Ⅲ.研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
内山真	睡眠障害の診断と治療	岡庭 豊	Year Note Selected Articles 主要病態・主要疾患の論文集2008-2009	メディックメディア	東京	2008	1603-1619
内山真	41 コンスタントルーチン	石田直理雄・本間研一	時間生物学辞典	朝倉書店	東京	2008	114-115
内山真	42 脱同調プロトコール	石田直理雄・本間研一	時間生物学辞典	朝倉書店	東京	2008	116-117
内山真	126 睡眠薬とリズム	石田直理雄・本間研一	時間生物学辞典	朝倉書店	東京	2008	310-311
内山真，栗山健一	時間生物学	上島国利・樋口輝彦・野村総一郎・大野裕・神庭重信・尾崎紀夫	気分障害	医学書院	東京	2008	253-260
内山真	睡眠障害：生物学的背景を中心に	松下正明・加藤敏・神庭重信	精神医学対話	弘文堂	東京	2008	373-392
内山真	脳を守る	脳の世紀推進会議	脳を知る・創る・守る・育む 10	株式会社クバプロ	東京	2008	93-124
赤柴恒人	睡眠時無呼吸症候群	竹内龍雄	新しい診断と治療のＡＢＣ	最新医学者	東京	2008	91-102
内村直尚	レストレスレッグス症候群の治療に用いられる薬物とその特徴	井上雄一、内村直尚、平田幸一	レストレスレッグス症候群（RLS）だからどうしても脚を動かしたい	アルタ出版	東京	2008	111-118
内村直尚	生徒の睡眠不足と解消法（連載）		体と心 保健総合大百科＜中・高校編＞	少年写真新聞社	東京	2008	105-108
内村直尚	糖尿病と睡眠障害		分子糖尿病学の進歩―基礎から臨床まで―2008	金原出版	東京	147-152	2008
橋爪祐二、内村直尚	睡眠薬・抗不安薬		治療薬ハンドブック	じほう	東京	22-25	2008

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kaneita Y, Uchiyama M, Yoshiike N, Ohida Y	Associations of Usual Sleep Duration with Serum Lipid and Lipoprotein Levels	SLEEP	31	645-652	2008
Nakajima H, Kaneita Y, Yokoyama E, Harano S, Tamaki T, Ibuka E , Kaneko A, Takahashi I, Umeda T, Nakaji S, Ohida T	Association between sleep duration and hemoglobin Alc level.	Sleep Medicine	9	745-752	2008
Yokoyama E, Saito Y, Kaneita Y, Ohida T, Harano S, Tamaki T, Ibuka E, Kaneko A, Nakajima H, Takeda F	Association between subjective well-being and sleep among the elderly in Japan.	Sleep Medicine	9	157-164	2008
Harano S, Ohida T, Kaneita Y, Yokoyama E, Tamaki T, Takemura S, Osaki Y, Hayashi K	Prevalence of restless legs syndrome with pregnancy and the relationship with sleep disorders in Japanese large population.	Sleep and Biological Rhythms	6	102-109	2008
Kaneita Y, Yokoyama E, Harano S, Tamaki T, Suzuki H, Munezawa T, Nakajima H, Asai T, Ohida T	Associations Between Sleep Disturbance and Mental Health Status: A Longitudinal Study of Japanese Junior High School Students.	Sleep Medicine	In press		
兼板佳孝, 大井田隆	日本人の睡眠障害の疫学的特徴	日本臨床	66	21-26	2008
兼板佳孝, 大井田隆	睡眠障害の診断・治療ガイドライン　学校との連携ガイドライン.	睡眠医療	3	330-332	2008
Uchiyama M	PREFACE	SLEEP AND BIOLOGICAL RHYTHMS	6	127	2008
内山真, 大川匡子	睡眠障害の概念と国際分野	臨床睡眠学	66・増刊	11-20	2008
降旗隆二, 久保英之, 鈴木正泰, 松・大和, 内山真	Huntington病に伴う幻覚妄想状態にRisperidoneが奏功した1例	東京精神医学会誌	25	21-25	2008
内山真	1.特集企画にあたってー睡眠障害の適切な理解と治療にむけてー	医薬ジャーナル	44	71-72	2008
内山真	7.睡眠薬の適正使用と服薬指導	医薬ジャーナル	44	110-114	2008
内山真	睡眠を科学する	臨床麻酔	32	885-893	2008

内山真	高齢者の睡眠障害	最新精神医学	13	347-353	2008
内山真	『ねむりと医療』の創刊にあたって	ねむりと医療	1	巻頭言	2008
内山真	不眠・睡眠不足とメタボリックシンドローム	ねむりと医療	1	1-4	2008
内山真	ねむりの達人がお応えします- Q&A第1回　高齢者の睡眠障害にどう対応するか？	ねむりと医療	1	40-42	2008
内山真	睡眠不足が代謝と内分泌機能に与える影響	ねむりと医療	1	43-45	2008
内山真	睡眠障害- 総論	心療内科	12	341-344	2008
内山真	睡眠障害の診断の進め方	日本医師会雑誌	137	1412-1416	2008
内山真	脳を休ませるしくみ	環境と健康	21	404-414	2008
内山真	睡眠薬の使用法とそのはたらき	こころの科学	143	32-39	2008
内山真	不眠症への対応--生活指導と薬物療法（第23回 生活習慣病指導専門職セミナー メンタルヘルスと生活習慣）	けんこうぶんか	37	2-13	2008
Akahoshi T, Akashiba T, et al.	Predicting optimal continuous positive airway pressure in Japanese patients with obstructive sleep apnea syndrome.	Respirology	13	1-13	2008
赤柴恒人	CPAP治療における治療圧の決定方法	Clinical Engineering	19	1153-1157	2008
赤柴恒人	ポリソムノグラフィー 簡易検査と精密検査 呼吸器疾患マニュアル	日本医師会雑誌	137	S135-S137	2008
赤柴恒人	睡眠と呼吸のかかわり	呼吸	27	753-754	2008
赤柴恒人	睡眠時無呼吸症候群の検査と診断のポイント- 外来における診断の実際	Medical Practice	25	1151-1154	2008
赤柴恒人	睡眠関連呼吸障害群、内科的疾患による睡眠関連低換気／低酸素血症、呼吸器疾患による睡眠関連低換気／低酸素血症	日本臨床	66(2S)	277-283	2008
赤柴恒人	肥満症・メタボリックシンドロームの治療・管理。睡眠時無呼吸症候群	治療	90	1733-1737	2008

赤柴恒人	睡眠障害	COPD Frontier	7	74-78	2008
内村直尚	睡眠障害の診断と治療	久留米医学会雑誌	71	221-228	2008
内村直尚	うつ病患者の不眠に対する超短時間型と長時間型ベンゾジアゼピン（ＢＺ）系睡眠薬の有用性の検討	Pharma Medica	26	95-101	2008
兒玉隆之、森田喜一郎、森圭一郎、小路純央、内村直尚	ERPのMicrostate法を用いたLORETA解析	臨床脳波	50	610-614	2008
大岡由佳、前田正治、大江美佐利、丸岡隆之、古賀章子、・松真理、原口雅浩、辻丸秀策、内村直尚	精神臨床現場における被害者・被災者支援の現状と課題　大学病院の過去10年間のＰＴＳＤ患者の調査から	精神医学	50	455-464	2008
石田　康、長友慶子、池田学、内村直尚、大内　清、小澤寛樹、北村俊則、近藤毅、赤崎安昭、佐野　輝、寺尾　岳、西村良二、山田茂人、神庭重信、中村　純	プライマリケア医のうつ病診療に関する実態調査	九州神経精神医学	54	120-126	2008
MISARI OE, MASAHARU MAEDA, NAOHISA UCHIMURA	Longitudinal Psychological Effects of the Garuda Indonesia Air Disaster in Japan	Kurume Medical Journal	55	1-6	2008

Ⅳ.研究成果の刊行物・別刷

Associations of Usual Sleep Duration with Serum Lipid and Lipoprotein Levels

Yoshitaka Kaneita, MD[1]; Makoto Uchiyama, MD[2]; Nobuo Yoshiike, MD[3]; Takashi Ohida, MD[1]

[1]Department of Public Health, Nihon University School of Medicine, Tokyo, Japan; [2]Department of Neuropsychiatry, Nihon University School of Medicine, Tokyo, Japan; [3]National Institute of Health and Nutrition, Tokyo, Japan

Study Objectives: We examined the individual association between sleep duration and a high serum triglyceride, low HDL cholesterol, or high LDL cholesterol level.

Design and Setting: The present study analyzed data from the National Health and Nutrition Survey that was conducted in November 2003 by the Japanese Ministry of Health, Labour and Welfare. This survey was conducted on residents in the districts selected randomly from all over Japan.

Participants: The subjects included in the statistical analysis were 1,666 men and 2,329 women aged 20 years or older.

