がメタボリックシンドロームのリスクファクターやタボリックシンドロームと有意な関連を示すことが明らかになった。また、睡眠呼吸障害群とメタボリックシンドロームリスクファクターとの関連が非肥満群で肥満群に比べより明らかであった。

表１　３%ＯＤＩ区分別年齢調整した循環器疾患リスクファクターの平均値と頻度

	男				女			
	3%ODI			*p* for trend	3%ODI			*p* for trend
	0-4	5-14	15+		0-4	5-14	15+	
人数	1,031	527	152		2,358	473	65	
年齢，歳	57.5 (0.2)	58.4 (0.3)	59.6 (0.6)	<0.001	55.8 (0.2)	59.5 (0.4)	60.7 (1.0)	<0.001
Body mass index, kg/m^2	23.2 (0.1)	25.0 (0.1)	26.4 (0.2)	<0.001	22.9 (0.1)	25.0 (0.1)	26.9 (0.4)	<0.001
飲酒量，g/day	22.3 (0.7)	25.1 (1.0)	28.5 (1.9)	0.006	1.7 (0.1)	1.9 (0.3)	2.4 (0.9)	0.36
現在喫煙，%	46	40	36	<0.001	5	4	2	0.15
最大血圧，mmHg	130 (0)	133 (1)	137 (1)	<0.001	125 (0)	127 (1)	135 (2)	<0.001
最小血圧，mmHg	81 (0)	83 (0)	85 (1)	<0.001	76 (0)	77 (0)	81 (1)	<0.001
血糖値，mg/dl	108.0 (1.0)	107.3 (1.4)	113.9 (2.6)	0.08	99.6 (0.4)	101.1 (0.9)	106.2 (2.4)	0.002
血清総コレステロール，mg/dl	201.9 (1.1)	209.1 (1.5)	213.6 (2.7)	<0.001	218.0 (0.7)	216.5 (0.9)	211.5 (4.4)	0.11
HDL-コレステロール，mg/dl	56.6 (0.5)	54.0 (0.6)	52.8 (1.2)	<0.001	63.9 (0.3)	59.1 (0.7)	58.1 (1.8)	<0.001
中性脂肪，mg/dl	134.1 (3.7)	156.8 (5.1)	168.8 (9.6)	<0.001	103.5 (1.9)	119.5 (4.3)	136.9 (11.5)	<0.001
空腹者，%	52	53	51	0.84	54	46	59	0.17
降圧剤服薬者，%	16	23	33	<0.001	15	24	38	<0.001
糖尿病薬服薬者，%	5	4	6	0.95	2	4	2	0.03

表２．年齢、性、多変量調整したメタボリックシンドロームリスクファクター2個以上集積のオッズ比

	非肥満群			肥満群			
	3%ODI			3%ODI			*p* for interaction
	0-4	5-14	15+	0-4	5-14	15+	
人数	2645	510	78	740	490	139	
血圧高値							
人数(%)	1185 (45)	293 (58)	63 (81)	472 (64)	369 (75)	114 (82)	
年齢、性調整 OR	1	1.2 (1.0, 14)	3.2 (1.8, 5.8)	1	1.5 (1.1, 1.9)	1.9 (1.2, 3.1)	
多変量調整 OR	1	1.0 (0.8, 1.3)	2.5 (1.4, 4.6)	1	1.4 (1.0, 1.8)	1.5 (0.9, 2.4)	0.006
高血糖							
人数(%)	288 (11)	74 (15)	19 (24)	110 (15)	85 (17)	40 (29)	
年齢、性調整 OR	1	1.1 (0.7, 1.3)	1.5 (0.9, 2.6)	1	1.1 (0.8, 1.5)	1.9 (1.2, 2.9)	
多変量調整 OR	1	1.0 (0.7, 1.3)	1.4 (0.9, 2.5)	1	1.1 (0.8, 1.5)	1.6 (1.0, 2.6)	0.56
HDL－コレステロール低値							
人数(%)	349 (13)	80 (15)	12 (15)	155 (21)	110 (22)	23 (17)	
年齢、性調整 OR	1	1.3 (1.0, 1.7)	1.4 (0.7, 2.6)	1	1.2 (0.9, 1.6)	0.9 (0.6, 1.5)	
多変量調整 OR	1	1.2 (0.9, 1.6)	1.3 (0.7, 2.6)	1	1.3 (1.0, 1.7)	1.0 (0.6, 1.8)	0.11
トリグリセライド高値							
人数(%)	433 (16)	131 (29)	38 (49)	288 (39)	222 (45)	77 (55)	
年齢、性調整 OR	1	1.5 (1.0, 1.7)	2.3 (1.4, 3.7)	1	1.1 (0.9, 1.5)	1.3 (0.9, 2.0)	
多変量調整 OR	1	1.2 (1.0, 1.6)	1.7 (1.0, 2.8)	1	1.2 (0.9, 1.5)	1.2 (0.8, 1.9)	0.08
リスクファクター2個以上							
人数(%)	454 (19)	122 (26)	35 (49)	239 (35)	205 (45)	71 (54)	
年齢、性調整 OR	1	1.3 (1.0, 1.6)	2.6 (1.6, 4.1)	1	1.1 (0.9, 1.5)	1.6 (1.1, 2.3)	
多変量調整 OR	1	1.1 (0.9, 1.4)	1.9 (1.2, 3.1)	1	1.2 (0.9, 1.5)	1.4 (0.9, 2.1)	0.002

*多変量調整因子を年齢、性、ＢＭＩ、現在喫煙、飲酒量、採血時間、女性の閉経有無とした。

E．結論

睡眠呼吸障害がメタボリックシンドロームのリスクファクターやメタボリックシンドロームと有意に関連することが示された。

対象地区からの転出は市町村と協力して調査を進めている。氏名や住所など個人を特定できる情報を削除し、解析を行う。このコホート研究全体については、2008年に大阪大学の倫理審査委員会で倫理審査を受け、承認を得ている。

F．データ管理・更新（倫理面への配慮）

G.論文発表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Muraki I, Tanigawa T, Yamagishi K, Sakurai S, Ohira T, Imano H, Kiyama M, Kitamura A, Sato S, Shimamoto T, Konishi M, Iso H.	Nocturnal intermittent hypoxia and metabolic syndrome; the effect of being overweight: the CIRCS study.	J Atheroscler Thromb	17	369-377	2010

H．　知的財産権の出願・登録状況

1．特許取得　なし。
2．実用新案登録　なし。
3．その他　なし

I．究協力者

崔　仁哲　大阪大学大学院医学系研究科

Original Article

Nocturnal Intermittent Hypoxia and Metabolic Syndrome; the Effect of being Overweight: the CIRCS Study

Isao Muraki[1,2], Takeshi Tanigawa[3], Kazumasa Yamagishi[4], Susumu Sakurai[3], Tetsuya Ohira[1], Hironori Imano[2], Masahiko Kiyama[2], Akihiko Kitamura[2], Shinichi Sato[2,5], Takashi Shimamoto[2], Masamitsu Konishi[2], and Hiroyasu Iso[1], for the CIRCS Investigators

[1]Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, Suita, Japan
[2]Osaka Medical Center for Health Science and Promotion, Osaka, Japan
[3]Department of Public Health, Doctoral Program in Social Medicine, Graduate School of Medicine, Ehime University, Toon, Japan
[4]Department of Public Health Medicine, Graduate School of Comprehensive Human Sciences, and Institute of Community Medicine, University of Tsukuba, Tsukuba, Japan
[5]Chiba Prefectural Institute of Public Health, Chiba, Japan

Aim: We investigated whether nocturnal intermittent hypoxia, a surrogate marker for obstructive sleep apnea, is associated with metabolic syndrome and its components among Japanese.
Methods: We examined 1,710 male and 2,896 female community-dwelling Japanese aged 40 to 69, who participated in annual cardiovascular examinations and investigations of sleep. Nocturnal intermittent hypoxia was estimated based on a 3% oxygen desaturation index measured with pulse-oximetry during sleep. No, mild and moderate-to-severe nocturnal intermittent hypoxia were defined by <5, 5 to <15 and ≥ 15 events/hour, respectively. Metabolic syndrome was defined by modified criteria of the Adult Treatment Panel III guidelines.
Results: Compared with no nocturnal intermittent hypoxia, the multivariable odds ratio of metabolic syndrome was 1.9 (95% confidence interval: 1.6–2.4) for mild and 3.2 (2.2–4.7) for moderate-to-severe nocturnal intermittent hypoxia among men; 2.6 (2.1–3.4) and 5.8 (3.4–9.8) among women, respectively. When stratified by overweight status (body mass index ≥ 25 kg/m^2), the multivariable odds ratio of two or more metabolic risk factors (other than overweight) associated with moderate-to-severe nocturnal intermittent hypoxia was 1.9 (1.2–3.1) among non-overweight subjects and 1.4 (0.9–2.1) among overweight subjects (p for interaction = 0.002).
Conclusions: Nocturnal intermittent hypoxia was associated with the accumulation of metabolic risk factors, especially among non-overweight individuals.

J Atheroscler Thromb, 2010; 17:369-377.

Key words; Metabolic syndrome, Intermittent hypoxia, Sleep-disordered breathing, Overweight, Cross-sectional study

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway obstruction during sleep, which cause enhanced sympathetic activity, elevated intrathoracic pressure, increased cytokine levels, increased oxidative stress and sleep deprivation[1]. OSA is associated with hypertension, dyslipidemia and glucose abnormality, independent of traditional confounding factors (e.g. age, sex and body mass index (BMI))[2]. In addition, prospective studies have shown that OSA increases the risk of cardiovascular disease, independently of traditional confounding factors[3]. Therefore, OSA has been noted as a new cardiovascular risk factor.

