracic and abdominal strain gauges. SaO_2 was monitored with an oximeter. Apnoea was defined as the absence of airflow for at least 10 s, as indicated by the thermistors and nasal cannula. Hypopnoea was defined as a reduction in airflow by at least 30%, lasting for at least 10 s, and associated with a 4% decrease in oxyhaemoglobin saturation or arousal, as indicated by the electroencephalogram. The AHI was calculated as the number of episodes of apnoea and/or hypopnoea per hour of sleep. PSG data were recorded overnight in the sleep laboratory between 21:00 and 06:00. The data for each patient were analysed manually according to standard criteria.[6] Blood pressure was measured twice in the outpatient clinic (between 09:00 and 11:00), with the patient in the sitting position after 5 min of rest. Fasting samples were obtained for haematology tests, biochemistry tests (total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol, fasting plasma glucose and HbA_{1C}) and urinalysis.

The MS was identified in accordance with the Japanese Diagnostic Standards for Metabolic Syndrome (2005).[7] MS was diagnosed if the waist circumference at the umbilicus was ≥85 cm in men or ≥90 cm in women, and the subject also had at least two of the following abnormalities: high blood pressure (systolic pressure ≥130 mm Hg and/or diastolic pressure ≥85 mm Hg), dyslipidaemia (TG ≥ 1.7 mmol/L and/or high-density lipoprotein cholesterol < 1.04 mmol/L) and fasting hyperglycaemia (fasting plasma glucose ≥6.1 mmol/L). Patients who were already receiving therapy for hypertension, hyperlipidaemia or diabetes were considered to have these diseases.

Non-obese patients with OSA were defined as having a BMI < 25.0 kg/m^2 and a waist circumference < 85 cm. Abnormal blood pressure, dyslipidaemia and glucose intolerance were investigated in these patients.

Statistical analyses

Results are presented as mean ± SD. The chi-square test was used to analyse the prevalence of the MS among patients stratified by the severity of OSA, as categorized according to AHI. The level of significance was set at $P < 0.05$. All statistical analyses were performed using the StatView version 5.0 software package (SAS Institute Inc., Cary, NC, USA).

RESULTS

Table 1 shows the sleep parameters, biochemical data, including lipid and blood glucose levels, and

Table 1 Demographic characteristics and metabolic parameters in the patients with OSA

Characteristic	
Number of patients	416
Age, years	52.8 ± 13.7
BMI, kg/m^2	28.0 ± 4.8
Waist circumference, cm	95.2 ± 11.9
AHI, events/h	46.6 ± 23.0
Arousal index, events/h	41.8 ± 21.7
Mean SaO_2, %	93.6 ± 3.4
Lowest SaO_2, %	74.9 ± 10.8
Systolic BP, mm Hg	134.3 ± 17.1
Diastolic BP, mm Hg	86.5 ± 10.9
Serum TC, mmol/L (normal 3.4–5.7)	5.3 ± 1.0
Serum HDL-C, mmol/L (normal 0.9–2.2)	1.3 ± 0.3
Serum TG, mmol/L (normal 0.6–1.7)	2.1 ± 1.5
FPG, mmol/L (normal 3.9–6.1)	6.3 ± 1.5
HbA_{1C}, % (normal 4.3–5.8)	5.7 ± 0.9

Values are mean ± SD.

BP, blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

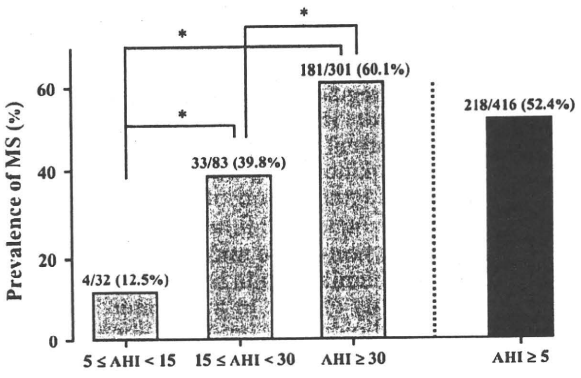

Figure 1 Prevalence of the metabolic syndrome (MS) in patients with OSA, stratified according to AHI. *$P < 0.01$.

