SMCs *(5)*. Therefore, the concentration of circulating sLR11, rather than the LR11 expression level in intimal SMCs, may be more effective as a novel marker for pathogenic changes in SMCs.

Recent studies have highlighted the pathological function of sLR11 in neurodegenerative diseases. Immunological analyses indicate that sLR11 exists in CSF at concentrations similar to those in serum. Neuronal LR11 expression is significantly reduced in individuals with mild cognitive impairment and AD *(10–13)*, and polymorphism of the gene for LR11 is highly associated with the onset of AD *(14)*. Therefore, methods for determining sLR11 concentrations in CSF may be vital for future research into neuronal diseases, particularly AD.

In conclusion, we established a sensitive ELISA method for determining sLR11 concentrations in serum and CSF. This ELISA method constitutes a useful tool for monitoring the pathological condition of intimal SMCs and the progression of atherosclerosis *(25)*. Use of this ELISA method to measure sLR11 as an indicator of intimal SMC function may enable novel strategies for treating atherosclerosis and help to determine risk factors for vascular disease. Furthermore, the ELISA described here has adequate sensitivity and dynamic range for determining sLR11 concentrations in CSF and may allow significant progress in AD-related research.

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分担研究報告書

職域における肥満と糖尿病発症との関連
富山職域コホート研究

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研究要旨

富山職域コホートは、富山県にある企業の従業員を追跡する職域コホートである。就労中の男女、特に地域ではコホート設定が困難な働き盛りの中高年男性における循環器疾患のリスクの評価や、リスクと就業状態の関連等の検討を行っている。

今回、ウエスト周囲径(WC)と糖尿病発症との関連につき検討を行った。35-55 歳の3,992 名を 8 年間追跡し、糖尿病発症を観察した。8 年間で 218 名の糖尿病発症を観察した。WC 5 分位の第 1 位（Q 1）から第 5 位（Q5）の糖尿病発症率（対 1,000 人年）は、Q1 6.3、Q2 4.0、Q3 6.0、Q4 11.1、Q5 12.8 であり、Q2 に対する年齢・性調整 HR(95%信頼区間)は、Q1 1.78（1.06-2.98)、Q4 3.11（1.92-5.04)、Q5 3.30（2.05-5.31)で有意に上昇した。比較的やせた日本人において肥満と糖尿病発症の関連は J カーブを示した。肥満に伴う糖尿病患者が増加するなかで、特定健診・特定保健指導では糖尿病等生活習慣病の発症予防を目標にした肥満者に対する介入が行われるが、糖尿病予防を考える上では、やせている者でも糖尿病リスクが高いことも考慮する必要がある。

A. 研究目的

富山県にある企業の従業員を追跡する職域コホートである。就労中の男女、特に地域ではコホート設定が困難な働き盛りの中高年男性における循環器疾患のリスクの評価や、リスクと就業状態の関連等の検討を行っている。

B. 研究方法

コホートの概要

富山県にあるアルミ製品製造業企業の黒部事業所及び滑川事業所従業員を対象としたコホートである。1980 年以降、研究者が産業医として従業員の健康管理を 25 年にわたり行っている。コホート規模は約 8,000 人で、男女比は約 2 対 1 である。

本コホートは職域コホートであるため、従業員全体が毎年 95%以上の受診率で健診を受診しており、各種検査値の高い率での経年追跡が可能である。また現業系従業員では転勤が少なく、また、途中退職も比較的少ないため長期の追跡が可能である。

本コホート研究グループは本事業所での産

業医活動を通して、詳細なエンドポイント発生の把握を実施している。すなわち、在職中の脳卒中、虚血性心疾患、悪性新生物、精神疾患等の発症および死亡の把握、健診データ追跡による在職中の高血圧、糖尿病、高脂血症等の発症の把握である。また、一般に職域コホートでは定年退職後の疾患発症の追跡が困難であるが、本コホートでは退職後も近隣に在住するものがほとんどのため、1990年以降退職者については郵送による退職後健康調査を毎年実施し、生活習慣病の治療状況、脳血管疾患・心疾患の発症および死亡を追跡している。在職中および退職後の脳心事故発症者については同意を得た上で、医療機関での医療記録調査を実施している。

以上より、本コホートの特色としては、(1)地域ではコホート設定が困難な青壮年期の男性を多く含むコホートであること、(2)青壮年期男性のライフスタイルや危険因子に影響が大きいと考えられる職業面での要因について詳細な情報が収集されていること、(3)各種危険因子の経年推移が高い追跡率で把握されていること、が挙げられる。

C. 研究結果

研究の成果

糖尿病発症とウエスト周囲径のＪ字型の関連 (Sakurai M, Miura K, Takamura T, Ishizaki M, Morikawa Y, Nakamura K, Yoshita K, Kido T, Naruse Y, Kaneko S, Nakagawa H. J-shaped relationship between waist circumference and subsequent risk for Type 2 diabetes: an 8-year follow-up of relatively lean Japanese individuals. Diabet Med. 2009; 26:753-759.)

【目的】日本人のコホート研究から、ウエスト周囲径（WC）と糖尿病発症との関連を検討した。

【方法】35-55歳の3,992名（男2,533, 女1,459）のWC測定、空腹時採血を行った。8年間追跡し、新規糖尿病発症を観察した。毎年の健診結果から、空腹時血糖値126mg/dl以上、HbA1c 6%以上のものに行った糖負荷試験で糖尿病型、糖尿病治療薬の開始、を糖尿病発症と定義した。WC5分位における糖尿病発症ハザード比(HR)を算出した。また、糖尿病発症者と非発症者でベースラインのインスリン抵抗性（HOMA-R）、インスリン分泌能（HOMA-B）を比較した。

【結果】8年間で218名（男175/女43）の糖尿病発症を観察した。WC5分位の第１位（Q１）から第5位(Q5)の糖尿病発症率(対1,000人年）は、Q1 6.3、Q2 4.0、Q3 6.0、Q4 11.1、Q5 12.8であり、Q2に対する年齢・性調整HR(95%信頼区間)は、Q1 1.78（1.06-2.98)、Q4 3.11（1.92-5.04)、Q5 3.30（2.05-5.31)で有意に上昇した。糖尿病発症者は非発症者と比較し、Q1ではHOMA-Bが有意に低く、Q4、Q5ではHOMA-Rが有意に高かった。

【まとめ】比較的やせた日本人において肥満と糖尿病発症の関連はＪカーブを示した。やせ型と肥満者の糖尿病発症にはインスリン分泌、インスリン抵抗性に関して異なる背景を有することを考慮する必要がある。

D. まとめ

富山職域コホートでは、職域の特徴を生かしたコホート研究を、引き続き継続して展開していく予定である。現在、働き盛りの中年労働者の生活習慣、職業的要因と循環器疾患危険因子との関連を検討中であり、今後横断研究、縦断研究として肥満・メタボリックシンドロームの疫学に関する研究の成果を発表していく。