Address for correspondence: Hiroyasu Iso, Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
E-mail: iso@pbhel.med.osaka-u.ac.jp
Received: July 20, 2009
Accepted for publication: October 6, 2009

Metabolic syndrome (MetS) reflects high cardiovascular risk conditions[4-6]. The prevalence of MetS defined by the Adult Treatment Panel III guidelines of the National Cholesterol Education Program (NCEP/ATPIII) was 2-fold higher among patients with an apnea-hypopnea index (AHI) ≥5 than among those with AHI <5[7, 8], 2- to 4-fold higher among those with AHI ≥15 than among those with AHI <15[8, 9], and 9-fold higher among those with AHI ≥15 and OSA-related symptoms (e.g. excessive daytime sleepiness) than among those without either[10]. Vgontzas and colleagues suggested that MetS manifests as OSA, because of the association of MetS with increased oxidative stress, insulin resistance and increased levels of cytokines, which are also associated with OSA[11, 12]. However, since most previous studies recruited mainly obese or overweight subjects (body mass index, BMI; 25.9–38.4 kg/m^2)[7-11], and both OSA and MetS were strongly associated with BMI, prior findings may not be applicable to non-overweight populations.

To examine whether these associations were extrapolated in a lean population, we examined the association between nocturnal intermittent hypoxia and MetS among community-dwelling Japanese, which consisted mainly of non-overweight subjects.

Methods

The Circulatory Risk in Communities Study (CIRCS) is a prospective community-based study that has been launched to prevent stroke in five communities across Japan since 1963, described in detail elsewhere[6, 13, 14]. Annual cardiovascular risk surveys and monitoring of cardiovascular events are systematically conducted by a research team of the Osaka Medical Center for Health Science and Promotion, the Osaka University and the University of Tsukuba. An investigation of sleep as part of the annual cardiovascular surveys was started in three communities (Ikawa; a northeast rural community, Yao; a mid-west suburban community, and Kyowa; a mid-east rural community) in 2000[15]. The study protocol was approved by the Institutional Review Board of the Osaka Medical Center for Health Science and Promotion, Osaka University and the University of Tsukuba.

Subjects

The participants in the 2001 to 2005 annual cardiovascular surveys aged 40 to 69 years were recruited for the present investigation. The numbers of participants were 448 men and 853 women from Yao (recruitment rate among the cardiovascular survey participants = 95% for men and 77% for women), 397 men and 571 women from Ikawa (93% and 88%), and 917 men and 1,507 women from Kyowa (89% and 87%). No subject had a history of OSA diagnosed by a physician. Subjects who had a history of stroke (n=55) or a history of heart disease (n=33) were excluded. A total of 1,710 men and 2,896 women were enrolled in the present study. For each subject, a physician and trained staff explained the protocol in detail, and obtained informed consent.

Measurement of Metabolic Risk Factors and Confounding Variables

Height in stocking feet and weight in light clothing were measured and BMI was calculated as weight (kg) divided by the square of height (m). Systolic and diastolic blood pressures (SBP and DBP) were measured by physicians using a standard mercury sphygmomanometer on the right arm while the subject was quietly seated after at least 5 min of rest.

For the measurement of serum lipids and glucose, venous blood was drawn from seated participants into a plain, siliconized glass tube and serum was separated within 30 min. The serum sample was transported on dry ice to the Osaka Medical Center for Health Science and Promotion, and stored at −70℃ prior to analysis. Serum total cholesterol, HDL-cholesterol, triglyceride and glucose levels were measured using enzymatic methods for lipids and the hexokinase method for glucose with an automatic analyzer (AU2700, Olympus Co., Tokyo, Japan) at the Osaka Medical Center for Health Science and Promotion, whose laboratory is an international member of the US National Cholesterol Reference Method Laboratory Network[16].

We measured several potential confounders that might also contribute to or aggravate OSA[2]. Interviews were conducted to determine alcohol intake per day, number of cigarettes smoked per day, time since last meal, use of antihypertensive and diabetes medication, and for women, menopausal status. An interviewer assessed normal weekly alcohol intake which was converted to grams of ethanol per day. Persons who smoked ≥1 cigarette/day were defined as current smokers. The distribution of time since the last meal did not differ between men and women; <2 hours (8% for men, 5% for women), 2 hours (9%, 7%), 3–7 hours (35%, 30%) and ≥8 hours (52%, 53%).

A modified definition of NCEP/ATPIII[17] was used to categorize subjects according to metabolic risk factors. Since waist circumference was not available in the present study, BMI was used for the assessment of obesity. The Asian criterion of obesity is a BMI ≥25.0 kg/m^2, or waist circumference ≥80 cm for women and

≥90 cm for men[18]. MetS was defined as three or more of the following metabolic risk factors: 1) BMI ≥25.0 kg/m^2, 2) fasting plasma glucose concentration ≥110 mg/dL (6.11 mmol/L) or non-fasting glucose concentration ≥140 mg/dL (7.77 mmol/L) or on medication, 3) SBP ≥130 mmHg or DBP ≥85 mmHg or on medication, 4) HDL-cholesterol concentration <40 mg/dL (1.03 mmol/L) for men and <50 mg/dL (1.29 mmol/L) for women, and 5) fasting or non-fasting triglyceride concentration ≥150 mg/dL (1.69 mmol/L). The presence of ≥2 metabolic risk factors was also defined as two or more metabolic risk factors other than overweight. We previously reported that MetS defined by these criteria was associated with incident ischemic stroke and heart disease[6].

Assessment of Nocturnal Intermittent Hypoxia

Nocturnal intermittent hypoxia was measured by Pulse-oximetry during one night's sleep using a pulse-oximeter (PULSOX-3Si, Minolta Co., Osaka, Japan) at the participants' own home[15]. The sensor probe was fitted to the fourth or fifth finger with tape. The device stores values of peripheral blood oxygen saturation by performing a moving average for the last 5 seconds, updated every second; this sampling time was short enough to avoid underestimation of oxygen desaturation[19]. Data were downloaded to a personal computer via an interface (PULSOX IF-3, Minolta) and analyzed by proprietary software (DS-3 ver. 2.0a, Minolta). Because the measurement time of pulse-oximetry is often longer than the true total sleep time, we used a single night's sleep log to exclude waking time from the analysis to minimize the potential for overestimating total sleep time. We used oxygen desaturation of 3% or more per hour of the adjusted measurement time (the 3% oxygen desaturation index, 3%ODI) as the indicator for nocturnal intermittent hypoxia. The severity of nocturnal intermittent hypoxia was defined by the 3%ODI level as 5 or 15 events per hour, corresponding to mild or moderate-to-severe nocturnal intermittent hypoxia, respectively.

The validity of pulse-oximetry using synchronous overnight recordings of both PULSOX-3Si and standard polysomnography (PSG) was confirmed previously among 256 consecutive patients in a sleep-disordered breathing center (mean body mass index, 26.8 kg/m^2). The sensitivity and specificity were 80% and 95%, respectively, for detecting an apnea-hypopnea index (AHI) of ≥5 by PSG using a cut-off threshold of 3%ODI=5. Similarly, the sensitivity and specificity for detecting AHI of ≥20 by PSG using a cut-off threshold of 3%ODI=15 were 85% and 100%, respectively[20]. To examine the reproducibility, pulse-oximetry was conducted for two nights among 61 men in the present study. The median values of 3%ODI were 5.4 on the first night and 4.8 on the second night (p for difference=0.95, Wilcoxon's signed-rank test). Spearman's rank correlation coefficient was 0.81 ($p<0.001$).

Statistical Analysis

Age and multivariable-adjusted mean values and prevalence of cardiovascular characteristics were calculated and tested by analysis of covariance according to 3%ODI. We used the logistic regression analysis to evaluate age- and multivariable-adjusted Odds ratios (ORs) of MetS according to 3%ODI. A trend test was performed with a regression model for mean values, and a logistic regression model for propotion and odds ratios, using median values of 3%ODI as representative of nocturnal intermittent hypoxia severity. The interactions of 3%ODI with sex, overweight and BMI in relation to MetS and its components were tested using cross-product terms of these variables in the logistic regression model. We included age (year), sex, smoking status (nonsmoker and current smoker), current ethanol intake (g/day), time since last meal (<2, 2, 3-7 and ≥8 hours) and for women, menopausal status (pre- and post-menopause), into the multivariable models. All analyses were conducted using the SAS statistical package, version 9.13 (SAS Institute Inc., Cary, NC). All p-values for statistical tests were two-tailed and $p<0.10$ to 0.05 and $p<0.05$ was regarded as borderline significance and statistical significance, respectively.

Results

The age-adjusted prevalence of mild and moderate-to-severe nocturnal intermittent hypoxia essentially did not differ among these three communities; the prevalence was 29 to 35% for mild and 8 to 9% for moderate-to-severe nocturnal intermittent hypoxia among men, and 15 to 17% for mild and 2 to 3% for moderate-to-severe nocturnal intermittent hypoxia among women.