other baseline measurements for the 416 men who were diagnosed as having OSA by PSG. Patients who were receiving therapy for hypertension, hyperlipidaemia or diabetes were considered to have these diseases. The mean age of the patients was 52.8 years and the mean BMI was 28.0 kg/m^2. Severe OSA was identified in 301 patients. The prevalence of the MS among patients with OSA was high at 52.4% (218/416 patients). When OSA was categorized as mild, moderate or severe, the prevalence of the MS was 12.5% (4/32 patients), 39.8% (33/83) and 60.1% (181/301) in these subgroups of patients. Although the number of patients varied between these subgroups, there was a significant increase in the prevalence of the MS with increasing severity of OSA (Fig. 1).

There were 101 non-obese patients with OSA (BMI < 25.0 kg/m^2 and waist circumference < 85 cm). Table 2 shows the sleep parameters, biochemical data and other baseline measurements for these patients. The mean age was 57.6 years and mean BMI was 22.7 kg/m^2. PSG revealed severe OSA in 59 patients. The prevalence of hypertension, dyslipidaemia and glucose intolerance was 69.3% (70/101 patients), 42.6% (43/101) and 19.8% (20/101), respectively. At least two of these factors were identified in 39.6% (40/101) of the non-obese patients with OSA, including 11.8% (2/17), 20.0% (5/25) and 55.9% (33/59) of those with mild, moderate or severe OSA, respectively. Although the number of non-obese patients in these OSA subgroups varied, the prevalence of at least two factors was significantly higher in the subgroup with severe OSA ($P < 0.01$).

DISCUSSION

The MS includes a constellation of metabolic derangements, including central obesity, hypertension, dyslipidaemia and glucose intolerance.[8,9] The majority of patients with OSA are also obese, and conditions related to obesity, such as hypertension, dyslipidaemia and glucose intolerance, may play a role in the development of cardiovascular disease. However, it is not clear whether OSA directly contributes to development of the MS and related disorders.

Table 2 Demographic characteristics and metabolic parameters in the non-obese patients with OSA

Characteristic	
Number of patients	101
Age, years	57.6 ± 13.5
BMI, kg/m^2	22.7 ± 1.8
Waist circumference, cm	79.1 ± 5.3
AHI, events/h	34.3 ± 16.7
Arousal index, events/h	34.0 ± 14.6
Mean SaO_2, %	95.4 ± 1.7
Lowest SaO_2, %	79.4 ± 7.3
Systolic BP, mm Hg	131.4 ± 17.5
Diastolic BP, mm Hg	83.1 ± 9.8
Subjects with hypertension	70/101 (69.3%)
Serum TC, mmol/L (normal 3.4–5.7)	5.2 ± 0.9
Serum HDL-C, mmol/L (normal 0.9–2.2)	1.3 ± 0.3
Serum TG, mmol/L (normal 0.6–1.7)	1.7 ± 1.6
Subjects with dyslipidaemia	43/101 (42.6%)
FPG, mmol/L (normal 3.9–6.1)	5.8 ± 0.9
HbA_{1C}, % (normal 4.3–5.8)	5.7 ± 0.9
Subjects with hyperglycaemia	20/101 (19.8%)
Subjects with at least two of hypertension, dyslipidaemia and hyperglycaemia	40/101 (39.6%)

Values are mean ± SD or number of patients (%).
BP, blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

