⑩-2 ウエスト周囲径と BMI の基準をともに満たさず，かつリスクファクター数 0 の者を対照群とした場合の解析

さらに，ウエスト周囲径と BMI の基準をともに満たさず，かつリスクファクター数 0 の者を対照群とした場合，全循環器疾患発症の年齢調整ハザード比は，動機づけ支援レベル群では男性 1.97，女性 2.79，積極的支援レベル群では男性 3.17，女性 3.78 で，ともに統計学に有意な上昇を認めた．但し，BMI とウエスト周囲径の基準値をともに満たさないが他のリスクファクターが存在あるいは集積している群においても，心血管疾患発症のハザード比が上昇していた．虚血性心疾患，虚血性循環器疾患についても同様な傾向が認められた．

保健指導レベル別にみた心血管疾患発症の年齢調整ハザード比（対照群を「ウエスト周囲径・BMI がともに基準値未満かつリスクファクター数 0 の者」とした場合）

男性

	情報提供レベル				動機づけ支援レベル	積極的支援レベル
	対照群					
男性	ウエスト周囲径＜85cmかつ BMI<25 +リスク0	ウエスト周囲径＜85cmかつ BMI<25 +リスク1個	ウエスト周囲径＜85cmかつ BMI<25 +リスク2個以上	ウエスト周囲径≧85cm+リスク数 0 or ウエスト周囲径＜85cmかつBMI ≧25+リスク数0	ウエスト周囲径≧85cm+リスク数 1 or ウエスト周囲径＜85cmかつBMI ≧25+リスク数1-2	ウエスト周囲径≧85cm+リスク数 2以上 or ウエスト周囲径＜85cmかつBMI ≧25+リスク数3以上
人数	2,048	2,775	2,141	683	2,816	2,794
平均BMI	21.2	21.5	22.0	25.1	25.5	26.3
平均ウエスト	75.7	77.3	78.8	88.0	89.6	91.0
虚血性心疾患、発症数	9	25	35	5	52	41
ハザード比	1.00	1.75 (0.81-3.76)	3.00 (1.43-6.28)	1.67 (0.56-5.01)	3.11 (1.52-6.38)	3.60 (1.74-7.44)
虚血性循環器疾患、発症数	30	96	82	13	128	115
ハザード比	1.00	1.91 (1.26-2.90)	1.93 (1.26-2.90)	1.31 (0.68-2.54)	2.02 (1.34-3.04)	3.40 (2.25-5.12)
全循環器疾患、発症数	37	117	113	14	150	134
ハザード比	1.00	1.91 (1.31-2.79)	2.22 (1.52-3.24)	1.14 (0.61-2.13)	1.97 (1.36-2.85)	3.17 (2.18-4.61)

女性

	情報提供レベル				動機づけ支援レベル	積極的支援レベル
	対照群					
女性	ウエスト周囲径＜90cmかつ BMI<25 +リスク0	ウエスト周囲径＜90cmかつ BMI<25 +リスク1個	ウエスト周囲径＜90cmかつ BMI<25 +リスク2個以上	ウエスト周囲径≧90cm+リスク数 0 or ウエスト周囲径＜90cmかつBMI ≧25+リスク数0	ウエスト周囲径≧90cm+リスク数 1 or ウエスト周囲径＜90cmかつBMI ≧25+リスク数1-2	ウエスト周囲径≧90cm+リスク数 2以上 or ウエスト周囲径＜90cmかつBMI ≧25+リスク数3以上
人数	4,938	4,222	2,139	921	2,947	864
平均BMI	21.2	21.8	22.2	26.3	27.0	27.8
平均ウエスト	73.8	76.3	78.0	87.3	89.4	94.2
虚血性心疾患、発症数	8	21	24	2	27	4
ハザード比	1.00	1.68 (0.74-3.83)	3.15 (1.39-7.13)	-	2.39 (1.06-5.36)	2.76 (0.83-9.22)
虚血性循環器疾患、発症数	29	91	84	3	98	24
ハザード比	1.00	2.19 (1.43-3.35)	3.42 (1.76-4.15)	-	2.70 (1.76-4.15)	4.46 (2.57-7.72)
全循環器疾患、発症数	43	134	113	6	131	31
ハザード比	1.00	2.39 (1.68-3.40)	3.51 (2.44-5.05)	0.67 (0.29-1.59)	2.79 (1.95-3.99)	3.78 (2.36-6.04)

⑩-3 非服薬者に限定した場合の解析

現行の保健指導対象者においては，服薬中の者は継続的に医療機関を受診しており原則として保健指導の対象とならないことから，非服薬者に限定して解析を行った．ウエスト周囲径と BMI の基準をともに満たさず，かつリスクファクター数 0 の者を対照群とした場合，全循環器疾患発症の年齢調整ハザード比は，動機づけ支援レベル群では男性 1.79，女性 2.14，積極的支援レベル群では男性 2.83，女性 3.88 で，ともに統計学に有意な上昇を認めた．虚血性心疾患，虚血性循環器疾患についても同様な傾向が認められた．

但し，情報提供レベルであるものの BMI とウエスト周囲径の基準値をともに満たさないが他のリスクファクターが存在あるいは集積している群においても，心血管疾患発症のハザード比が上昇していた．

保健指導レベル別にみた心血管疾患発症の年齢調整ハザード比（非服薬者に限定：対照群を「ウエスト周囲径・BMI がともに基準値未満かつリスクファクター数 0 の者」とした場合）

男性

	情報提供レベル				動機づけ支援レベル	積極的支援レベル
	対照群					
男性	ウエスト周囲径＜85cmかつ BMI<25 +リスク0	ウエスト周囲径＜85cmかつ BMI<25 +リスク1個	ウエスト周囲径＜85cmかつ BMI<25 +リスク2個以上	ウエスト周囲径≧85cm+リスク数 0 or ウエスト周囲径＜85cmかつBMI ≧25+リスク数0	ウエスト周囲径≧85cm+リスク数 1 or ウエスト周囲径＜85cmかつBMI ≧25+リスク数1-2	ウエスト周囲径≧85cm+リスク数 2以上or ウエスト周囲径＜85cmかつBMI ≧25+リスク数3以上
人数	2,048	2,451	1,609	683	2,189	2,033
平均BMI	21.2	21.5	21.9	25.1	25.4	26.1
平均ウエスト	75.7	77.3	78.7	88.0	89.3	90.6
虚血性心疾患、発症数	9	18	23	5	33	26
ハザード比	1.00	1.49 (0.67-3.33)	2.79 (1.28-6.06)	1.67 (0.56-5.01)	2.79 (1.32-5.88)	3.19 (1.49-6.85)
虚血性循環器疾患、発症数	30	72	53	13	82	70
ハザード比	1.00	1.71 (1.11-2.63)	1.79 (1.13-2.82)	1.31 (0.68-2.54)	1.86 (1.21-2.86)	2.93 (1.89-4.54)
全循環器疾患、発症数	37	86	74	14	97	83
ハザード比	1.00	1.66 (1.12-2.46)	2.05 (1.37-3.07)	1.14 (0.61-2.14)	1.79 (1.21-2.64)	2.83 (1.90-4.22)