Sex-specific age-adjusted distributions of cardiovascular risk factors according to 3%ODI are shown in **Table 1**. Mean values of age, BMI, SBP, DBP, serum glucose, triglyceride, and the proportion of antihypertensive medication use were higher, and mean values of HDL-cholesterol were lower, with increased 3%ODI among both sexes. Current ethanol intake and currently smoking were positively associated with 3%ODI among men. Mean values of serum total cholesterol were positively associated with 3%ODI among

Table 1. Sex-specific age-adjusted mean values (standard error) and prevalence of cardiovascular risk factors according to a 3% oxygen desaturation index

	Men				Women			
	3%ODI			*p* for trend	3%ODI			*p* for trend
	0 to <5	5 to <15	≥15		0 to <5	5 to <15	≥15	
No.	1,031	527	152		2,358	473	65	
Age, year	57.5 (0.2)	58.4 (0.3)	59.6 (0.6)	<0.001	55.8 (0.2)	59.5 (0.4)	60.7 (1.0)	<0.001
Body mass index, kg/m^2	23.2 (0.1)	25.0 (0.1)	26.4 (0.2)	<0.001	22.9 (0.1)	25.0 (0.1)	26.9 (0.4)	<0.001
Current ethanol intake, g/day	22.3 (0.7)	25.1 (1.0)	28.5 (1.9)	<0.001	1.7 (0.1)	1.9 (0.3)	2.4 (0.9)	0.36
Current smoker, %	46	40	36	<0.001	5	4	2	0.15
Systolic blood pressure, mmHg	130 (0)	133 (1)	137 (1)	<0.001	125 (0)	127 (1)	135 (2)	<0.001
Diastolic blood pressure, mmHg	81 (0)	83 (0)	85 (1)	<0.001	76 (0)	77 (0)	81 (1)	<0.001
Serum blood glucose, mg/dL	108.0 (1.0)	107.3 (1.4)	113.9 (2.6)	0.08	99.6 (0.4)	101.1 (0.9)	106.2 (2.4)	0.002
Serum total cholesterol, mg/dL	201.9 (1.1)	209.1 (1.5)	213.6 (2.7)	<0.001	218.0 (0.7)	216.5 (0.9)	211.5 (4.4)	0.11
HDL-cholesterol, mg/dL	56.6 (0.5)	54.0 (0.6)	52.8 (1.2)	<0.001	63.9 (0.3)	59.1 (0.7)	58.1 (1.8)	<0.001
Triglyceride, mg/dL	134.1 (3.7)	156.8 (5.1)	168.8 (9.6)	<0.001	103.5 (1.9)	119.5 (4.3)	136.9 (11.5)	<0.001
Fasting blood drawing, %	52	53	51	0.84	54	46	59	0.17
Use of antihypertensive medication, %	16	23	33	<0.001	15	24	38	<0.001
Use of diabetic medication, %	5	4	6	0.95	2	4	2	0.03

men, but inversely associated among women.

Table 2 shows the age- and multivariable-adjusted ORs of MetS and its components according to the severity of nocturnal intermittent hypoxia. Overweight, high blood pressure, a low HDL-cholesterol level and a high triglyceride level were positively associated with the severity of nocturnal intermittent hypoxia after adjustments for the confounding factors among both sexes. Glucose abnormality was associated with moderate-to-severe nocturnal intermittent hypoxia among men, but not among women. After further adjustment for BMI, the association of nocturnal intermittent hypoxia with each of these metabolic risk factors was weakened except for glucose abnormality. The age-adjusted prevalence of MetS was 2-fold and 4-fold higher for mild and moderate-to-severe nocturnal intermittent hypoxia, respectively among men, and 3-fold and 5-fold higher for mild and moderate-to-severe nocturnal intermittent hypoxia, respectively among women. After adjustments for the confounding factors, these associations did not change materially. The interaction of mild and moderate-to-severe nocturnal intermittent hypoxia with sex in relation to MetS was statistically significant (p for interaction=0.03 for mild and 0.04 for moderate-to-severe nocturnal intermittent hypoxia).

Since the impact of being overweight on both nocturnal intermittent hypoxia and metabolic risk factors seemed to be large, we further examined associations between nocturnal intermittent hypoxia and metabolic risk factors stratified by overweight status (**Table 3**). The associations did not vary with the presence and absence of this factor although they tended to be stronger for high blood pressure and high triglyceride among overweight individuals. After further adjustment for BMI, the associations for high blood pressure and high triglyceride were weakened, but remained statistically significant among non-overweight subjects. The interaction between nocturnal intermittent hypoxia and BMI in relation to high blood pressure, a high triglyceride level, and the presence of 2 or more metabolic risk factors was statistically significant or borderline significant (p for interaction=0.006 for high blood pressure, 0.08 for high triglyceride and 0.002 for the presence of 2≥ metabolic risk factors).

Discussion

Nocturnal intermittent hypoxia was positively associated with MetS and its components among both men and women. The prevalence of MetS associated with nocturnal intermittent hypoxia was 2 to 3-fold higher for persons with a ODI of 5 to <15 and 4 to 5-fold higher for persons with an ODI of ≥15 compared with those with an ODI of <5. The magnitude of these associations was similar to those in previous studies of American and Chinese[7-9]. As for the components of MetS, previous studies reported that nocturnal intermittent hypoxia was associated with

Table 2. Sex-specific age- and multivariable-adjusted odds ratios (95% confidence intervals) of metabolic risk factors and MetS according to the 3% oxygen desaturation index

	Men			Women			*p* for interaction	
	3%ODI			3%ODI			Mild SDB × Sex	Moderate-to-severe SDB × Sex
	0 to <5	5 to <15	≥15	0 to <5	5 to <15	≥15		
No. at risk	1,031	527	152	2,358	473	65		
Overweight								
No. of cases (%)	234 (23)	256 (49)	97 (64)	507 (22)	234 (49)	42 (65)		
Age-adjusted OR	1.0	3.2 (2.6, 4.1)	6.1 (4.3, 8.8)	1.0	3.5 (2.8, 4.3)	6.5 (3.8, 10.9)		
Multivariable-adjusted OR	1.0	3.3 (2.6, 4.1)	6.1 (4.2, 8.8)	1.0	3.5 (2.9, 4.4)	7.2 (4.2, 12.1)	0.46	0.63
High blood pressure								
No. of cases (%)	625 (61)	378 (72)	125 (82)	1,033 (44)	284 (60)	52 (80)		
Age-adjusted OR	1.0	1.6 (1.3, 2.0)	2.8 (1.8, 4.3)	1.0	1.5 (1.2, 1.9)	3.9 (2.1, 7.3)		
Multivariable-adjusted OR	1.0	1.5 (1.2, 1.9)	2.6 (1.6, 4.0)	1.0	1.5 (1.2, 1.9)	4.0 (2.1, 7.5)	0.84	0.33
Further adjustment for BMI	1.0	1.2 (1.9, 1.5)	1.7 (1.0, 2.6)	1.0	1.1 (0.8, 1.4)	2.2 (1.1, 4.2)		
Glucose abnormality								
No. of cases (%)	202 (20)	96 (18)	46 (30)	197 (8)	63 (13)	13 (20)		
Age-adjusted OR	1.0	0.9 (0.7, 1.2)	1.7 (1.2, 2.5)	1.0	1.4 (1.0, 1.9)	2.1 (1.1, 3.9)		
Multivariable-adjusted OR	1.0	0.9 (0.7, 1.2)	1.7 (1.2, 2.6)	1.0	1.5 (1.1, 2.1)	1.9 (1.0, 3.7)	0.009	0.78
Further adjustment for BMI	1.0	0.9 (0.7, 1.2)	1.7 (1.1, 2.5)	1.0	1.2 (0.9, 1.6)	1.2 (0.6, 2.3)		
Low HDL cholesterol								
No. of cases (%)	110 (11)	64 (12)	18 (12)	394 (17)	126 (27)	17 (26)		
Age-adjusted OR	1.0	1.3 (0.8, 1.6)	1.1 (0.6, 1.8)	1.0	1.7 (1.3, 2.1)	1.5 (0.9, 2.7)		
Multivariable-adjusted OR	1.0	1.3 (0.9, 1.8)	1.3 (0.8, 2.2)	1.0	1.7 (1.3, 2.2)	1.2 (0.6, 2.3)	0.28	0.70
Further adjustment for BMI	1.0	1.2 (0.8, 1.6)	1.1 (0.6, 2.0)	1.0	1.3 (1.0, 1.7)	1.0 (0.6, 1.9)		
High triglyceride								
No. of cases (%)	294 (29)	197 (37)	60 (39)	363 (15)	110 (23)	28 (43)		
Age-adjusted OR	1.0	1.5 (1.2, 1.9)	1.8 (1.2, 2.5)	1.0	1.5 (1.2, 1.9)	3.6 (2.2, 6.1)		
Multivariable-adjusted OR	1.0	1.6 (1.3, 2.1)	1.8 (1.3, 2.6)	1.0	1.5 (1.1, 1.9)	3.8 (2.3, 6.5)	0.64	0.02
Further adjustment for BMI	1.0	1.1 (0.9, 1.5)	1.1 (0.7, 1.5)	1.0	1.1 (0.9, 1.4)	2.3 (1.3, 4.0)		
Metabolic syndrome								
No. of cases (%)	178 (17)	145 (28)	61 (40)	243 (10)	121 (26)	28 (43)		
Age-adjusted OR	1.0	1.8 (1.6, 2.3)	3.2 (2.2, 4.6)	1.0	2.6 (2.0, 3.4)	5.5 (3.3, 9.3)		
Multivariable-adjusted OR	1.0	1.9 (1.6, 2.4)	3.2 (2.2, 4.7)	1.0	2.6 (2.1, 3.4)	5.8 (3.4, 9.8)	0.03	0.04

Multivariable-adjusted OR was adjusted for age (year), smoking status (nonsmoker and current smoker), current ethanol intake (g/day), time since last meal (<2, 2, 3–7 and ≥8 hours) and for women, menopausal status (pre- and post-menopause).