The main findings from the present study can be summarized as follows. First, the overall prevalence of the MS among Japanese men with OSA was 52.4% (218/416 patients). The prevalence of the MS increased with increasing severity of OSA, as stratified according to the AHI, and the MS was identified in 60.1% of patients with severe OSA. Interestingly, comparison with the results of the 2004 National Health/Nutrition Survey by the Japanese Ministry of Health, Labour and Welfare, suggests that the prevalence of the MS was higher in OSA patients in the present study than in the general population (52.4% vs 23.4%), although direct statistical comparison of the data is not possible. Thus, it may be concluded that Japanese patients with OSA are very likely to suffer from the MS. Second, 39.6% of non-obese patients with OSA had at least two of components of the MS other than obesity (hypertension, dyslipidaemia and/or glucose intolerance). This suggests that even non-obese patients with OSA may have multiple metabolic abnormalities and that OSA *per se* may play a role in the development of the MS, independently of obesity.

Obesity, with accumulation of visceral fat, is an important risk factor for both OSA and the MS. According to the 2005 'Sleep in America' survey, one in every four adults in the USA is obese, and 57% of obese people have OSA.[10] Young *et al.*[11] suggested that sleep-disordered breathing (SDB) was related to weight gain in 41%–58% of patients aged 30–69 years. Accumulation of visceral fat is significantly correlated with AHI and low SaO_2, which are indicators of the

severity of OSA,[12] while nasal CPAP therapy decreases the accumulation of visceral fat and reduces serum leptin levels, without any change in bodyweight.[13] Therefore, OSA may be closely related to obesity, with accumulation of visceral fat, which is an important factor in the pathogenesis of the MS.

Coughlin *et al.* reported that the MS occurred in 87% of OSA patients,[14] which was a far greater prevalence than in the present study. However, the mean BMI in those OSA patients was 35.8 ± 0.9 kg/m^2, while in the present population it was 28.0 ± 4.8 kg/m^2. Thus, the difference in the prevalence of the MS among OSA patients in the two studies is presumably attributable to ethnic differences in BMI and/or craniofacial anatomy between Westerners and Asians. It was previously reported that the prevalence of the MS in Japan was 49.5% among men with OSA (n = 719, mean BMI 27.7 ± 0.2 kg/m^2) and 59.0% among men with severe OSA.[15] In the present study, the MS was identified in 52.4% of the 416 patients with OSA and 60.1% of those with severe OSA, which was not appreciably different from the previously reported prevalence among Japanese patients with OSA.

Insulin resistance and the accumulation of visceral fat appear to be key factors in the pathogenesis of the MS, and it has been suggested that OSA is also related to insulin resistance.[16,17] Epidemiological data from the Sleep Heart Health Study suggested that patients with mild or moderate to severe OSA have an increased risk of fasting glucose intolerance,[18] and that the hypoxaemia caused by SDB was significantly correlated with insulin resistance. In patients with dyslipidaemia, abnormalities in various lipid parameters (except cholesterol) have been reported to increase with increasing AHI.[19] In the Wisconsin Sleep Cohort Study, the contribution of AHI ≥ 15 to diabetes was 2.3-fold greater than that of AHI < 5.[20] Thus, the severity of OSA may influence insulin resistance, although concomitant obesity with accumulation of visceral fat represents a greater risk for insulin resistance.

CPAP therapy significantly improved insulin sensitivity,[21] and decreased HbA_{1C} in OSA patients with type 2 diabetes.[22] Cholesterol levels also decreased after 4 weeks of CPAP therapy,[23] and a number of studies have demonstrated that treatment of OSA leads to a decrease in blood pressure.[24–27] OSA has various adverse metabolic effects, but adequate treatment reverses these to a considerable extent. However, the detailed mechanisms by which OSA influences hypertension, insulin resistance, glucose intolerance and dyslipidaemia have not been elucidated.

An earlier study by Parish *et al.*[28] indicated that the prevalence of the MS was significantly correlated with the severity of OSA (n = 228, mean BMI 32.2 ± 7.7 kg/m^2). In addition, the present study showed that at least two components of the MS were present in 39.6% of non-obese patients with OSA. This was a relatively high prevalence compared with that reported for the general Japanese population in the 2004 National Health/Nutrition Survey (23.4%). Therefore, it may be useful for clinicians to include assessment of components of the MS in their evaluation of non-obese patients with OSA.