E. 研究発表

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F. 知的財産権の出願・登録状況（予定を含む）

なし

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表雑誌	巻号	ページ	出版年
Sakurai M, Miura K, Takamura T, Ishizaki M, Morikawa Y, Nakamura K, Yoshita K, Kido T, Naruse Y., Kaneko S, Nakagawa H.	J-shaped relationship between waist circumference and subsequent risk for Type 2 diabetes: an 8-year follow-up of relatively lean Japanese individuals.	Diabet Med	26	753-759	2009.
Sakurai M, Takamura T, Miura K, Kaneko S, Nakagawa H.	Middle-aged Japanese women are resistant to obesity-related metabolic abnormalities.	Metabolism	58	456-459	2009
Kitaoka-Higashiguchi K, Morikawa Y, Miura K, Sakurai M, Ishizaki M, Kido T, Naruse Y, Nakagawa H.	Burnout and Risk Factors for Arteriosclerotic Disease: Follow-up Study.	J Occup Health	59	123-31	2009.

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Burnout and Risk Factors for Arteriosclerotic Disease: Follow-up Study

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Abstract: Burnout and Risk Factors for Arteriosclerotic Disease: Follow-up Study: Kazuyo KITAOKA-HIGASHIGUCHI, *et al.* Department of Public Health, Kanazawa Medical University—Objectives: The purpose of this longitudinal study was to investigate the effects of burnout on risk factors for arteriosclerotic disease. **Methods:** Baseline data were collected from 442 male middle managers working for a manufacturing company in Japan. All participants had a physical health check-up and completed the Japanese Maslach Burnout Inventory-General Survey. We calculated the Japanese-specific cut-off points of the MBI-GS and applied "exhaustion +1" criterion to define subjects as healthy or burnout at baseline. Follow-up measures were collected 4–5 yr later for 383 middle managers. Changes in the subjects' waist circumference, body weight, body mass index (BMI), blood pressure, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, fasting blood sugar, fasting insulin, HOMA-R, and HbA1c over a time period of 4 to 5 yr were compared between the healthy and burnout groups. New cases of large waist circumference, high BMI, metabolic syndrome, hypertension, hypercholesterolemia, high triglycerides, low HDL cholesterol, high LDL cholesterol, and impaired fasting glucose were detected at follow-up. **Results:** Changes in waist circumference, body weight, and BMI were significantly greater in burned-out managers than in healthy managers. Furthermore, compared to other variables (age and health behaviors such as smoking), burnout was a significant explanatory variable. The odds ratio of the burnout group was 2.80 for hypercholesterolemia with statistical significance after adjusting for age. After adjusting for age, health behaviors, and baseline total cholesterol, the results were similar. **Conclusions:** Burnout, which results from prolonged exposure to chronic work stress, may be associated with risk factors for arteriosclerotic disease.
(J Occup Health 2009; 51: 123–131)

Key words: Arteriosclerotic disease, Burnout, Longitudinal study, Maslach Burnout Inventory (MBI), Working population

Burnout is the result of prolonged exposure to chronic work stress with insufficient recovery[1–5]. Maslach and Jackson[6,7] provided an operational definition of burnout in terms of the demands of human service work and developed the primary measure of the burnout construct, the Maslach Burnout Inventory (MBI). Given the increasing interest in burnout within occupations that are not clearly people-oriented[8], the MBI-General Survey (MBI-GS)[9] was developed. In the MBI-GS, the three components of the burnout construct are conceptualized in slightly broader terms with respect to occupation, and not just to the personal relationships that may be part of the job. The three components are labeled exhaustion, cynicism, and diminished professional efficacy.

A large number of burnout studies have examined the correlates and the causes of burnout, but a few studies have focused on its attitudinal and organizational consequences and its negative impact on mental health. Moreover, there are scant data available on the impact that burnout has on physical health[5,10,11]. A prospective cohort study dealing with job stress found that chronic work stress is an important risk factor for the development of metabolic syndrome[12]. This study provides evidence for the biological plausibility of a link between everyday life psychosocial stressors and heart disease. On the other

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hand, physical health problems that are more or less objectively diagnosed have been investigated with respect to burnout[10, 11, 13–16]. Other studies have investigated the relationship between burnout and objectively diagnosed physical health problems. The relationships between burnout and indicators such as cholesterol and lipid peroxidation have been examined[13, 17, 18]. Burnout has been found to be associated with cardiovascular disease (CVD) in a few studies[19–23]. However, no definitive, longitudinal studies dealing with the relationship between burnout as assessed using the MBI and objectively diagnosed health problems have been published.

In the present longitudinal study, the effects of burnout on risk factors for arteriosclerotic disease were assessed.

Subjects and Methods

Study population and data collection

The study population included male middle managers working for a manufacturing company in Japan. The company has approximately 7,000 employees: upper managers, middle managers, and general employees. Middle managers predominantly manage clerical work and supervisory work in the manufacturing sections. The target company had three types of health examinations for employees: an annual health examination as mandated by law in Japan; a comprehensive health check-up program, involving a physical health examination, including laboratory tests, and a questionnaire concerning health behaviors and mental health held in the health care unit of the company; and intensive health examinations held in hospital. Middle managers were encouraged to participate in the health check-up program. The MBI-GS was performed as part of the mental health examination in the health check-up program for middle managers at baseline in 2001.

The final study population for which all necessary data for this study were available included 442 men aged less than 55 yr at baseline. Changes in the physical condition 4 to 5 yr later were analyzed in relation to burnout. When we could not obtain enough data for subjects in 2005, because they had other types of health check-ups or other reasons, we used data obtained in 2006 to achieve a higher follow-up rate. Thus, in total, 383 male middle managers were followed up 4 to 5 yr after baseline, and the follow-up rate was 86.7%.

The following risk factors for arteriosclerotic disease were assessed: waist circumference, body weight, body mass index (BMI), blood pressure, total cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, fasting blood sugar, fasting insulin, HOMA-R (see below), and HbA1c. HOMA-R was calculated on the basis of fasting blood sugar and insulin: fasting blood sugar (mg/d*l*) × fasting insulin (μU/m*l*) / 405. Waist circumference was measured to the nearest 0.5 cm above the iliac crests and below the lowest rib margin at minimal respiration in a standing position. Body weight was measured in light clothing without shoes using a standard scale and height was measured to the nearest 0.1 cm without socks using a stadiometer. Blood pressure was determined with a mercury sphygmomanometer in a sitting position after rest for 5 min. Fasting blood samples were taken from the subjects at least 10 hours after their last meal. Laboratory tests were performed by a laboratory test center. Total cholesterol, triglycerides, and LDL cholesterol were measured by enzyme assay. HDL cholesterol was measured by the direct method. The hexokinaze method, chemiluminescence immunoassay, and latex agglutination method were used respectively, to measure fasting blood sugar, fasting insulin, and HbA1c.