MetS[7-10] as well as obesity, hypertension, glucose abnormality and high triglyceride levels[2]. Our results generally confirmed these previous findings.

OSA and MetS were each associated strongly with BMI. Then, we examined the association between the severity of nocturnal intermittent hypoxia and each metabolic risk factor after stratification by overweight status. The associations with high blood pressure, a high triglyceride level and the presence of two or more metabolic risk factors were modified by overweight and BMI. To our knowledge, this study is the first to show significant interaction between nocturnal intermittent hypoxia and BMI in relation to metabolic risk factors.

Several mechanisms, other than being overweight, for nocturnal intermittent hypoxia affect metabolic risk factors. First, reduced blood oxygen saturation stimulates peripheral arterial chemoreceptors, especially carotid bodies, and enhances sympathetic drive, an effect which appears to be carried over into normal waking hours, leading to elevated blood pressure[21]. This mechanism was supported by reports that nasal continuous positive pressure reduced baroreceptor sensitivity[22] and ambulatory blood pressure[23]. Second, increased sympathetic tone also raised serum catecholamine levels, leading to elevated serum glu-

Table 3. Age, sex- and multivariable-adjusted odds ratios (95% confidence intervals) of metabolic risk factors and the presence of ≥2 metabolic risk factors according to the 3% oxygen desaturation index, stratified by overweight

	Not overweight			Overweight			*p* for interaction	
	3%ODI			3%ODI			Moderate-to-severe SDB×Overweight	Moderate-to-severe SDB×BMI
	0 to <5	5 to <15	≥15	0 to <5	5 to <15	≥15		
No. at risk	2,645	510	78	740	490	139		
High blood pressure								
No. of cases (%)	1,185 (45)	293 (58)	63 (81)	472 (64)	369 (75)	114 (82)		
Age, sex-adjusted OR	1.0	1.2 (1.0, 1.4)	3.2 (1.8, 5.8)	1.0	1.5 (1.1, 1.9)	1.9 (1.2, 3.1)		
Multivariable-adjusted OR	1.0	1.1 (0.9, 1.4)	2.9 (1.6, 5.3)	1.0	1.5 (1.1, 1.9)	2.0 (1.2, 3.2)	0.16	0.006
Further adjustment for BMI	1.0	1.0 (0.8, 1.3)	2.5 (1.4, 4.6)	1.0	1.4 (1.0, 1.8)	1.5 (0.9, 2.4)		
Glucose abnormality								
No. of cases (%)	288 (11)	74 (15)	19 (24)	110 (15)	85 (17)	40 (29)		
Age, sex-adjusted OR	1.0	1.1 (0.7, 1.3)	1.5 (0.9, 2.6)	1.0	1.1 (0.8, 1.5)	1.9 (1.2, 2.9)		
Multivariable-adjusted OR	1.0	1.0 (0.7, 1.4)	1.5 (0.9, 2.7)	1.0	1.2 (0.8, 1.6)	1.9 (1.2, 3.1)	1.00	0.56
Further adjustment for BMI	1.0	1.0 (0.7, 1.3)	1.4 (0.8, 2.5)	1.0	1.1 (0.8, 1.5)	1.6 (1.0, 2.6)		
Low HDL cholesterol								
No. of cases (%)	349 (13)	80 (16)	12 (15)	155 (21)	110 (22)	23 (17)		
Age, sex-adjusted OR	1.0	1.3 (1.0, 1.7)	1.4 (0.7, 2.6)	1.0	1.2 (0.9, 1.6)	0.9 (0.6, 1.5)		
Multivariable-adjusted OR	1.0	1.4 (1.0, 1.8)	1.6 (0.8, 3.0)	1.0	1.3 (1.0, 1.8)	1.1 (0.7, 1.9)	0.34	0.11
Further adjustment for BMI	1.0	1.2 (0.9, 1.6)	1.3 (0.7, 2.6)	1.0	1.3 (1.0, 1.7)	1.0 (0.6, 1.8)		
High triglyceride								
No. of cases (%)	433 (16)	131 (26)	29 (37)	224 (30)	176 (36)	59 (42)		
Age, sex-adjusted OR	1.0	1.5 (1.0, 1.7)	2.3 (1.4, 3.7)	1.0	1.1 (0.9, 1.5)	1.3 (0.9, 2.0)		
Multivariable-adjusted OR	1.0	1.5 (1.0, 1.8)	2.2 (1.4, 3.7)	1.0	1.2 (0.9, 1.6)	1.4 (0.9, 2.1)	0.12	0.08
Further adjustment for BMI	1.0	1.2 (1.0, 1.6)	1.7 (1.0, 2.8)	1.0	1.1 (0.9, 1.5)	1.2 (0.8, 1.9)		
The presence of ≥2 metabolic risk factors								
No. of cases (%)	538 (19)	149 (29)	38 (49)	288 (39)	222 (45)	77 (55)		
Age, sex-adjusted OR	1.0	1.3 (1.0, 1.6)	2.6 (1.6, 4.1)	1.0	1.1 (0.9, 1.5)	1.6 (1.1, 2.3)		
Multivariable-adjusted OR	1.0	1.3 (1.0, 1.6)	2.5 (1.5, 4.0)	1.0	1.2 (1.0, 1.6)	1.7 (1.1, 2.5)	0.09	0.002
Further adjustment for BMI	1.0	1.1 (0.9, 1.4)	1.9 (1.2, 3.1)	1.0	1.2 (0.9, 1.5)	1.4 (0.9, 2.1)		

Multivariable-adjusted OR was adjusted for age (year), sex, body mass index (kg/m^2), smoking status (nonsmoker and current smoker), current ethanol intake (g/day), time since last meal (<2, 2, 3–7 and ≥8 hours) and for women, menopausal status (pre- and post-menopause).

cose levels[24]. Third, oxidative stress owing to repetitive hypoxia elevated cytokine levels (e.g. tumor necrosis factor-α; TNF-α and interleukin-6; IL-6)[25], which led to increased insulin resistance[26]. Fourth, sleep deprivation and the stress there from inhibited slow wave sleep and activated the hypothalamic-pituitary-adrenal axis[27]. Inhibition of slow wave sleep decreased growth hormone levels, leading to a reduction in metabolism, and serum leptin levels and increased serum grhelin levels, leading to the stimulation of appetite. Activation of the hypothalamic-pituitary-adrenal axis increased serum cortisol levels[28], leading to hyperglycemia and insulin resistance[29]. Lastly, an experimental study has shown that intermittent hypoxia caused an increase in hepatic levels of triglyceride and phospholipid, and upregulated the expression of genes involved in lipid biosynthesis in mice[30]. Therefore, nocturnal intermittent hypoxia may increase serum triglyceride levels.

To explain the interaction between nocturnal intermittent hypoxia and BMI in relation to high blood pressure and high triglyceride levels, we considered whether BMI affects metabolic risk factors both directly and indirectly. Being overweight is associated with the accumulation of fat, which increases levels of free fatty acids and adipokines (e.g. TNF-α and IL-6)[31, 32]. An increase in adipokines causes elevated blood pressure[33]. An increase in free fatty acids causes

lipoprotein synthesis in the liver and raises serum triglyceride levels[34]. Being overweight may also be associated with metabolic risk factors indirectly, mediated by nocturnal intermittent hypoxia. For example, reduced oxygen saturation enhances sympathetic activity to raise blood pressure[23] and the production of VLDL in liver, and raises blood triglyceride levels[30], common pathways in overweight individuals. Therefore, being overweight may weaken the effect of nocturnal intermittent hypoxia on high blood pressure and high triglyceride levels.

The strengths of the present study were the large sample size ($n \approx 4{,}000$), and community-based approach. Another strength was that we investigated lean persons in Asia, whereas previous large studies were mainly of obese or overweight persons in the United States.

Several limitations of the present study need to be discussed. First, the study had a cross-sectional design. Therefore, we cannot prove the causality between nocturnal intermittent hypoxia and MetS. Second, we measured oxygen desaturation during sleep by pulse-oximetry to estimate OSA. Since apneic episodes do not always cause oxygen desaturation, we could not accurately estimate very mild OSA. However, the specificity of the screening remained high[20]. Third, we used BMI as the definition of MetS. Some studies reported that abdominal obesity had a stronger association with OSA than did high BMI[35]. Therefore, there may be some, though not substantial, misclassification because a previous study reported that BMI was highly correlated with abdominal fat as well as waist circumference ($r=0.87$ for BMI and $r=0.91$ for waist circumference)[36]. Fourth, the same cutoff point of serum triglycerides was used for fasting and non-fasting data as the criterium for high triglyceride levels. Although justification of the use of the same cutoff point as fasting status is under debate, the data of non-fasting triglycerides can be used because it is a significant predictor for ischemic heart disease[14]. Fifth, we used a non-fasting glucose concentration $\geq$140 mg/dL (7.77 mmol/L) as a component of MetS. Although we defined fasting status as more than 8 hours after the last meal, plasma glucose levels returned to pre-prandial levels in 2–3 hours after the last meal among subjects with normal glucose tolerance[37]. The proportion of participants with glucose abnormality for each definition of fasting status (more than 8 hours after the last meal vs. more than 3 hours after the last meal) was 14% vs. 25% for non-fasting and 26% vs. 24% for fasting in men, and in women, 14% vs. 11% and 12% vs. 12%, respectively. Therefore, we may have underestimated the number of participants with glucose abnormality among men. However, there was no difference change in our results between definitions of fasting status.