女性

	情報提供レベル				動機づけ支援レベル	積極的支援レベル
	対照群					
女性	ウエスト周囲径＜90cmかつ BMI<25 +リスク0	ウエスト周囲径＜90cmかつ BMI<25 +リスク1個	ウエスト周囲径＜90cmかつ BMI<25 +リスク2個以上	ウエスト周囲径≧90cm+リスク数 0 or ウエスト周囲径＜90cmかつBMI ≧25+リスク数0	ウエスト周囲径≧90cm+リスク数 1 or ウエスト周囲径＜90cmかつBMI ≧25+リスク数1-2	ウエスト周囲径≧90cm+リスク数 2以上 or ウエスト周囲径＜90cmかつBMI ≧25+リスク数3以上
人数	4,938	3,484	1,428	921	2,012	521
平均BMI	21.2	21.7	22.1	26.3	26.8	27.6
平均ウエスト	73.8	76.2	77.7	87.3	89.1	93.8
虚血性心疾患、発症数	8	12	10	2	12	3
ハザード比	1.00	1.24 (0.50-3.08)	2.13 (0.83-5.50)	-	1.79 (0.72-4.46)	3.78 (0.99-14.4)
虚血性循環器疾患、発症数	29	59	38	3	47	13
ハザード比	1.00	1.84 (1.17-2.90)	2.51 (1.53-4.13)	-	2.18 (1.35-3.51)	4.29 (2.21-8.34)
全循環器疾患、発症数	43	91	53	6	62	18
ハザード比	1.00	2.08 (1.43-3.01)	2.61 (1.72-3.95)	0.67 (0.29-1.59)	2.14 (1.43-3.21)	3.88 (2.22-6.80)

D.結果のまとめと考察

日本人において，ウエスト周囲径は BMI と同様にリスクファクター集積と明らかな関連があり，ウエスト周囲径の測定は有用であると考えられた．

ウエスト周囲径が増加するに伴い，メタボリックシンドロームの平均リスクファクター数・リスクファクター集積者の割合は増加した．平均リスクファクター数が 1 を超えるウエスト周囲径のカテゴリーは男性では 80-85cm から，女性では 90-95cm からであり，内臓脂肪面積から求めた現行のウエスト周囲径の基準値とほぼ合致した[絶対的リスクの検討]．また，ROC 曲線解析でリスクファクター集積を予測するウエスト周囲径に関して検討すると，感度 70%以上となるウエスト周囲径は男性 83cm 以下，女性 80cm 以下で，感度 60%以上となるウエスト周囲径は男性 85cm 以下，女性 83cm 以下であった．一方，特異度が 70%以上となるウエスト周囲径は男性 87cm 以上，女性 84cm 以上で，特異度が 60%以上となるウエスト周囲径は男性 85cm 以上，女性 81cm 以上であった．そのため，感度と特異度の和を最大にするウエスト周囲径は，男性 85cm 前後，女性 80cm 前後と算出された[相対的リスクの検討]．ウエスト周囲径以外のリスクファクターのカットオフ値を日本基準に準拠した場合，リスクファクター集積(2 個以上)の年齢調整オッズ比は，男性ではウエスト周囲径のカットオフ値を 85cm とすると 3.06，女性ではウエスト周囲径のカットオフ値を 80cm とすると 2.79 であった．

次に，ROC 曲線解析で心血管疾患発症を予測するウエスト周囲径を検討したところ，男女ともに ROC 曲線がほぼフラットであったため，感度と特異度の和を最大にするウエスト周囲径のカットオフ値の決定は困難であった．そこで，メタボリックシンドロームのリスクファクターを考慮した総合判別改善度（IDI）が最大値を呈するウエスト周囲径のカットオフ値を検討したところ，虚血性循環器疾患ならびに全循環器疾患発症に関しては男性 83～85 cm，女性 80～83cm と算出された．

ウエスト周囲径を必須項目としたわが国の診断基準によるメタボリックシンドロームでは，心血管疾患発症のリスクが有意に高かった．ウエスト周囲径の基準値を 75～90cm の間で検討した場合，非メタボリックシンドローム群に対するメタボリックシンドローム群の心血管疾患発症の年齢調整ハザード比は男性 1.5～1.8，女性 1.5～1.7 であった．ウエスト周囲径の基準値を低く設定するほどメタボリックシンドロームに該当する者は増加し，メタボリックシンドローム群は常に非メタボリックシンドローム群と比較して心血管疾患発症のリスクが高いため，メタボリックシンドローム群が寄与する心血管疾患発症の割合，PAF(population attributable risk fraction:人口寄与危険度割合)はいずれも増加した．また，腹部肥満（ウエスト周囲径の基準）を診断の必須項目としない海外のメタボリックシンドロームの診断基準に準拠させて解析した場合，心血管疾患発症の年齢調整ハザード比に大きな変化は認められなかった．

ウエスト周囲径の基準値を男性 85cm，女性 90cm とする現行の特定保健指導の階層化基準で選定された群の心血管疾患発症のリスクは，選定されない群より高いことが示された．但し，今まで国内の複数の疫学研究で指摘されてきたように BMI とウエスト周囲径の基準値をともに満たさなくともリスクファクターが存在あるいは集積している群では，心血管疾患発症のリスクが上昇していた．従って，現行の事業として推奨にとどまっている「非肥満者でリスクファクターが存在あるいは集積している群に対する保健指導」に関してはその制度的対応の必要性が示された．

メタボリックシンドロームの診断基準はあくまでも病態医学的な観点で検討されるべきであるが，保健医療制度としての特定健診・保健指導におけるウエスト周囲径の位置付けと基準値の設定，保健指導対象者の抽出アルゴリズムに関しては，本研究のエビデンスに加えて，社会的な保健医療資源のより効率的な活用等を勘案することにより，公衆衛生的見地から再検討すべきものであると判断する．

E. 研究発表

研究成果の刊行に関する一覧表を参照.

F. 知的所有権の取得状況

該当するものはない.

研究成果の刊行に関する一覧表

＊厚生労働科学研究費の補助を受けたことが明記された主なものを記載

著者名	タイトル	雑誌名	巻号	開始頁	年
Watanabe M, Kokubo Y, Higashiyama A,他	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	88	20	2010
Okamura T, Kokubo Y, Watanabe M,他	Triglycerides and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort: The Suita study.	Atherosclerosis	209	290	2010
Takamoto I, Kadowaki T	Controversies about the importance of increased waist circumference	International Diabetes Monitor	22	10	2010
Higashiyama A, Okamura T, Ono Y, 他	Risk of smoking and metabolic syndrome for incidence of cardiovascular disease--comparison of relative contribution in urban Japanese population: the Suita study.	Circ J	73	2258	2009
櫻井勝, 三浦克之, 中村幸志,他	中年期日本人男性における腹部肥満の有無別に見た代謝異常集積と脳心血管疾患発症との関連	日循予防誌	44	1	2009

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International Diabetes Federation

Brief report

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

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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].

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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

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.

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Triglycerides and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort: The Suita study

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ABSTRACT

Objective: The impact of elevated triglycerides (TG) and non-high density lipoprotein cholesterol (non-HDLC) on the incidence of stroke and myocardial infarction (MI) has not been well evaluated in Asian populations such as in Japan, which have a lower incidence of myocardial infarction, but a higher risk of stroke than Western populations.
Methods: The authors conducted an 11.7-year prospective study ending in 2005 of 5098 Japanese aged 30–79 living in an urban population, initially free of stroke or MI. The relationship between serum lipids and the risk for stroke and MI was determined by dividing the participants into four groups stratified by the combination of serum levels of TG and non-HDLC. The cut-off value was 1.7 mmol/L for TG and 4.9 mmol/L for non-HDLC.
Results and conclusion: The total person-years were 59,774 (27,461 for men and 32,313 for women). During the follow-up period, there were 113 cases of MI and 180 of stoke (with 116 cerebral infarctions). Compared with the low TG/low non-HDLC group, the hazard ratio (95% confidence interval) for MI in the high TG/high non-HDLC group was 2.55 (1.53–4.24) after adjustment for other cardiovascular risk factors. The hazard ratio for cerebral infarction in the high TG alone group was 1.63 (1.03–2.56); however, the risk of cerebral infarction was not significantly increased in the other groups. High serum levels of TG and non-HDLC are both important targets for the prevention of cardiovascular disease in Japan.