OSA may promote the onset of the MS through several mechanisms, including enhanced sympathetic activity, intermittent hypoxaemia, fragmentation of sleep, dysregulation of the hypothalamic-pituitary-adrenal axis, impaired vascular endothelial function, and abnormal production of inflammatory cytokines and adipokines.[29] In particular, intermittent hypoxaemia and fragmentation of sleep caused by SDB may influence metabolic function. Iiyori *et al.*[30] reported that when non-obese mice were exposed to intermittent hypoxaemia, insulin resistance occurred independently of any change in autonomic activity, together with dyslipidaemia and an increase in hepatic TG.[31] When mice exposed to intermittent hypoxaemia were fed a high-cholesterol diet, both dyslipidaemia and progression of arteriosclerosis were observed.[32] These data strongly suggest that intermittent hypoxaemia may induce or promote metabolic abnormalities.

Fragmentation of sleep in patients with OSA may also be a risk factor for the MS. Spiegel *et al.*[33] observed enhanced sympathetic activity and impaired secretion of insulin in healthy young people who were subjected to sleep deprivation for 6 days. When deep sleep was inhibited, insulin sensitivity decreased and fragmentation of sleep was correlated with plasma catecholamine levels.[34] Thus, insufficient or fragmented sleep due to OSA may promote catecholamine secretion and enhance sympathetic activity, resulting in adverse effects on insulin sensitivity and metabolic function. Interestingly, insufficient or fragmented sleep may also influence the neuroendocrine regulation of hunger and appetite through factors such as leptin and ghrelin.[35] Thus, insufficient or fragmented sleep in patients with OSA may be a risk factor for increased weight and accumulation of visceral fat by affecting energy balance, thereby resulting in the development of the MS. In the present study, the prevalence of at least two components of the MS was significantly higher in the subgroup of non-obese patients with severe OSA, suggesting that OSA may predispose even non-obese patients to developing components of the MS.

There are several limitations to the present study that need consideration. First, given the cross-sectional nature of the study, inferences regarding causal relationships were not possible and it could not be determined whether OSA directly enhances risk factors for the MS. Second, the study only included Japanese men with OSA, and there was no healthy control group that was matched for age, waist circumference and BMI. Therefore, the results cannot be extrapolated to other cohorts or ethnic groups. Finally, the non-obese subjects were defined as having both a BMI < 25.0 kg/m^2 and a waist circumference < 85 cm, in order to exclude suspected central obesity, as defined by national health/nutrition surveys in Japan. However, accumulation of visceral fat, which is an important contributor to metabolic dysfunction, was not directly assessed by abdominal CT or MRI.

In conclusion, the present study demonstrated that the prevalence of the MS was high among Japanese male patients with OSA, and that it increased with increasing severity of OSA. Asians are generally less

obese than Westerners, but risk factors for the MS, including hypertension, dyslipidaemia and glucose intolerance, were identified even in non-obese patients with OSA. Early identification of such metabolic risk factors may be beneficial in the clinical management of OSA.