Mean BMI is much lower in Asia[38], and the prevalence of OSA was reported to be less than half that in the United States[39]. However, our findings suggest that OSA affects cardiovascular risk factors more strongly among lower BMI populations. Therefore, the impact of OSA on cardiovascular risk factors may be potentially large in Asia.

Acknowledgements

We thank Dr. Mitsumasa Umesawa, MD, PhD, Ms. Yukiko Ichikawa and Ms. Miyuki Notsute for technical assistance, and Ms. Minako Kudo, Ms. Kazuyo Kamei and staff of the Osaka Medical Center for Health Science and Promotion, Osaka University and the University of Tsukuba for data collection.

Notice of Grant Support

This was not an industry supported study. This study was supported in part by grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology (Grant-in-Aid for research B: 14370132) and the Health and Labor Sciences Research Grant (Clinical Research for Evidence Based Medicine), Ministry of Health, Welfare and Labor, the FULLHAP, Japan, and the University Research Project Research Grant (B), University of Tsukuba. Drs. Muraki, Tanigawa, Yamagishi, Sakurai, Cui, Imano, Sato, Kitamura, Shimamoto, Konishi and Iso have indicated no conflicts of interest.

References

1) Caples SM, Garcia-Touchard A, Somers VK: Sleep-disordered breathing and cardiovascular risk. Sleep, 2007; 30: 291-303
2) Young T, Peppard PE, Gottlieb DJ: Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med, 2002; 165: 1217-1239
3) Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T: Sleep apnea and cardiovascular disease: an American Heart Association/ American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol, 2008; 52: 686-717
4) Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, Daida H, Biro S, Hirobe K, Funahashi T,

Yokote K, Yokode M: Metabolic syndrome. J Atheroscler Thromb, 2008; 15: 1-5
5) Teramura M, Emoto M, Araki T, Yokoyama H, Motoyama K, Shinohara K, Mori K, Koyama H, Shoji T, Inaba M, Nishizawa Y: Clinical impact of metabolic syndrome by modified NCEP-ATPIII criteria on carotid atherosclerosis in Japanese adults. J Atheroscler Thromb, 2007; 14: 172-178
6) Iso H, Sato S, Kitamura A, Imano H, Kiyama M, Yamagishi K, Cui R, Tanigawa T, Shimamoto T: Metabolic syndrome and the risk of ischemic heart disease and stroke among Japanese men and women. Stroke, 2007; 38: 1744-1751
7) Lam JC, Lam B, Lam CL, Fong D, Wang JK, Tse HF, Lam KS, Ip MS: Obstructive sleep apnea and the metabolic syndrome in community-based Chinese adults in Hong Kong. Respir Med, 2006; 100: 980-987
8) Parish JM, Adam T, Facchiano L: Relationship of metabolic syndrome and obstructive sleep apnea. J Clin Sleep Med, 2007; 3: 467-472
9) Sasanabe R, Banno K, Otake K, Hasegawa R, Usui K, Morita M, Shiomi T: Metabolic syndrome in Japanese patients with obstructive sleep apnea syndrome. Hypertens Res, 2006; 29: 315-322
10) Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM, Wilding JP: Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. Eur Heart J, 2004; 25: 735-741
11) Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP: Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab, 2000; 85: 1151-1158
12) Vgontzas AN, Bixler EO, Chrousos GP: Sleep apnea is a manifestation of the metabolic syndrome. Sleep Med Rev, 2005; 9: 211-224
13) Imano H, Kitamura A, Sato S, Kiyama M, Ohira T, Yamagishi K, Noda H, Tanigawa T, Iso H, Shimamoto T: Trends for blood pressure and its contribution to stroke incidence in the middle-aged Japanese population: the Circulatory Risk in Communities Study (CIRCS). Stroke, 2009; 40: 1571-1577
14) Iso H, Naito Y, Sato S, Kitamura A, Okamura T, Sankai T, Shimamoto T, Iida M, Komachi Y: Serum triglycerides and risk of coronary heart disease among Japanese men and women. Am J Epidemiol, 2001; 153: 490-499
15) Tanigawa T, Tachibana N, Yamagishi K, Muraki I, Umesawa M, Shimamoto T, Iso H: Usual alcohol consumption and arterial oxygen desaturation during sleep. JAMA, 2004; 292: 923-925
16) Nakamura M, Sato S, Shimamoto T: Improvement in Japanese clinical laboratory measurements of total cholesterol and HDL-cholesterol by the US cholesterol reference method laboratory network. J Atheroscler Thromb, 2003; 10: 145-153
17) National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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: 3143-3421
18) World Health Organization Western Pacific Region, International Association for the Study of Obesity and the International Obesity Task Force. The Asia-Pacific perspective: Redefining obesity and its treatment. Health Communications Australia Pty Limited: Australia; 2000
19) Clark JS, Votteri B, Ariagno RL, Cheung P, Eichhorn JH, Fallat RJ, Lee SE, Newth CJ, Rotman H, Sue DY: Noninvasive assessment of blood gases. Am Rev Respir Dis 1992; 145: 220-232
20) Nakamata M, Kubota Y, Sakai K, Kinebuchi S, Nakayama S, Ohira T, Sato S, Shinoda S, Kawano S: The limitation of screening test for patients with sleep apnea syndrome using pulse oximetry. J Jpn Soc Respir Care, 2003; 12: 401-406 (in Japanese)
21) Narkiewicz K, van de Borne PJ, Montano N, Dyken ME, Phillips BG, Somers VK: Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea. Circulation, 1998; 97: 943-945
22) Coughlin SR, Mawdsley L, Mugarza JA, Wilding JP, Calverley PM: Cardiovascular and metabolic effects of CPAP in obese males with OSA. Eur Respir J, 2007; 29: 720-727
23) Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ: Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. Lancet, 2002; 359: 204-210
24) Nonogaki K: New insights into sympathetic regulation of glucose and fat metabolism. Diabetologia, 2000; 43: 533-549
25) Ciftci TU, Kokturk O, Bukan N, Bilgihan A: The relationship between serum cytokine levels with obesity and obstructive sleep apnea syndrome. Cytokine, 2004; 28: 87-91
26) Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS: Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature, 1997; 389: 610-614
27) Van Cauter E, Spiegel K, Tasali E, Leproult R: Metabolic consequences of sleep and sleep loss. Sleep Med, 2008; 9 Suppl 1: S23-S28
28) Spiegel K, Leproult R, Van Cauter CE: Impact of sleep debt on metabolic and endocrine function. Lancet, 1999; 354: 1435-1439
29) Follenius M, Brandenberger G, Bandesapt JJ, Libert JP, Ehrhart J: Nocturnal cortisol release in relation to sleep structure. Sleep, 1992; 15: 21-27
30) Li J, Nanayakkara A, Jun J, Savransky V, Polotsky VY: Effect of deficiency in SREBP cleavage-activating protein on lipid metabolism during intermittent hypoxia. Physiol Genomics, 2007; 31: 273-280
31) Chudek J, Wiecek A: Adipose tissue, inflammation and endothelial dysfunction. Pharmacol Rep, 2006; 58 Suppl: 81-88
32) Zimmermann R, Strauss JG, Haemmerle G, Schoiswohl G, Birner-Gruenberger R, Riederer M, Lass A, Neuberger G, Eisenhaber F, Hermetter A, Zechner R: Fat mobiliza-

tion in adipose tissue is promoted by adipose triglyceride lipase. Science, 2004; 306: 1383-1386
33) Guzik TJ, Mangalat D, Korbut R: Adipocytokines - novel link between inflammation and vascular function? J Physiol Pharmacol, 2006; 57: 505-528
34) Jensen MD, Haymond MW, Rizza RA, Cryer PE, Miles JM: Influence of body fat distribution on free fatty acid metabolism in obesity. J Clin Invest, 1989; 83: 1168-1173
35) Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP: Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab, 2000; 85: 1151-1158
36) Hwang MJ, Chung WS, Gallagher D, Kim DY, Shin HD, Song MY: How useful is waist circumference for assessment of abdominal obesity in Korean pre-menopausal women during weight loss? Asia Pac J Clin Nutr, 2008; 17: 229-234
37) American Diabetes Association. Postprandial blood glucose. American Diabetes Association. Diabetes Care, 2001; 24: 775-778
38) Balkau B, Deanfield JE, Després JP, Bassand JP, Fox KA, Smith SC Jr, Barter P, Tan CE, Van Gaal L, Wittchen HU, Massien C, Haffner SM: International Day for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. Circulation, 2007; 116: 1942-1951
39) Lam B, Lam DC, Ip MS: Obstructive sleep apnoea in Asia. Int J Tuberc Lung Dis, 2007; 11: 2-11

厚生労働省科学研究費補助金循環器疾患等生活習慣病対策総合研究事業：「保健指導への活用を前提としたメタボリックシンドロームの診断・管理のエビデンス創出のための横断・縦断研究」分担研究者報告書