1. Introduction

Previous studies suggested that high levels of serum total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) are causal risk factors for coronary artery disease (CAD) [1–4] and possibly for ischemic stroke [5]. However, less attention has been paid to high serum levels of triglycerides (TG) [6–8]. Furthermore, although the US National Cholesterol Education Program Adult Treatment Panel guideline III (NCEP-ATP III) has set goals for non-high-density lipoprotein cholesterol (non-HDLC) after the achievement of LDL-C goals in patients with elevated TG [9], the impact of TG and non-HDLC on the incidence of cardiovascular disease (CVD) has not been evaluated in the Japanese population, which has a lower incidence of CAD but a higher risk of stroke than Western populations [10].

Therefore, our a priori hypothesis was that the coexistence of high serum TG and non-HDLC increases the risk of CAD and stroke in the Japanese population. To investigate this hypothesis, we performed a long-term prospective study in an urban, community-dwelling Japanese population.

2. Methods

2.1. Populations

The Suita study, a cohort study for CVD of urban residents was established in 1989. The details of this study have been described elsewhere [4,11–14]. Briefly, 6485 men and women aged 30–79 years had a baseline survey at the National Cardiovascular Center between September 1989 and March 1994. Of these, a total of 1387 were excluded for the following reasons: past history of coronary heart disease or stroke (n = 210), lack of participation in the baseline survey (n = 79), non-fasting visit (n = 166), use of lipid-lowering agents (n = 125), missing data (n = 109), and lost to follow-up (n = 698). Data from the remaining 5098 participants (2404 men and 2694 women) were included in the analysis. This

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cohort study was approved by the Institutional Review Board of the National Cardiovascular Center.

2.2. Baseline examination

Blood samples were collected after the participants had fasted for at least 10 h. The samples were centrifuged immediately and a routine blood examination was performed that included serum total cholesterol (TC), HDL cholesterol, TG and glucose levels.

Blood pressure was measured in triplicate on the right arm after 5 min of rest by well-trained physicians using a standard mercury sphygmomanometer. The average of the second and third measurements was used for analysis. Hypertension was defined as either a systolic blood pressure (SBP) ≥ 140 mmHg, a diastolic blood pressure (DBP) ≥ 90 mmHg or the use of antihypertensive agents. Diabetes was defined as a fasting serum glucose ≥ 7.0 mmol/L (126 mg/dL), the use of anti-diabetic agents, or both. Height with bare feet and weight in light clothing were measured. Waist circumference (WC) was measured at umbilical level in a standing position. Metabolic syndrome (MetS) was defined using modified NCEP-ATP III criteria [13], of which abdominal obesity was defined according to the International Obesity Task Force central obesity criteria for Asia [15].

Public health nurses obtained information on the smoking, drinking and medical histories.

2.3. Endpoint determination

The endpoint determination was previously reported [4,11–14]. The endpoints of the present study were: (1) the first myocardial infarction (MI) or stroke event; (2) death; (3) leaving Suita city; or (4) December 31, 2005.

The first step in the survey for MI and stroke involved checking the health status of all participants by repeated clinical visits every two years and yearly questionnaires by mail or telephone. In the second step, in-hospital medical records of participants who were suspected of having an MI or stroke were reviewed by registered hospital physicians or research physicians, who were blinded to the baseline information. The criteria for stroke were defined according to the US National Survey of Stroke criteria [16]. For each stroke subtype [i.e., cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage], a definite diagnosis was established based on the computed tomography, magnetic resonance imaging, or autopsy. The criteria for definite and probable MI were defined according to the criteria of the MONICA (Monitoring Trends and Determinants of Cardiovascular Disease) project [17]. Sudden deaths of unknown origin that occurred within 24 h of the onset were classified as MI in the present study.

2.4. Statistical analysis

The relationship between serum lipids and the risk of MI and stroke was described by dividing the participants into four groups stratified by the combination of serum levels of TG and non-HDLC. We used 1.7 mmol/L (150 mg/dL) of serum TG as a cut-off point for high serum TG according to the classification of NCEP-ATP III [9] and that of the Japan Atherosclerosis Society [3]. The category of non-HDLC ≥4.9 mmol/L (190 mg/dL) was defined as a high serum non-HDLC, which was equivalent to 6.2 mmol/L (240 mg/dL) of TC or 4.1 mmol/L (160 mg/dL) of LDL-C, because non-HDLC was usually 0.8 mmol/L (30 mg/dL) higher than LDL-C [9,18–19].

Continuous variables between groups were compared by analysis of variance and categorical variables were compared by a chi-square test. The hazard ratio (HR) for MI or stroke was calculated using a proportional hazards model adjusted for age, hypertension (dichotomous variable), diabetes, HDL-C, body mass index (BMI), smoking (never-smoked; ex-smoker; current smoker) and drinking (never-drank; ex-drinker; regular drinker) (model 1). Sex-combined analysis with further adjustment for sex was also performed. Another statistical model after replacement of BMI and hypertension with WC and SBP level (continuous variable) was also performed (model 2).

All confidence intervals were estimated at the 95% level and significance was set at a P value of <0.05. The Statistical Package for the Social Sciences (SPSS Japan Inc. version 15.0J, Tokyo, Japan) was used for all the analyses.

3. Results

The median and interquartile range of serum TG in the baseline survey was 1.29 mmol/L (0.90, 1.90) in men and 0.98 mmol/L (0.73, 1.41) in women. The mean baseline serum non-HDLC was 3.93 ± 0.91 mmol/L in men and 4.03 ± 1.03 mmol/L in women.

The means or prevalence of major cardiovascular risk factors in each group stratified by the combination of serum levels of TG and non-HDLC are summarized in Table 1. There was no significant difference in mean age and the prevalence of smoking among the TG and non-HDLC groups for men. There were significant differences in all other variables. Mean BMI, waist circumference and the prevalence of hypertension and diabetes were highest in the high-TG/high non-HDLC group, whereas the values of these parameters were lowest in the low-TG/low-non-HDLC group for both sexes. The prevalence of Mets was much higher in the high-TG groups than in the low-TG groups irrespective of non-HDLC level.

The total person-years were 59,774 (27,461 for men and 32,313 for women), with a mean follow-up period of 11.7 years. During the follow-up period, there were 113 first MIs and 180 first strokes. The strokes consisted of 28 intracerebral hemorrhages, 116 cerebral infarctions, 21 subarachnoid hemorrhages and 15 unclassified cases.

Table 2 shows the number of cases, age and multivariable-adjusted HRs for MI stratified by TG and non-HDLC. Compared with the low TG/low non-HDLC group, the HR for MI in the high TG/high non-HDLC group was 2.05 (95% confidence interval, CI, 1.08–3.90) in men, 3.79 (95% CI, 1.58–9.14) in women and 2.55 (95% CI, 1.53–4.24) in both sexes combined in multivariable adjusted model 1. We did not observe a significant increase in the HR for MI in the other groups. Similar results were observed after replacement of BMI and hypertension with WC and SBP level (model 2).

Table 3 shows the multivariable-adjusted HRs for cerebral infarction stratified by levels of TG and non-HDLC. Compared with the low TG/low non-HDLC group, the HR for cerebral infarction in the high TG alone group (high TG/low non-HDLC group) was 1.45 (95% CI, 0.84–2.50) in men, 2.09 (95% CI, 0.92–4.73) in women and 1.63 (95% CI, 1.03–2.56) in both sexes combined in statistical model 1. There was no significant increase of cerebral infarction in the other groups. Similar results were also observed in statistical model 2.

The incidence of total stroke, intracerebral hemorrhage and subarachnoid hemorrhage was not related to TG and non-HDLC levels in either sex. When the participants were divided into two groups by age (<60 and ≥60), the results of all the analyses listed above were similar in both age groups (data not shown).

4. Discussion

To our knowledge, this is the first cohort study in Japan to clarify the risk for MI and ischemic stroke of high serum level of TG, non-HDLC and both. The risk for MI of both high serum TG and non-HDLC was considerably higher than the risk without both or with only one. This relationship was similarly observed in both men and

Table 1
Means and prevalence of major cardiovascular risk factors in each group stratified by the combination of serum levels of triglycerides (TG) and non-high-density lipoprotein cholesterol (non-HDLC).

Variables	Low TG/low Non-HDLC		Low TG/high Non-HDLC		High TG/low Non-HDLC		High TG/high Non-HDLC		*P* value
Men									
No. of subjects	1532		117		550		205		
Non-HDLC (stratum mean), mmol/L	3.6	(0.7)	5.4	0.4	4.0	0.6	5.5	0.5	
Triglycerides (stratum median), mmol/L	1.0	(0.8, 1.3)	1.3	(1.0, 1.5)*	2.2	(1.9, 2.9)	2.4	(2.0, 3.7)*	
Age, years	55.8	(13.5)	57.4	(12.9)	54.8	(12.7)	54.8	(11.8)	0.16
HDLC, mmol/L	1.4	(0.3)	1.3	(0.3)	1.1	(0.3)	1.1	(0.2)	<0.01
BMI, kg/m^2	22.2	(2.8)	23.1	(3.1)	23.8	(2.6)	24.2	(2.6)	<0.01
Waist circumference, cm	80.8	(7.9)	82.7	(8.6)	85.7	(7.0)	86.3	(6.9)	<0.01
Systolic blood pressure, mmHg	127	(21)	129	(20)	130	(20)	132	(21)	<0.01
Diastolic blood pressure, mmHg	78	(12)	79	(12)	81	(11)	82	(11)	<0.01
Hypertension, %	30.0		35.0		36.4		38.0		0.01
Diabetes, %	4.8		4.3		7.5		9.3		0.02
Metabolic syndrome, %	4.5		4.3		45.1		47.8		<0.01
Smoking, %									
Current smoker	49.9		43.6		53.5		47.3		0.51
Ex-smoker	30.3		35.0		28.4		32.7		
Never-smoker	19.8		21.4		18.2		20.0		
Drinking, %									
Current drinker	76.0		63.2		76.4		69.3		0.02
Ex-drinker	3.6		6.0		2.9		5.4		
Never-drinker	20.4		30.8		20.7		25.4		
Women									
No. of subjects	1956		290		256		192		
Non-HDLC (stratum mean), mmol/L	3.6	(0.7)	5.5	(0.5)	4.2	(0.5)	5.8	(0.8)	
Triglycerides (stratum median), mmol/L	0.9	(0.7, 1.1)*	1.2	(0.9, 1.4)*	2.0	(1.8, 2.4)*	2.4	(2.0, 3.0)*	
Age, years	51.5	(12.9)	59.3	(9.6)	57.9	(11.2)	60.7	(8.8)	<0.01
HDLC, mmol/L	1.5	(0.3)	1.4	(0.3)	1.2	(0.3)	1.1	(0.3)	<0.01
BMI, kg./m2	21.7	(3.1)	22.9	(3.1)	23.6	(3.3)	24.2	(3.1)	<0.01
Waist circumference, cm	75.5	(9.8)	79.8	(9.7)	82.7	(10.0)	83.5	(9.7)	<0.01
Systolic blood pressure, mmHg	121	(21)	131	(21)	132	(21)	137	(21)	<0.01
Diastolic blood pressure, mmHg	73	(12)	79	(12)	79	(12)	80	(13)	<0.01
Hypertension, %	20.4		37.9		37.1		48.4		<0.01
Diabetes, %	2.4		4.5		6.6		7.8		<0.01
Metabolic syndrome, %	7.5		19.3		66.8		74.5		<0.01
Smoking, %									
Current smoker	11.8		8.6		14.5		16.1		0.04
EX-smoker	3.5		2.8		2.7		6.3		
Never-smoker	84.7		88.6		82.8		77.6		
Drinking, %									
Current drinker	34.9		29.3		28.5		24.5		<0.01
Ex-drinker	1.8		0.3		0.8		4.2		
Never-drinker	63.3		70.3		70.7		71.4		

TG, triglycerides; non-HDLC, non-high-density lipoprotein cholesterol; BMI, body mass index. Brackets indicate standard deviation.
Analysis of variance was used for comparisons of multiple group means and the chi-square test was used to compare proportions.
* Inter-quartile range.
** MetS was defined using modified NCEP-ATP III. Abdominal obesity was defined as a waist circumference ≥0.90 m in men and ≥ 0.80 m in women. High blood pressure was defined as average systolic/diastolic blood pressures of ≥ 130/85 mm Hg and/or current medication for hypertension. High triglyceride was defined as serum triglycerides of ≥1.7 mmol/L. Low HDL cholesterol was defined as serum HDL cholesterol levels of <1.03 mmol/L in men and of <1.29 mmol/L in women. High blood glucose was defined as fasting blood glucose of ≥6.1 mmol/L and/or current use of anti-diabetic medication. MetS was defined as the presence of three or more of these components.

women. In contrast, the risk for ischemic stroke was highest in the participants with high TG alone.

TG-rich lipoproteins have been shown to be atherogenic, and thus, they are associated with coronary atherosclerosis [9,19–20]. As NCEP-ATP III pointed out [9], elevated non-HDLC is a good therapeutic target in patients with high TG, because the serum concentration of non-HDLC reflects not only LDL-C but also the cholesterol content of all other TG-rich and apolipoprotein B containing lipoproteins, such as very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), small dense LDL particles and their remnant lipoproteins [19–20]. In the Helsinki Heart study [21], most of the risk for coronary heart disease (CHD) was confined to participants with high levels of both TG and LDL-C. In the West of Scotland Coronary Prevention Study [22], a higher incidence of CHD was observed in men in both the pravastatin and placebo groups when TG was at or above the median level. Pischon et al. suggested that TG added significant information to non-HDLC for CAD risk prediction in a nested case-control study [23]. Our findings are consistent with previous studies.

Similar to previous studies in Japan [4,10], we found no association between non-HDLC and cerebral infarction even in the presence of high serum TG, which may be due to a lower prevalence of atherothrombotic infarction than in Western populations. The ARIC study indicated that TC was associated with increased risk of non-lacunar, non-embolic stroke (atherothrombotic infarction), but not with lacunar or embolic stroke [24]. A recent report from a Japanese rural population showed that LDL-C is a risk factor for only atherothrombotic infraction [25]. Unfortunately, due to the relatively small stroke cases in our study, we were not able to demonstrate an association between any subtype of cerebral infarction and non-HDLC.

It is not clear why participants with high TG alone showed the increased risk for cerebral infarction in the present study. In a meta-analysis of 26 cohort studies in Asia-Pacific area, partici-

Table 2
Age and multivariable-adjusted hazard ratios (95% confidence intervals) for myocardial infarction stratified by TG and non-HDLC groups in an 11.7-year prospective study of 5098 Japanese men and women.

	Low TG/low Non-HDLC	Low TG/high Non-HDLC	High TG/low Non-HDLC	High TG/high Non-HDLC
Men				
Person-years	17410	1288	6358	2404
Case, *n*	45	6	11	14
Age adjusted	1.00	1.63 (0.70-3.83)	0.76 (0.39-1.48)	2.74(1.50-5.02)
Model 1[a]	1.00	1.48 (0.62-3.49)	0.63 (0.32-1.26)	2.05(1.08-3.90)
Model 2[b]	1.00	1.55 (0.66-3.66)	0.64 (0.32-1.29)	2.10 (1.10-3.98)
Women				
Person-years	23652	3455	2936	2270
Case, *n*	14	5	6	12
Age adjusted	1.00	1.59 (0.57-4.40)	2.28 (0.88-5.94)	4.88 (2.25-10.6)
Model 1[a]	1.00	1.63 (0.58-4.26)	1.99 (0.71-5.57)	3.79 (1.58-9.14)
Model 2[b]	1.00	1.55 (0.55-4.38)	1.92 (0.69-5.34)	3.18 (1.34-7.52)
Men and women				
Person-years	41062	4743	9294	4674
Case, *n*	59	11	17	26
Age adjusted	1.00	1.51 (0.79-2.89)	1.04 (0.60-1.78)	3.42 (2.15-5.44)
Model 1[a]	1.00	1.42 (0.74-2.74)	0.86 (0.49-1.53)	2.55 (1.53-4.24)
Model 2[b]	1.00	1.45 (0.75-2.79)	0.87 (0.49-1.54)	2.48 (1.49-4.10)

TG, triglycerides; non-HDLC, non high-density lipoprotein cholesterol.
[a] Multivariable adjusted for age, body mass index, hypertension, diabetes, HDL (high-density lipoprotein) cholesterol, cigarette smoking and alcohol intake by a Cox proportional hazard model. Sex was also adjusted in the men and women combined model.
[b] Replacement of body mass index and hypertension as covariates in model 1 with waist circumference and systolic blood pressure level.

pants grouped in the highest fifth of serum TG had a 50% increased risk of stroke compared with those in the lowest fifth [26]. Recent reviews have also concluded that hypertriglyceridemia seems to be a causal risk factor for ischemic stroke [7–8]. However, above-mentioned findings were not able to explain the low incidence of cerebral infarction in the high TG/high non-HDLC group in the present study. An elevated risk for MI might mask the relationship between TG and cerebral infarction; because there would be no further follow-up after a first MI. Another large study concerning about the relationship between serum TG and stroke should be needed.

Recently, we have reported that high serum LDLC and non-HDLC are both associated with an increased risk of MI; and the predictive value of non-HDLC for MI is almost similar to that of LDL-C [4]. However, we did not use serum TG as a covariate to avoid over-adjustment, because difference between serum level of LDLC and non-HDLC was automatically determined by serum TG level when serum LDLC value was calculated by the Friedewald formula [27]. Considering all the findings together, non-HDLC and TG may be recommended as beneficial screening markers for primary prevention of CAD in the Japanese community, as they are less expensive and more convenient because non-HDLC can be calculated irrespective of serum TG level.

The present study has some limitations. First, the single TG and non-HDLC measurement at the baseline survey may have underestimated the relationship between these lipids and cardiovascular disease due to regression dilution bias. Furthermore, we did not evaluate longitudinal trend for each risk factor and its medication status after baseline survey. Especially, hypertriglyceridemia is associated with not only present existence of metabolic components, such as hypertension and diabetes, but also new onset

Table 3
Age and multivariable-adjusted hazard ratios (95% confidence intervals) for cerebral infarction stratified by TG and non-HDLC groups in an 11.7-year prospective study of 5098 Japanese men and women.

	Low TG/low Non-HDLC	Low TG/high Non-HDLC	High TG/low Non-HDLC	High TG/high Non-HDLC
Men				
Person-years	17410	1288	6358	2404
Case, *n*	46	2	22	5
Age adjusted	1.00	0.53 (0.13-2.19)	1.51 (0.91-2.52)	0.99 (0.39-2.51)
Model 1[a]	1.00	0.54 (0.13-2.25)	1.45 (0.84-2.50)	0.92 (0.35-2.38)
Model 2[b]	1.00	0.56 (0.14-2.31)	1.48 (0.86-2.56)	0.75 (0.26-2.14)
Women				
Person-years	23652	3455	2936	2270
Case, *n*	20	8	10	3
Age adjusted	1.00	1.77 (0.78-4.02)	2.62 (1.23-5.60)	0.81 (0.24-2.72)
Model 1[a]	1.00	1.52 (0.66-3.50)	2.09 (0.92-4.73)	0.69 (0.20-2.44)
Model 2[b]	1.00	1.54 (0.67-3.54)	2.10 (0.93-4.73)	0.77 (0.22-2.71)
Men and women				
Person-years	41062	4743	9294	4674
Case, *n*	66	10	32	8
Age adjusted	1.00	1.14 (0.58-2.23)	1.82 (1.19-2.79)	0.94 (0.45-1.95)
Model 1[a]	1.00	1.12 (0.57-2.20)	1.63 (1.03-2.56)	0.79 (0.37-1.69)
Model 2[b]	1.00	1.12 (0.57-2.21)	1.62 (1.03-2.55)	0.69 (0.62-1.88)

TG, triglycerides; non-HDLC, non high-density lipoprotein cholesterol.
[a] Multivariable adjusted for age, body mass index, hypertension, diabetes, HDL (high-density lipoprotein) cholesterol, cigarette smoking and alcohol intake by a Cox proportional hazard model. Sex was also adjusted in the men and women combined model.
[b] Replacement of body mass index and hypertension (prevalence) as covariates in model 1 with waist circumference and systolic blood pressure levels.

of them in the future [28,29]. Second, we did not measure serum apolipoprotein B (apoB) [22], apolipoprotein A1 (ApoA1) and LP(a) [30], which some previous studies have shown to be strong risk factors for CAD [22]. Third, a recent study indicated that non-fasting TG is a better predictor of CAD than fasting TG [31]. However, in a large individual based meta-analysis in the Asia-Pacific region [26], most blood samples were collected during fasting, and there was a significant positive relationship between serum TG and CAD or stroke.

In conclusion, a combination of higher serum levels of TG and non-HDLC is associated with an increased risk of MI in a Japanese population. Furthermore, the risk for ischemic stroke was highest in the participants with high TG alone; however, further research should be needed. High serum levels of TG and non-HDLC are both important targets for the prevention of cardiovascular disease, which requires evidence-based guidelines for management in the primary care setting.

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Controversies about the importance of increased waist circumference

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Abstract

Obesity is defined as a condition of excess body fat accumulation mainly in the adipose tissue. Obesity increases the risk of type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease (CVD) and, ultimately, death. BMI measures general obesity but cannot take into account the distribution of body fat. By contrast, waist circumference is one of the indices of abdominal obesity.

Over the past two decades considerable attention has been paid to the metabolic syndrome. However, partially due to a lack of unified diagnostic criteria for the metabolic syndrome, heated arguments have arisen about the importance of increased waist circumference. These can be summarized as follows. (1) The correlation coefficients between waist circumference and visceral fat area measured by computed tomography are above $r = 0.7$ in both men and women. (2) No single waist circumference measurement is recommended as a protocol for predicting health risks, but we must be aware of the level used to measure waist circumference. (3) Measuring waist circumference provides additional information, beyond that provided by BMI. (4) Increased waist circumference itself is thought to be a simple and useful indicator of an elevated risk of metabolic abnormalities, CVD and death. (5) Independently of arguments over the metabolic syndrome, it is possible that population-specific cut-off points for waist circumference will be established in the near future.

Key words:
Waist circumference, body mass index (BMI), abdominal obesity, cardiovascular disease (CVD), metabolic syndrome

Introduction

The prevalence of obesity is rising rapidly in many parts of the world. Obesity is defined as a condition of excessive body fat accumulation mainly in adipose tissue, which increases the risk of type 2 diabetes, hypertension, dyslipidemia and cardiovascular disease (CVD) [1]. Recent data have shown that obesity is associated with the risk of death: average life expectancy has been shown to be reduced in obese subjects [2, 3]. BMI is the best-established index worldwide to assess and classify obesity. BMI cut-off points are 25 kg/m² for overweight (preobese) and 30 kg/m² for obesity, regardless of gender, age and ethnicity *(Table I)* [4]. However, in Asian populations the risk of developing type 2 diabetes and CVD is substantially higher at a BMI lower than the cut-off point for overweight. Nevertheless, a WHO expert consultation concluded that the WHO BMI cut-off points should be retained for international classifications [5].

Table I: *Classification of adults according to BMI [4].*

BMI (kg/m²)	Classification
<18.5	Underweight
18.5–24.9	Normal weight
25.0–29.9	Overweight
30.0–34.9	Class I obesity
35.0–39.9	Class II obesity
≥40.0	Class III obesity

In Asian populations the risk of developing type 2 diabetes and CVD is substantially higher at a BMI lower than the cut-off point for overweight

BMI cannot be used to distinguish between excess adipose tissue and high muscle mass. In addition, BMI measures general obesity but cannot take into account the distribution of body fat. Abdominal obesity or visceral obesity is thought to be more closely associated with insulin resistance and the metabolic abnormalities commonly referred to as the metabolic syndrome [6–9]. Although the mechanisms underlying the relationship of abdominal obesity to the metabolic syndrome have yet to be fully elucidated, abdominal obesity is a highly prevalent feature of the metabolic syndrome.

Table II: Comparison of various diagnostic criteria for the metabolic syndrome [10–14].

IDF (2006)		Revised NCEP ATP III (2005)		Japan (2005)	
Risk factor	Cut-off point	Risk factor	Cut-off point	Risk factor	Cut-off point
1. Waist circumference measurement level	Midpoint	1. Waist circumference measurement level	Iliac crest	1. Waist circumference measurement level	Umbilicus
Men	≥94 cm[a]	Men	≥102 cm	Men	≥85 cm
Women	≥80 cm[a]	Women	≥88 cm	Women	≥90 cm
2. Triglycerides	≥150 mg/dl	2. Triglycerides	≥150 mg/dl	2. Triglycerides and/or	≥150 mg/dl
3. HDL cholesterol		3. HDL cholesterol		3. HDL cholesterol	<40 mg/dl
Men	<40 mg/dl	Men	<40 mg/dl		
Women	<50 mg/dl	Women	<50 mg/dl		
4. Blood pressure		4. Blood pressure		4. Blood pressure	
Systolic and/or	≥130 mmHg	Systolic and/or	≥130 mmHg	Systolic and/or	≥130 mmHg
Diastolic	≥85 mmHg	Diastolic	≥85 mmHg	Diastolic	≥85 mmHg
5. Fasting blood sugar	≥100 mg/dl	5. Fasting blood sugar	≥100 mg/dl	5. Fasting blood sugar	≥110 mg/dl
1 is essential Any two of 2–5		No essential factor Any three of 1–5		1 is essential Any two of 2–4	

[a]For Europids.

Waist circumference is one of the indices of abdominal obesity, as are waist-hip ratio and waist-height ratio. Current widely used diagnostic criteria for the metabolic syndrome, including the original Japanese criteria, define abdominal obesity by waist circumference *(Table II)* [10–14]. Considerable attention has been paid to the metabolic syndrome over the past two decades. However, partially due to the lack of unified diagnostic criteria, heated arguments have arisen about the actual existence of a so-called 'syndrome', its clinical usefulness and its predictive power for CVD [15]. As a result, there are several controversies about the importance of increased waist circumference in relation to the metabolic syndrome, as discussed in this article.

Does waist circumference reflect visceral obesity?

According to imaging studies using computed tomography (CT) or magnetic resonance imaging, which can directly measure abdominal adiposity in detail, excess intra-abdominal or visceral adipose tissue, but not the amount of subcutaneous abdominal fat, correlates strongly with the metabolic abnormalities observed in overweight or obese patients [7, 16]. However, such accurate measurements of visceral adipose tissue are expensive and not always available in clinical practice, even in Japan where CT scanners are in abundance.

Waist circumference is weakly related to height [17], correlates closely with BMI [9] and waist-hip ratio [18], and is expected to be an appropriate index of visceral obesity. In theory, waist circumference is a simple index of overall abdominal obesity but is not a specific index of visceral obesity. Therefore the relationship between waist circumference and visceral obesity has become a matter of importance.

A recent Japanese study provides an answer to this fundamental question [19]. Abdominal CT was performed in 1617 subjects (1101 men and 516 women) undergoing general health examinations. Both visceral fat area at the level of the umbilicus and waist circumference anthropometrically measured at the same level in the upright posture were collected. The correlation coefficients between visceral fat area and waist circumference were $r = 0.755$ in men and $r = 0.715$ in women. This result is probably open to a variety of interpretations, though we consider it to be within a reasonable range.

What is the optimal measurement level of waist circumference?

At present, no consensus exists on the optimal protocol for measuring waist circumference, and

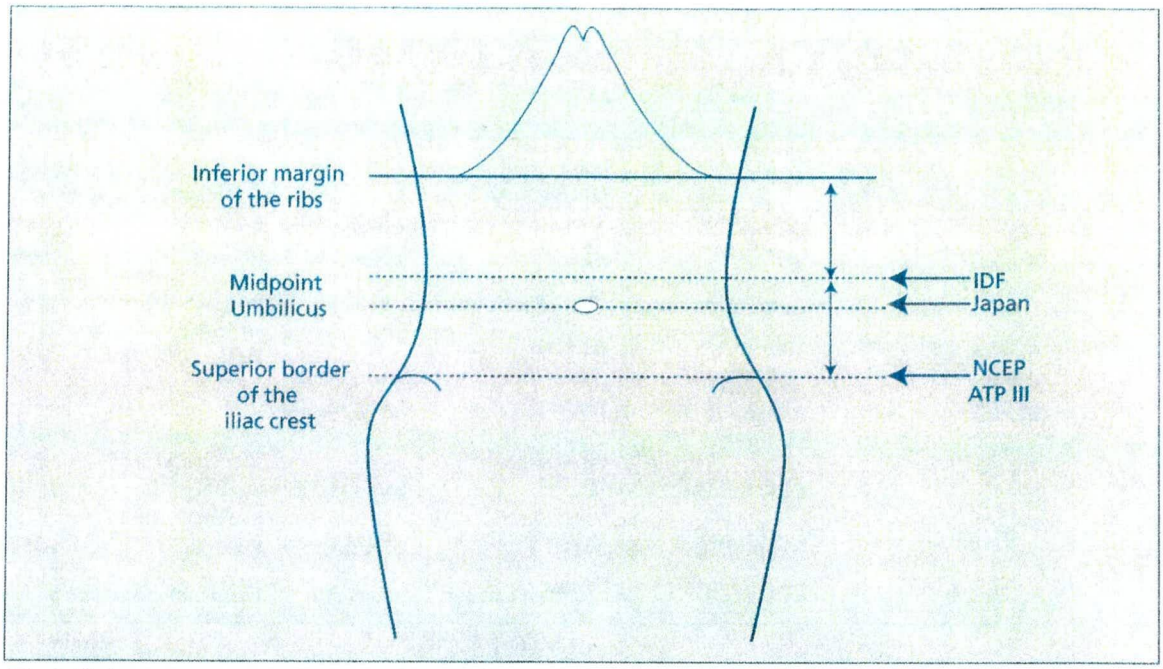

Fig. 1: *Various measurement levels of waist circumference [11, 12, 14].*

this gives rise to confusion regarding the waist circumference cut-off point for diagnosing the metabolic syndrome *(Table II)*. Indeed, waist circumference measurement levels are not uniform *(Fig. 1)*. According to the International Diabetes Federation (IDF) criteria published in 2006 [11], waist circumference should be measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest (the midpoint). In the revised National Cholesterol Education Program–Adult Treatment Panel III (NCEP ATP III) diagnostic criteria published in 2005 [12], however, waist circumference is to be measured in a horizontal plane around the abdomen at the iliac crest level. In addition, the original Japanese criteria published in 2005 clearly noted that waist circumference should be measured in a horizontal plane around the abdomen at the level of the umbilicus except in extremely obese persons with a definite downshift of the umbilicus, in whom waist circumference should be instead measured at the midpoint [14].

No consensus exists on the optimal protocol for measuring waist circumference, and this gives rise to confusion regarding the waist circumference cut-off point for diagnosing the metabolic syndrome

Although there may be some differences that cannot be ignored in absolute waist circumference between the selected measurement sites, few studies have directly compared measures at the sites recommended by these diagnostic criteria. Wang et al. [20] compared the three levels of waist circumference measurements, i.e. immediately below the lowest ribs (LR), the midpoint between the lowest ribs and the iliac crest (MP), and immediately above the iliac crest (IC). The mean values of waist circumferences were LR < MP < IC in females, while no differences were seen among LR, MP and IC in males. Thus there are no differences between the iliac crest and midpoint protocols for men, but there is an absolute difference for women, as conceptually illustrated by the cylinder model for men and the hourglass model for women *(Fig. 2)*.

There are no differences between the iliac crest and midpoint protocols for men, but there is an absolute difference for women

The next question is whether the optimal waist circumference measurement level can be determined. A recent systematic review suggested that the waist circumference measurement protocol selected had no substantial influence on the associations of waist circumference with all-cause mortality, CVD mortality, CVD or dia-

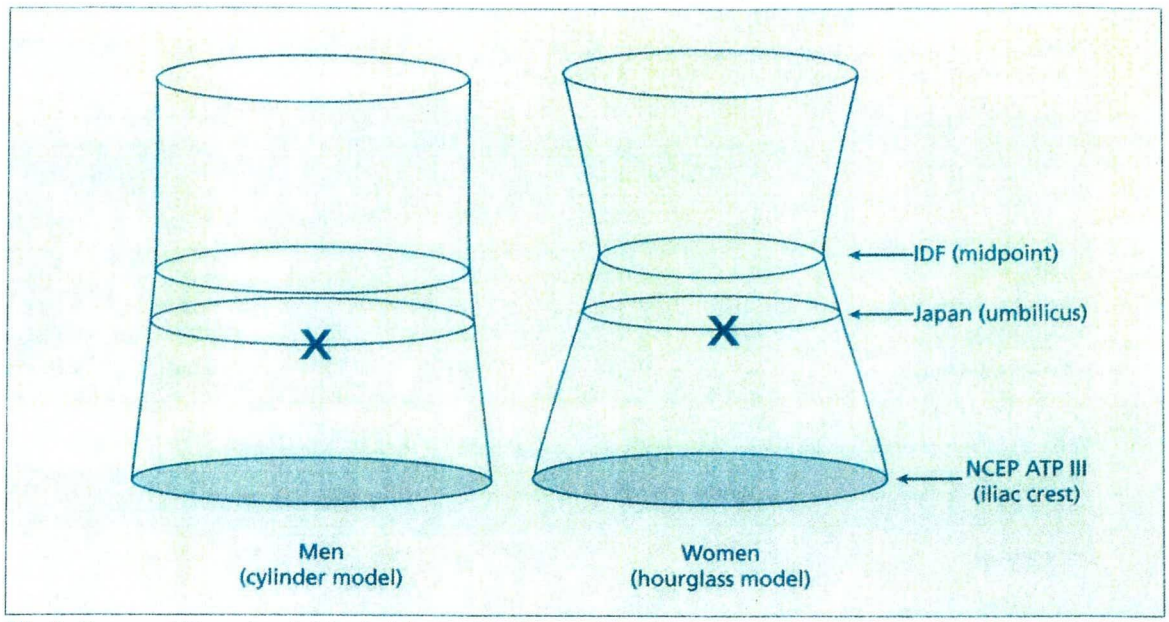

Fig. 2: *Conceptual illustration of abdominal shape and each waist circumference.*

betes [21]. Therefore no single waist circumference measurement is recommended as a protocol for predicting health risks, but awareness of the level of waist circumference measurement is essential.

Can measuring waist circumference provide additional information beyond that given by BMI?

From a clinical perspective, abdominal obesity is closely associated with metabolic abnormalities and should therefore be more informative than general obesity, i.e. BMI. As mentioned above, waist circumference correlates closely with BMI and correlation coefficients between the two are reportedly often at or above $r = 0.80$ [9]. Because of this high correlation, from a statistical perspective BMI and waist circumference are unlikely to yield different answers. Therefore the clinically important question arises of whether or not, for any given BMI, variation in waist circumference affects metabolic markers, CVD events or death.

One meta-analysis was performed using 32 studies out of 432 publications initially identified [22]. The pooled relative risks (95% CI) for incident diabetes were 1.87 (1.67–2.10), 1.87 (1.58–2.20) and 1.88 (1.61–2.19) per standard deviation of BMI, waist circumference and waist-hip ratio, respectively, demonstrating that these three obesity indicators have similar associations with incident diabetes. By contrast, according to another meta-analysis which included studies that used receiver operating characteristics (ROC) curve analysis and published area under the ROC curves (AUC) for obesity indices with type 2 diabetes, hypertension and dyslipidemia, statistical evidence supported the superiority of measures of abdominal obesity (especially waist-height ratio) over BMI for detecting metabolic abnormalities in both men and women *(Table III)* [23].

Redefinition of obesity based on waist-hip ratio instead of BMI is expected to increase the estimate of myocardial infarction attributable to obesity

Using data from the INTERHEART study representing several major ethnic groups, a standardized cross-sectional case-control study of acute myocardial infarction with 27,098 participants in 52 countries (12,461 cases and 14,637 controls) was conducted [24]. Waist circumference showed a significant association with myocardial infarction risk after adjustment for BMI (adjusted odds ratio 1.77; 95% CI 1.59–1.97). Strikingly, waist-hip ratio showed a graded and highly significant association with myocardial infarction risk worldwide. Therefore redefinition of obesity based on waist-hip ratio instead of BMI is expected to increase the estimate of myocardial infarction attributable to

Table III: *Comparison of the discriminatory power (pooled AUC) for metabolic abnormalities with hypertension among BMI, waist circumference, waist-hip ratio and waist-height ratio. Adapted from [23].*

Obesity indices	Metabolic abnormalities					
	Type 2 diabetes		Hypertension		Dyslipidemia	
	Men	Women	Men	Women	Men	Women
BMI	0.672	0.693	0.641	0.693	0.647	0.639
Waist circumference	0.701	0.744	0.669	0.715	0.653	0.663
Waist-hip ratio	0.721	0.748	0.673	0.709	0.639	0.656
Waist-height ratio	0.726	0.756	0.684	0.732	0.665	0.676

Table IV: *Country/ethnic-specific values for waist circumference according to the IDF. Adapted from [11].*

Country/ethnic group	Waist circumference (cm)	
Europids[a]	Men	94
	Women	80
South Asians	Men	90
	Women	80
Chinese	Men	90
	Women	80
Japanese[b]	Men	90
	Women	80
Ethnic South and Central Americans	Use South Asian data	
Sub-Saharan Africans	Use European data	
Eastern Mediterranean and Middle East (Arab) populations	Use European data	

[a]In the United States, the NCEP ATP III values (102 cm in males, 88 cm in females) are likely to continue to be used for clinical purposes.
[b]Different values were originally proposed for Japanese people, but new data support the use of the values shown above.

obesity. Moreover, in a European prospective investigation of 24,508 men and women 45–79 years of age, indices of abdominal obesity were more consistently and strongly predictive of coronary heart disease in comparison with BMI [25]. Hazard ratios (95% CI) of the top vs. the bottom fifth of waist-hip ratio were 1.55 (1.28–1.73) in men and 1.91 (1.44–2.54) in women after adjustment for BMI and other coronary heart disease risk factors. Hazard ratios also increased with waist circumference, but risk estimates for waist circumference without hip circumference adjustment were lower by 10–18%. Overall, measuring waist circumference and hip circumference is anticipated to provide additional information over BMI from both cross-sectional and prospective studies of CVD events. Even among subjects within a normal BMI range, those with an increased waist circumference can have up to double the CVD risk.

A recent study from Europe directly examined the associations of BMI, waist circumference and waist-hip ratio with the risk of death in 359,387 participants from nine countries [3]. After adjustment for BMI, waist circumference and waist-hip ratio were strongly associated with the risk of death. Relative risks (95% CI) among men and women in the highest quintile of waist circumference were 2.05 (1.80–2.33) and 1.78 (1.56–2.04), respectively, and in the highest quintile of waist-hip ratio the relative risks were 1.68 (1.53–1.84) and 1.51 (1.37–1.66), respectively. These data suggested that abdominal obesity as well as general obesity was associated with the risk of death and supported the use of waist circumference or waist-hip ratio in addition to BMI in assessing the risk of death.

How should the appropriate cut-off point for waist circumference be determined?

Although measuring waist circumference must be an independent step in refining the assessment of a patient's risk, proposing cut-off points to define abdominal obesity based on a scientific or clinical rationale poses another inherent diffi-

culty, as the relationship of waist circumference to metabolic abnormalities is quite linear [26]. As an obvious threshold is difficult to establish, or even recognize, the appropriateness of cut-off points depends on particular circumstances. However, we would like to emphasize that these challenges do exist in the decision-making process used to establish cut-off points for BMI as well as waist circumference.

The most common, widespread cut-off points for waist circumference are 102 cm and 94 cm for men, and 88 cm and 80 cm for women [10–12], although these cut-off points are mainly based on epidemiological studies in North Americans and Europeans. The cut-off points adopted in the United States (102 cm for men and 88 cm for women) were employed by the NCEP ATP III to define central obesity and correspond in Europid populations to a BMI of approximately 30 kg/m^2. However, the NCEP ATP III recognized that people with lower waist circumferences can manifest characteristics of the metabolic syndrome and, if so, should be treated similarly to those who have higher waist circumferences plus two other risk factors [27]. In 2006 the IDF produced a new set of criteria for use both epidemiologically and in clinical practice worldwide with the aim of identifying people with the metabolic syndrome. The cut-off points adopted by the IDF (94 cm for Europid males and 80 cm for Europid females) were based on cross-sectional data from individuals of European ethnic origin and were the best values for identifying people with increased adiposity, defined as a BMI of 25 kg/m^2 or a waist-hip ratio of 0.90 for men and 0.85 for women [11]. In addition, the IDF recommended country/ethnicity-specific values for waist circumference *(Table IV)*. In particular, cut-off points for South Asians, Chinese and Japanese should be 90 cm for men and 80 cm for women, which were supported by a recently published retrospective cohort study in the Japanese population to predict CVD events [28].

By contrast, the cut-off points decided by the Examination Committee of Criteria for the Metabolic Syndrome in Japan (85 cm for men and 90 cm for women) were based on the original Japanese cross-sectional data and were the corresponding value for a visceral fat area of 100 cm^2, rather than a specific value of BMI. The inverse relation between men and women in terms of the cut-off point for waist circumference has produced controversies. Visceral fat area, the most direct index of visceral obesity, is clearly associated with the accumulation of metabolic abnormalities in Japanese [13, 14, 19, 29], but whether visceral fat area can predict future CVD events more reliably than other obesity indices is still under study. Moreover gender differences in fat distribution and cardiovascular morbidity cannot be ignored.

It is also important in the implementation of public health policy to balance the sensitivity and specificity for screening of a disease or 'pre-disease' such as the metabolic syndrome. To identify those who are at high risk of future CVD events, cut-off points need to be more sensitive. Previously, we proposed optimal cut-off points of waist circumference (measured at the level of the midpoint) for the diagnosis of metabolic syndrome in the Japanese population (85 cm for men and 78 cm for women), yielding the maximal sensitivity plus specificity, or 83 cm for men and 73 cm for women, yielding at least 80% sensitivity for predicting the presence of multiple risk factors [30]. Consistently, recent reports have revealed that the optimal calculated cut-off visceral fat area is 94–100 cm^2 for men and 60–65 cm^2 for women, yielding the maximal sensitivity and specificity. Waist circumferences (measured at the level of the umbilicus) corresponding to these data were calculated to be 86 cm for men and 77–82 cm for women [19, 29].

Perspective

Increased waist circumference itself is thought to be a simple and useful indicator of elevated risk of metabolic abnormalities, CVD and death. Over the past two decades, waist circumference has become the focus of public attention in association with the metabolic syndrome. However, at the same time, this association has given rise to various forms of confusion. Critics of the metabolic syndrome have highlighted scientific shortcomings, inconsistent criteria and uncertain medical value. Controversies regarding the importance of increased waist circumference have thus persisted [31–33]. The minimal requirement for reducing this confusion is one definition and unified criteria for the metabolic syndrome. It is especially necessary to deliberate as to whether increased abdominal circumference is an essential component of the metabolic syndrome or just one component that is occasionally present [15]. A joint interim statement by several major organizations including the IDF and the American Heart Association was recently published, in which it was agreed that there should not be an obligatory component in the diagnosis of the metabolic syndrome, but that waist measurement would continue to be a

useful preliminary screening tool [34]. We are currently conducting a nationwide survey to optimize the Japanese criteria for the metabolic syndrome by integrating 12 cross-sectional and prospective cohort studies performed in Japan, through which some controversies are expected to be resolved [35].

Cut-off points for waist circumference as an index of abdominal obesity vary in the context of diagnostic criteria for the metabolic syndrome, though BMI cut-off points for general obesity are common regardless of gender, age and ethnicity. Independently of arguments over the metabolic syndrome, it is possible that population-specific cut-off points for waist circumference will be established in the near future, as the levels of abdominal obesity at which the risk of other morbidities begins to rise appears to vary among populations [36].

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