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ORIGINAL ARTICLE

Insomnia symptoms associated with hyperglycemia

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Abstract

In recent years, insomnia and short sleep duration have been reported to worsen glucose tolerance. Because only a few prospective studies have investigated this issue in Japan, various aspects have yet to be elucidated. Therefore, we conducted a 2-year prospective study of Japanese local residents in order to examine the association between the onset of glucose tolerance disorders and insomnia/short sleep duration. In 2005 and 2007, residents of a rural community in Aomori Prefecture, Japan, were sent a self-administered questionnaire, and peripheral blood samples were collected to measure their fasting plasma glucose levels. A total of 497 residents participated in both of the surveys. The incidence of hyperglycemia was calculated as the number of people who had had neither hyperglycemia nor diabetes mellitus at the baseline survey but had eventually developed hyperglycemia at the time of the follow-up survey. Logistic regression analyses were used to examine the association between the onset of hyperglycemia and insomnia/sleep duration. Depression status, which had not been adjusted for in previous studies, was included as a covariate in the logistic regression analyses. A total of 429 participants had neither hyperglycemia nor diabetes mellitus at the baseline; of these, 12 were found to have hyperglycemia at the follow-up survey. Thus, the calculated incidence of hyperglycemia was 2.8%. Multiple logistic regression analyses revealed that the odds ratio for difficulty in initiating sleep with regard to the onset of hyperglycemia was 5.27 (95% confidence interval, 1.48–18.77; $P = 0.01$). Difficulty in initiating sleep is a risk factor for hyperglycemia.

Key words: diabetes, epidemiology, impaired fasting glucose, sleep disorder.

INTRODUCTION

Factors such as a family history or genetic background of diabetes mellitus, obesity,[1–3] aging,[4] smoking,[5–7] exercise habits,[8–10] and eating habits[11–13] are known to affect the onset of diabetes mellitus. In recent years, the association of sleep disorders such as short sleep duration and insomnia with worsening of glucose tolerance and the onset of diabetes has been studied.[14–18]

From a physiological viewpoint, insomnia stimulates the cerebral cortex, cerebral limbic system, and hypothalamus; this induces secretion of catecholamine from the sympathetic ganglia and adrenal medulla, and secretion of cortisol from the pituitary-adrenal system.[19] These hormones may in turn increase the level of plasma glucose. Furthermore, several studies have revealed that sleep restriction increases the blood cortisol concentration and insulin resistance.[20–22]

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Previous epidemiological cross-sectional studies of the association between sleep and diabetes mellitus have revealed that the prevalence of sleep disorders, such as difficulty in initiating sleep, maintaining sleep, and remaining alert, is higher in patients with diabetes.[23,24] Several prospective studies in Western countries have reported that glucose tolerance is worsened by sleep disorders such as short sleep duration, difficulty in initiating sleep, and difficulty in maintaining sleep.[16,17,25] Our previous cross-sectional study of the residents of a Japanese rural community revealed a U-shaped association between sleep duration and HbA_{1c} (hemoglobinA_1c) level: the HbA_{1c} level was higher in subjects with shorter or longer sleep duration than in those with normal sleep duration.[26] Prospective studies by Kawakami *et al.* which followed 2649 employees over 8 years,[27] and by Hayashino *et al.* which followed 6509 employees over 4.2 years,[28] found an association between insomnia and the risk of diabetes onset.

To date, these are the only two large-scale prospective epidemiological studies conducted in the Japanese general population to have found an association between sleep and diabetes onset. As the subjects of those studies were limited to employees, they may not have been wholly representative of the general population of Japan. Therefore, we conducted a prospective study to clarify the association between insomnia and impaired glucose tolerance among residents of a rural community.

METHODS

Subjects

The study population comprised residents of Iwaki-machi (a municipality name that is now defunct due to elimination and consolidation of local municipalities), Nakatsugaru-gun, Aomori, Japan. We started a longitudinal survey in 2005 to collect and accumulate data on the lifestyle habits and health status of the local residents in order to contribute to the maintenance and promotion of their health. We recruited all adult residents of the community to participate in this study and did not perform sampling. Thus, the distributions of gender and age were not considered. From the 1067 people who participated in the survey conducted in 2005, the base year of this prospective study, 497 (male, 187; female, 310) also participated in the follow-up survey conducted in 2007. The data for these 497 subjects were used for all analyses.