コホート研究におけるヘモグロビンA1cと大血管障害（心筋梗塞、脳卒中）の関連：吹田研究

研究分担者　岡村　智教　国立循環器病センター予防検診部
研究協力者　小久保 喜弘　同上
渡邉　至　同上
東山　綾　同上

研究要旨：International Expert Committeeは、2009年にヘモグロビンA1cを用いた新しい糖尿病の診断基準を提唱した。この基準は主に細小血管障害の出現率に基づいて決められているが、大血管障害についても評価しておく必要がある。そこで都市住民コホートである吹田研究において、ヘモグロビンA1cで分類した糖尿病（および境界域）と大血管障害（心筋梗塞、脳卒中）の発症との関連を検討した。1990年6月～1991年2月にヘモグロビンA1cの測定を受け、循環器疾患の既往歴がない1607人（男性764人、女性843人）を2005年末まで追跡した。正常群（-5.9%）を基準として、境界群(6.0-6.4%)、糖尿病群(6.5%以上)の大血管障害発症のハザード比を算出した（性、年齢、BMI、高血圧、高コレステロール血症、糖尿病治療の有無、喫煙、飲酒を調整)。ヘモグロビンA1c（JDS値）は換算式を用いて、IFCC値→NGSP値に変換され、本研究ではすべてNGSP値で表記した。平均追跡期間は12.7年であり、この間に70件の大血管障害の発症を確認した。そのうち24件は心筋梗塞、44件は脳卒中（出血性19件、梗塞性22件、不明3件)、2件は内因性突然死であった。大血管障害全体の多変量調整ハザード比は、正常群を1.0とすると、境界群で1.2（95% 信頼区間 CI, 0.6-2.5)、糖尿病群で3.0（95% CI, 1.2-7.4)であった。心筋梗塞や脳卒中のハザード比も同様の傾向であり、それぞれ傾向性の検定で有意差を認めた。日本人の大血管障害の予防という観点からも6.5%（NGSP値）というヘモグロビンA1cを用いた糖尿病診断基準は妥当と考えられた。

A. 研究目的

International Expert Committeeは、2009年にヘモグロビンA1cを用いた新しい糖尿病の診断基準を提唱した。この基準は主に細小血管障害の出現率に基づいて決められているが、同時に大血管障害についても評価しておく必要がある。特に循環器疾患の疾病構造として欧米では冠動脈性心疾患が多いのに対し、本邦では脳卒中が多く、ヘモグロビンA1cと大血管障害の関連は独自に検証しておく必要がある。またヘモグロビンA1cの測定は、本邦のJDS値、NGSP値（米国)、IFCC値（主に欧州）と3通りの測定法が存在しており、単純な比較は困難である。したがって国際比較の観点からは、JDS値ではなく、最も普及しているNGSP

値に基づいてリスク評価を行うことが望ましい。

本研究では約 20 年前に測定されたヘモグロビン A1c 値（JDS 値）を NGSP 値に換算し、15 年間の追跡期間中に発症した大血管障害との関連を検討した。

B. 研究方法

吹田研究は、1989 年に吹田市の住民台帳から 30～79 歳の 12,200 名を無作為抽出し、その中で同意が得られた 6,485 名を第一次コホートとして追跡している。このうちヘモグロビン A1c の測定を実施した者を今回の解析対象とし、2005 年末まで追跡した。

1）ベースライン調査

吹田研究の一次コホートのベースライン調査は、1989 年 9 月～1993 年 3 月である。このうち 1990 年 6 月～1991 年 2 月の期間だけヘモグロビン A1c の測定が実施されていた。本研究の対象者は、吹田研究の一次コホート対象者のうちヘモグロビン A1c の測定値があり、循環器疾患の既往歴がない 1607 人である（男性 764 人、女性 843 人、平均年齢 51.2 歳）。既往歴・喫煙及び飲酒習慣は、保健師が聴取した。血圧は 3 回測定し、2 回目と 3 回目の平均値を使用した。血清総コレステロール、ヘモグロビン A1c は国立循環器病センター検査部で測定した。ヘモグロビン A1c は、高速液体クロマトグラフィで測定された。ヘモグロビン A1c（JDS 値）は換算式を用いて、IFCC 値→NGSP 値に変換され、本研究ではすべて NGSP 値で表記した（臨床化学 37; 393-409, 2008）。

2）追跡方法：大血管障害（脳卒中・心筋梗塞）の発症をエンドポイントとして追跡を行った。発症の転帰は以下の方法により把握した。① 毎年、脳卒中・心筋梗塞発症状況調査票を送付して、脳卒中・心筋梗塞の発症を把握する。調査票が未返送の場合、電話等で確認する。② 2 年に 1 回の健診受診時に発症の既往を聞き取る。③ 人口動態統計（死因統計）から循環器疾患死亡を確認する。①～③の内容を研究者が確認し、同意が得られた者を対象に入院時のカルテ調査を行って確定診断を得ている。なおカルテ調査が不能または人口動態統計では循環器疾患死亡が確認できるが発症歴が確認できなかったもの場合は「疑い」扱いとしている。

対象者は、提唱されているヘモグロビン A1c を用いた糖尿病の診断基準に基づいて -5.9%、6.0-6.4%、6.5%以上の 3 群に分類した。Cox の比例ハザードモデルで性、年齢、BMI、高血圧、高コレステロール血症、糖尿病治療の有無、喫煙、飲酒を調整した時の、ヘモグロビン A1c 群別の大血管障害の多変量調整ハザード比を算出した。本研究は観察研究であり、疫学研究に関する倫理指針に従い国立循環器病センター倫理委員会の承認を得て研究を実施している。

C. 研究結果

ベースライン時の検査結果は、BMI 22.5 kg/m^2±3.0、ヘモグロビン A1c 5.3%±0.7、高血圧（収縮期血圧 140 mmHg 以上 and/or 拡張期血圧 90 mmHg 以上 and/or 治療中）25.8 %、高コレステロール血症（総コレステロール 220 mg/dl 以上 and/or 服薬中）38.9%、糖尿病治療中 0.9%であった。

平均追跡期間は 12.7 年であり、この間に 70 件の大血管障害の発症を確認した。そのうち 24 件は心筋梗塞、44 件は脳卒中（出血性

19 件、梗塞性 22 件、不明 3 件)、2 件は内因性突然死であった。

大血管障害全体の多変量調整ハザード比は、-5.9%群を 1.0 とすると、6.0-6.4%群で 1.2 (95% 信頼区間 CI, 0.6-2.5)、6.5%以上群で 3.0 (95% CI, 1.2-7.4)であった。同じく心筋梗塞のハザード比は、0.8 (95% CI, 0.2-3.3)、2.5 (95% CI, 0.5-11.6)、脳卒中は、1.5 (95% CI, 0.7-3.6)、3.4 (95% CI, 1.1-10.8)、脳梗塞は、1.6 (95% CI, 0.5-4.9)、6.4 (95% CI, 1.4-30.4)であった。また傾向性の検定では、心筋梗塞以外は有意な関連を示し、ヘモグロビン A1c の増加とともに発症率が高くなる傾向を認めた。

D. 考察

本研究の結果から、日本人集団において、ヘモグロビン A1c の基準で糖尿病と判定された群では有意に大血管障害の発症率が高いことが示され、ハザード比は約 3 倍であった。また例数が少ないので断定的には言えないが、糖尿病の脳梗塞発症に対するハザード比は他の病型よりも大きい傾向を示した。したがって日本人の大血管障害の予測という観点からも 6.5% (NGSP 値による) という糖尿病診断のカットオフポイントは有用と考えられた。一方、いずれの群でも境界域 (6.0-6.4%) では有意差を認めていないが、正常、境界域、糖尿病と全体の傾向としてはリスクの上昇を認めた。

なおヘモグロビン A1c 値は貧血等の影響を受けるが、本研究参加者のうち血中ヘモグロビンが 11.0 g/dl 未満または貧血治療中の者は合わせて 2.7%しかおらず、ほとんどその影響は受けていない。

一次コホートの対象者約 6000 人全員にヘモグロビン A1c のデータがなかったため、本研究では男女別の解析ができておらず、性別は調整変数として組み入れた。またヘモグロビン A1c の下限値や糖尿病領域の中でも更に値の上昇に伴ってリスクが増加するかなど詳細な検討ができていない。したがって大規模なデータでの再検証が必要であろう。

D. 結論

ヘモグロビン A1c で判定された糖尿病は、日本人都市一般住民の大血管障害 (心筋梗塞、脳卒中) の発症リスクであった。日本人の大血管障害の予防という観点からも 6.5%以上(NGSP 値)というヘモグロビン A1c を用いた糖尿病診断基準は妥当と考えられた。

F. 健康危険情報

なし

G. 研究発表

1. Watanabe M, Kokubo Y, Higashiyama A, Ono Y, Okayama A, Okamura T. New diagnosis criteria for diabetes with hemoglobin A1c and risks of macro-vascular complications in an urban Japanese cohort: The Suita Study. ***Diabetes Res Clin Pract***, in press
2. 渡邉 至、岡村智教. 疫学：循環器疾患の危険因子としての糖尿病. 日本糖尿病学会(編), 糖尿病の療養指導 2009, pp 118-121, 診断と治療社, 東京, 2009

H. 知的財産権の出願・登録状況

なし

別紙４

研究成果の刊行に関する一覧表レイアウト

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
渡邉 至、岡村智教	疫学：循環器疾患の危険因子としての糖尿病.	日本糖尿病学会	糖尿病の療養指導 2009	診断と治療社	東京	2009	118-121

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
Watanabe M, Kokubo Y, Higashiyama A, Ono Y, Okayama A, Okamura T.	New diagnosis criteria for diabetes with hemoglobin A1c and risks of macro-vascular complications in an urban Japanese cohort: The Suita Study.	Diabetes Res Clin Pract	In press	－	－
				－	－

DIABETES RESEARCH AND CLINICAL PRACTICE XXX (2010) XXX–XXX

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Brief report

New diagnosis criteria for diabetes with hemoglobin A1c and risks of macro-vascular complications in an urban Japanese cohort: The Suita Study

Makoto Watanabe[a,*], *Yoshihiro Kokubo*[a], *Aya Higashiyama*[a], *Yuu Ono*[a], *Akira Okayama*[a,b], *Tomonori Okamura*[a]

[a] *Department of Preventive Cardiology, National Cardiovascular Center, 5-7-1, Fujishiro-dai, Suita, Osaka, 565-8565, Japan*
[b] *The First Institute for Health Promotion and Health Care, Japan Anti-Tuberculosis Association, Tokyo, Japan*

ARTICLE INFO

Article history:
Received 15 July 2009
Received in revised form
12 January 2010
Accepted 18 January 2010

Keywords:
Hemoglobin A1c
Diagnosis criteria
Macro-vascular complications
Cohort study
Japanese

ABSTRACT

The association of the new diagnosis criteria for diabetes adopting hemoglobin A1c, recently proposed by the international expert committee, with macro-vascular complications was tested in a 12-year population-based cohort. The present analysis suggested that this new criteria were applicable to macro-vascular complications in the Japanese.

1. Introduction

Recently, an international expert committee proposed the new diagnosis criteria for diabetes with hemoglobin A1c (HbA1c) mainly on the basis of the relation of HbA1c with micro-vascular complications [1]. It would be also important to estimate the association of HbA1c with macro-vascular complications, although they are not specific to diabetes. Since these new criteria are worldwide, evidence for macro-vascular complications would be needed from diverse populations. Several population-based studies chiefly in the Western have investigated the association of HbA1c with macro-vascular complications [2–5], but there have been few reports from other areas including Asia [6,7]. Therefore, we tested the association of the new proposed criteria of HbA1c with macro-vascular complications in a 12-year cohort study in a Japanese urban area where incidence of strokes was higher than myocardial infarction (MI) [8].

* *Corresponding author.* Tel.: +81 6 6833 5012x2186; fax: +81 6 6833 5300.
E-mail address: makotow@hsp.ncvc.go.jp (M. Watanabe).
0168-8227/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.diabres.2010.01.019

Please cite this article in press as: M. Watanabe, et al., New diagnosis criteria for diabetes with hemoglobin A1c and risks of macro-vascular complications in an urban Japanese cohort: The Suita Study, Diab. Res. Clin. Pract. (2010), doi:10.1016/j.diabres.2010.01.019

2. Materials and methods

The details of the Suita study have been described elsewhere [9–11]. Briefly, the Suita study is a population-based cohort study in a Japanese urban area. From the Suita city residents, 6406 men and women (aged 30–79 years) were randomly sampled and participated in a baseline survey from September 1989 to March 1994, and were followed up to December 2005. The individuals with a history of MIs or strokes were excluded at enrollment. Informed consent was obtained from all subjects, and this study was approved by the institutional review board at the National Cardiovascular Center.

In the enrollment period, HbA1c measurements were conducted from June 1990 to February 1991. The present analysis was conducted in 1607 initially healthy subjects (764 men and 843 women, mean age: 51.2 years) who had HbA1c measurements at baseline.

A baseline survey included questionnaires, anthropometric measurements, or fasting blood sample tests. All blood samples were analyzed immediately after blood sampling by an automatic analyzer at the laboratory of the National Cardiovascular Center. HbA1c was measured by the high performance liquid chromatography method (coefficient of variance was 1.5%). It was known that HbA1c values in Japan were lower than those mainly in the United States which adopted the National Glycohemoglobin Standardization Program (NGSP) method [12]. Converting formula from the HbA1c values by the Japan Diabetes Society (JDS) method to the ones by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) method was as follows; IFCC value (mmol/mol) = 10.39 × JDS value (%) − 16.8 [12]. Converting formula from the HbA1c values by the IFCC method to the ones by the NGSP method was as follows; NGSP value (%) = 0.0981 × IFCC value (mmol/mol) + 1.95 [12]. All present analysis adopted the HbA1c values by the NGSP method.

To detect MI or stroke events, each subject was checked by physicians or nurses at clinical visits every 2 years. In addition, yearly questionnaires by mail or telephone were completed for all participants. We also reviewed in-hospital medical records. MIs were defined according to the criteria by the MONICA project [13]. Strokes were defined according to the National Survey of Stroke criteria [14]. Death certificates were also searched systematically to complete surveillance for fatal strokes and MIs.

HbA1c levels were divided into 3 categories according to the proposed new criteria (i.e., ≤5.9%, 6.0–6.4%, ≥6.5%) to calculate crude incidence rates (per 1000 person-years), or estimate age- and multivariate-adjusted hazard ratios (HRs) by subtypes of cardiovascular diseases (CVD) (all CVDs, MIs, all strokes, ischemic strokes). HRs with confidence intervals (CIs) were estimated using a Cox regression model. The multivariate-adjusted model adjusted for age, sex, body mass index, hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication), use of antidiabetic medication, hypercholesterolemia (total cholesterol ≥5.7 mmol/L or use of antihypercholesterolemic medication), current cigarette use, and current alcohol consumption at baseline. The P values for trend (2-tailed) were calculated to test for linearity of HRs.

Table 1 – Baseline characteristics in a cohort study of a Japanese urban area, 1989–2005.

Number of subjects	1607
Sex (men/women)	764/843
Age (years)	51.2 (11.9)
Body mass index (kg/m^2)	22.5 (3.0)
Hemoglobin A1c (%)	5.3 (0.7)
Hypertension (%)[a]	25.8
Hypercholesterolemia (%)[b]	38.9
Use of antidiabetic medication (%)	0.9
Cigarette use	
Non (%)	54.8
Past (%)	12.6
Current (%)	32.6
Alcohol consumption	
Non (%)	42.3
Past (%)	1.4
Current (%)	56.3

Averages in continuous variables are shown with standard deviation in parentheses.
[a] Hypertension was defined by systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication.
[b] Hypercholesterolemia was defined by total cholesterol ≥5.7 mmol/L (220 mg/dL) or use of antihypercholesterolemic medication.

3. Results

The mean follow-up duration was 12.7 years, and 70 cases of CVDs were observed; 24 MIs, 44 strokes (19 hemorrhagic, 22 ischemic, 3 unclassified), and 2 sudden deaths.

Baseline characteristics were demonstrated in Table 1. The average of HbA1c levels was 5.3%, and current cigarette use was 32.6%. Use of antidiabetic medication was 0.9%.

Age- and multivariate-adjusted HRs by HbA1c levels are shown in Table 2. Regardless of subtype of CVDs, a graded increase in crude incidence rates was observed. Age- and multivariate-adjusted HRs for all CVDs, all strokes and ischemic strokes increased linearly with increases in HbA1c, and the multivariate-adjusted HRs in subjects with HbA1c of 6.5% or more were 3.0 (95% CI 1.2–7.4), 3.4 (95% CI 1.1–10.8), 6.4 (95% CI 1.4–30.4), respectively. In the relation between HbA1c and MIs, a significant graded increase in the adjusted HRs was not observed although the HRs were higher in HbA1c of 6.5% or more than that of 5.9% or less.

4. Discussion

The present study in Japan demonstrated that risks for all CVDs or strokes, especially for ischemic strokes, increased with increases in HbA1c levels, and were clearly higher in subjects with HbA1c levels of 6.5% or more. With regard to MIs, graded increase in the HRs was not observed. The results for MIs may be due to the fact that the incidence of MIs is considerably lower than strokes in the Japanese [8]. However, from the view point of prevention of macrovascular complications, defining HbA1c of 6.5% as a cut-off

Please cite this article in press as: M. Watanabe, et al., New diagnosis criteria for diabetes with hemoglobin A1c and risks of macrovascular complications in an urban Japanese cohort: The Suita Study, Diab. Res. Clin. Pract. (2010), doi:10.1016/j.diabres.2010.01.019

Table 2 – Incident rates and adjusted HRs with 95% CIs for cardiovascular diseases by HbA1c levels in a cohort study of the Japanese men and women, 1989–2005.

HbA1c levels	N	Number of events	Person-years	Crude incidence rates (per 1000 person-years)	Age-adjusted		Multivariate-adjusted[a]	
					HRs	95%CIs	HRs	95%CIs
All cardiovascular diseases								
≤5.9	1451	54	18627	2.9	1	(reference)	1	(reference)
6.0–6.4	108	9	1289	7.0	1.5	(0.7–3.0)	1.2	(0.6–2.5)
≥6.5	48	7	479	14.6	3.5	(1.6–7.7)	3.0	(1.2–7.4)
					Trend P = 0.003		Trend P = 0.04	
Myocardial infarctions								
≤5.9	1451	20	18627	1.1	1	(reference)	1	(reference)
6.0–6.4	108	2	1289	1.6	0.9	(0.2–3.9)	0.8	(0.2–3.3)
≥6.5	48	2	479	4.2	2.8	(0.6–11.9)	2.5	(0.5–11.6)
					Trend P = 0.32		Trend P = 0.48	
All strokes								
≤5.9	1451	32	18627	1.7	1	(reference)	1	(reference)
6.0–6.4	108	7	1289	5.4	1.9	(0.8–4.3)	1.5	(0.7–3.6)
≥6.5	48	5	479	10.4	4.2	(1.6–10.8)	3.4	(1.1–10.8)
					Trend P = 0.002		Trend P = 0.03	
Ischemic strokes								
≤5.9	1451	15	18627	0.8	1	(reference)	1	(reference)
6.0–6.4	108	4	1289	3.1	2.2	(0.7–6.5)	1.6	(0.5–4.9)
≥6.5	48	3	479	6.3	5.2	(1.5–18.1)	6.4	(1.4–30.4)
					Trend P = 0.006		Trend P = 0.03	

[a] Multivariate-adjusted HRs adjusted for age, sex, body mass index, hypertension, use of antidiabetic medication, hypercholesterolemia, current cigarette use and current alcohol consumption.

point for diabetes seemed to be reasonable in this Japanese population. The international expert committee of the new criteria also recommended that individuals with HbA1c levels of 6.0–6.4% should receive effective preventive intervention [1]. The present analysis demonstrated a graded risk increase in CVDs with HbA1c, so this recommendation also seemed to be applicable to macro-vascular complications.