Intervention: N/A

Measurements and Results: Among women, both short and long sleep durations are associated with a high serum triglyceride level or a low HDL cholesterol level. Compared with women sleeping 6 to 7 h, the relative risk of a high triglyceride level among women sleeping <5 h was 1.51 (95% CI, 0.96-2.35), and among women sleeping ≥8 h was 1.45 (95% CI, 1.00-2.11); the relative risk of a low HDL cholesterol level among women sleeping <5 h was 5.85 (95% CI, 2.29-14.94), and among women sleeping ≥8 h was 4.27 (95% CI, 1.88-9.72). On the other hand, it was observed that the risk of a high LDL cholesterol level was lower among men sleeping ≥8 h. These analyses were adjusted for the following items: age, blood pressure, body mass index, plasma glucose level, smoking habit, alcohol consumption, dietary habits, psychological stress, and taking cholesterol-lowering medications.

Conclusions: Usual sleep duration is closely associated with serum lipid and lipoprotein levels.

Keywords: Dyslipidemia; triglyceride; high density lipoprotein cholesterol; low density lipoprotein cholesterol; sleep duration

Citation: Kaneita Y; Uchiyama M; Yoshiike N; Ohida T. Associations of usual sleep duration with serum lipid and lipoprotein levels. *SLEEP* 2008;31(5):645-652.

IN THE LATE 1960S, IT WAS REVEALED THAT SHORTER OR LONGER SLEEP DURATION RESULTED IN AN INCREASED RISK OF MORTALITY IN HUMANS, AND that there was a U-shaped association between sleep duration and mortality risk.[1] Subsequently, several large-scale studies demonstrated similar findings.[2-4] In recent years, U-shaped associations have been demonstrated between sleep duration and morbidity risk for diabetes mellitus,[5-7] obesity,[8] hypertension,[9] coronary heart disease (CHD),[10] and atherosclerosis.[11] It has been increasingly recognized that sleep habits, along with other lifestyle habits, such as eating, exercising, smoking, and drinking, are potential risk factors for diabetes mellitus, obesity, hypertension, and cardiovascular disease (CVD).

Dyslipidemia, such as an increase in the level of triglyceride, a decrease in the level of high-density-lipoprotein (HDL) cholesterol, and an increase in the level of low-density-lipoprotein (LDL) cholesterol, increases the risk of CVD morbidity.[12-14] In order to prevent CVD, it is important to identify and change lifestyles that are associated with serum triglyceride, HDL cholesterol or LDL cholesterol level. It is well known that these serum lipid and lipoprotein levels are strongly influenced by lifestyles. Smoking decreases the level of HDL cholesterol and increases the level of triglyceride in blood, whereas alcohol consumption increases the levels of both.[15] Exercise increases the HDL cholesterol level and decreases the triglyceride level in blood.[15] In addition, alcohol consumption is reported to decrease the level of LDL cholesterol.[16,17]

In 1999, Nakanishi et al. indicated that there was no significant association between sleep duration and serum lipid and lipoprotein levels among men.[18] However, their sample was comprised of male office workers from a single company and these findings cannot reasonably be extrapolated to the general Japanese population. To clarify this issue, the present study examined the individual associations of sleep duration with the levels of serum triglyceride, HDL cholesterol and LDL cholesterol.

METHODS

Study Subjects and Data Collection

The present study was performed using data collected by the National Health and Nutrition Survey that was conducted in November 2003 by the Japanese Ministry of Health, Labour and Welfare. The National Health and Nutrition Survey is a cross-sectional survey that is conducted annually in order to obtain epidemiological data for national health promotion.[19] The subjects of this national survey comprised approximately 15,000 residents aged 1 year or more in the 300 districts randomly selected from the national census unit districts.

The survey comprised three parts: (1) examination of physical status, (2) dietary intake survey, and (3) questionnaire on lifestyles. Actual data collection was performed by the staff of the local public health centers that exercised jurisdiction over the selected districts.

Disclosure Statement

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

Submitted for publication January, 2007
Accepted for publication February, 2008

Address correspondence to: Dr. Makoto Uchiyama, Department of Neuropsychiatry, School of Medicine, Nihon University, 30-1, Ohyaguchikamimachi, Itabashi-ku, Tokyo 173-8610, Japan; Tel: +81-3-3972-8111 ext.2430; Fax: +81-3-3974-2920; E-mail: maco.uchiyama@nifty.com

For the physical status examination, the subjects were invited to public facilities within the districts. The heights and weights of all the participants aged 1 year or older, abdominal circumference, and blood pressure of all participants aged 15 years or older were measured. In addition, participants aged 20 years or older were interviewed with regard to any medications taken on a regular basis, and blood samples were taken from each subject for subsequent analysis.

For dietary assessment, the staff of the public health centers visited the subjects' households, distributed the recording sheets, and explained how to complete them. The subjects were requested to record the name and amount of all food consumed by each household member aged 1 year or older on a selected weekday.

The lifestyle questionnaire, which was self-administered, was issued to all participants older than 15 years of age, with instructions on how to complete it. The lifestyle questionnaire included items related to diet, smoking, drinking, exercise, sleep, and dental hygiene. When the staff of the public health centers visited the subjects' households, the subjects were informed of the due consideration given to confidentiality of all personal data based on the Health Promotion Law.

Measures and Definitions

According to criteria determined by the Japan Society for the Stûdy of Obesity, a BMI of 25 kg/m^2 or higher was considered to indicate overweight.[20] Before recording the blood pressure, activities that might potentially affect the blood pressure readings (blood sampling, exercise, eating, and smoking) were prohibited. Each participant was instructed to urinate prior to recording the blood pressure. After 5 min of rest, blood pressure was measured in the right upper arm with the participant seated on a chair. Blood pressure was measured twice with an interval of 1 minute between the 2 measurements, and the 2 measurements were used for statistical analyses.

In accordance with criteria determined by the World Health Organization, International Society of Hypertension, and Japanese Society of Hypertension, a mean systolic blood pressure of 140 mm Hg or higher or a mean diastolic blood pressure of 90 mm Hg or higher was considered to indicate hypertension.

Blood tests included the following items: white blood cell count, red blood cell count, platelet count, hemoglobin concentration, ferritin level, total protein level, albumin level, total cholesterol level, HDL cholesterol level, triglyceride level, glucose level, and hemoglobin A1c level. The serum triglyceride and HDL cholesterol levels were measured using the enzyme and direct methods, respectively. In the participants whose serum triglyceride level was lower than 400 mg/dL, the level of LDL cholesterol was calculated from total cholesterol, HDL cholesterol and triglyceride levels using Friedewald's formula.[21] The serum triglyceride level was 400 mg/dL or more in 93 participants (2.3%), and we excluded cases showing this value from statistical analysis involving LDL cholesterol. In accordance with the criteria determined by the Japan Atherosclerosis Society, a serum triglyceride level ≥150 mg/dL was considered to be high, an HDL cholesterol level <40 mg/dL was defined as low, and an LDL cholesterol level ≥140 mg/dL was considered to be high. Furthermore, in accordance with the criteria determined by the Japan Diabetes Society, a fasting glucose level ≥126 mg/dL was considered to represent hyperglycemia.

The questionnaire on lifestyles included the question: "What was your daily average sleep duration during the past month?" The 6 options provided as responses to this question were: (a) less than 5 h, (b) 5 h or more but less than 6 h, (c) 6 h or more but less than 7 h, (d) 7 h or more but less than 8 h, (e) 8 h or more but less than 9 h, and (f) 9 h or more. Categories (e) and (f) were integrated for the purpose of statistical analysis. Subjects who answered "every day" and "sometimes" to the question "Do you smoke currently? (*within one month*)" were categorized as current smokers. Those who answered "3 days or more per week" to the question "How many days per week do you consume alcoholic beverages?" were categorized as habitual drinkers. Those who had exercised twice or more per week for ≥30 min over the past one year or more were categorized as habitual exercisers. Questions regarding the frequencies of skipping meals, eating between meals, and eating out were asked separately. If the frequency of any of the above eating patterns was once or more per week, it was considered to be a habit. The questionnaire also included a question on psychological stress levels. To the question "Have you felt stress caused by dissatisfaction, worries, or troubles during the past month?" the following 4 options were provided: definitely, occasionally, not much, and never. The participants who selected "definitely" as the answer to this question were regarded as those "Definitely feeling psychological stress."

Statistical Analyses

After seeking permission from the Ministry of Health, Labour and Welfare, we performed statistical analysis of the anonymized dataset obtained from the National Health and Nutrition Survey.

A total of 11,630 individuals participated in at least one of the three parts of the National Health and Nutrition Survey, and the response rate was approximately 77.5%. Of these participants, the following were sequentially excluded from the dataset; those aged 20 years or younger (2,199); those who did not participate in a blood test (4,124); pregnant women or women who had given birth in the last 6 months (43); those from whom blood was collected within 4 h after a meal (1,234); those for whom the serum triglyceride and HDL cholesterol levels could not be measured due to technical errors such as an insufficient quantity of collected blood (8); and those who did not answer the question on sleep duration (27). The data for the remaining 3,995 cases (men: 1,666, women: 2,329) were used for statistical analyses.

All statistical analyses were conducted separately by gender. Unadjusted differences in continuous and categorical variables across sleep duration categories were assessed for significance using single-factor analysis of variance or contingency table analysis, as appropriate. Logistic regression analyses were conducted to assess the relation of usual sleep duration to a high triglyceride, low HDL cholesterol or high LDL cholesterol level, adjusting for relevant covariates. Covariates included in the model were age, blood pressure, BMI, fasting plasma glucose level, smoking habit, alcohol consumption, dietary habits, psychological stress, and taking cholesterol-lowering medications.

Table 1—Characteristics of the Male Participants According to Reported Usual Sleep Duration

Characteristic	Reported Usual Sleep Duration, h/night					P value
	<5	5 to <6	6 to <7	7 to <8	≥8	
No. of participants	70	318	596	455	227	
Age, y	52.7 (19.9)	52.4 (16.8)	53.6 (15.6)	56.3 (16.1)	64.1 (15.2)	<0.001
BMI	22.9 (3.2)	23.9 (3.5)	23.6 (3.1)	23.2 (3.2)	23.1 (3.4)	0.008
Systolic blood pressure, mm Hg	133.4 (17.1)	134.0 (21.3)	134.3 (19.6)	136.4 (19.1)	136.7 (18.1)	0.181
Diastolic blood pressure, mm Hg	78.5 (10.4)	81.3 (13.0)	82.2 (11.5)	82.7 (11.0)	80.6 (11.2)	0.015
Drinking alcohol ≥3 days/week, %	44.3	50.8	57.0	61.3	59.5	0.009
Current smoking, %	43.3	47.9	42.5	46.9	45.9	0.515
Exercising at least twice per week, %	40.0	28.6	29.8	29.3	29.2	0.433
Skipping meal ≥1 time/day, %	21.4	5.4	7.9	7.7	3.5	<0.001
Eating between meals ≥1 time/day, %	28.6	31.6	27.7	28.1	34.8	0.273
Eating out ≥1 time/day, %	22.9	12.6	9.7	5.5	2.6	<0.001
Definitely feeling psychological stress, %	37.1	18.6	9.2	7.0	4.0	<0.001
Fasting plasma glucose, mg/dL	101.6 (26.6)	104.8 (32.3)	104.5 (29.5)	108.8 (43.9)	112.6 (44.8)	0.021
Hemoglobin A1c, %	5.41 (0.97)	5.33 (0.78)	5.40 (0.86)	5.47 (1.07)	5.55 (1.03)	0.069
Triglyceride, mg/dL	134.5 (70.9)	159.0 (110.3)	155.3 (120.6)	157.7 (115.4)	141.7 (94.1)	0.198
HDL cholesterol, mg/dL	57.8 (16.2)	56.1 (14.6)	56.1 (14.4)	56.5 (15.7)	56.1 (15.6)	0.915
LDL cholesterol, mg/dL	109.0 (29.0)	113.1 (31.7)	116.4 (32.3)	112.7 (31.1)	107.2 (29.6)	0.004
Total cholesterol, mg/dL	193.7 (33.9)	199.5 (34.2)	202.1 (37.0)	199.3 (33.4)	191.8 (35.2)	0.003

Data are presented as mean (SD) or percentages.
Significance tests for the unadjusted difference across categories of sleep duration are based on the contingency table analysis for categorical variables and single-factor analysis of variance for continuous variables.

Odds ratios were calculated from logistic regression analyses with 95% confidence intervals. Finally, participants who were taking cholesterol-lowering medications were excluded, and the same analyses as described above were performed. All analyses were performed using SPSS 12.0 for Windows.

RESULTS

Among men, the percentages of subjects who slept <6 h and ≥8 h per night were 23.3% and 13.6%, respectively. Among women, the corresponding percentages were 31.2% and 8.2%, respectively. The number of subjects with shorter sleep duration was greater for women than for men, and the number of subjects with longer sleep duration was smaller for women than for men ($P < 0.001$). The mean (standard deviation [SD]) serum triglyceride level was 153.9 (112.2) mg/dL for men and 123.2 (86.5) mg/dL for women, and was thus significantly higher among men ($P < 0.001$). The mean (SD) serum HDL cholesterol level was 56.3 (15.0) mg/dL for men and 64.8 (15.6) mg/dL for women, and was thus significantly lower among men ($P < 0.001$). The mean (SD) serum LDL cholesterol level was 113.2 (31.5) mg/dL for men and 118.6 (32.0) mg/dL for women, and was thus significantly higher among women ($P < 0.001$). The prevalence of a high triglyceride level was 36.5% among men and 24.0% among women, and was thus significantly higher among men ($P < 0.001$). The prevalence of a low HDL cholesterol level was 12.1% among men and 3.4% among women, and was thus significantly higher among men ($P < 0.001$). The prevalence of a high LDL cholesterol level was 17.6% among men and 23.9% among women, and was thus significantly higher among women ($P < 0.001$).

Among men with shorter sleep duration, the number of men who answered that they skipped meals or ate out once or more per day was observed to be high (Table 1). Additionally, a high number of men in this group answered that they experienced high levels of psychological stress. A significant association was observed between serum LDL cholesterol levels and sleep duration among men. The mean serum LDL cholesterol level of those who slept ≥8 h was approximately 9.2 mg/dL lower than that of those who slept for 6 to 7 h. Among men, there were no evident significant associations between sleep duration and serum triglyceride or serum HDL cholesterol level.

Similarly, among women with shorter sleep duration, the number of subjects who skipped meals, ate out, or experienced heavy psychological stress was large (Table 2). The mean serum triglyceride level was lowest in women who slept 6 to 7 h and

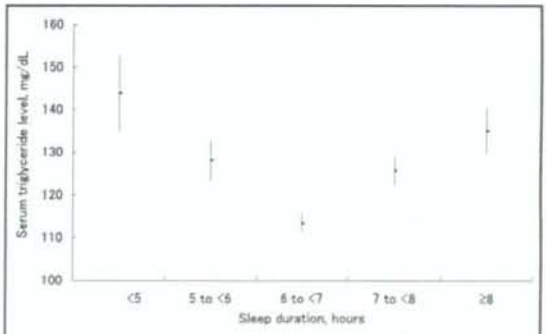

Figure 1—The relationship between serum triglyceride level and sleep duration. The mean value (point) and standard error (bar) of the serum triglyceride level for different sleep duration groups are shown. A U-shaped association is observed between serum triglyceride level and sleep duration.

Table 2—Characteristics of the Female Participants According to Reported Usual Sleep Duration

Characteristic	Reported Usual Sleep Duration, h/night					P value
	<5	5 to <6	6 to <7	7 to <8	≥8	
No. of participants	125	601	919	493	191	
Age, y	56.6 (16.7)	53.2 (15.1)	53.2 (15.3)	57.1 (17.2)	65.0 (16.9)	<0.001
BMI	23.3 (4.2)	22.8 (3.6)	22.7 (3.4)	22.8 (3.3)	22.6 (3.6)	0.457
Systolic blood pressure, mm Hg	133.9 (21.7)	128.4 (20.7)	128.6 (20.6)	131.0 (22.0)	134.9 (19.3)	<0.001
Diastolic blood pressure, mm Hg	77.9 (11.6)	76.8 (11.4)	77.5 (11.2)	77.2 (12.1)	77.9 (12.0)	0.691
Drinking alcohol ≥3 days/week, %	8.0	15.5	15.3	12.4	13.1	0.127
Current smoking, %	12.8	12.5	10.2	6.9	7.9	0.023
Exercising at least twice per week, %	21.8	26.1	25.5	25.3	20.6	0.535
Skipping meal ≥1 time/day, %	11.2	3.7	4.0	4.3	6.8	0.002
Eating between meals ≥1 time/day, %	40.8	52.8	49.0	47.6	52.9	0.086
Eating out ≥1 time/day, %	5.6	4.3	2.1	1.6	0.5	0.001
Definitely feeling psychological stress, %	29.6	18.1	11.6	7.3	4.7	<0.001
Fasting plasma glucose, mg/dL	105.0 (35.0)	103.3 (25.3)	102.2 (26.3)	104.7 (25.7)	110.9 (36.9)	0.002
Hemoglobin A1c, %	5.39 (0.72)	5.34 (0.77)	5.30 (0.74)	5.34 (0.68)	5.39 (0.83)	0.427
Triglyceride, mg/dL	143.9 (100.0)	128.1 (115.7)	113.4 (66.0)	125.8 (77.2)	135.0 (74.1)	<0.001
HDL cholesterol, mg/dL	63.2 (17.4)	65.3 (16.2)	66.3 (14.8)	63.4 (15.5)	60.2 (15.4)	<0.001
LDL cholesterol, mg/dL	117.4 (31.4)	116.7 (31.8)	118.1 (32.3)	120.7 (31.4)	122.6 (32.9)	0.114
Total cholesterol, mg/dL	209.6 (38.4)	207.0 (37.1)	207.1 (35.9)	208.8 (34.8)	209.5 (34.5)	0.770

Data are presented as mean (SD) or percentages.
Significance tests for the unadjusted difference across categories of sleep duration are based on the contingency table analysis for categorical variables and single-factor analysis of variance for continuous variables.

became higher as the sleep duration became shorter than 6 h or longer than 7 h. Compared with those who slept for 6 to 7 h, the mean serum triglyceride level in those who slept <5 h, and in those who slept ≥8 h, was approximately 30.5 mg/dL and 21.6 mg/dL higher, respectively. Thus, a U-shaped association was observed between sleep duration and serum triglyceride level (Figure 1). In contrast, the mean serum HDL cholesterol level was highest for sleep durations of 6 to 7 h, and became lower as the sleep duration became shorter than 6 h or longer than 7 h. Compared with those who slept for 6 to 7 h, the mean serum HDL cholesterol level in those who slept <5 h, and in those who slept ≥8 h was approximately 3.1 mg/dL and 6.1 mg/dL lower, respectively. Thus, an inverted U-shaped association was observed (Figure 2). Furthermore, U-shaped associations were observed between sleep duration and systolic blood pressure, and sleep duration and fasting plasma glucose. Among women, there was no significant association between sleep duration and serum LDL cholesterol level.

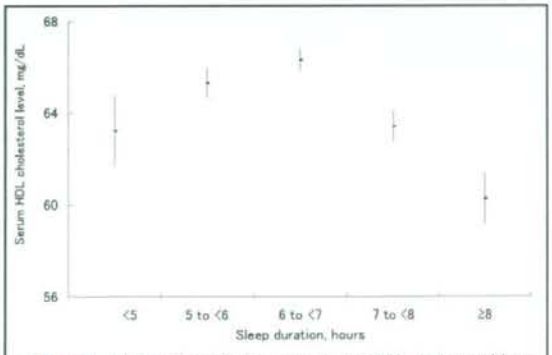

Figure 2—The relationship between serum HDL cholesterol level and sleep duration. The mean value (point) and standard error (bar) of serum HDL cholesterol level for different sleep duration groups are shown. An inverted U-shaped association is observed between serum HDL cholesterol level and sleep duration.

Among women, both univariate and multivariate logistic models showed statistically significant associations between sleep duration and a high triglyceride level and sleep duration and a low HDL cholesterol level (Table 3). Both the associations were U-shaped. The ORs for a high triglyceride and a low HDL cholesterol levels were the lowest for sleep durations of 6 to 7 h and became higher as the sleep duration became shorter or longer than 6 to 7 h. Among men, no statistically significant association was observed between sleep duration and a high triglyceride level, or sleep duration and a low HDL cholesterol level.

A significant association was observed among men with regard to LDL cholesterol level and sleep duration. Specifically, the OR with regard to a high LDL cholesterol level among those who slept ≥8 h was significantly lower than for those who slept for 6 to 7 h. On the other hand, there was no significant association between sleep duration and LDL cholesterol level among women.

Finally, 370 participants (9.3%) who took cholesterol-lowering medications were excluded, and the same analyses as those described above were performed. There were no substantial differences between the results of those analyses and the above-mentioned analyses.

DISCUSSION

In the present study, we found U-shaped associations between sleep duration and a high triglyceride or a low HDL cho-

Table 3—Odds Ratios for Dyslipidemia by Reported Sleep Duration

Reported Usual Sleep Duration, h/night	High triglyceride Crude odds ratio	95% CI	P value	Adjusted odds ratio*	95% CI	P value
Male			0.364			0.229
<5	1.02	0.61-1.71		1.52	0.85-2.70	
5 to <6	1.25	0.95-1.66		1.36	1.00-1.84	
6 to <7	1.00	referent		1.00	referent	
7 to <8	1.10	0.85-1.41		1.24	0.94-1.63	
≥8	0.89	0.64-1.23		1.09	0.76-1.56	
Female			<0.001			0.048
<5	1.82	1.21-2.75		1.51	0.96-2.35	
5 to <6	1.41	1.10-1.80		1.42	1.09-1.84	
6 to <7	1.00	referent		1.00	referent	
7 to <8	1.28	0.98-1.66		1.15	0.87-1.53	
≥8	1.98	1.41-2.79		1.45	1.00-2.11	
Reported Usual Sleep Duration, h/night	**Low HDL cholesterol**					
Male			0.951			0.694
<5	1.15	0.54-2.41		1.35	0.60-3.03	
5 to <6	1.02	0.67-1.57		0.95	0.60-1.50	
6 to <7	1.00	referent		1.00	referent	
7 to <8	1.16	0.80-1.68		1.19	0.80-1.77	
≥8	1.09	0.68-1.75		0.87	0.51-1.46	
Female			<0.001			0.001
<5	6.40	2.60-15.78		5.85	2.29-14.94	
5 to <6	3.14	1.51-6.52		3.25	1.55-6.85	
6 to <7	1.00	referent		1.00	referent	
7 to <8	3.86	1.85-8.02		3.15	1.49-6.65	
≥8	7.04	3.18-15.57		4.27	1.88-9.72	
Reported Usual Sleep Duration, h/night	**High LDL cholesterol**					
Male			0.005			0.048
<5	0.49	0.23-1.06		0.66	0.29-1.48	
5 to <6	0.90	0.64-1.28		0.91	0.62-1.31	
6 to <7	1.00	referent		1.00	referent	
7 to <8	0.80	0.59-1.11		0.80	0.57-1.13	
≥8	0.42	0.26-0.68		0.45	0.27-0.76	
Female			0.333			0.515
<5	1.28	0.84-1.96		1.24	0.78-1.97	
5 to <6	0.87	0.68-1.12		0.88	0.67-1.14	
6 to <7	1.00	referent		1.00	referent	
7 to <8	1.10	0.85-1.42		1.10	0.84-1.45	
≥8	1.11	0.78-1.59		0.98	0.66-1.45	

*Multivariate logistic regression analyses were conducted with adjustment for age, blood pressure, body mass index, fasting plasma glucose level, smoking habit, alcohol consumption, dining habits, psychological stress, and using anti-cholesterol medicine.

lesterol level among women. Using the data of a cohort study conducted on 71,617 women in the USA, Ayas et al. examined the associations between sleep duration and CHD.[10] They reported that the relative risk of CHD was significantly higher among those with shorter or longer sleep durations, and that the association was U-shaped.[10] Recently, in a study comprising 2,437 participants from the general population in Germany, Wolff et al. reported that the carotid intima-media thickness was greater among those with short and long sleep durations.[11] From these study results, it is suggested that both short and long sleep durations can be regarded as individual risk factors of CVDs such as CHD and atherosclerosis. Since an increase in the triglyceride level or a decrease in the HDL cholesterol level in blood are risk factors for the onset of CVD,[12-14] the present results are important for explaining the association between sleep duration and CVD. It is logical to consider that the incidence or prevalence of a high triglyceride or a low HDL cholesterol level are high among individuals with short and long sleep durations, predisposing them to a higher relative risk of CVD. There are associations between two of the three elements (sleep duration, dyslipidemia, and CVD) and each element can produce a confounding effect on the association between the other two elements. These associations must be examined individually in the future using a study design that can account for the confounding effects of all the above elements.

While we were preparing the present report, a study on the associations between sleep duration and dyslipidemia was published by another group.[22] Williams et al. examined the asso-

ciations between sleep duration and biomarkers that could be risk factors for CVDs in 935 women with type 2 diabetes. They indicated that among the subjects whose blood pressure was within the normal range, the serum HDL cholesterol level was low among those with both short and long sleep durations. They stated that the result partially explained how sleep habit could become a risk factor for CVDs. A simple comparison between their study and ours is not warranted because in their study the subjects were limited to women with type 2 diabetes. However, the data are helpful for clarifying the associations between dyslipidemia and sleep duration, i.e., an inverted U-shaped association was observed between serum HDL cholesterol levels and sleep duration in both studies.

Recently, it has become increasingly clear that sleep has a strong influence on the metabolic hormones that regulate energy balance. Sleep restriction lowers the blood concentration of leptin, which acts to suppress appetite, and increases the blood concentration of ghrelin, which promotes appetite.[8,23-25] In addition, it is known that administration of leptin decreases serum triglyceride level.[26,27] In addition, it was recently reported that short sleep duration was associated with a reduced leptin level and being overweight.[28] Mechanisms such as a decrease in the blood concentration of leptin or an increase in the blood concentration of ghrelin due to sleep restriction may be involved in the biological mechanisms responsible for the associations between short sleep duration and dyslipidemia: associations that were observed among women.

Meanwhile, it is not easy to explain the biological mechanism responsible for the association between long sleep duration and a high triglyceride or a low HDL cholesterol level. Existing knowledge of metabolic hormones and sleep duration cannot explain this association. Certain metabolic endocrinological changes caused by long sleep duration may result in increased triglyceride level and decreased HDL cholesterol level. However, because it is difficult to experimentally induce individuals to sleep for long periods, data related to this field are sparse. Meanwhile, there is a possibility that a specific factor may be associated separately with long sleep duration and a high triglyceride or a low HDL cholesterol level, and that through this unidentified confounding factor, an apparent association between long sleep duration and these dyslipidemia becomes evident. In this study, as age, overweight, hypertension, and glucose intolerance could have been potential confounding elements, various covariates, including the above factors, were fed into multivariate logistic models to study the association between long sleep duration and serum lipid and lipoprotein levels. However, the associations were independent of these factors, and could not be justified using them. Several previous studies have reported that various pathologic features such as obesity, hypertension, and glucose intolerance are associated with long sleep duration.[5-9] However, in those studies, biological mechanisms responsible for such associations were not completely elucidated. Therefore, studies on the physiological characteristics of long sleep must be conducted in the future.

Previous studies have reported that the relative risk of death or CHD was lowest among those who slept for 7 to 8 h.[1-4,10,29] Meanwhile, in the present study, the relative risk of a high triglyceride level or a low HDL cholesterol level was lowest among women who slept for 6 to 7 h. Thus, the optimal sleep duration suggested in the present study was not in accord with those indicated by previous studies. However, the results of the present and the previous studies are similar in that the relative risks were lowest among the categories of sleep duration to which the largest numbers of participants belonged. In an attempt to interpret the optimal sleep durations for disease prevention based on epidemiological data, it is inferred that the optimal sleep durations vary with the target population. In addition, when considering optimal sleep duration, bidirectional causal relationships must be taken into consideration from a biological viewpoint. In other words, sleep duration may affect physical status, but conversely, physical status may also affect sleep duration. It must be recognized that according to the type of disease being examined, the optimal sleep duration may differ.

With regard to the associations between sleep duration and mortality among Japanese, 3 cohort studies have been reported so far, but their results were discordant.[4,29,30] Kojima et al. reported that a U-shaped association was observed among male subjects,[29] whereas Tamakoshi et al. reported that a U-shaped association was observed among women.[4] Conversely, Amagai et al. reported that a U-shaped association was not observed among either men or women.[30] The reason for these gender-based differences in the associations between sleep duration and mortality among the studies is unclear. In the present study, a U-shaped association between sleep duration and dyslipidemia was recognized among women. Our data support the results of Tamakoshi et al. Further studies will be necessary to clarify the associations of sleep duration with dyslipidemia and mortality among Japanese.

In this study, unlike the situation in women, no significant associations were observed between sleep duration and serum triglyceride or HDL cholesterol level among men. However, the risk of a high LDL cholesterol level was lower among men who slept ≥8 h. From the viewpoint of CVD prevention, it was suggested that long sleep duration was not favorable for women, whereas it was favorable for men. Many previous studies have already reported that there is a gender-specific difference in the prevalence of dyslipidemia because sex hormones (estrogen, in particular) strongly affect lipoprotein metabolism.[31-33] It has also been reported that certain gender-specific differences in sleep habits are influenced by differences in social or household roles,[34] or in sex hormones.[35] Since there are gender-based differences in the onset of dyslipidemia and sleep habits, it is not unusual to observe a gender-specific difference in the association between them. In any event, until the biological mechanisms associated with the relationship between sleep duration and dyslipidemia are elucidated, the reasons for the gender-specific difference in these associations will remain unclear. This issue should be addressed in future epidemiological and physiological investigations.

Several studies have reported U-shaped associations between sleep duration and various diseases. On the other hand, several studies have reported that the associations were negative linear, and not U-shaped (i.e., the risk was higher only among those with short sleep durations).[36-39] In the present study, adjusted analyses failed to detect any significant associations of BMI, blood pressure, and fasting plasma glucose level with sleep duration; this was despite the fact that significant associations were recognized during unadjusted analyses (data not shown). Thus, the results

of the present study did not always agree with those of previous ones. It is inferred that these differences were due to firstly, differences in the sampling of subjects, and secondly, differences in adjustment factors. It is important that future epidemiological studies regarding the associations between sleep duration and diseases are carefully designed to minimize the selection bias and are adjusted for confounding factors. Subsequently, the results from such studies should be integrated through a meta-analysis, and a consensus should be reached. Future development of studies along these lines is expected.

The present study had several limitations. First, as this was a cross-sectional study, causal relationships could not be determined, even for items between which an association was indicated. When examining a causal relationship, a longitudinal study such as a cohort study is required, and such a study will be required in the future. Second, there may have been a non-response bias. Since the subjects were asked to come to public facilities in each district on a particular day during the survey period for examination of physical status, many of them may not have been able to participate because they had to go to work. The percentage of subjects who did not participate in the survey of physical status is estimated to have been approximately 37%. Among the cases analyzed, the number of subjects in the 20 to 49-yr age group and that of male participants were relatively small. Third, objective data could not be used for the present evaluation of sleep habits. Lauderdale et al. showed that the self-reported sleep duration was systematically biased along gender and race line when compared to measured sleep duration.[40] Therefore, the bias due to the use of self-reported data on sleep duration in this study remains to be resolved. Hereafter, the advantages of using measured data, such as those obtained with an actigraph, should be examined in a future study.

In conclusion, the results of this study indicate that both short and long sleep durations are associated with a high serum triglyceride level or a low HDL cholesterol level among women. Conversely, it was observed that the risk of a high LDL cholesterol level was lower among men who slept ≥8 h. Usual sleep duration is closely associated with serum lipid and lipoprotein levels.

ACKNOWLEDGMENTS

We wish to express our thanks to Eise Yokoyama M.D., Satoru Harano M.D., and Tetsuo Tamaki M.D. (Department of Public Health, School of Medicine, Nihon University) for their help in this study. This study was supported by a Health Science Research Grant from the Ministry of Health, Labour and Welfare of the Japanese Government.

REFERENCES

1. Hammond EC. Some preliminary findings on physical complaints from a prospective study of 1,064,004 men and women. Am J Public Health Nations Health 1964;54:11-23.
2. Kripke DF, Simons RN, Garfinkel L, et al. Short and long sleep and sleeping pills. Is increased mortality associated? Arch Gen Psychiatry 1979;36:103-16.
3. Kripke DF, Garfinkel L, Wingard DL, et al. Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry 2002;59:131-6.
4. Tamakoshi A, Ohno Y; JACC Study Group. Self-reported sleep duration as a predictor of all-cause mortality: results from the JACC study, Japan. Sleep 2004;27:51-4.
5. Ayas NT, White DP, Al-Delaimy WK, et al. A prospective study of self-reported sleep duration and incident diabetes in women. Diabetes Care 2003;26:380-4.
6. Gottlieb DJ, Punjabi NM, Newman AB, et al. Association of sleep time with diabetes mellitus and impaired glucose tolerance. Arch Intern Med 2005;165:863-7.
7. Yaggi HK, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of type 2 diabetes. Diabetes Care 2006;29:657-61.
8. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med 2004;1:e62.
9. Gottlieb DJ, Redline S, Nieto FJ, et al. Association of usual sleep duration with hypertension: the Sleep Heart Health Study. Sleep 2006;29:1009-14.
10. Ayas NT, White DP, Manson JE, et al. A prospective study of sleep duration and coronary heart disease in women. Arch Intern Med 2003;163:205-9.
11. Wolff B, Volzke H, Schwahn C, Robinson D, Kessler C, John U. Relation of self-reported sleep duration with carotid intima-media thickness in a general population sample. Atherosclerosis (in press).
12. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Relation of high TG-low HDL cholesterol and LDL cholesterol to the incidence of ischemic heart disease. An 8-year follow-up in the Copenhagen Male Study. Arterioscler Thromb Vasc Biol 1997;17:1114-20.
13. Gaziano JM, Hennekens CH, O'Donnell CJ, Breslow JL, Buring JE. Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. Circulation 1997;96:2520-5.
14. Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final report. Circulation 2002;106:3143-421.
15. Hata Y, Nakajima K. Life-style and serum lipids and lipoproteins. J Atheroscler Thromb 2000;7:177-97.
16. Choudhury SR, Ueshima H, Kita Y, et al. Alcohol intake and serum lipids in a Japanese population. Int J Epidemiol 1994;23:940-7.
17. Nakanishi N, Tatara K, Nakamura K, Suzuki K. Association of lifestyle with serum lipid levels: a study of middle-aged Japanese men. J Epidemiol 2000;10:216-25.
18. Nakanishi N, Nakamura K, Ichikawa S, Suzuki K, Tatara K. Relationship between lifestyle and serum lipid and lipoprotein levels in middle-aged Japanese men. Eur J Epidemiol 1999;15:341-8.
19. Ministry of Health, Labour and Welfare, Report of National health and nutrition survey 2003, www.mhlw.go.jp/bunya/kenkou/eiyou-chosa2-01/index.html
20. Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan [in Japanese]. Journal of Japan Society for the Study of Obesity 2000;6:18-28.
21. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
22. Williams CJ, Hu FB, Patel SR, Mantzoros CS. Sleep duration and snoring in relation to biomarkers of cardiovascular disease risk among women with type 2 diabetes. Diabetes Care 2007;30:1233-40.
23. Guilleminault C, Powell NB, Martinez S, et al. Preliminary observations on the effects of sleep time in a sleep restriction paradigm. Sleep Med 2003;4:177-84.
24. Spiegel K, Leproult R, L'hermite-Baleriaux M, Copinschi G, Pe-