Alcohol consumption, smoking, and physical activity were assessed using a questionnaire. Alcohol consumption was classified into three categories: almost no drinks, drinks 1–4 days per week, and drinks more than 5 days per week. Smoking was categorized as either a current smoker or not a current smoker. Physical activity was categorized as either participating in at least one exercise session per week or not.

Burnout

Burnout was assessed using the Japanese version of the MBI-GS[24, 25]. The Japanese MBI-GS is a 16-item measure containing five items dealing with exhaustion, five dealing with cynicism, and six dealing with professional efficacy. The original version responses were used: never, a few times a year, once a month, a few times a month, once a week, a few times a week, and everyday. All 16 items of the MBI-GS are scored ranging from "0" (never) to "6" (everyday), and the total scores for each subscale were divided by the number of items for the subscale.

Except for studies done in The Netherlands[26] and Sweden[27], there are no clinically valid cut-off points available for the MBI that allow differentiation between levels of burnout. The MBI test manual presents numerical cut-off points based on arbitrary statistical norms[9]. The test authors divided the normative sample into tertiles, but since this was done using a Canadian sample[28], the classification in the manual cannot be applied to workers in Japan; only nation-specific cut-off points should be used[29, 30]. For this reason, cut-off points were determined based on data obtained from the many different studies[24, 25, 31–35] conducted by us so far, including the MBI-GS data obtained at the baseline of the present study. Overall, there were 5,621 samples (3,042 males, 2,515 females, 64 unknown). Although the average age differed among the studies, the overall average age was 37.8 yr (±S.D. 11.6), and age groups ranging from the 20s through the 60s were included. Subjects' occupations included company employees (new employees, general employees, and managers), civil servants, medical doctors (medical doctors and residents), clinical nurses, and teachers. The Japanese data were divided into tertiles. For exhaustion and cynicism, the cut-off point was set between the upper third and the lower two thirds, and for professional efficacy, the cut-off point was set between the higher two thirds and the lower third. Thus, for exhaustion, the cut-off point was 3.60 or higher; for cynicism, the cut-off point was 2.20 or higher; and for professional efficacy, the cut-off point was 1.83 or lower. It is commonly held that, in the process of burnout, exhaustion comes first, followed by cynicism and diminished professional efficacy[3]. In line with this idea, subjects with intense exhaustion and either a high level of cynicism or a low level of professional efficacy, or both, were considered to have burned out. In short, the "exhaustion + 1" criterion recommended by Brenninkmeijer and VanYperen[36] was applied. In accordance with this criterion, the baseline MBI-GS scale scores were divided into a healthy group and a burnout group. As a result, 46 subjects were categorized as belonging to the burnout group, and the remaining 337 as belonging to the healthy group. The average age was 48.3 yr (± S.D. 4.6) for the healthy group and 47.3 yr (± S.D. 4.8) for the burnout group; the difference was not statistically significant.

Statistical methods

First, health behaviors of the healthy group and the burnout group at baseline and follow-up were compared using the Chi-square test. Means of subjects' waist circumference, body weight, BMI, blood pressure, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, fasting blood sugar, fasting insulin, HOMA-R, and HbA1c at baseline were compared between the healthy and burnout groups using the *t*-test. The distribution of triglycerides, fasting blood sugar, fasting insulin, and HOMA-R was not normal, so a logarithmic transformation to normalize the distribution was applied.

Next, changes in the parameters over a time period of 4 to 5 yr were compared between the two groups. In order to compare the averages, the *t*-test and analyses of covariance (ANCOVA) were performed. Since changes in all parameters were distributed normally, mean and standard deviation were used. The baseline values of the corresponding variables were adjusted as the covariates.

Furthermore, the relationship between burnout and changes of the parameters was evaluated. Multiple regression analyses were done to determine the effect of burnout on each variable, after adjusting for the other factors. The input variables were burnout (1=healthy, 2=burned out), age (continuous variable), alcohol consumption (1=almost no drinks, 2=drinks 1–4 days per week, 3=drinks more than 5 days per week), smoking (1=a current smoker, 2=not a current smoker), and physical activity (1=no exercise, 2=participating in at least one exercise session per week). Ordinal numbers were used to categorize alcohol consumption.

New cases of large waist circumference (waist circumference ≥85 cm), high BMI (BMI ≥25), metabolic syndrome, hypertension (blood pressure ≥140/90 mmHg), hypercholesterolemia (total cholesterol ≥220 mg/d*l*), high triglycerides (triglycerides ≥150 mg/d*l*), low HDL cholesterol (HDL cholesterol <40 mg/d*l*), high LDL cholesterol (LDL cholesterol ≥140 mg/d*l*), and impaired fasting glucose (fasting blood sugar ≥110 mg/d*l*) were detected at follow-up. The definition of the Japanese Society of Internal Medicine[37] was used for metabolic syndrome. According to this definition, metabolic syndrome is defined as the presence of waist circumference larger than 85 cm in males and two or more risk factors: blood pressure ≥130/85 mmHg, fasting blood sugar ≥110 mg/d*l*, triglycerides ≥150 mg/d*l* or HDL cholesterol <40 mg/d*l*. Those considered as new cases were subjects who fell short of the diagnostic criteria at baseline and either met the criteria at follow-up or were undergoing medical treatment. Multiple logistic regression analyses were carried out to evaluate the effects of burnout on the onset of those cases after adjusting for confounding factors. Two models were tested: model 1, with adjustment for age; model 2, with adjustment for age, health behaviors (alcohol consumption, smoking, physical activity), and baseline value of the corresponding variable.

Significance levels were set at $p<0.05$. All statistical analyses were performed using SPSS 15.0 software for Windows Vista.

Ethics

Ethical approval was obtained from the Kanazawa Medical University Epidemiological Research Ethics Committee.

Results

Table 1 shows the prevalence of habitual drinking, smoking, and exercise in the two groups; there were no differences between the groups at baseline and at follow-up. Additionally, there was no significant change in the prevalence of these habits between baseline and follow-up.

Table 2 compares the baseline risk factors for arteriosclerotic diseases between the healthy and burnout groups; there were no significant differences between the two groups.

Table 3 compares the changes in the risk factors at follow-up between the two groups. It shows both a simple comparison and the results of the co-variance analyses that used the baseline values of the corresponding variables as the covariates.