Recently Kilpatrick et al. pointed the problem that anemias or hemoglobinopathies influenced on HbA1c levels and might give misleading results [15]. Present dataset included hemoglobin concentration and current treatment status for any anemia, although it did not include information for hemoglobinopathies. Prevalence of subjects with hemoglobin levels of less than 11.0 g/dl or on treatment for anemia was only 2.7% in total. In addition, excluding such anemic subjects from the analysis or adjusting for hemoglobin levels in the multivariate analysis hardly altered the results. Accordingly, we think anemias did not influence on present results so much, although present results could not be applied to individuals with anemia or hemoglobinopathies, considering lack of the reliability in HbA1c levels.

There were several limitations in this analysis. First, compared to the whole cohort, the number of samples was considerably smaller. However, since study subjects were determined only by timing of enrollment to the baseline survey, not by arbitrary reasons, this would not bias the results. Second, the single HbA1c measurement at baseline may have underestimated the relationship due to regression dilution bias [16].

In conclusion, the present results suggested that the new worldwide diagnosis criteria for diabetes with HbA1c were applicable to macro-vascular complications in the Japanese population. However, since the present study was conducted in a limited Japanese population, these new criteria should be tested further in various populations.

Conflict of interest

There are no conflicts of interest.

Acknowledgements

We would like to express our gratitude to all members of the Suita City Health Center and the Suita Medical Association. We also thank all researchers and the staffs of the Division of Preventive Cardiology for performing medical examinations and the follow-up. We also thank Satsuki-Junyukai, the volunteers for the administration of the Suita study.

Grant support: This work was supported by grant-in-aids from the Japanese Ministry of Health, Labor and Welfare (H20-SeiShu-013 and H19-SeiShu-021); and the Research Grant for Cardiovascular Disease from the Ministry of Health, Labor and Welfare (20K-6 and 21S-1).

Please cite this article in press as: M. Watanabe, et al., New diagnosis criteria for diabetes with hemoglobin A1c and risks of macro-vascular complications in an urban Japanese cohort: The Suita Study, Diabet. Res. Clin. Pract. (2010), doi:10.1016/j.diabres.2010.01.019

REFERENCES

[1] The International Expert Committee, International expert committee report on the role of the A1c assay in the diagnosis of diabetes, Diab. Care 32 (2009) 1–8.
[2] E. Selvin, J. Coresh, S.H. Golden, F.L. Brancati, A.R. Folsom, M.W. Steffes, Glycemic control and coronary heart disease risk in persons with and without diabetes. The atherosclerosis risk in communities study, Arch. Int. Med. 165 (2005) 1910–1916.
[3] E. Selvin, J. Coresh, E. Shahar, L. Zhang, M. Steffes, A.R. Sharrett, Glycaemia (haemoglobin A1c) and incident ischaemic stroke: the atherosclerosis risk in communities (ARIC) study, Lancet Neurol. 4 (2005) 821–826.
[4] P.K. Myint, S. Sinha, N.J. Wareham, S.A. Bingham, R.N. Luben, A.A. Welch, et al., Glycated hemoglobin and risk of stroke in people without known diabetes in the European prospective investigation into cancer (EPIC)-Norfolk prospective population study: a threshold relationship? Stroke 38 (2007) 271–275.
[5] D.A. Lawlor, A. Fraser, S. Ebrahim, G. Davey Smith, Independent associations of fasting insulin, glucose, and glycated haemoglobin with stroke and coronary heart disease in older women, PLoS Med. 4 (2007) e263.
[6] K. Sunaga, K. Miura, Y. Naruse, M. Sakurai, Y. Morikawa, Y. Kurosawa, et al., Glycated hemoglobin and risk of stroke, ischemic and hemorrhagic, in Japanese men and women, Cerebrovasc. Dis. 26 (2008) 310–316.
[7] S. Nakanishi, M. Yamada, N. Hattori, G. Suzuki, Relationship between HbA1c and mortality in a Japanese population, Diabetologia 48 (2005) 230–234.
[8] H. Ueshima, A. Sekikawa, K. Miura, T.C. Turin, N. Takashima, Y. Kita, et al., Cardiovascular disease and risk factors in Asia: a selected review, Circulation 118 (2008) 2702–2709.
[9] Y. Kokubo, K. Kamide, T. Okamura, M. Watanabe, A. Higashiyama, K. Kawanishi, et al., Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita study, Hypertension 52 (2008) 652–659.
[10] T. Okamura, Y. Kokubo, M. Watanabe, A. Higashiyama, Y. Miyamoto, Y. Yoshimasa, et al., Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: the Suita study, Atherosclerosis 203 (2009) 587–592.
[11] M. Watanabe, T. Okamura, Y. Kokubo, A. Higashiyama, A. Okayama, Elevated serum creatine kinase predicts first-ever myocardial infarction: a 12-year population-based cohort study in Japan, the Suita study, Int. J. Epidemiol. 38 (2009) 1571–1579.
[12] Committee on Diabetes Mellitus Indices, Japan Society of Clinical Chemistry (Chair: Izumi Takei), Japanese guideline for reporting HbA1c results reported in IFCC units and JDS units. *Rinsho Kagaku* 37 (2008):393–409, (Japanese).
[13] H. Tunstall-Pedoe, K. Kuulasmaa, P. Amouyel, D. Arveiler, A.M. Rajakangas, A. Pajak, Myocardial infarction and coronary deaths in the World Health Organization MONICA project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents, Circulation 90 (1994) 583–612.
[14] A.E. Walker, M. Robins, F.D. Weinfeld, The national survey of stroke. Clinical findings, Stroke 12 (1981) I13–44.
[15] E. Kilpatrick, Z. Bloomgarden, P. Zimmet, Is haemoglobin A1c a step forward for diagnosing diabetes? BMJ 339 (2009) b4432.
[16] S. MacMahon, R. Peto, J. Cutler, R. Collins, P. Sorlie, J. Neaton, et al., Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias, Lancet 335 (1990) 765–774.

Please cite this article in press as: M. Watanabe, et al., New diagnosis criteria for diabetes with hemoglobin A1c and risks of macrovascular complications in an urban Japanese cohort: The Suita Study, Diab. Res. Clin. Pract. (2010), doi:10.1016/j.diabres.2010.01.019

厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）
分担研究報告書

大阪府八尾市南高安地区地域コホート研究

分担研究者　北村明彦　大阪府立健康科学センター健康開発部長

研究要旨

地域対策として脳卒中や虚血性心疾患等の循環器疾患の罹患率を減少させるために重点的に予防、管理すべき危険因子を明らかにすることを目的として、大阪、秋田、茨城、高知の４地域の 40～69 歳男性住民計 4599 人を平均 14 年間追跡し、脳卒中、虚血性心疾患の発生に対する相対危険度、集団寄与危険割合を検討した。脳卒中発生の相対危険度は心房細動が 3.1 と最も高く、集団寄与危険割合は、高血圧が 35%と最も高かった。虚血性心疾患発生の相対危険度は、高コレステロール血症 2.1 が最も高く、集団寄与危険割合は、喫煙が 26%と最も高かった。

A．研究目的

平成２０年度より、わが国では生活習慣病予防対策として、メタボリックシンドロームの発見と管理に主眼を置いた特定健診・特定保健指導が開始された。しかしながら、地域住民におけるメタボリックシンドロームの実態や予後については不明の点が多い。

こうした背景より、メタボリックシンドローム等の危険因子に対する系統的な対策が地域住民の循環器疾患発生の予防にどの程度効果的であるかについて、疫学的見地からの検証を行った。すなわち、地域住民の壮年男性の追跡調査を行い、循環器疾患の発生に関してメタボリックシンドロームのみならず、他の危険因子を含めて、相対危険度のみでなく、集団寄与危険割合を検討した。社会的対策を設計する上では、相対危険度のみでなく、集団寄与危険割合の考え方が重要であり、それらの結果をもとに集団全体の疾病への影響力がより大きい要因の管理・予防に重点を置いた施策展開を行うことがより大きな予防効果をもたらす。本研究を通じて、地域対策として脳卒中や虚血性心疾患等の循環器疾患の罹患率を減少させるために重点的に予防、管理すべき危険因子を明らかにしたい。

B．研究方法

対象は、われわれが循環器疾患の疫学調査を実施している大阪府八尾市南高安地区地域コホートに、秋田、茨城、高知の３地域コホートを加えた４地域において、1985-94 年に地域の循環器健診を受診した 40～69 歳男性住民計 4738 人の中で、循環器疾患の既往の有る 139 人を除いた 4599 人である。この 4599 人を 2002 年まで平均 14 年間追跡し、追跡期間内の脳卒中、虚血性心疾患の発生を調査した。脳卒中・虚血性心疾患の発生調査は、４地域ともに同一の方法により毎年実施し、既定の疫学分類基準に基づき、脳卒中（脳出血、脳梗塞、くも膜下出血、分類不能の脳卒中）、および虚血性心疾患（心筋梗塞、労作性狭心症）の発生の有無を判定した。

循環器健診の手技、測定、判定も４地域同一の方法、基準で行った。循環器疾患のリスクファクターは、1985-94 年のベースライン健診時の所見に基づき、高血圧（最大血圧値