nev PD, Van Cauter E. Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. J Clin Endocrinol Metab 2004;89:5762-71.
25. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med 2004;141:846-50.
26. Oral EA, Simha V, Ruiz E, et al. Leptin-replacement therapy for lipodystrophy. N Engl J Med 2002;346:570-8.
27. Petersen KF, Oral EA, Dufour S, et al. Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. J Clin Invest 2002;109:1345-50.
28. Chaput JP, Despres JP, Bouchard C, Tremblay A. Short sleep duration is associated with reduced leptin levels and increased adiposity: Results from the Quebec family study. Obesity (Silver Spring). 2007;15:253-61.
29. Kojima M, Wakai K, Kawamura T, et al. Sleep patterns and total mortality: a 12-year follow-up study in Japan. J Epidemiol 2000;10:87-93.
30. Amagai Y, Ishikawa S, Gotoh T, et al. Sleep duration and mortality in Japan: the Jichi Medical School Cohort Study. J Epidemiol 2004;14:124-8.
31. Godsland IF, Wynn V, Crook D, Miller NE. Sex, plasma lipoproteins, and atherosclerosis: prevailing assumptions and outstanding questions. Am Heart J 1987;114:1467-503.
32. Sacks FM, Gerhard M, Walsh BW. Sex hormones, lipoproteins, and vascular reactivity. Curr Opin Lipidol 1995;6:161-6.
33. Sattler AM, Soufi M, Maisch B, Schaefer JR. Lipids and lipoproteins in women. Herz 2005;30:368-74.
34. Park YM, Matsumoto K, Shinkoda H, Nagashima H, Kang MJ, Seo YJ. Age and gender difference in habitual sleep-wake rhythm. Psychiatry Clin Neurosci 2001;55:201-2.
35. Antonijevic IA, Murck H, Frieboes R, Holsboer F, Steiger A. On the gender differences in sleep-endocrine regulation in young normal humans. Neuroendocrinology 1999;70:280-7.
36. Hasler G, Buysse DJ, Klaghofer R, et al. The association between short sleep duration and obesity in young adults: a 13-year prospective study. Sleep 2004;27:661-6.
37. Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB. Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. Sleep 2005;28:1289-96.
38. Mallon L, Broman JE, Hetta J. High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population. Diabetes Care 2005;28:2762-7.
39. Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. Hypertension 2006;47:833-9.
40. Lauderdale DS, Knutson KL, Yan LL, et al. Objectively measured sleep characteristics among early-middle-aged adults: the CARDIA study. Am J Epidemiol 2006;164:5-16.

ELSEVIER

Sleep Medicine 9 (2008) 745–752

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Original Article

Association between sleep duration and hemoglobin A_{1c} level

Hiromi Nakajima [a], Yoshitaka Kaneita [a,*], Eise Yokoyama [a], Satoru Harano [a], Tetsuo Tamaki [a], Eiji Ibuka [a], Akiyo Kaneko [a], Ippei Takahashi [b], Takashi Umeda [b], Shigeyuki Nakaji [b], Takashi Ohida [a]

[a] *Division of Public Health, Department of Social Medicine, Nihon University, Tokyo, Japan*
[b] *Department of Social Medicine, School of Medicine, Hirosaki University, Hirosaki, Japan*

Received 19 April 2007; accepted 17 July 2007
Available online 24 October 2007

Abstract

Objective: The association between sleep habits and hemoglobin A_{1c} (HbA_{1c}) level has not been sufficiently examined. In the present study of residents in a local community, the associations between sleep duration and HbA_{1c} level were examined.
Methods: Self-administered questionnaires were mailed to 1062 residents in a rural community in Japan, and completed questionnaires were collected. At the time of collection, the fasting plasma glucose and HbA_{1c} levels were measured using peripheral blood samples. For the analyses, values that were considered to represent high levels were a fasting plasma glucose level of $\geqslant 126$ mg/dl and a HbA_{1c} level of $\geqslant 6.5\%$. Logistic regression analyses were performed to examine the associations between sleep duration and high fasting plasma glucose or high HbA_{1c} levels.
Results: The prevalence of high fasting plasma glucose and high HbA_{1c} levels was significantly high ($p < 0.01$) in subjects with a short or a long sleep duration. Logistic regression analyses demonstrated a significant association between high HbA_{1c} level and sleep duration. The adjusted odds ratios for a high HbA_{1c} level showed high values with regard to both short and long sleep durations.
Conclusions: HbA_{1c} level showed a U-shaped association with sleep duration. These results suggest that there may be an appropriate range of sleep duration in individuals with glucose tolerance disorders. It is expected that the present findings will contribute to the treatment and prevention of diabetes mellitus.

Keywords: Sleep; Diabetes mellitus; Hemoglobin A_{1c}; Glucose; Epidemiology; U-shaped association

1. Introduction

According to a fact-finding survey of diabetes mellitus conducted in 2002 by the Ministry of Health, Labour and Welfare in Japan, the number of people with a hemoglobin A_{1c} (HbA_{1c}) level of $\geqslant 6.1\%$ (those who were strongly suspected to have diabetes) and those currently receiving treatment for diabetes mellitus was approximately 7.4 million, and the number of people with an HbA_{1c} level of $\geqslant 5.6\%$ but $<6.1\%$ (those in whom the possibility of diabetes could not be ruled out) was approximately 8.8 million, giving an overall total of approximately 16.2 million [1]. These figures were higher than those reported in an earlier survey conducted in 1997. Diabetic nephropathy was ranked first (41.3%) among the diseases that necessitated dialysis. In addition, diabetic retinopathy-induced visual impairment is detected in approximately 3000 people annually [1]. Therefore, diabetes mellitus is currently recognized to be an important public health issue in Japan Fig. 1.

* Corresponding author. Tel.: +81 3 3972 8111x2272; fax: +81 3 3972 5878.
E-mail address: kaneita@med.nihon-u.ac.jp (Y. Kaneita).

1389-9457/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.sleep.2007.07.017

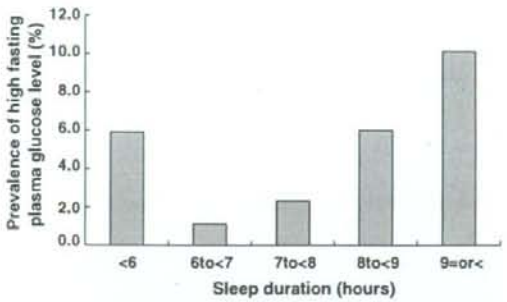

Fig. 1. (Title) Association between prevalence of high fasting plasma glucose level and sleep duration. *Note:* A U-shaped association was recognized between prevalence of high fasting plasma glucose level and sleep duration. A fasting plasma glucose level of ⩾126 mg/dl was considered to be a "high plasma glucose level."

In addition to diet, exercise habits, alcohol consumption, and smoking habits, sleep habits are considered to be a particularly important factor associated with lifestyle-related diseases, including diabetes. Moreover, changes in social habits, as exemplified by the increase in the number of shops and restaurants that stay open until late at night, coupled with the increase in the number of people who stay up until late at night browsing the Internet (an outcome of the popularization of the Internet), have resulted in a new nightlife culture in Japanese society. Hence, an increase in the prevalence of sleep disturbance has been recognized as a social problem in recent years. According to large-scale epidemiological studies on sleep in Japan, approximately one out of five Japanese adults has some type of sleep problem [2], and sleep duration among Japanese adults tends to decrease year after year [3]. For example, in the general Japanese population, the average sleep duration on weekdays was reported to have decreased by more than 30 minutes over the 35 years between 1970 and 2005 [3].

With the increase in the number of studies on sleep, it has been revealed that sleep disturbance may cause various mental and physical problems [4–7]. Various studies have reported associations between depression, a mental disease, and sleep disturbance [8,9]. Several studies have also reported that sleep disturbances such as insomnia and short sleep duration impair glucose tolerance [4,5,10]. In addition, it is known that the complication rate of depression developed by diabetic patients is high because of their fear of developing complications [11]. Other contributing factors include stressful lifestyles that involve regular insulin injections, and strict diet and exercise therapies [12,13].

For the prevention and treatment of diabetes, it is important to clarify the associations between sleep and both glucose tolerance and diabetes. In comparison with the plasma glucose level, the HbA_{1c} level shows less fluctuation and is less influenced by short-term lifestyle habits such as calorie intake. Therefore, the HbA_{1c} level is considered to be an important test parameter during the management of diabetes, a disease that has a prolonged course of development. However, to date, only a few large-scale studies have been conducted on the associations between sleep habits and HbA_{1c}. In the present study of residents in a rural community in Japan, the associations between sleep duration and fasting plasma glucose and HbA_{1c} level were examined under the situation in which depression was adjusted Fig. 2.

2. Methods

2.1. Subjects

We started a longitudinal survey in 2005 to collect and accumulate data on the lifestyle habits and health status of the residents of Iwaki-machi in order to contribute to the maintenance and promotion of their good health. To recruit the study participants, we mailed written notifications about the present longitudinal survey to residents aged 20 years or above as of March 31, 2005. Those interested in participating were requested to reply by mailing a consent letter. On the day of the survey, the survey details were verbally explained to the participants and they were instructed to sign the consent forms for participation and cooperation. At the beginning of this longitudinal survey, there were 1067 entries.