Data collection

The baseline survey was conducted from 19–28 April 2005, and the follow-up survey from 15–26 April 2007. For both surveys, the local residents were asked to visit the Iwaki-machi Municipal Health and Welfare Center for data collection after we had mailed written notifications and self-administered questionnaires to the participants beforehand, and instructed them to bring the questionnaires on the days of the survey. At the time of collection, we confirmed whether the questionnaires were complete; participants who had submitted an incomplete questionnaire were instructed to complete the missing parts immediately. The questionnaire included items on history of diabetes, presence/absence of diseases for which the patient was receiving treatment at the time, smoking status, exercise habits, sleep habits, depression quotient, physical parameters (height, weight, and blood pressure), laboratory parameters, electrocardiogram, and X-ray findings. Plasma was separated from the blood samples, refrigerated, and then sent to a laboratory for measurement of plasma glucose levels using an enzymatic method. The Japanese version of the Center for Epidemiologic Studies Depression Scale (CES-D)[29] was used to assess the depression quotient. The CES-D, which is a 20-item inventory designed specifically to assess symptoms of depression in the general population, was used to screen for current depressive states. The CES-D yields an item score (range, 0–3) and the sum of the scores for the 20 items is determined (range, 0–60). Higher scores indicate increasing severity of depression symptoms. Although this scale is designed to screen, but not diagnose, major depression, a score of 16 or higher is highly suggestive of symptoms of depression. Shima *et al.* developed the Japanese version of the CES-D, examined its reliability and validity, and recommended that the cut-off point be set at 16, as with the US version of the CES-D.[30]

Questions included in the self-administered questionnaire

Seven questions on sleep during the past month included in the self-administered questionnaire were as follows:

1 (Sleep duration): What was your actual daily sleep duration? Please also include the duration of your naps.
2 (Difficulty initiating sleep [DIS]): How often did you find it difficult to fall asleep within 30 min of retiring to bed?

3 (Difficulty remaining alert): How often did you have trouble staying alert when you were required to refrain from sleep (at work, etc.)?
4 (Difficulty maintaining sleep [DMS]): How often do you find it difficult to go back to sleep after you have woken up during the night or too early in the morning?
5 (Use of hypnotic medication): How often have you taken medication to induce sleep?
6 (Use of the toilet): How often have you found it difficult to resume sleep after getting up in the middle of the night to use the toilet?
7 (Pain): How often have you found it difficult to fall asleep because of pain?

The subjects were instructed to answer question 1 by entering the value of their average daily sleep duration. For questions 2 to 7, the following four options were provided: (a) never; (b) less than once per week; (c) once or twice per week; and (d) three times or more per week. For each question, subjects who selected (c) or (d) as the answer were considered to have the symptoms related to the question.

For questions on sleep, we used part of the Japanese version of the Pittsburgh Sleep Quality Index (PSQI) without modification.

With regard to smoking, the current smoking status was taken as the reference. If a subject did not smoke at the time of the survey, he/she was classified as a non-smoker even if he/she had a history of smoking.

With regard to exercise habits, for the question "Do you exercise regularly?," the following five options were provided: (a) seldom; (b) once a week; (c) twice or three times a week; (d) four or five times a week; and (e) nearly every day. Those who selected (b) (c) (d), or (e) were considered to be those who routinely exercise.

Definition of high fasting plasma glucose level

For the purpose of our analyses, we defined hyperglycemia as a fasting plasma glucose level of ≥100 mg/dL. Recently, this level has often been used by the Japan Diabetes Society and the American Diabetes Association as a cut-off point for assessing the risk of glucose tolerance disorders, including diabetes mellitus.[31] As stipulated for the particular health check-up system initiated in Japan in 2008, detection of this high plasma glucose level is considered to indicate the need for health counseling.[32]