Table 1. Health behaviors of the healthy group (n=337) and the burnout group (n=46) at baseline and follow-up

Health behavior	Baseline				Follow-up			
	Healthy		Burnout		Healthy		Burnout	
	n	(%)	n	(%)	n	(%)	n	(%)
Alcohol consumption								
Almost no drinks	60	(17.8)	8	(17.4)	62	(18.4)	10	(21.7)
Drinks 1–4 days per week	78	(23.1)	10	(21.7)	65	(19.3)	9	(19.6)
Drinks more than 5 days per week	199	(59.1)	28	(60.9)	210	(62.3)	27	(58.7)
Smoking								
A current smoker	169	(50.1)	22	(47.8)	142	(42.1)	21	(45.7)
Not a current smoker	168	(49.9)	24	(52.2)	195	(57.9)	25	(54.3)
Physical activity								
No exercise	192	(57.0)	29	(63.0)	199	(59.1)	29	(63.0)
Exercise	145	(43.0)	17	(37.0)	138	(40.9)	17	(37.0)

Table 2. Means of risk factors for arteriosclerotic disease of the healthy group (n=337) and the burnout group (n=46) at baseline

Risk factors	Healthy group		Burnout group		*p* value [a]
Waist circumference (cm)	83.3	7.5	82.4	7.7	0.43
Body weight (kg)	68.6	8.7	68.2	10.0	0.73
Body mass index (kg/m^2)	23.9	2.7	23.5	2.8	0.39
Systolic blood pressure (mmHg)	121.6	14.3	122.1	12.0	0.84
Diastolic blood pressure (mmHg)	76.2	10.2	75.8	9.0	0.80
Total cholesterol (mg/d*l*)	202.4	30.8	204.9	30.9	0.61
Triglycerides (mg/d*l*)	114.8	(67.5–195.2)	107.2	(56.4–203.7)	0.49
HDL cholesterol (mg/d*l*)	51.1	13.0	52.7	11.9	0.43
LDL cholesterol (mg/d*l*)	124.4	30.9	124.6	36.8	0.98
Fasting blood sugar (mg/d*l*)	93.3	(77.8–112.0)	93.3	(77.8–112.0)	0.71
Fasting insulin (μU/m*l*)	4.8	(2.8–8.2)	4.7	(2.8–8.0)	0.76
HOMA-R	1.1	(0.7–1.9)	1.1	(0.6–2.0)	0.70
HbA1c (%)	5.1	0.5	5.1	0.6	0.82

a: *t*-test. Data are mean and SD (standard deviation). Triglycerides, fasting blood sugar, fasting insulin, and HOMA-R are changed from logarithmic value and numbers in parentheses of them are range.

There were significant differences between the healthy and burnout groups in regard to waist circumference, body weight, and BMI. While the healthy group had an estimated average change of 0.6 cm in waist circumference, the average change in the burnout group was 2.4 cm, which was significantly greater than that of the healthy group. The estimated average change in body weight was −0.4 kg in the healthy group and 1.2 kg in the burnout group. While the healthy group generally lost weight, the burnout group gained weight; the difference between the groups was significant. The estimated average change in BMI was −0.1 for the healthy group and 0.4 for the burnout group. As with body weight, the BMI of the healthy group decreased while that of the burnout group increased; again, the difference between the groups was significant.

There was no significant difference in systolic blood pressure or diastolic blood pressure between the healthy group and the burnout group.

While the healthy group had an estimated average change of 6.6 mg/d*l* on total cholesterol, the estimated average change (12.8 mg/d*l*) tended to be larger in the burnout group; but it was not statistically significant. A significant difference in HDL and LDL cholesterol as well as triglycerides was not found between the two groups.

No significant difference between the healthy and burnout groups was found regarding fasting blood sugar, fasting insulin, HOMA-R, and HbA1c.

Using the variables (waist circumference, body weight,

Table 3. Changes in risk factors for arteriosclerotic disease at follow-up of the healthy group (n=337) and the burnout group (n=46)

Risk factors	Healthy group		Burnout group			Healthy group		Burnout group		
						Adjusted		Adjusted		
	Mean	SD	Mean	SD	*p* value [a]	mean	SE	mean	SE	*p* value [b]
Waist circumference (cm)	0.5	4.5	2.6	5.9	0.01	0.6	0.2	2.4	0.7	0.01
Body weight (kg)	−0.4	3.9	1.3	6.6	0.01	−0.4	0.2	1.2	0.6	0.01
Body mass index (kg/m²)	−0.1	1.3	0.4	2.2	0.01	−0.1	0.1	0.4	0.2	0.02
Systolic blood pressure (mmHg)	1.9	13.4	2.1	16.7	0.94	1.9	0.7	2.2	1.9	0.89
Diastolic blood pressure (mmHg)	5.1	9.6	6.9	12.0	0.25	5.1	0.5	6.8	1.4	0.25
Total cholesterol (mg/d*l*)	6.7	22.0	12.3	27.3	0.12	6.6	1.2	12.8	3.2	0.07
Triglycerides (mg/d*l*)	1.1	95.0	11.7	182.3	0.54	0.8	5.4	13.1	14.6	0.43
HDL cholesterol (mg/d*l*)	5.6	9.2	4.7	9.2	0.52	5.6	0.5	4.9	1.3	0.61
LDL cholesterol (mg/d*l*)	0.9	23.2	5.3	31.7	0.25	0.9	1.2	5.3	3.3	0.21
Fasting blood sugar (mg/d*l*)	4.4	17.6	2.9	7.3	0.58	4.4	0.9	2.7	2.3	0.48
Fasting insulin (μU/m*l*)	−1.0	3.9	−0.7	2.8	0.59	−1.0	0.2	−0.8	0.5	0.71
HOMA-R	−0.1	1.1	−0.1	0.7	0.98	−0.1	0.1	−0.2	0.2	0.94
HbA1c (%)	0.1	0.5	0.1	0.3	0.44	0.1	0.1	0.1	0.1	0.46

a: *t*-test. b: Co-variance analyses adjusted for baseline value of the corresponding variable. SD indicates standard deviation. SE indicates standard error.

Table 4. Summary of multiple regression analyses of changes in waist circumference, body weight, BMI on explanatory variables of age, health behaviors, and burnout

	Waist circumference			Body weight			BMI		
Variables	B	SE	*p* value	B	SE	*p* value	B	SE	*p* value
Burnout	1.93	0.74	<0.01	1.67	0.68	0.01	0.54	0.22	0.01
Age	−0.13	0.05	0.01	−0.09	0.05	0.07	−0.02	0.02	0.14
Alcohol consumption	0.09	0.31	0.76	−0.03	0.29	0.93	0.02	0.09	0.86
Smoking	−0.41	0.48	0.40	−0.25	0.44	0.57	−0.07	0.14	0.63
Physical activity	−0.03	0.49	0.94	−0.02	0.45	0.97	−0.02	0.14	0.91

Burnout: 1=healthy, 2=burned out. Age: continuous variable. Alcohol consumption: 1=almost no drinks, 2=drinks 1–4 days per week, 3=drinks more than 5 days per week. Smoking: 1=a current smoker, 2=not a current smoker. Physical activity: 1=no exercise, 2=exercise. BMI indicates Body Mass Index. B indicates unstandardized coefficients. SE indicates standard error.

and BMI) that showed significant differences between the healthy and burnout groups, multiple regression analyses were performed. In all cases, burnout was a significant explanatory variable (Table 4).

Table 5 shows that odds ratios of the burnout group compared with the healthy group for the onsets of large waist circumference, high BMI, metabolic syndrome, hypertension, hypercholesterolemia, high triglycerides, low HDL cholesterol, high LDL cholesterol, and impaired fasting glucose. For large waist circumference, high BMI, metabolic syndrome, hypertension, high triglycerides, and impaired fasting glucose, the odds ratios of the burnout group were not high. The odds ratio of the burnout group was 2.80 for hypercholesterolemia with statistical significance after adjusting for age (model 1). After adjusting for age, health behaviors, and baseline total cholesterol (model 2), the results were similar. However, there was no significantly high odds ratio for low HDL cholesterol or high LDL cholesterol.

Discussion

This is the first longitudinal study of the effects of burnout on risk factors for arteriosclerotic disease. Burnout was measured using the Japanese version of the MBI-GS[24,25]. Japanese-specific cut-off points of the MBI-GS were used and the "exhaustion + 1" criterion recommended by Brenninkmeijer and VanYperen[36] was applied to classify Japanese subjects into two groups at

Table 5. Odds ratios of the burnout group compared with the healthy group for onset of large waist circumference, high BMI, metabolic syndrome, hypertension, hypercholesterolemia, high triglycerides, low HDL cholesterol, High LDL cholesterol, and impaired fasting glucose

Risk factors for arteriosclerotic disease			Odds ratio (95% CI)			
	Subjects [a]	No. of cases	Model 1	p value	Model 2	p value
Large waist circumference (waist circumference ≥85 cm)						
Healthy group	198	41	1		1	
Burnout group	28	7	1.28 (0.44–3.78)	0.65	1.46 (0.49–4.38)	0.50
High BMI (BMI ≥25)						
Healthy group	224	19	1		1	
Burnout group	32	4	2.37 (0.64–8.75)	0.20	1.97 (0.49–7.92)	0.34
Metabolic syndrome [b]						
Healthy group	306	20	1		1	
Burnout group	42	3	1.14 (0.32–4.03)	0.84	1.17 (0.33–4.15)	0.81
Hypertension (blood pressure ≥140/90 mmHg)						
Healthy group	295	46	1		1	
Burnout group	44	6	0.62 (0.23–1.66)	0.34	0.67 (0.25–1.77)	0.41
Hypercholesterolemia (total cholesterol ≥220 mg/d*l*)						
Healthy group	242	52	1		1	
Burnout group	34	15	2.80 (1.23–6.39)	0.01	2.78 (1.20–6.46)	0.02
High triglycerides (triglycerides ≥150 mg/d*l*)						
Healthy group	241	38	1		1	
Burnout group	35	6	1.21 (0.45–3.29)	0.71	1.19 (0.43–3.30)	0.74
Low HDL cholesterol (HDL cholesterol <40 mg/d*l*)						
Healthy group	279	9	1		1	
Burnout group	39	1	0.95 (0.11–0.79)	0.96	0.83 (0.09–7.50)	0.87
High LDL cholesterol (LDL cholesterol ≥140 mg/d*l*)						
Healthy group	243	39	1		1	
Burnout group	32	7	1.28 (0.17–3.48)	0.62	1.34 (0.49–3.69)	0.57
Impaired fasting glucose (fasting blood sugar ≥110 mg/d*l*)						
Healthy group	307	34	1		1	
Burnout group	43	2	0.62 (0.13–2.87)	0.54	0.58 (0.12–2.71)	0.49

a: Number of those who fell short of the diagnostic criteria at baseline. b: The presence of waist circumference ≥85 cm, and two or more risk factors: blood pressure ≥130/85 mmHg, fasting blood sugar ≥110 mg/d*l*, triglycerides ≥150 mg/d*l* or HDL cholesterol <40 mg/d*l*. Model 1: Adjusted for age. Model 2: Adjusted for age, health behaviors (alcohol consumption, smoking, physical activity), and baseline value of the corresponding variable. BMI indicates Body Mass Index.

baseline: a healthy group and a burnout group.

Changes in the values of risk factors for arteriosclerotic disease from baseline to follow-up were compared between the healthy group and the burnout group. Compared to healthy male middle managers, burned out managers had significant increases in their waist circumference, body weight, and BMI at the time of follow-up, 4 to 5 yr later. It is important to note that the associations identified in this study were independent of other risk factors for arteriosclerotic disease, such as age, alcohol consumption, smoking, and physical activity. Some studies have found an association between high job strain and increased BMI[38, 39]. Others have reported no associations between these psychosocial characteristics of the work environment and BMI[40–43]. In some samples, high job strain was associated with a lower BMI[44, 45]. The associations of job strain and its components with BMI have been found to vary by gender, but not in a consistent manner[46, 47]. The mixed findings that have been reported with respect to work stress and obesity may reflect a failure to take into account the possibility that stress may cause some people to eat more, but others to eat less[48, 49]. Moreover, the design of those studies was mostly cross-sectional. The Whitehall 2 study of Brunner *et al.*[50] examined cumulative job strain as a predictor of obesity in a prospective 19-yr study. That study provided prospective evidence that chronic work stress predicts obesity. To the best of our knowledge, there is only one prospective study that has investigated the association between burnout and obesity[51], but it did not provide evidence that burnout predicts obesity. The present study provides the first prospective evidence that burnout predicts general and central obesity.

With respect to lipid metabolism disorders, the burned out group showed a larger increase of total cholesterol and a significantly higher risk for hypercholesterolemia, independent of the other factors (age, baseline total cholesterol, and health behaviors), compared with healthy managers. However, other metabolic indicators and blood pressure were not different between the two groups. Melamed *et al.*[22] examined the association between burnout and risk factors for cardiovascular disease (CVD). They found in a cross-sectional study that scores for burnout plus tension were significantly associated with cholesterol, triglycerides, and glucose levels, while scores for burnout plus listlessness were significantly associated with glucose and diastolic blood pressure levels. Shirom *et al.*[17] also performed a follow-up study on the effects of burnout on cholesterol and triglyceride levels. They found that physical and emotional burnout were both positive predictors of the change of total cholesterol levels. Those results about total cholesterol were similar to our results. Nonetheless, they did not assess burnout using the MBI, which is almost universally accepted as the standard for assessing burnout. In fact, the MBI has been used in over 90% of the empirical publications dealing with burnout[4]. Instead, Melamed *et al.* and Shirom *et al.* used their own definition of burnout and their own scale, the Shirom-Melamed Burnout Measure (SMBM). Our results might be significant because the are based on the MBI for burnout measurement.

What kind of biological mechanism is behind the fact that burnout tended to be associated with a larger waist circumference, body weight, and BMI, as well as a higher incidence rate of hypercholesterolemia? Although the biological mechanisms remain unclear, Brunner and Marmot[52], in the Whitehall 2 study, presented a hypothetical model of the biological mechanism at work between job strain and cardiovascular diseases. We use this model to consider the mechanism in question. The hypothalamic-pituitary-adrenal (HPA) axis may be involved due to a direct effect of burnout. Burnout that arises as a result of prolonged exposure to chronic job strain results in the body always being on the alert for another stressor. As a result, the HPA axis remains hyperactive and fat accumulates, which leads to lipid abnormalities and results in general obesity and central obesity. Moreover, this mechanism could lead to appetite stimulation. In addition to these direct effects, burnout may also have indirect effects. After leaving work, many people release their stress by eating and/or drinking alcoholic beverages. This style of coping could lead to the excessive intake of fat and sugar, which in turn could lead to weight gain and increase of cholesterol.

The present study had some limitations. First, at the time of follow-up, individuals suffering from burnout at baseline significantly increased their waist circumference, body weight, and BMI, and they had a higher incidence of hypercholesterolemia. However, among these subjects no significant difference was observed in any of the other factors. If the significant increase in the waist circumference and the body weight had been associated with a significant increase in triglycerides and LDL cholesterol levels, and a significant decline in HDL cholesterol levels, this would have made the study's results easier to interpret. In fact, such trends were observed, but they were not statistically significant, primarily because the study population was rather small and thus lacked statistical power. Furthermore, the follow-up study period was too short to properly explore the effects of burnout on physical health. Therefore, we should be mindful of the possibilities of the under estimation of the effects of burnout on those variables. Second, MBI-GS was not measured at the follow-up. Accordingly, we could not assess the changes of burnout level in the subjects at follow-up, 4 to 5 yr later. However, because burnout arises as a result of prolonged exposure to chronic job strain, burnout is characterized by its chronic nature. Hence, baseline evaluation of burnout level might predict health in the future. Third, since all of the middle managers were male, the results may not be generalizable to women. Finally, none of the study participants were on sick leave, which indicates that the sample employees with burnout were relatively healthy. The physiological correlates of more advanced burnout may therefore be different from those observed in the present study. Nonetheless, our study is still significant one because of the study design, a follow-up study with measurement of burnout using the standard scale, MBI.

In conclusion, burnout, which results from prolonged exposure to chronic work stress, may be associated with risk factors for arteriosclerotic disease.

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Middle-aged Japanese women are resistant to obesity-related metabolic abnormalities

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Abstract

We attempted to determine sex differences in obesity-related metabolic abnormalities in a relatively large middle-aged Japanese population. The study population consisted of 2935 men and 1622 women who were 35 to 59 years old. Metabolic abnormalities were determined using the Japanese criteria for metabolic syndrome, and we evaluated the number of metabolic abnormalities discriminated by waist circumference. In men, the mean number of metabolic abnormalities increased as the waist circumference increased. In women, although the mean number of metabolic abnormalities increased as the waist circumference increased, the mean number was less than 1 even in those with a waist circumference of at least 95 cm. According to the receiver operating characteristic curve, the cutoff levels yielding the maximal sensitivity plus specificity for predicting the prevalence of one or more obesity-related metabolic abnormalities were 80 cm in men and 73 cm in women. However, the positive predictive value was as low as 28.8% in men and 7.1% in women, which may not be suitable for a screening test, especially in women. Middle-aged Japanese women seem to be resistant to obesity-induced metabolic abnormalities, and waist circumference would not effectively predict the existence of metabolic syndrome. In setting the cutoff points in guidelines, a greater emphasis should be placed on the absolute risk of having abnormalities or diseases.

1. Introduction

Cutoff points for waist circumference have been proposed for each racial/ethnic group in diagnosing abdominal obesity and metabolic syndrome [1]. However, the Japanese cutoff points for waist circumference are still controversial. The Japanese cutoff points proposed by the Japan Society of Study for Obesity were derived from a 100-cm^2 area for visceral fat at the umbilical level on computed tomography imaging and are unique in that the value for women (90 cm) is larger than that for men (85 cm) [2,3]. On the other hand, the International Diabetes Federation proposes to use the cutoff point of waist circumference of 90 cm for men and 80 cm for women [1]; and some reports proposed lowering the cutoff point of waist circumference for Japanese women [4,5]. However, previous reports did not pay attention to the absolute risk of the accumulation of metabolic abnormalities in Japanese women. We attempted to determine sex differences in the accumulation of metabolic abnormalities in relation to obesity in a relatively large-scale middle-aged Japanese population.

2. Research design and methods

The study population consisted of 4557 Japanese employees (2935 men and 1622 women) of a metal products factory who were aged 35 to 59 years. Detailed information on this study population has been provided elsewhere [6,7]. The physical examinations for this analysis were held in 1996. Anthropometric markers including waist circumference and blood pressure were measured, and venous blood samples after an overnight fast were withdrawn from each subject during a routine annual medical checkup. Three obesity-related abnormalities—high blood

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pressure, dyslipidemia, and high fasting plasma glucose—were defined by the Japanese guidelines of metabolic syndrome [3]. *High blood pressure* was defined as a systolic blood pressure of at least 130 mm Hg or a diastolic blood pressure of at least 85 mm Hg. *Dyslipidemia* was defined as serum triglycerides of at least 150 mg/dL or high-density lipoprotein cholesterol not exceeding 40 mg/dL, and *high fasting plasma glucose* was defined as a fasting plasma glucose of at least 110 mg/dL. We evaluated the number of obesity-related abnormalities discriminated by waist circumference and body mass index (BMI). We plotted receiver operating characteristic (ROC) curves for waist circumference to predict one or more obesity-related metabolic abnormalities and calculated sensitivity, specificity, and positive predictive value.

3. Results

The participants had a mean age of 45.5 years for men and 45.3 years for women, a mean BMI of 23.3 kg/m^2 for men and 22.6 kg/m^2 for women, and a mean waist circumference of 80.1 cm for men and 72.7 cm for women.

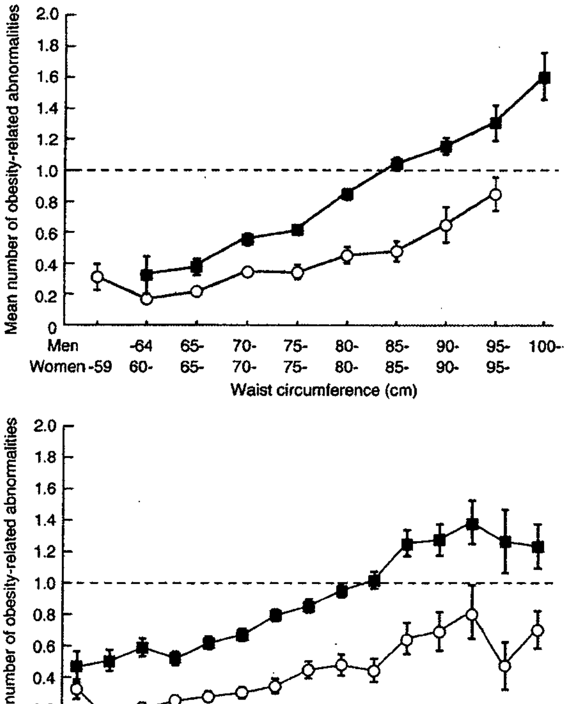


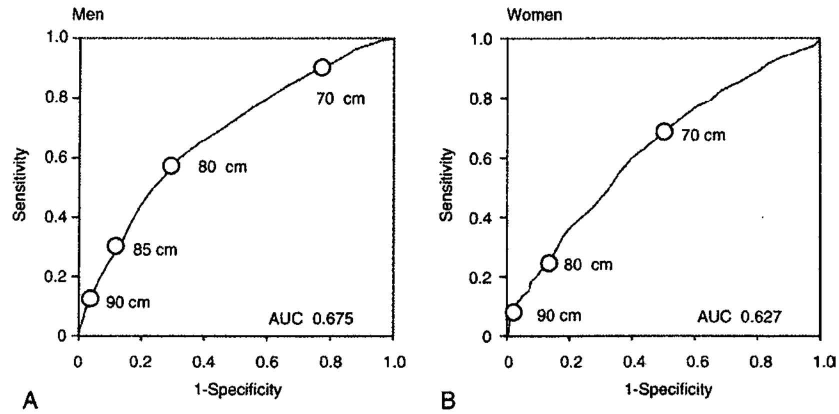
Fig. 1. The mean number of obesity-related abnormalities discriminated by waist circumference or BMI in men (■) and women (O). Obesity-related abnormalities included hypertension, dyslipidemia, and glucose intolerance. The horizontal dotted line shows a mean number of obesity-related abnormalities of 1.0. Data are presented as means ± standard error.

We evaluated the association between waist circumference or BMI and the mean number of obesity-related abnormalities (Fig. 1). In men, the mean number of abnormalities increased as waist circumference or BMI increased. When the waist circumference was 85 cm, which is the cutoff point for the diagnosis of metabolic syndrome in Japanese men [3], the mean number of complicated metabolic abnormalities was approximately 1. In women, although the mean number of abnormalities increased as the waist circumference increased, it was less than 1 even in women with a waist circumference of at least 95 cm or BMI of at least 30 kg/m^2.

The prevalence of one or more obesity-related abnormalities was 50% in men and 21% in women. According to the ROC curve, the area under the curve was higher for men (0.675; 95% confidence interval, 0.655-0.694) than for women (0.627; 95% confidence interval, 0.596-0.657) (Fig. 2). The cutoff levels yielding the maximal sensitivity plus specificity for predicting the prevalence of one or more obesity-related abnormalities were 80 cm in men (sensitivity, 0.59; specificity, 0.69) and 73 cm in women (sensitivity, 0.55; specificity, 0.64). However, the positive predictive value was as low as 28.8% in men and 7.1% in women at these cutoff points.

4. Discussion

Hara et al [4] and Ohkubo et al [5] proposed a cutoff point regarding waist circumference for detecting metabolic syndrome or insulin resistance in Japanese based on relatively small, older, and somewhat higher-risk populations. Both reports proposed lowering the cutoff point of waist circumference for Japanese women to 76 cm. We found that a similar cutoff point of 73 cm for women provided the highest sensitivity and specificity for detecting metabolic syndrome as was recently observed [4,5]. Theoretically, sensitivity and specificity (therefore, the ROC curves) are not affected by the prevalence of the detected disease in various populations. However, the positive predictive value was as low as 7.1% in our population of middle-aged Japanese women, which means that only 7.1% of women with waist circumference of 73 cm or higher had the accumulation of metabolic abnormalities. Therefore, this cutoff point may not be suitable for a screening test in women. Two previous reports from Japan did not give the positive predictive values for their cutoff points. The low positive predictive value was caused by the low prevalence of metabolic abnormalities in middle-aged Japanese women and, possibly, the relatively higher resistance of Japanese women than men to obesity-induced metabolic abnormalities. As proposed in previous reports [4,5], lower cutoff points for



Cutoff point for waist circumference

		Sensitivity	Specificity
Men			
	70 cm	0.94	0.16
	80 cm	0.59	0.69
	85 cm	0.32	0.86
	90 cm	0.13	0.96
Women			
	70 cm	0.67	0.52
	73 cm	0.55	0.64
	80 cm	0.27	0.85
	90 cm	0.09	0.98

C

Fig. 2. The predictive performance of waist circumference for one or more obesity-related metabolic abnormalities. The ROC curves for one or more obesity-related metabolic abnormalities in men (A) and in women (B) are shown. The sensitivity and specificity of each cutoff point of waist circumference are given (C).

waist circumference might detect more people with metabolic abnormalities with high sensitivity. However, in a population with a low prevalence of metabolic abnormalities, lower cutoff points would also result in a greater proportion of false positives, with more healthy women in particular being screened as abnormal. Furthermore, because the mean number of complicated metabolic abnormalities was lower than 1 even in those with a waist circumference of at least 95 cm and the area under the ROC curve was lower in women than in men, waist circumference would not effectively predict the existence of metabolic syndrome in Japanese women.

In this study, similar to previous reports [2,4,5,8], cutoff points of waist circumference were proposed using ROC curves for predicting the metabolic abnormalities. However, abdominal obesity is important in metabolic syndrome because it has been linked to the development of cardiovascular disease. Further investigations are needed to evaluate the association between waist circumference and future incidence of cardiovascular events to establish an appropriate cutoff point for waist circumference. Another limitation was that the participants of this study did not include older people and might be healthier than general Japanese people because they were identified at a work place. Similar analyses are needed in older Asian populations.

In conclusion, middle-aged Japanese women seem to be resistant to obesity-related metabolic abnormalities; and waist circumference would not effectively predict the existence of metabolic syndrome. In setting cutoff points in guidelines, a greater emphasis should be placed on the absolute risk of having abnormalities or diseases.

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J-shaped relationship between waist circumference and subsequent risk for Type 2 diabetes: an 8-year follow-up of relatively lean Japanese individuals

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Abstract

Aims This study investigated the relationship between waist circumference and the subsequent incidence of Type 2 diabetes and the association with insulin resistance and pancreatic B-cell function in relatively lean Japanese individuals.

Methods The study participants were 3992 employees (2533 men and 1459 women, aged 35–55 years) of a metal-products factory in Japan. The incidence of diabetes was determined in annual medical examinations during an 8-year follow-up. We calculated age- and sex-adjusted hazard ratios (HRs) according to the sex-specific quintile of waist circumference at baseline. Differences in baseline insulin resistance [homeostatis model assessment (HOMA)-IR] and pancreatic B-cell function (HOMA-B) were compared between participants who developed diabetes and those who did not.

Results During the follow-up, 218 participants developed diabetes. Age- and sex-adjusted HRs across the quintiles of waist circumference were 1.78, 1.00 (reference), 1.59, 3.11 and 3.30, respectively (P for trend, < 0.0001). The HR for the lowest quintile was significantly higher than that for the second quintile. Among participants with waist circumference of the lowest quintile, HOMA-B was lower in those who developed diabetes than in those who did not [33.1 (24.1–45.0) vs. 54.3 (37.9–74.6) median (interquartile range), $P < 0.0001$], but HOMA-IR did not differ between these groups.

Conclusions There was a J-shaped relationship between waist circumference and subsequent risk for Type 2 diabetes in relatively lean Japanese individuals; lower pancreatic B-cell function may also increase the risk of diabetes in very lean Japanese people.

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Keywords Incidence, insulin resistance, insulin secretion, Type 2 diabetes, waist circumference

Abbreviations BMI, body mass index; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; HOMA-B, homeostasis model assessment of pancreatic B-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; OGTT, oral glucose tolerance test

Introduction

Obesity increases the risk for Type 2 diabetes [1–7], with previous reports indicating a linear association between the degree of obesity and the incidence of Type 2 diabetes in Western populations [1–5]. Although the prevalence of obesity is much lower in Asian countries than in Western countries, the prevalence of Type 2 diabetes has been reported to be similar [8], suggesting that the association between obesity and diabetes may be different in Asian countries compared with Western countries.

One possible reason for the high frequency of Type 2 diabetes in Asians is the presence of prominent abdominal fat in Asians compared with Caucasians with a similar body mass index (BMI)

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[9,10]; however, few studies have analysed the association between waist circumference and diabetic risk in Asians [11]. Waist circumference might be a useful predictor for diabetes in Asians with high abdominal fat.

In addition to obesity, impairment of early phase insulin secretion and low pancreatic B-cell mass may play important roles in the development of Type 2 diabetes in lean Asians [12–15]. Decreased B-cell function can cause hyperglycaemia prior to the onset of obesity. It is possible that not only obese people with insulin resistance but also lean people with lower B-cell function are at high risk for developing Type 2 diabetes. Recently, a J-curve association between BMI and the incidence of diabetes was reported in older Japanese adults [16]. This report suggested that older Japanese people with low BMI would also be at higher risk for developing diabetes. However, there have been few prospective studies investigating the relationship of waist circumference to future development of diabetes in lean Asian people which have also assessed B-cell function and insulin resistance.

In this large, 8-year prospective study of relatively lean Japanese men and women, we investigated the relationship between anthropometric indices (BMI and waist circumference) and the subsequent risk for developing Type 2 diabetes. The objectives of this study were: (i) to investigate whether waist circumference is associated with the future risk of diabetes; (ii) to determine whether the relationship is linear or J-shaped; (iii) to investigate how this relationship is influenced by insulin resistance and B-cell function.

Research design and methods

The participants were employees of a factory that produces zip fasteners and aluminum sashes in Toyama Prefecture, Japan. Detailed information about the study population has been described [17–19]. The Industrial Safety and Health Law in Japan requires employers to conduct annual health examinations of all employees. A survey of the incidence of diabetes mellitus was performed during the annual medical examinations between 1996 and 2004. At the baseline examination in 1996, 4274 (90%) of 4757 employees aged 35–55 years received health examinations. Of these 4274 potential participants, 282 (6.6%) were excluded: 199 had pre-existing diabetes or had high fasting plasma glucose (≥ 7.0 mmol/l) at the time of the baseline examination, 16 had missing data in baseline anthropometric indices and 67 did not participate in consecutive follow-up annual health examinations. The final study population consisted of 3992 employees (2533 men and 1459 women).

The baseline health examination included a medical history, physical examination, anthropometric measurements (waist circumference and BMI) and the determination of fasting plasma glucose, fasting insulin, glycated haemoglobin (HbA_{1c}) and serum lipid levels. Height was measured, without shoes, to the nearest 0.1 cm using a stadiometer. Weight was measured, with participants wearing only light clothing and no shoes, to the nearest 0.1 kg using a standard scale. BMI was calculated as weight/height^2 (kg/m^2). Waist circumference was determined to the nearest 0.5 cm by measuring from a point above the iliac crest and below the lowest rib margin, during minimal respiration in a standing position. Blood pressure was measured once with a mercury sphygmomanometer after the subjects had rested for 5 min in a seated position. Trained staff took all of the measurements.

Plasma glucose levels were measured enzymatically (Abbott glucose UV test; Abbott Laboratories, Chicago, IL, USA) and plasma insulin levels were determined by radioimmunoassay (Shionogi Co., Tokyo, Japan). HbA_{1c} was measured by high-velocity liquid chromatography using a fully automated analyser (Kyoto Daiichi Kagaku, Kyoto, Japan). Total cholesterol and triglycerides were measured by enzyme assay. High-density lipoprotein (HDL) cholesterol was measured by direct method. Insulin resistance was calculated by the homeostasis model assessment (HOMA) method [20], using the following;

$$\text{HOMA-IR} = \text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting plasma glucose (mmol/l)}/22.5$$

The HOMA of pancreatic B-cell function (HOMA-B) [20] was calculated using the following;

$$\text{HOMA-B} = 20 \times \text{fasting insulin } (\mu\text{U/ml})/[\text{fasting plasma glucose (mmol/l)} - 3.5]$$

Participants with $HbA_{1c} > 6.0\%$ underwent a 75-g oral glucose tolerance test (OGTT). According to the definitions of the American Diabetes Association [21] and the Japanese Diabetes Society [22], the diagnosis of diabetes is confirmed by at least one of the following observations: (i) fasting plasma glucose concentration ≥ 7.0 mmol/l; (ii) 2-h glucose level ≥ 11.1 mmol/l in a 75-g OGTT; or (iii) treatment with insulin or oral glucose-lowering agents.

A questionnaire was used to identify lifestyle behaviours such as alcohol consumption, smoking and regular exercise. Participants were classified as either non-drinkers or active drinkers. Active drinkers were further divided into occasional (less than 5 days/week), light (more than 5 days/week and average amounts less than 40 g alcohol/day for men and 20 g/day for women) or moderate/heavy (more than 5 days/week and average amounts of more than 40 g alcohol/day for men and 20 g/day for women) drinkers. Data were also collected concerning smoking habits (never, ex-smoker or current smoker) and frequency of exercise (none, weak, moderate or strong). Exercise was defined as the participation in any physical activity such as jogging, cycling, swimming or tennis that was performed long enough to cause sweating. A self-administered questionnaire was also used to collect information about a medical history of hypertension, dyslipidaemia, diabetes and the use of glucose-lowering medication. High blood pressure and dyslipidaemia were defined by the Japanese criteria of the