2.2. Data collection

Approval of the Ethics Committee of the institutions to which the authors belong was obtained prior to the start of the study. The first data collection was performed from April 19–28, 2005. During this period,

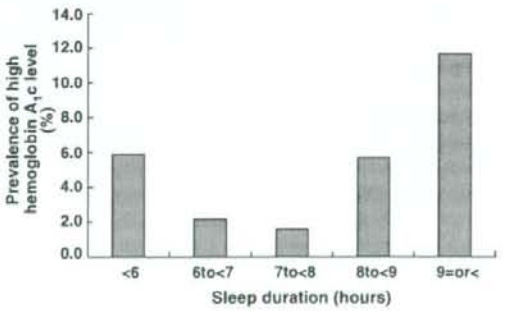

Fig. 2. (Title) Association between prevalence of high hemoglobin A_{1c} level and sleep duration. *Note:* A U-shaped association was recognized between prevalence of high hemoglobin A_{1c} level and sleep duration. A hemoglobin A_{1c} level of ⩾6.5% was considered to be a "high hemoglobin A_{1c} level."

the participants were instructed to report to the Health and Welfare Center of the municipality. A self-administered questionnaire was mailed to the participants 2–3 weeks before the day of the survey, and completed questionnaires were collected on the day of the survey. At the time of collection, we confirmed whether or not the questionnaires were complete; any participants with an incomplete questionnaire were instructed to complete the questionnaire immediately. Data on sleep habits, physical measurements (height, weight, and blood pressure), blood samples for laboratory examinations, and electrocardiogram and X-ray findings were collected.

2.3. Measures

The self-administered questionnaire consisted of queries concerning the following three items: (1) sonodemographic information, (2) sleep habits and sleep problems, and (3) the Center for Epidemiologic Studies Depression Scale (CES-D) [14].

Five questions on sleep during the past month included in this 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 maintaining sleep (DMS)]: "How often do you find it difficult to go back to sleep after waking during the night or too early in the morning?"
(4) "How often do you have trouble staying alert when you are required to refrain from sleep (at work, etc.)?"
(5) "How often have you taken medication to induce sleep?"

The subjects were instructed to answer question (1) by entering the value of their average daily sleep duration. For questions (2)–(5), the following four options were provided: "never," "less than once per week," "once or twice per week," and "three times or more per week". The option "three times or more per week" was taken as an affirmative answer for questions (2)–(5).

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 20-item scores (range: 0–60). Higher scores indicate increasing severity of symptoms of depression. 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 the cutoff point to be set at 16, as with the United States version of the CES-D [15].

Blood samples were collected when participants were in the fasting state. The plasma was separated, refrigerated, and then consigned to a laboratory for measurement of the HbA_{1C} and fasting plasma glucose levels. The fasting plasma glucose level was measured using the enzyme method, and the HbA_{1c} level was measured using the latex agglutination turbidimetric immunoassay [16,17].

2.4. Statistical analysis

Of the 1067 participants of the first survey, five were excluded from the analysis because either they did not complete the questionnaire or did not undergo determination of the HbA_{1c} level. The data for the remaining 1062 participants were analyzed statistically.

In the present study, in accordance with the diagnostic criteria of diabetes [18], a fasting plasma glucose level of $\geqslant 126$ mg/dl was considered to be a "high plasma glucose level" and a HbA_{1c} level of $\geqslant 6.5\%$ as a "high HbA_{1c} level." A HbA_{1c} value of 6.5% is the cutoff point that is often used as one of the target levels for preventing complications of diabetes, according to the diagnostic criteria for diabetes [18].

First, the mean values and standard deviations of the fasting plasma glucose and HbA_{1c} levels based on gender and age class were calculated. Second, the prevalence of high plasma glucose and high HbA_{1c} levels was calculated, and the associations of the sleep items with high plasma glucose and high HbA_{1c} levels were examined using χ^2 test. Finally, logistic regression analyses were performed to examine the associations of sleep duration with high plasma glucose and high HbA_{1c} levels. The high plasma glucose and high HbA_{1c} levels were input as response variables in Models I and II, respectively. The following parameters were input as covariates in both models: age, gender, obesity, systolic blood pressure, high-density lipoprotein level, triglyceride level, CES-D score, and answers to questions on sleep. SPSS14.0J for Windows was used for all statistical analyses.

3. Results

The distributions of the analyzed subjects based on gender and age classification are presented in Table 1. Among both men and women, participants aged 50 years and above accounted for approximately 70% of the study population.

The prevalence of high fasting plasma glucose and HbA_{1c} levels based on gender and age classification and the mean values and standard deviations of the fasting plasma glucose and HbA_{1c} levels are presented in Table 2. The prevalence of high plasma glucose and high

Table 1
The distributions of the analyzed subjects by gender and age classification

Age classification	Male *N* (%)	Female *N* (%)	Total *N* (%)
20–39	57(14.0)	86(13.1)	143(13.5)
40–49	61(15.0)	81(12.3)	142(13.4)
50–59	99(24.4)	163(24.8)	262(24.7)
60–69	94(23.2)	189(28.8)	283(26.6)
70–	95(23.4)	137(20.9)	232(21.8)
Total	406(100.0)	656(100.0)	1062(100.0)

HbA_{1c} levels was higher among men and women aged 60 years and above.

The associations of each sleep item with fasting plasma glucose and HbA_{1c} level are presented in Table 3. A significant association was demonstrated between sleep duration and the prevalence of a high plasma glucose level ($p < 0.01$). The prevalence of a high plasma glucose level was lowest for sleep durations of $\geqslant 6$ h but <7 h. The prevalence of a high plasma glucose level tended to become higher for sleep durations shorter or

Table 2
Prevalence of glucose intolerance by gender and age classification

Age classification	*N*	Prevalence of high fasting plasma glucose level (%)	95% CI	Mean ± SD	Prevalence of high HbA_{1c} level (%)	95% CI	Mean ± SD
Male							
20–39	57	1.8	0.0–5.3	79 ± 12	1.8	0.0–5.3	4.8 ± 0.5
40–49	61	3.3	0.0–7.8	84 ± 10	1.6	0.0–4.7	4.9 ± 0.4
50–59	99	6.1	1.4–10.8	93 ± 29	8.1	2.7–13.5	5.3 ± 0.9
60–69	94	9.6	3.6–15.6	96 ± 27	11.7	5.2–18.2	5.4 ± 0.9
70–	95	10.5	4.3–16.7	96 ± 21	10.5	4.3–16.7	5.4 ± 0.9
Total	406	6.9	4.4–9.4	91 ± 23	7.6	5.0–10.2	5.2 ± 0.9
Female							
20–39	86	0.0	0.0–0.0	77 ± 6	0.0	0.0–0.0	4.7 ± 0.5
40–49	81	1.2	0.0–3.6	83 ± 18	1.2	0.0–3.6	5.0 ± 0.4
50–59	163	1.2	0.0–2.9	87 ± 15	1.8	0.0–3.8	5.1 ± 0.6
60–69	189	6.3	2.8–9.8	93 ± 19	5.3	2.1–8.5	5.2 ± 0.6
70–	137	5.8	1.9–9.7	95 ± 27	5.8	1.9–9.7	5.3 ± 0.9
Total	656	3.5	2.1–4.9	88 ± 19	3.4	2.0–4.8	5.1 ± 0.7
Total	1062	4.8	3.5–6.1	89 ± 21	5.0	3.7–6.3	5.2 ± 0.7

CI, confidence interval; SD, standard deviations; HbA_{1c}, hemoglobin A_{1c}.

Table 3
Prevalence of glucose intolerance by sleep duration and sleep problems

	N	Prevalence of high fasting plasma glucose level (%)	95% CI	*P*-value	Mean ± SD	Prevalence of high HbA_{1c} level (%)	95% CI	*P*-value	Mean ± SD
Sleep duration (h)				<0.01				<0.01	
<6	51	5.9	0.0–12.4		93 ± 39	5.9	0.0–12.4		5.2 ± 1.0
6 to <7	183	1.1	0.0–2.6		85 ± 12	2.2	0.0–4.2		5.1 ± 0.5
7 to <8	308	2.3	0.6–4.0		86 ± 15	1.6	0.2–3.0		5.0 ± 0.5
8 to <9	332	6.0	3.4–8.6		91 ± 21	5.7	3.2–8.2		5.1 ± 0.8
9 = or <	188	10.1	5.8–14.4		95 ± 27	11.7	7.1–16.3		5.4 ± 1.1
Difficulty intiating sleep				0.68				0.85	
No	970	4.7	3.4–6.0		89 ± 21	5.1	3.7–6.5		5.1 ± 0.8
Yes	87	5.7	0.8–10.6		91 ± 21	4.6	0.2–9.0		5.2 ± 0.7
Difficulty maintaining sleep				0.24				0.46	
No	958	4.9	3.5–6.3		89 ± 21	5.0	3.7–6.5		5.1 ± 0.8
Yes	92	2.2	0.0–5.2		91 ± 17	3.3	0.0–7.0		5.2 ± 0.6
Use of hypnotic medication				0.75				0.02	
No	1018	4.7	0.6–8.8		89 ± 21	4.6	3.3–5.9		5.1 ± 0.7
Yes	29	3.4	0.0–10.0		92 ± 26	13.8	1.2–26.4		5.3 ± 1.0
Difficulty remaining alert				0.64				0.70	
No	1034	4.5	3.2–5.8		89 ± 20	4.8	3.5–6.1		5.1 ± 0.7
Yes	14	7.1	0.0–20.6		97 ± 60	7.1	0.0–20.6		5.3 ± 1.3

CI, confidence interval; SD, standard deviations; HbA_{1c}, hemoglobin A_{1c}. *P*-values were calculated by χ^2 test.

longer than the above-mentioned range. A significant association was also demonstrated between sleep duration and the prevalence of a high HbA_{1c} level. Similarly to a high plasma glucose level, the prevalence of a high HbA_{1c} level was lowest for sleep durations of ⩾6 h but <7 h. The prevalence tended to become higher for sleep durations that were shorter and longer than the above-mentioned range.

The results of logistic regression analyses are presented in Table 4. The adjusted odds ratio for a high plasma glucose level was significantly higher for a sleep duration of ⩾9 h than for a sleep duration of ⩾7 h but <8 h. Logistic regression analysis using high HbA_{1c} as a response variable revealed significant associations with gender, sleep duration, and triglyceride level. The adjusted odds ratio for a high HbA_{1c} level was

Table 4
The results of logistic regression analyses

	High fasting plasma glucose level			High HbA_{1c} level		
	AOR	95% CI	*P*-value	AOR	95% CI	*P*-value
Age classification			0.07			0.12
30–39	2.10	0.19–23.84		2.15	0.19–24.50	
40–49	3.85	0.46–32.46		5.07	0.62–41.69	
50–59	9.07	1.15–71.63		9.02	1.14–71.60	
60–69	8.18	1.00–66.86		6.60	0.80–54.60	
70–	1.00			1.00		
Gender			0.13			0.03
Male	1.00			1.00		
Female	0.61	0.32–1.16		0.49	0.26–0.94	
Sleep duration (h)			0.07			0.02
<6	3.60	0.79–16.41		4.96	1.03–23.96	
6 to <7	0.59	0.12–3.00		0.97	0.22–4.26	
7 to <8	1.00			1.00		
8 to <9	2.03	0.76–5.41		2.92	1.03–8.27	
9 = or <	3.16	1.14–8.75		4.96	1.70–14.50	
Systolic blood pressure			0.32			0.11
<130 mm Hg	1.00			1.00		
130 mm Hg = or <	1.41	0.72–2.8		1.75	0.89–3.45	
Body mass index			0.35			0.26
<25	1.00			1.00		
25 = or <	0.73	0.38–1.41		0.68	0.35–1.33	
High-density lipoprotein cholesterol level			0.28			0.45
<40 mg/dl	1.00			1.00		
40 mg/dl = or <	0.32	0.04–2.53		1.55	0.49–4.89	
Triglyceride level			0.39			0.05
<150 mg/dl	1.00			1.00		
150 mg/dl = or <	1.51	0.59–3.85		2.27	1.00–5.16	
Difficulty remaining alert			0.48			0.49
No	1.00			1.00		
Yes	2.27	0.42–1.62		2.22	0.23–21.17	
Difficulty intiating sleep			0.26			0.80
No	1.00			1.00		
Yes	1.90	0.62–5.78		0.85	0.25–2.91	
Difficulty maintaining sleep			0.17			0.20
No	1.00			1.00		
Yes	0.34	0.07–1.58		0.37	0.08–1.67	
Use of hypnotic medication			0.62			0.17
No	1.00			1.00		
Yes	0.57	0.06–5.15		2.71	0.66–11.13	
Going to the rest room during night			0.58			0.57
No	1.00			1.00		
Yes	0.83	0.42–1.62		0.82	0.43–1.59	
Having a pain			0.61			0.29
No	1.00			1.00		
Yes	1.31	0.46–3.76		1.70	0.63–4.57	
CES-D score			0.36			0.73
<16	1.00			1.00		
16 = or <	0.67	0.28–1.60		0.87	0.39–1.93	

CI, confidence interval; HbA_{1c}, hemoglobin A_{1c}; AOR, adjusted odds ratio; CES-D, the Center for Epidemiologic Studies Depression Scale. In each section, the missing data have been excluded from the statistical analyses.

significantly higher for sleep durations of <6 h and ≥8 h than for a sleep duration of ≥7 h but <8 h. Thus, a U-shaped association was recognized between high HbA_{1c} and sleep duration. No significant association was found between a high fasting plasma glucose level and the CES-D score or between a high HbA_{1c} level and the CES-D score.

4. Discussion

This is the first report to demonstrate that the adjusted odds ratio for HbA_{1c} level is significantly high for both short and long sleep durations. Previous cross-sectional studies that examined the association between diabetes mellitus and sleep showed that the prevalences of DIS, DMS, and excessive daytime sleepiness were high among diabetics [6,7]. In a prospective study of 8269 Germans, Meisinger et al. reported that DMS might be a risk factor for onset of Type 2 diabetes [19]. Similar results were reported in prospective studies conducted in other Western countries [20,21]. In Japan, Kawakami et al. followed 2649 subjects over eight years and reported that DMS and DIS might be risk factors for the onset of diabetes [22]. With regard to the association between diabetes and sleep duration, the Sleep Heart Health Study conducted in the United States with approximately 1500 subjects revealed that glucose tolerance was impaired at sleep durations of ≤6 h or ≥9 h [23]. In the present study, a U-shaped association was recognized between glucose tolerance and sleep duration, even when glucose tolerance was assessed using the plasma HbA_{1c} level as a measure. This result was rationally in agreement with the result of the above-mentioned study.

The association between short sleep duration and impaired glucose tolerance can be explained in terms of the functions of several hormones. It is known that insomnia stimulates the cerebral cortex, cerebral limbic system, and hypothalamus, which in turn induces the secretion of catecholamines from the sympathetic ganglion and adrenal medulla and of cortisol from the pituitary–adrenal system [4]. These hormones may function to increase the plasma glucose level. Moreover, physiological experiments have shown that the blood cortisol concentration and insulin resistance are increased when sleep is prevented [4,24,25]. Furthermore, recently, it has recently been clarified that the blood concentration of leptin, which suppresses appetite, is decreased and that the blood concentration of ghrelin, which promotes appetite, is increased when individuals are deprived of sleep [19,26]. The association between short sleep duration and impaired glucose tolerance may be explained in terms of the function of these appetite-regulating hormones. Unfortunately, since measurement of hormone concentrations was not included in the present study, any associations among short sleep duration, glucose tolerance, and hormone concentrations could not be elucidated. We intend to investigate such associations in future studies.

Although it can be reasonably argued that an association exists between short sleep duration and impaired glucose tolerance, the biological mechanisms underlying the association between long sleep duration and impaired glucose tolerance cannot be explained easily. It is known that neuropathic pain or nocturia leads to disturbed sleep [27] and increases the prevalence of insomnia symptoms such as DIS and DMS among diabetics [6,21]. It is possible that sleep duration increases to compensate for the shallow sleep caused by neuropathic pain or nocturia among diabetics. Therefore, we performed a logistic regression analysis using "having pain" and "going to the toilet during the night" as covariates. However, these two factors did not explain the association between long sleep duration and high HbA_{1c} level. A possibility that various other complications of diabetes may be associated with long sleep duration and impaired glucose tolerance, and that they act as confounding factors, cannot be refuted. Future studies on long sleep duration in the light of physiologic and epidemiologic data are expected to yield information on this issue.

Since the prevalences of depression and depressive symptoms among diabetic patients have been reported to be high [11], an association between a high HbA_{1c} level and the CES-D score was examined. However, no significant association was observed in the present study. In addition, the possibility that depression may have produced a confounding effect on the association between HbA_{1c} and sleep was considered. However, after depression was adjusted for, the significant association between sleep duration and HbA_{1c} continued to exist.

Since the latter half of the 1960s, it has been known that the mortality risk is high for individuals with both short and long sleep durations, and that there is a U-shaped association between sleep duration and mortality risk [28–31]. In recent years, U-shaped associations have been recognized between sleep duration and the morbidity risks of diabetes, obesity, hypertension, and coronary heart disease (CHD) [32–35]. It is well known that diabetes mellitus, obesity, and hypertension are morbidity risk factors for CHD. The fact that U-shaped associations exist between these pathological conditions and sleep duration may explain the U-shaped association between CHD and sleep duration, and consequently between the mortality risk of CHD and sleep duration. Diabetes mellitus, obesity, and hypertension are pathological conditions that have a tendency to develop simultaneously and affect each other. Therefore, when examining an association between one of these pathological conditions and sleep duration, it is necessary to adjust for the remaining two. In the present