Statistical analyses

First, we calculated the prevalence of hyperglycemia in 2005 and 2007. Then, after identifying subjects whose fasting glucose level was <100 mg/dL and who did not have a medical history of diabetes mellitus at the time of the baseline survey, we calculated the incidence of new-onset hyperglycemia over the 2 years. Finally, we conducted logistic regression analyses to determine the association between sleep habits and the onset of hyperglycemia. We considered the incidence of new-onset hyperglycemia between 2005 and 2007 as the response variable, and used the following items as covariates: age of the subjects in 2005, gender, body mass index (BMI), smoking status, presence/absence of exercise habits, systolic blood pressure, difficulty in initiating sleep, difficulty in remaining alert, difficulty in maintaining sleep, use of hypnotic medication, use of the restroom during the night, experiencing pain, sleep duration, high-density lipoprotein level, triglyceride level, and CES-D score. We also performed gender-specific logistic regression analyses. SPSS 14.0J for Windows (SPSS, Chicago, IL, USA) was used for all statistical analyses.

Ethical considerations

We obtained approval from the ethics committee of our institution prior to initiation of the study. The survey details and the purpose of the study were explained both verbally and on a printed form to the participants, and they were instructed to sign the consent forms for participation. The privacy of the participants was strictly protected.

RESULTS

The number of participants in the baseline survey and the follow-up survey was 1067 and 814, respectively. Of these participants, 497 participated in both surveys. In the baseline survey, 68 participants had a fasting glucose level of ≥100 mg/dL or a medical or treatment history of diabetes mellitus, while 429 participants had a fasting glucose level of <100 mg/dL and had neither a medical nor a treatment history of diabetes mellitus (Table 1: Changes in the plasma glucose levels of the participants in 2005 and 2007). Among these 429 participants, the fasting glucose level in 12 increased to ≥100 mg/dL at the follow-up survey; the incidence of hyperglycemia was 2.8% during this time period (Table 2). No participants were diagnosed as having diabetes mellitus at any medical institution during these 2 years.

Table 1 Changes in the plasma glucose levels of the participants in 2005 and 2007

	In 2007 FPG < 100 mg/dL	In 2007 FPG ≥ 100 mg/dL	Total (%)
In 2005 FPG <100 mg/dL and history of diabetes (–)	417 (83.9)	12 (2.4)	429 (86.3)
In 2005 FPG ≥ 100 mg/dL or history of diabetes (+)	26 (5.2)	42 (8.5)	68 (13.7)
Total	443 (89.1)	54 (10.9)	497 (100.0)

FPG, fasting plasma glucose.

The results of logistic regression analyses are presented in Table 3. The results of univariate logistic regression analyses showed that the incidence of hyperglycemia was significantly associated with that of systolic blood pressure ($P = 0.02$), difficulty in initiating sleep ($P < 0.01$), and difficulty in maintaining sleep ($P = 0.02$). The results of multiple logistic regression analyses revealed a significant association between difficulty in initiating sleep and the incidence of hyperglycemia after 2 years ($P = 0.01$; adjusted odds ratio [OR], 5.27; 95% confidence interval [CI], 1.48–18.77).

The results of gender-specific analyses are presented in Table 4. The univariate analysis showed significantly high odds ratios between new onset of hyperglycemia and difficulty in initiating sleep for both men and women (males: $P = 0.04$; crude OR, 5.48; 95% CI, 1.04–28.83, females: $P = 0.01$; crude OR, 8.60; 95% CI, 1.53–48.27). However, the multivariate analysis showed a significantly high odds ratio only in women ($P = 0.02$; adjusted OR, 7.91; 95% CI, 1.38–45.42).

DISCUSSION

Many epidemiological studies of sleep disorders and impaired glucose tolerance have been conducted in Western countries.[14–17] However, only two large-scale epidemiological prospective studies – one by Kawakami *et al.*[27] and the other by Hayashino[28] – have been conducted with a Japanese cohort; the study populations in their studies were limited to employees. Our prospective study was significant in that it included residents of a local Japanese community, and our results suggested that difficulty in initiating sleep may be a risk factor for hyperglycemia, which might develop after 2 years of sleep disturbance.

Spiegel *et al.* demonstrated that insomnia could be a risk factor for impaired glucose tolerance on the basis of physiological experiments that measured the levels of various hormones such as catecholamines and cortisol.[21,22] In addition, it has been reported that adrenocorticotropic hormone (ACTH) and cortisol secretion were significantly higher in patients with chronic insomnia symptoms than in non-insomnia controls. As the severity of insomnia increased, the levels of hormones also increased; in addition, sympathetic nervous system activity increased, and a higher blood noradrenaline concentration was observed.[19,33] Such endocrinological changes accompanying insomnia are considered to induce an increase in the plasma glucose level. Recently, sleep and appetite-regulating hormones (leptin and ghrelin) were also reported to be closely associated with saccharometabolism: when sleep was prevented, the blood leptin concentration decreased and the blood ghrelin concentration increased, which led to an increase in appetite and a sense of hunger.[34–36] Furthermore, the melanin-concentrating hormone (MCH) system, which is considered to regulate these hormones, is reportedly involved in sleep as well as eating habits, energy metabolism, and stress responses such as depression and anxiety;[37] therefore, it was inferred that insomnia induces dysregulation of these hormones, which in turn increases insulin resistance, and consequently, an increase in blood glucose levels. Future epidemiological studies should include measurements of the blood concentrations of these hormones.

Nilsson *et al.* conducted a cohort study involving 6599 Swedish men and investigated the association between difficulty in initiating sleep and impaired glucose tolerance; they reported that glucose tolerance worsened in subjects with insomnia, including those having difficulty in initiating sleep and those who used hypnotic medication.[18] Large-scale prospective studies with Japanese subjects were conducted by Kawakami *et al.*[27] and Hayashino *et al.*[28] Kawakami *et al.* followed up 2649 employees over 8 years, and Hayashino *et al.* followed up 6509 employees over 4.2 years; the results of both studies indicated that difficulty in initiating sleep could be a risk factor for diabetes mellitus. The

Table 2 Incidence of hyperglycemia

		Incidence of hyperglycemia	
	n	%	95% CI
Overall	429	2.8	0.0–12.1
Gender			
Male	155	3.9	0.9–6.9
Female	274	2.2	0.5–3.9
Age classification (years)			
<50	112	0.9	0.0–2.6
50–59	109	1.8	0.0–4.3
60–69	134	4.5	1.0–8.0
70≤	74	4.1	0.0–8.6
BMI			
<25	311	2.6	0.8–4.4
≥25	118	3.4	0.1–6.7
Systolic blood pressure			
<130	246	1.2	0.0–2.6
≥130	183	4.9	1.8–8.0
Smoking			
No	358	2.8	1.1–4.5
Yes	71	2.8	0.6–6.6
Exercise			
No	334	2.1	0.6–3.6
Yes	95	5.3	0.8–9.8
Sleep disorder			
Difficulty initiating sleep			
No	346	1.4	0.2–2.6
Yes	80	8.8	2.6–15.0
Difficulty remaining alert			
No	404	2.7	1.1–4.3
Yes	23	4.3	0.0–12.6
Difficulty maintaining sleep			
No	331	1.8	0.4–3.2
Yes	95	6.3	1.4–11.2
Use of hypnotic medication			
No	407	2.7	1.1–4.3
Yes	20	5.0	0.0–14.6
Going to the restroom during night			
No	323	2.2	0.6–3.8
Yes	103	4.9	0.7–9.1
Having pain			
No	399	2.8	1.2–4.4
Yes	24	4.2	0.0–12.2
Sleep duration (h)			
<7	110	0.0	
7 to <8	124	1.6	0.0–3.8
8 to <9	129	5.4	1.5–9.3
9= or <	64	4.7	0.0–9.9
CES-D			
<16	349	2.0	0.5–3.5
≥16	80	6.3	1.0–11.6
High-density lipoprotein cholesterol level			
<40	411	2.7	1.1–4.3
≥40	18	5.6	0.0–16.2
Triglyceride level			
<150	389	2.3	0.8–3.8
≥150	40	7.5	0.0–15.7

BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval.