Table 2 Prevalence of retinal microvascular signs by presence of metabolic syndrome components

Metabolic syndrome components		Prevalence (%)	Unadjusted Odds ratio (95% CI)	Adjusted Model 1 Odds ratio (95% CI)	Adjusted Model 2 Odds ratio (95% CI)
Severe focal arteriolar narrowing					
Large waist	Present/absent	8.5/7.7	1.11 (0.70 to 1.75)	1.39 (0.83 to 2.30)	1.21 (0.71 to 2.07)
High triglyceride	Present/absent	8.3/7.8	1.07 (0.67 to 1.72)	1.10 (0.68 to 1.80)	1.07 (0.63 to 1.82)
Low HDL cholesterol	Present/absent	7.5/8.0	0.93 (0.54 to 1.59)	0.88 (0.51 to 1.53)	0.81 (0.45 to 1.46)
High blood pressure	Present/absent	12.3/3.7	3.70 (2.37 to 5.77)	2.78 (1.73 to 4.47)	2.76 (1.71 to 4.45)
High glucose	Present/absent	9.4/7.2	1.33 (0.90 to 1.99)	1.08 (0.71 to 1.64)	0.93 (0.60 to 1.44)
Moderate to severe arteriovenous nicking					
Large waist	Present/absent	19.9/15.5	1.35 (0.98 to 1.87)	1.31 (0.92 to 1.87)	1.16 (0.80 to 1.69)
High triglyceride	Present/absent	19.0/15.8	1.25 (0.89 to 1.73)	1.19 (0.85 to 1.67)	1.28 (0.88 to 1.84)
Low HDL cholesterol	Present/absent	12.7/17.2	0.70 (0.46 to 1.06)	0.71 (0.47 to 1.09)	0.62 (0.39 to 0.97)
High blood pressure	Present/absent	21.9/11.3	2.21 (1.66 to 2.95)	1.89 (1.39 to 2.57)	1.84 (1.35 to 2.52)
High glucose	Present/absent	19.3/15.2	1.33 (1.00 to 1.78)	1.18 (0.87 to 1.59)	1.05 (0.77 to 1.44)
Severe enhanced arteriolar wall reflex					
Large waist	Present/absent	22.3/19.3	1.20 (0.89 to 1.63)	1.30 (0.93 to 1.81)	1.11 (0.78 to 1.58)
High triglyceride	Present/absent	24.7/18.8	1.42 (1.05 to 1.92)	1.46 (1.07 to 2.00)	1.49 (1.06 to 2.09)
Low HDL cholesterol	Present/absent	19.2/20.1	0.95 (0.66 to 1.35)	0.94 (0.65 to 1.35)	0.77 (0.52 to 1.14)
High blood pressure	Present/absent	25.6/14.5	2.03 (1.56 to 2.63)	1.71 (1.29 to 2.26)	1.64 (1.23 to 2.18)
High glucose	Present/absent	23.5/18.3	1.37 (1.05 to 1.79)	1.24 (0.94 to 1.64)	1.12 (0.84 to 1.50)
Retinopathy					
Large waist	Present/absent	14.0/8.1	1.85 (1.26 to 2.70)	1.83 (1.20 to 2.79)	1.61 (1.03 to 2.50)
High triglyceride	Present/absent	14.0/8.1	1.39 (0.92 to 2.08)	1.36 (0.90 to 2.06)	1.13 (0.72 to 1.78)
Low HDL cholesterol	Present/absent	11.6/8.9	1.34 (0.86 to 2.09)	1.42 (0.90 to 2.25)	1.26 (0.77 to 2.06)
High blood pressure	Present/absent	11.4/7.3	1.64 (1.15 to 2.34)	1.19 (0.82 to 1.74)	1.06 (0.72 to 1.57)
High glucose	Present/absent	13.0/7.7	1.80 (1.26 to 2.56)	1.51 (1.05 to 2.18)	1.36 (0.93 to 1.98)

Model 1, adjusted for age, gender and smoking status. Model 2, multiple linear regression model includes model 1 plus all other metabolic syndrome components.
CI, confidence interval.

diameter may reflect increased blood volume.[24] Our findings are in keeping with such previous studies.

Although an increase in number of metabolic syndrome components was associated with higher likelihood of having retinal vessel signs, the metabolic syndrome per se was only associated with retinopathy and wider venular diameter. However, the magnitude of the associations between larger waist circumference and retinopathy (OR 1.61) or wider venular diameter (difference in venular diameter: 3.73 μm) was similar to the magnitude of associations found between the metabolic syndrome and retinopathy (CR: 1.64) or wider venular diameter (difference in venular diameter: 4.69 μm). Thus, components of the metabolic syndrome seem not to have synergistic effects beyond individual effects of each component.

In contrast, in the ARIC study population,[12] the metabolic syndrome, defined using the NCEP-ATPIII criteria, was associated with focal arteriolar narrowing, arteriovenous nicking and generalised arteriolar narrowing.[13] It is unclear why there is a discrepancy in findings between our study and the ARIC study. One possible explanation is the difference between the definition of metabolic syndrome by the IDF and by the NCEP-ATPIII criteria, especially for cut-offs for a larger waist circumference. In this study, we found that the associations between metabolic syndrome and retinal microvascular signs appear mainly driven by the associations with larger waist circumference. This might reflect the main emphasis of the IDF definition of the metabolic syndrome on obesity (larger waist circumference) by definition. Especially for Japanese, the IDF

Table 3 Mean difference in retinal vessel measurements by presence of metabolic syndrome components

Metabolic syndrome components		Mean diameter (μm)	Unadjusted Difference in mean diameter (μm) (95% CI)	Adjusted Model 1 Difference in mean diameter (μm) (95% CI)	Adjusted Model 2 Difference in mean diameter (μm) (95% CI)
CRAE (μm)					
Large waist	Present/absent	179.12/178.66	0.46 (−2.90 to 3.81)	−1.79 (−4.78 to 1.21)	−1.07 (−4.16 to 2.02)
High triglyceride	Present/absent	178.90/178.73	0.17 (−3.42 to 3.75)	−1.85 (−4.82 to 1.12)	−1.37 (−4.61 to 1.87)
Low HDL cholesterol	Present/absent	179.34/178.65	0.69 (−3.13 to 4.50)	−0.49 (−3.60 to 2.63)	0.20 (−3.14 to 3.54)
High blood pressure	Present/absent	175.39/181.85	−6.46 (−9.25 to −3.68)	−3.29 (−5.74 to −0.83)	−3.07 (−5.59 to −0.56)
High glucose	Present/absent	178.59/178.85	−0.26 (−3.26 to 2.75)	−0.67 (−3.20 to 1.85)	0.11 (−2.48 to 2.70)
CRVE (μm)					
Large waist	Present/absent	219.70/213.73	5.97 (2.70 to 9.24)	4.72 (1.80 to 7.64)	3.73 (0.72 to 6.76)
High triglyceride	Present/absent	219.02/214.16	4.86 (1.35 to 8.37)	3.82 (0.90 to 6.73)	2.84 (−0.33 to 6.02)
Low HDL cholesterol	Present/absent	216.18/214.87	1.30 (−2.44 to 5.05)	1.65 (−1.41 to 4.72)	−0.01 (−3.28 to 3.27)
High blood pressure	Present/absent	213.62/216.43	−2.81 (−5.56 to −0.05)	0.93 (−1.50 to 3.37)	−0.08 (−2.56 to 2.39)
High glucose	Present/absent	217.17/214.08	3.08 (0.14 to 6.02)	3.06 (0.59 to 5.53)	2.23 (−0.30 to 4.77)

Data presented are the difference in mean diameter (μm) and 95% confidence interval (95% CI). Model 1, adjusted for age, gender, and smoking status; for CRAE, the model also includes CRVE and vice versa. Model 2, multiple linear regression model includes model 1 plus all other metabolic syndrome components.

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Table 4 Associations of the metabolic syndrome with retinal vascular signs

	Prevalence (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Severe focal arteriolar narrowing			
Metabolic syndrome (present/absent)	8.3/7.8	1.06 (0.60 to 1.87)	1.09 (0.59 to 1.98)
No. of components: each increase in number of components		1.28 (1.10 to 1.49)	1.22 (1.03 to 1.44)
No. of components (4 or more vs 0)	2.7/16.7	2.58 (0.87 to 7.65)	2.17 (0.71 to 6.65)
Moderate to severe arteriovenous nicking			
Metabolic syndrome (present/absent	21.6/15.7	1.48 (1.01 to 2.16)	1.32 (0.88 to 1.98)
No. of components: each increase in number of components		1.22 (1.10 to 1.37)	1.16 (1.03 to 1.31)
No. of components (4 or more vs 0)	10.5/25.0	2.58 (1.38 to 4.83)	2.09 (1.09 to 4.02)
Severe enhanced arteriolar wall reflex			
Metabolic syndrome (present/absent	25.1/19.2	1.41 (0.98 to 2.03)	1.40 (0.95 to 2.05)
No. of components: each increase in number of components		1.25 (1.12 to 1.38)	1.21 (1.08 to 1.35)
No. of components (4 or more vs 0)	13.3/33.3	3.59 (2.08 to 6.21)	3.19 (1.80 to 5.65)
Retinopathy			
Metabolic syndrome (present/absent)	15.0/8.5	1.89 (1.21 to 2.95)	1.64 (1.02 to 2.64)
No. of components: each increase in number of components		1.36 (1.19 to 1.56)	1.27 (1.10 to 1.47)
No. of components (4 or more vs 0)	6.3/50.0	3.02 (1.48 to 6.15)	2.16 (1.03 to 4.53)

*Adjusted for age, gender and smoking status.

Table 5 Associations of the metabolic syndrome with retinal vessel diameters

	Mean diameter (μm)	Unadjusted mean difference (μm) (95% CI)	Adjusted mean difference* (μm) (95% CI)
Central retinal arteriolar equivalents (CRAE)			
Metabolic syndrome (present/absent)	177.27/178.97	−4.35 (−7.78 to −0.92)	−2.95 (−6.51 to 0.61)
No. of components: each increase in number of components		−1.76 (−2.69 to −0.82)	−1.10 (−2.10 to −0.11)
No. of components (4 or more vs 0)	180.25/177.52	−5.92 (−11.26 to −0.58)	−3.57 (−9.09 to 1.94)
Central retinal venular equivalents (CRVE)			
Metabolic syndrome (present/absent)	218.57/214.80	5.73 (2.39 to 9.07)	4.69 (1.20 to 8.19)
No. of components: each increase in number of components		1.86 (0.95 to 2.77)	1.75 (0.78 to 2.73)
No. of components (4 or more vs 0)	213.91/219.24	6.89 (1.68 to 12.11)	6.29 (0.88 to 11.69)

*Adjusted for age, gender, smoking status and CRVE in the model for CRAE, or vice versa.

definition provides different cut-offs for a larger waist circumference (for Japanese men ≥85 cm and women ≥90 cm). Following these criteria, more Japanese men were likely to be diagnosed as having the metabolic syndrome compared with women, as we found in this study (77.7% of persons with the IDF defined metabolic syndrome were men in this study). And this might also underestimate the impact of the metabolic syndrome by including more men who are not so obese. Recently, the IDF have recommended using new cut-offs of larger waist circumference for Japanese (men ≥90 cm and women ≥80 cm) (http://www.idf.org/webdata/docs/MetS_def_update2006.pdf accessed 20 August 2007). Thus, with this new definition of the metabolic syndrome and the NCEP-ATPIII definition of the metabolic syndrome, we repeated the analyses. After all, those findings did not change. Alternatively (this might be specific to Japanese), the study suggested that the IDF definition of the metabolic syndrome appeared to have less predictive power, even for cardiovascular disease among Japanese with diabetes;[28] further studies might be needed to answer this question.

There are several limitations to our study. The response rate was low (53.3% of eligible), and a further proportion of persons (8.9%) did not have photographs, so the study sample could be subject to selection bias. Furthermore, we took only one non-mydriatic fundus photograph from one eye of each subject. Although there is a good correlation between right and left eyes for retinal vessel diameter,[26] this may have led to an underestimation of the prevalence of retinopathy and other microvascular signs.

In summary, in this Japanese sample, individual components of the metabolic syndrome were associated with different retinal microvascular signs. Although the metabolic syndrome per se was found to be associated with the presence of retinopathy lesions and wider venular diameter, these associations were mainly driven by a larger waist circumference and were not beyond the associations of individual metabolic syndrome components. These data suggest that there are no synergistic effects among these components on the presence of retinal microvascular signs.

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Competing interests: None.

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分担研究報告書

生体インピーダンス測定原理による腹部脂肪分布測定に関する研究

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研究要旨
生体インピーダンス測定原理を応用した内臓脂肪および腹部皮下脂肪定量装置を開発し、CTで測定した内臓脂肪面積値との相関を肥満の程度の異なる複数の集団において検討した。人間ドック受診者では、同装置による測定値とCTでの測定値との相関係数は男性0.81、女性0.90であり、病的肥満被験者では相関係数は0.78であった。病的肥満被験者の減量過程で内臓脂肪面積の減少率は中性脂肪およびHDLコレステロールの変化と有意な相関を示した。

A．研究目的
メタボリックシンドロームが国民の健康に与える影響を評価するためには、内臓脂肪蓄積状態を簡便に測定できる、疫学研究に有用性の高い方法が必要である。生体インピーダンス（BIA）法に基づくDual BIA法を用いて内臓脂肪蓄積状態の評価を簡便かつ高精度に測定する装置を開発した。本装置を用いてメタボリックシンドロームと関連する臨床データとの関連性ついて、検討を行った。

B．研究方法
人間ドック受診者男性83名（平均年齢51.1歳、BMI 24.3kg/m²）、女性86名、（平均年齢 54.5歳、平均BMI 23.1kg/m²）についてDual BIAおよび臍レベルCTによる内臓脂肪面積（VF-BIAおよびVF-CT）収縮期血圧（SBP）拡張期血圧（DBP）、HDL-C、TG、LDL-C、空腹時血糖値（FPG）を同日空腹時に測定した。
肥満症治療目的入院中男性26名女性24名（平均年齢54.7歳、平均BMI:29.5kg/m²）について、Dual BIAおよびCTによる腹部内臓脂肪測定を行ない、減量経過が3週間以上観察できた被験者17名については、SBP、DBP、HDL-C、TG、LDL-C、FPGを毎週1回測定した。
（倫理面への配慮）
書面で同意を得た被験者のみで測定を行ない、匿名化したうえで、解析した。

C．研究結果
人間ドック受診者のVF-BIAとVF-CTの相関係数は男性0.81、女性0.90で、有意な相関を示し、VF-BIAとメタボリックシンドローム診断項目との相関では、男性で、SBP、DBP、TG、FPGとVF-BIAの間に有意な相関が認められ、女性ではSBP、DPB、TG、HDL-C、FPGとVF-BIAの間に有意な相関が認められた。肥満症患者では、VF-BIAとVF-CTとの相関係数は0.78であった。患者の減量期間のVF-BIA減少率は、TGとHDL-Cの変化率と有意に相関した。

D．考察
Dual Impedance法による内臓脂肪蓄積測定は、病的な肥満を対象にした測定においても、人間ドックの受診者を対象にした測定においても、CTによる測定と同程度の相関を示し。広い範囲の腹部脂肪分布の定量的評価が可能であった。

E．結論
メタボリックシンドロームの診断において重要と考えられる腹部脂肪分布の定量的評価法としてDual BIA法は有用と考えられ、本装置は疫学的研究にも有用と考えられる。

G．研究発表
1．論文発表
投稿準備中
2．学会発表
小林望美、他．肥満研究 15巻 suppl. P136, 2008.
井田みどり、他．肥満研究 15巻 suppl. Pp136, 2008.

H．知的財産権の出願・登録状況
なし

別紙4

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
平田雅一、森栄作、井田みどり、小鳥真司、細田公則、小林望美、宮脇尚志、志賀利一，大島秀武，中尾一和	非侵襲的内臓脂肪量の定量	内分泌・糖尿病科	27巻	68-73	2008

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分担研究報告

内臓脂肪面積と腹囲からみた metabolic syndrome 頻度および腹囲の測定方法に関する検討

分担研究者　伊藤千賀子　ｸﾞﾗﾝﾄﾞﾀﾜｰ　ﾒﾃﾞｨｶﾙｺｰﾄ　所長

研究要旨：2,433 例を対象に内臓脂肪面積(VFA)、腹囲(WC)等を計測して以下の結果を得た。VFA と WC は高い相関がみられた。Metabolic syndrome の頻度は日本の基準で男性 23.8%,女性 2.4%であった。臍周囲径と WHO の WC は極めて高い相関がみられ、臍周囲径から WHO の WC に換算することは可能である。危険因子から MS screening 精度を臍周囲径は男性 85cm、女性 80cm が cut off として妥当と思われる。

A. 研究目的

疫学的な立場から metabolic syndrome (MS) の頻度を日本の臍周囲径や内臓脂肪面積 100 cm^2 以上を基準にした場合について年齢・性別に比較した。

腹囲の測定部位が施設や国によって異なっており、内臓脂肪面積と臍周囲径、WHO や NCEP の WC との関連を検討した。腹囲(WC)と risk factor 重積との関連から MS screening の至適 WC 基準値を検討した

B. 研究方法

対象は 2005 年 10 月から 2008 年 11 月の間、当所で人間ドック健診を受けた 2,433 例（男性 1,404 例、女性 1,029 例）で、早朝空腹時の血清脂質、血糖値、IRI、アディポネクチン値、血圧値を測定した。WC 径は臍周囲、WHO（肋骨下縁と腸骨上縁の中間点）と NCEP（腸骨上縁）の方法で測定した。低線量 CT で内臓脂肪面積と皮下脂肪面積を測定した。本研究は Grand Tower Medical Court Life Care Clinic 治験審査委員会で承認を受け、対象例は全て文書による同意を得ている

C. 研究結果

1) Metabolic syndrome の頻度

内臓脂肪面積が 100cm^2 を基準にした場合の MS の頻度は男性では＜40 歳が 8.7%、40～49 歳が 21.1%、50～59 歳が 30.6%、60 歳以上が 33.3%、女性ではそれぞれ 0.3%、1.3%、5.5%、8.8%であり、男女とも年齢と共に上昇したが、女性では何れの年代も極めて低率であった。全体では男性 20.9%、女性 2.4%であった。

臍周囲径（男性 85cm 以上、女性 90cm 以上）を用いると、MS の頻度は男性では＜40 歳が 11.7%、40～49 歳が 25.6%、50～59 歳が 30.3%、60 歳以上が 40.4%、女性ではそれぞれ 1.2%、1.0%、4.6%、8.8%であり、全体では男性 23.8%、女性 2.4%であった。男性では内臓脂肪面積よりも臍周囲径を基準にした方が若干高率であった。

2) WC と内臓脂肪面積の関連

男性について内臓脂肪面積(x)と WC(y)との関連をみると臍周囲径では y=0.140x+73.1 の回帰式と r=0.746 (P<0.0001)の相関係数が得られた。WHO の WC で y=0.147x+71.3、r=0.765 (P<0.0001) 、NCEP の WC では y=0.140x+73.1、r=0.746 (P<0.0001) で何れもほぼ同様の高い相関が見られた。

女性についてみると臍周囲径では y=0.224x+68.4、r=0.742 (P<0.0001) 、WHO の WC では y=0.228x+63.0 r=0.754 (P<0.0001) 、NCEP の WC では y=0.189x+76.0、r=0.691 (P<0.0001) と NCEP の WC が若干相関が低くなっていた。

3) 臍周囲径と WHO および NCEP による測定値との関連

臍周囲径(x)として WHO および NCEP の WC(y)との関連を、男性についてみると WHO とは極めて高い相関がみられ、y=0.993x-0.529 の回帰式と r=0.970 (P<0.0001) の相関係数が得られた。同様に NCEP とは y=0.822x+17.71 、r=0.920 (P<0.0001) であった。

女性についてみると WHO とは

y=1.075x-10.22 r=0.949 (P<0.0001) で極めて高い相関がみられたが、NCEP とは y=0.743x+25.35 、r=0.919 (P<0.0001) であった。しかし、女性では WC サイズにもよるが、臍周囲径が WHO に比して 5～6cm 大きくなっていた。

4) 臍周囲径、WHO や NCEP の WC からみた metabolic syndrome screening 精度の比較 (ROC による)

男性についてみると日本の基準では精度が最も良いのは WC が 87cm で Sensitivity・Specificity は 67 %であった。WHO では WC 86cm で、Sensitivity・Specificity は 68 %, NCEP では WC 89.3cm で Sensitivity・Specificity は 66 % であった。

女性についてみると日本の基準では WC 80.7cm が精度が良く、Sensitivity・Specificity は 72 %。WHO では WC 73.8 cm で Sensitivi -ty・Specificity が 70 %、NCEP では WC 87.2 cm で Sensitivity・Specificity は 72 % であった。

D.考察

内臓脂肪面積 100cm^2 を基準にした場合の MS の頻度は男女とも年齢と共に上昇したが、女性では何れの年代も極めて低率で男性の 1/10 程度であった。日本の WC 基準で診断すると男性23.8%、女性2.4%であった。男性では内臓脂肪面積よりも臍周囲径を基準にした方が若干高率であったが、何れも女性が著しく低率になっているのは男性と同様の内臓脂肪面積 100 cm^2 を基準としていることにある。男女差のない基準が適切か否かは十分検討する必要がある。そこで WC 基準に耐糖能異常、脂質異常、血圧異常の 2 項目以上のあるものを MS として screening 精度を比較すると、男性は臍周囲径が 87cm、女性は 80 cm となる。この値は WHO WC では 86 cm および 73.8 cm となる。

WC 測定で広く行われている方法が 3 種類あるが、それぞれの方法による差は男性では大きくないが、女性では差が大きい。WC は NCEP 日本、WHO の順に小さくなっている。国際的には WHO の WC 測定方法が広く用いられており、内臓脂肪面積との関連からどの測定方法が適切かを検討したが、男性についてみると相関係数は 0.746～0.765 と殆ど差がみられない。一方、女性では NCEP が 0.691 と若干相関係数が低くなっており、臍周囲径や WHO の WC が良いと思われる。その理由として女性では所謂ヒップに近い位置で WC を測定する NCEP は個人によって皮下脂肪量が異なるために差が拡大すると思われる。しかし、日本では臍周囲径が用いられているので、国際基準と比較するときに問題が出る。そこで日本の基準を中心に WHO と NCEP の WC との相関を検討した。男性では WHO の WC が日本の基準とは若干低値を示しているものの臍周囲径が 85 cm のところで 1cm 程度にすぎない。一方女性では WHO との相関は r=0.949 と高いものの WHO の WC の WC に比して 5～6 cm 大きいなど問題がある。しかし、今まで述べてきたように日本の臍周囲径は男女とも WHO の WC と高い相関があるので、臍周囲径は WHO の WC に換算可能である。

E. 結論

内臓脂肪面積と WC は高い相関がみられる。また、臍周囲径と WHO の WC は極めて高い相関がみられ、臍周囲径から WHO の WC に換算することは可能である。MS の危険因子から MS screening 精度を ROC でみると臍周囲径は男性 85cm、女性 80cm が cut off として妥当と思われる。

別紙4

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
伊藤千賀子　藤川るみ	糖尿病とアディポネクチン	門脇孝編集	アディポネクチンとその受容体	フジメディカル出版	大阪	2008	242-249
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雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
伊藤　千賀子 藤川　るみ	メタボリックシンドロームにおける「糖尿病」発症のリスク	診断と治療	96巻・第2号	41-46	2008
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「保健指導への活用を前提としたメタボリックシンドロームの診断・管理のエビデンス創出のための縦断・横断研究」分担報告書

茨城県筑西市協和地区における疫学研究
所属：大阪大学大学院医学系研究科公衆衛生学
研究者：磯　博康

研究要旨：茨城県筑西市協和地区では、昭和56年より脳卒中を中心とした循環器疾患病予防対策事業が開始され、現在まで継続している。本研究では、地域住民における心血管イベント並びに、ウエスト周囲径以外のメタボリックシンドロームリスク２つ以上集積とウエスト周囲径のROC曲線から、最適なウエスト周囲径を解析することを目的とした。本検討では、メタボリックシンドロームリスクファクターのカウントにおいて、脂質異常については空腹時・非空腹時ともにTG≧150mg/dL and/or HDL-コレステロール＜40mg/dl、高血糖については空腹時血糖≧110mg/dL、非空腹時血糖≧140mg/dL、血圧高値はSBP≧130mmHg and/or DBP≧85mmHgとし、それぞれ薬物療法の有無は考慮しなかった。その結果、虚血性心疾患の発症をアウトカムにした場合とウエスト周囲径高値以外のリスクファクター2つ以上の集積をアウトカムとした場合、いずれの場合もウエスト周囲径の最適のカットオフ値は、男性84cm、女性82-83cmであった。

A．研究目的

茨城県筑西市協和地区（旧・真壁郡協和町）では、1981 年より健診による高血圧の把握と高血圧管理、食事改善指導を中心とする脳卒中の一次・二次予防対策を、町、医師会、保健所、健診機関、住民組織および大阪府立成人病センター（現・大阪府立健康科学センター）、筑波大学、大阪大学等の研究機関の組織的な協力の下に進めてきた。

平成 17 年にメタボリックシンドロームに関する我が国の診断基準が策定され、平成 20 年度よりメタボリックシンドロームの概念に着目した特定健診・特定保健指導が開始された。メタボリックシンドロームを診断する意義は心血管疾患の高リスク者をスクリーニングすることにあり、メタボリックシンドロームを診断することの臨床的有用性については一定の根拠がある。我が国においては、メタボリックシンドロームの診断基準におけるウエスト周囲径のカットオフ値を、日本内科学会など 8 学会が共同で科学的根拠に基づいて男性で 85cm、女性で 90cm と定めている。しかしながらこの基準が、主に企業勤務者や外来患者におけるデータに基づいて設定されており、一般住民の成績などに基づいたメタボリックシンドロームの診断基準の再検討が必要である。そこで、本研究では、ウエスト周囲径以外のメタボリックシンドロームのリスクファクターである高血糖、高トリグリセライド・低 HDL-コレステロール、血圧高値のうち２つ以上有している者、および心血管イベントとウエスト周囲径の ROC 曲線から、日本人に最適なウエスト周囲径のカットオフ値を ROC 解析により算出することを目的とした。

B. 研究対象と方法

対象は茨城農村の筑西市K地区(人口1.7万人)の住民で、1990～1993年の循環器検診でウエスト周囲径(臍レベル)を測定し、虚血性心疾患と脳卒中の既往がある者を除いた2,017(男769、女1,248)人である。1990～1993年から12.6年間(2005年12月末まで)追跡した。また、1990～1993年の検診で腹囲を測定した40～74歳の男女2,571(男965、女1,606)人について心血管疾患のリスクファクターであるウエスト周囲径高値、高血糖(空腹時≧110 mg／dl、非空腹時≧140 mg／dl)、高トリグリセライド(空腹、非空腹時いずれも150 mg／dl)、低HDL-コレステロール(＜40 mg／dl)、血圧高値(収縮期≧130mmHg または拡張期≧85mmHg)のうち2つ以上保持している者、および心血管イベントとウエスト周囲径のROC曲線から、日本人に最適なウエスト周囲径のカットオフ値をROC解析により算出した。リスクファクターのカウントにおいて、なお、解析にあたって糖尿病・高血圧・脂質異常に対する薬物療法の有無は考慮しなかった。

C．研究結果

(1) メタボリックシンドロームリスクとウエスト周囲径とのROC解析

1990-93年におけるウエスト周囲径の平均値は男性で84cm、女性で81cmであり、男性でウエスト周囲径高値以外のメタボリックシンドロームのリスクファクター2つ以上を有する者は55%、女性では35%にみられた。アウトカムをウエスト周囲径高値以外のリスクファクター2つ以上の集積とした場合、ウエスト周囲径の最適のカットオフ値は、男性84cm、女性82cmであった。

(2) 虚血性心疾患・脳卒中発症とウエスト周囲径とのROC解析

平均12.6年間の追跡調査の結果、虚血性心疾患(虚血性心疾患＋突然死)29人、全脳卒中125人、全循環器疾患(虚血性心疾患＋脳卒中)146人の発症が認められた。虚血性心疾患(初発の急性心筋梗塞＋急性死)の発症とした場合、最適のカットオフ値は男性84cm、女性83cmであった。この結果は、急性心筋梗塞単独で解析した場合もほぼ同様であった。

また、脳卒中の発症に関しても解析を行ったが、ROCカーブはほぼ直線状でカットオフ値の算出は困難であった。

D. 考察

ウエスト周囲径高値以外のメタボリックシンドロームリスクファクター2つ以上の集積をアウトカムとした場合、ウエスト周囲径の最適のカットオフ値は、男性84cm、女性82cmと算出された。

虚血性心疾患(初発の急性心筋梗塞＋急性死)の発症とした場合、最適のカットオフ値は男性84cm、女性83cmと算出された。但し、ROCカーブのふくらみは少なく、特に女性ではその傾向は顕著でウエスト周囲径のみによる虚血性心疾患発症リスクの予測は男性に比べて困難と考えられた。また、脳卒中の発症に関するROCカーブはほぼ直線状でカットオフ値の算出は困難であった。今後、脳卒中のなかで、メタボリックシンドロームとの関連性が高い脳梗塞の発症を抽出して解析を行う予定である。

メタボリックシンドロームのリスクファクターの集積と虚血性心疾患の発症予測において、いずれもウエスト周囲径の最適のカットオフ値は、男性では現行の基準の85cmに近かった。女性では現行の基準の90cmよりも低い値であった。これらの値は他のコホート集団を合わせたメタ解析の結果とほぼ同様であった。

E. 結論

茨城県農村の一般住民において、メタボリックシンドロームのリスクファクターの集積と心血管イベント発症の予測のためのウエスト周囲径の最適のカットオフ値を算出することができ、研究班全体のメタ解析と同様の結果が得られた。

F．データ管理・更新（倫理面への配慮）

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

G. 論文発表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Chei CL, Yamagishi K, Tanigawa T, Kitamura A, Imano H, Kiyama M, Sato S, Iso H.	Metabolic syndrome and the risk of ischemic heart disease and stroke among middle-aged Japanese.	Hypertens Res	31	1887-94	2008

H. 知的財産権の出願・登録状況

1．特許取得　なし。
2．実用新案登録　なし。
3．その他　なし

Original Article

Metabolic Syndrome and the Risk of Ischemic Heart Disease and Stroke among Middle-Aged Japanese

Choy-Lye CHEI[1], Kazumasa YAMAGISHI[1], Takeshi TANIGAWA[1,2], Akihiko KITAMURA[3], Hironori IMANO[3], Masahiko KIYAMA[3], Shinichi SATO[4], and Hiroyasu ISO[5]

Limited information is available regarding risk of cardiovascular disease and trends for the metabolic syndrome in Asia. We examined the impact of the metabolic syndrome and its components on risk of cardiovascular disease among middle-aged Japanese according to four criteria. We followed 2,613 subjects from a rural Japanese community who participated in cardiovascular health examinations between 1990 and 1993. After 27,477 person-years of follow-up through 2003, there were 42 incidents of ischemic heart disease, 73 total strokes (54 ischemic and 18 hemorrhagic), and 115 total cases of cardiovascular disease. The metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII), American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), International Diabetes Federation (IDF), and Japanese criteria. The multivariable hazard ratios (95%CI) associated with the metabolic syndrome based on NCEP-ATPIII criteria were 2.1 (1.1–4.0) for ischemic heart disease, 1.7 (1.0–2.7) for total stroke, 2.0 (1.2–3.5) for ischemic stroke, 1.1 (0.4–2.8) for hemorrhagic stroke, 2.0 (1.3–3.1) for ischemic cardiovascular disease, and 1.7 (1.2–2.5) for total cardiovascular disease. The population-attributable fractions of the metabolic syndrome based on NCEP-ATPIII criteria were 26–27% for ischemic heart disease and ischemic stroke and 20% for total cardiovascular disease. The metabolic syndrome based on AHA/NHLBI, IDF and Japanese criteria had weaker associations with risk of cardiovascular disease, and the association with risk of ischemic heart disease was not statistically significant. The metabolic syndrome based on NCEP-ATP III criteria predicted risks of ischemic heart disease, ischemic stroke and total cardiovascular disease, whereas that based on three other criteria predicted them less effectively. (*Hypertens Res* 2008; 31: 1887–1894)

Key Words: **metabolic syndrome, ischemic heart disease, stroke, follow-up study, Japanese**

Introduction

The metabolic syndrome is associated with increased risks of both type 2 diabetes and cardiovascular disease (*1–8*). The criteria of metabolic syndrome defined by the Third Report of the National Cholesterol Educational Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cho-

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lesterol in Adults (Adult Treatment Panel III; NCEP-ATP III) (*9*) have been widely accepted. Recently, the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) provided new guidelines for the diagnosis of the metabolic syndrome (*10*). The definition adopted by both NCEP-ATP III and AHA/NHLBI was based on five commonly measured clinical criteria whereas the criteria proposed by the International Diabetes Federation (IDF) (*11*) and the new Japanese definition (*12*) were based on a precondition for the presence of abdominal obesity.

A recent prospective study in Japan has shown that the metabolic syndrome and its components, defined by modified NCEP-ATP III criteria, were associated with an increased risk of ischemic cardiovascular disease (*13*). Another Japanese study of diabetic patients showed an increased risk of cardiovascular disease associated with the metabolic syndrome based on NCEP-ATPIII but not IDF criteria (*14*, *15*). To our knowledge, there are no studies that have examined whether the criteria of the metabolic syndrome can accurately predict the risk of incident cardiovascular disease among the general Japanese population. Limited prospective studies have been undertaken in Asian populations (*13*, *16–18*).

In the present study, we examined the association between the metabolic syndrome and risks of ischemic heart disease and stroke in Japanese men and women according to four different criteria of the metabolic syndrome.

Methods

Study Populations

The subjects were residents of Kyowa, a rural farming community in the Ibaraki Prefecture, mid-eastern Japan (census population in 1990 of ages 40–69: n=6,520), where annual cardiovascular health examinations have been conducted since 1981 (*19*). Residents aged ≥40 years old were invited annually by the municipal government to be assessed for several cardiovascular risk factors as a part of community stroke prevention program. Overall participation rates were approximately 60–70% from 1990 to 2003.

In the present study, we included a total of 2,660 subjects (998 men and 1,662 women) aged 40–69 who participated in cardiovascular health examinations between 1990 and 1993 that included waist circumference measurements. After exclusion of persons with a history of ischemic heart disease (n=15) or stroke (n=32) at baseline, a total of 2,613 subjects were followed-up through 2003 to examine the association between the metabolic syndrome and risks of ischemic heart disease and stroke. There were 17 individuals (0.7%) who moved out of the community during the follow-up period, according to municipal emigration office records. Forty-three (1.6%) people died during the follow-up. These cases were censored at the date of emigration or death, respectively. The median follow-up period was 10.5 years.

The study was approved by the Medical Ethics Committee of the University of Tsukuba.

Endpoint Determination

The follow-up was conducted by annual cardiovascular risk surveys in order to obtain information about ischemic heart disease and stroke incidents from the participants. For non-participants, these endpoints were ascertained by mailed questionnaire and by the use of death certificates. From death certificates, cases with stroke as an underlying cause of death ("International Classification of Diseases," 9th ed., pp. 410–414, 428, 429 and 430–438) were selected. We also used national insurance claims, ambulance records, reports by local physicians and public health nurses for case ascertainment. To confirm the diagnosis, all living patients were telephoned or visited to obtain their medical history and records. For deaths, we obtained information from families and reviewed medical records.

The criteria for ischemic heart disease were modified from those of the WHO Expert Committee (*20*). Definite myocardial infarctions were indicated by typical chest pain, lasting for ≥30 min with the appearance of abnormal and persistent Q or QS waves on the electrocardiogram, changes in cardiac enzyme activity, or both. Probable myocardial infarctions were indicated by typical chest pain for which the findings of electrocardiogram or enzyme activity were not available. Angina pectoris was defined as repeated episodes of chest pain during effort, especially when walking, usually disappearing rapidly after the cessation of effort or use of sublingual nitroglycerin. Sudden cardiac death was defined as death within 1 h of symptom onset, a witnessed cardiac arrest, or abrupt collapse not preceded by more than 1 h of symptoms. Ischemic heart disease included definite or probable myocardial infarction, angina pectoris, and sudden cardiac death.

Stroke was defined as a focal neurological disorder with rapid onset that persisted at least 24 h or until death. The determination of incident stroke was based on clinical criteria (*21*). Stroke events were further subclassified as subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic stroke (non-embolic or embolic), primarily based on CT and/or MRI (*22*). Stroke cases without the imaging studies were subclassified according the clinical criteria (*21*) as subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic stroke, or stroke of undetermined type. The proportion of stroke cases confirmed by CT or MRI was 92% for total stroke, 100% for subarachnoid hemorrhage, 86% for intraparenchymal hemorrhage, and 94% for ischemic stroke.

A panel of three or four physician-epidemiologists made the final diagnosis of ischemic heart disease and stroke, blinded to the data of risk factor surveys.

Measurements

Height in stocking feet and weight in light clothing were measured. Body mass index was calculated as weight (kg) divided

by square of height (m^2). Well-trained observers measured the waist circumference of the subjects at the level of the umbilicus to the nearest 1 cm while subjects were standing and breathing normally. Blood pressure was measured by well-trained technicians using mercury sphygmomanometers on the right arm of seated participants after at least 5 min of rest. Blood was drawn from seated participants into a plain, siliconized glass tube, and serum was separated. Serum glucose was measured by the hexokinase method. Fasting was not required. The distribution of time since the last meal was <2 h (40%), 2 h (35%), 3–7 h (19%) and ≥8 h (6%).

An interview was conducted to ascertain daily alcohol intake, number of cigarettes smoked per day, use of medication for diabetes mellitus and hypertension, and past history of stroke and ischemic heart disease. Persons who smoked at least 1 cigarette/d were defined as current smokers, and those who had not smoked for ≥3 months were defined as former smokers.

Serum total cholesterol and high-density lipoprotein (HDL)-cholesterol after heparin-manganese precipitation were measured by the Liebermann-Burchard direct method using the Autoanalyzer II (Technicon, Tarrytown, USA) at the Osaka Medical Center for Health Science and Promotion. The laboratory has been standardized under the CDC-NHLBI Lipid Standardization Program, Centers for Disease Control and Prevention, Atlanta, and successfully met the criteria for precision and accuracy of triglyceride and total and HDL-cholesterol measurements as an international member of the US National Cholesterol Reference Method Laboratory Network (CRMLN) (*23*).

Definition of the Metabolic Syndrome

According to the modified NCEP-ATPIII definition (*9*), subjects who had three or more of the following criteria were identified as having the metabolic syndrome: 1) triglycerides ≥1.69 mmol/L (≥150 mg/dL), 2) HDL cholesterol <1.03 mmol/L (<40 mg/dL) for men and <1.29 mmol/L (<50 mg/dL) for women, 3) blood pressure ≥130/85 mmHg, or use of antihypertensives, 4) fasting glucose ≥6.11 mmol/L (≥110 mg/dL) or non-fasting glucose ≥7.77 mmol/L (≥140 mg/dL), or on treatment, or 5) abdominal obesity—modified waist circumference cutoffs (≥90 cm for men and ≥80 cm for women) were used (*24*) instead of the waist circumference cutoffs (>102 cm for men and >88 cm for women) proposed in the existing NCEP-ATPIII criteria.

According to the AHA/NHLBI definition (*10*), the metabolic syndrome was defined as the presence of three or more of the following: 1) elevated triglyceride level ≥1.69 mmol/L (≥150 mg/dL) or on treatment, 2) reduced HDL-cholesterol <1.03 mmol/L (<40 mg/dL) for men and <1.29 mmol/L (<50 mg/dL) for women, or on treatment, 3) elevated blood pressure ≥130/85 mmHg, or use of antihypertensive medication, 4) elevated fasting glucose ≥5.56 mmol/L (≥100 mg/dL) or non-fasting glucose ≥7.22 mmol/L (≥130 mg/dL), or on treatment, or 5) abdominal obesity, waist circumference ≥90 cm for men and ≥80 cm for women.

According to the new IDF definition (*11*) (the IDF consensus worldwide definition of the metabolic syndrome [article online]: available from http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf/), Japanese people were defined as having the metabolic syndrome if the subjects had abdominal obesity (waist circumference cutoffs ≥90 cm for men and ≥80 cm for women) plus two or more of the following risk factors: 1) elevated triglyceride level ≥1.69 mmol/L (≥150 mg/dL) or on treatment, 2) low HDL cholesterol <1.03 mmol/L (<40 mg/dL) for men and <1.29 mmol/L (<50 mg/dL) for women or on treatment, 3) high blood pressure ≥130/85 mmHg or use of antihypertensives, or 4) high fasting glucose ≥5.56 mmol/L (≥100 mg/dL) or non-fasting glucose ≥7.22 mmol/L (≥130 mg/dL) or on treatment.

According to the Japanese definition (*12*), the metabolic syndrome was identified if subjects had abdominal obesity (waist circumference ≥85 cm for men and ≥90 cm for women), in addition to two or more of the following criteria: 1) triglyceride level ≥1.69 mmol/L (≥150 mg/dL) or on treatment, 2) HDL cholesterol <1.03 mmol/L (<40 mg/dL) or on treatment, 3) blood pressure ≥130/85 mmHg or use of antihypertensive medication, or 4) fasting glucose ≥6.11 mmol/L (≥110 mg/dL) or non-fasting glucose ≥7.77 mmol/L (≥140 mg/dL) or on treatment.

Statistical Analysis

Age-adjusted mean values or the prevalence of metabolic syndrome, its components and other cardiovascular risk factors were compared between incident cases of ischemic heart disease and stroke and non-cases using the analysis of covariance or χ^2 tests.

Person-years were calculated as the sum of individual follow-up time until the occurrence of incident ischemic heart disease, stroke, death, emigration, or until the end of 2003. The hazard ratios of ischemic heart disease and stroke and the respective 95% confidence intervals (CI) were calculated with reference to the risk of individuals without the metabolic syndrome using the Cox proportional hazards model. The results were adjusted for age (years), and other potential confounding variables such as smoking status (never, former, and current smokers), alcohol intake category (never, former, and current <46, 46–68 and ≥69 g/d ethanol), time since last meal (<2, 2, 3–7, and ≥8 h), and total serum cholesterol levels (mmol/L). The proportional hazards assumption was tested using an interaction terms of time by metabolic syndrome and was not violated for each analysis. We also calculated the population attributable fraction (PAF) to examine the contribution of the metabolic syndrome to risk of cardiovascular disease using multivariable hazard ratios of statistical significance and the proportions of cases in each categories (*25*). PAF was estimated as Pd × (HR − 1)/HR, where Pd is the proportion of cases falling into the metabolic syndrome category

Table 1. Sex-Specific Baseline Characteristics of Cardiovascular Disease Cases and Non-Cases among Japanese Aged 40–69 Years

	Ischemic heart disease	Total stroke	Ischemic stroke	Hemorrhagic stroke	Ischemic cardiovascular disease	Total cardiovascular disease	Non-cases
Men							
n	28	31	26	5	52	60	908
Age, years	59.5±2*	60.2±2†	60.0±2*	61.6±4	59.6±1*	59.9±1‡	55.6±0.3
Systolic blood pressure, mmHg	138±3	146±3‡	147±3‡	139±7	141±2‡	141±2‡	134±0.5
Diastolic blood pressure, mmHg	82±2	84±2*	84±2	85±5	83±2*	83±1	80±0.3
Use of antihypertensive medication, %	32*	18	19	14	25	23	17
High blood pressure, %	47†	34	34	34	39*	36*	24
Body mass index, kg/m^2	23.5±0.5	23.6±0.5	23.8±0.5	22.6±1.3	23.7±0.4	23.5±0.4	23.7±0.1
Waist circumference, cm	82.9±1.5	84.0±1.4	85.1±1.6	78.3±3.5	84.4±1.1	83.5±1.0	84.0±0.3
Waist circumference (≥85 cm), %	42	50	53	38	49	46	49
Waist circumference (≥90 cm), %	24	41*	41	38	34	32	24
Serum total cholesterol, mmol/L	5.13±0.16	4.87±0.16	4.97±0.17	4.35±0.39	5.06±0.12	5.00±0.11	4.96±0.03
Hypercholesterolemia, %	15	14	17	2	16	16	20
Serum triglycerides, mmol/L	2.13±0.21	1.82±0.20	1.96±0.21	1.13±0.49	2.07±0.15	1.95±0.14	1.79±0.04
Hypertriglyceridemia, %	49	40	47	1	50	43	42
Serum HDL-cholesterol, mmol/L	1.25±0.07	1.36±0.06	1.33±0.07	1.49±0.16	1.29±0.05	1.33±0.05	1.33±0.01
Low HDL-cholesterol, %	10	16	19	1	15	13	19
Serum glucose, mmol/L	8.16±0.45*	8.90±0.41‡	9.09±0.44‡	7.79±0.99	8.61±0.33‡	8.46±0.31‡	7.02±0.08
Glucose abnormality, % (≥6.11mmol/L)	6	28‡	30‡	19	18‡	17†	7
Current smokers, %	59	66	67	62	61	61	53
Ethanol intake, g/d	28.0±4.6	25.4±4.3	26.9±4.7	17.1±10.8	27.8±3.4	27.1±3.1	22.9±0.8
Women							
n	14	42	28	13	40	55	1,590
Age, years	65.6±2‡	62.9±1‡	63.0±2‡	62.2±2†	63.9±1‡	63.6±1‡	54.8±0.2
Systolic blood pressure, mmHg	130±4	136±3*	135±3	139±4*	133±3	134±2	130±0.4
Diastolic blood pressure, mmHg	75±3	79±2	77±2	83±3*	77±2	78±1	77±0.3
Use of antihypertensive medication, %	21	30	35	21	31*	28	19
High blood pressure, %	35	34	39	28	38*	35	24
Body mass index, kg/m^2	24.4±0.8	25.5±0.5‡	25.7±0.6†	25.4±0.9	25.3±0.5†	25.3±0.4‡	23.8±0.1
Waist circumference, cm	84.4±2.5	84.1±1.4*	84.7±1.7*	82.9±2.6	84.6±1.5*	84.0±1.3*	81.0±0.2
Waist circumference (≥90 cm), %	41*	27	29	25	33*	29*	18
Waist circumference (≥80 cm), %	64	56	34	36	65	59	55
Serum total cholesterol, mmol/L	5.41±0.25	5.07±0.15	5.02±0.18	5.15±0.26	5.18±0.15	5.19±0.13	5.26±0.02
Hypercholesterolemia, %	34	22	22	24	27	27	31
Serum triglycerides, mmol/L	1.52±0.23	1.47±0.13	1.49±0.16	1.46±0.24	1.49±0.14	1.48±0.12	1.47±0.02
Hypertriglyceridemia, %	40	43*	46*	40	42	41*	29
Serum HDL-cholesterol, mmol/L	1.32±0.09	1.40±0.05	1.40±0.06	1.40±0.09	1.38±0.05	1.39±0.05	1.46±0.01
Low HDL-cholesterol, %	61*	41	44	36	50*	45*	32
Serum glucose, mmol/L	7.11±0.50	6.96±0.29	7.12±0.36	6.42±0.52	6.90±0.30	6.83±0.26	6.42±0.05
Glucose abnormality, % (≥6.11 mmol/L)	12	15‡	16†	7	13†	13‡	4
Current smokers, %	8	8	8	9	9	8	5
Ethanol intake, g/d	0.4±1.4	2.2±0.8	2.5±1.0	1.8±1.5	1.9±0.9	1.8±0.7	1.1±0.1

Values are mean±SEM, or proportions, adjusted for age. Serum triglycerides and glucose values were also adjusted for time since last meal. Test for significance from non-cases: *$p<0.05$, †$p<0.01$, ‡$p<0.001$. HDL, high-density lipoprotein.

Table 2. Hazard Ratios (HR), Population Attributable Fraction (PAF), and 95% Confidence Interval (CI) of Cardiovascular Disease Associated with the Metabolic Syndrome in Japanese Aged 40–69 Years

Metabolic syndrome	NCEP-ATP III criteria		AHA/NHLBI criteria		IDF criteria		Japanese criteria	
	No	Yes	No	Yes	No	Yes	No	Yes
No. at risk	1,808	805	1,750	863	1,919	694	2,174	439
Person-years	18,999	8,478	18,373	9,104	20,142	7,336	22,838	4,639
Ischemic heart disease								
No. of cases	20	22	20	22	25	17	30	12
Age-adjusted HR (95% CI)	1.0	1.9 (1.1–3.6)*	1.0	1.7 (0.9–3.2)	1.0	1.4 (0.8–2.7)	1.0	1.6 (0.8–3.1)
Multivariable HR (95% CI)	1.0	2.1 (1.1–4.0)*	1.0	1.9 (1.0–3.5)	1.0	1.8 (0.9–3.4)	1.0	1.1 (0.5–2.2)
PAF (95% CI), %		27 (−0.5–48)		—		—		—
Total stroke								
No. of cases	38	35	37	36	43	30	50	23
Age-adjusted HR (95% CI)	1.0	1.6 (1.0–2.6)*	1.0	1.5 (1.0–2.4)	1.0	1.5 (0.9–2.4)	1.0	1.9 (1.1–3.1)*
Multivariable HR (95% CI)	1.0	1.7 (1.0–2.7)*	1.0	1.6 (1.0–2.5)	1.0	1.6 (1.0–2.7)	1.0	1.8 (1.1–3.1)*
PAF (95% CI), %		19 (−1–35)		—		—		14.0
Ischemic stroke								
No. of cases	26	28	26	28	29	25	35	19
Age-adjusted HR (95% CI)	1.0	1.9 (1.1–3.3)*	1.0	1.7 (1.0–2.9)	1.0	1.9 (1.1–3.2)*	1.0	2.2 (1.3–3.9)†
Multivariable HR (95% CI)	1.0	2.0 (1.2–3.5)*	1.0	1.8 (1.0–3.1)*	1.0	2.2 (1.2–3.9)†	1.0	2.0 (1.1–3.6)*
PAF (95% CI), %		26 (2–44)		23 (−3–42)		25 (4–42)		18 (−0.6–33)
Hemorrhagic stroke								
No. of cases	11	7	10	8	13	5	14	4
Age-adjusted HR (95% CI)	1.0	1.1 (0.4–2.9)	1.0	1.2 (0.5–3.2)	1.0	0.8 (0.3–2.3)	1.0	1.2 (0.4–3.5)
Multivariable HR (95% CI)	1.0	1.1 (0.4–2.8)	1.0	1.2 (0.5–3.2)	1.0	0.7 (0.3–2.2)	1.0	1.4 (0.5–4.6)
PAF (95% CI), %		—		—		—		—
Ischemic cardiovascular disease								
No. of cases	44	48	44	48	51	41	62	30
Age-adjusted HR (95% CI)	1.0	1.9 (1.3–2.9)†	1.0	1.7 (1.1–2.6)*	1.0	1.7 (1.1–2.6)*	1.0	2.0 (1.3–3.0)†
Multivariable HR (95% CI)	1.0	2.0 (1.3–3.1)†	1.0	1.8 (1.2–2.7)†	1.0	2.0 (1.3–3.2)†	1.0	1.5 (1.0–2.4)
PAF (95% CI), %		26 (8–41)		23 (4–38)		23 (7–36)		—
Total cardiovascular disease								
No. of cases	59	56	58	57	68	47	81	34
Age-adjusted HR (95% CI)	1.0	1.7 (1.2–2.4)†	1.0	1.5 (1.1–2.2)*	1.0	1.5 (1.0–2.1)*	1.0	1.7 (1.1–2.5)*
Multivariable HR (95% CI)	1.0	1.7 (1.2–2.5)†	1.0	1.6 (1.1–2.3)*	1.0	1.6 (1.1–2.4)*	1.0	1.4 (0.9–2.1)
PAF (95% CI), %		20 (4–33)		18 (1–31)		16 (2–28)		—

*$p<0.05$, †$p<0.01$. Multivariable HR adjusted for age, time since last meal, cigarette smoking, alcohol intake and serum total cholesterol.

and HR is hazard ratio in that category. The Greenland formula was used to calculate 95% CI (*26*).

SAS statistical software (version 9.13; SAS Institute Inc., Cary, USA) was used for the analyses, and $p<0.05$ was regarded as statistically significant

Results

After 27,477 person-years of follow-up, we documented 42 incident cases of ischemic heart disease (1.5 per 1,000 person-years), 73 incident cases of total stroke (2.7 per 1,000 person-years), 54 incident cases of ischemic stroke (2.0 per 1,000 person-years), 18 incident cases of hemorrhagic stroke (0.7 per 1,000 person-years), 92 incident cases of ischemic cardiovascular disease (3.4 per 1,000 person-years), and 115 incident cases of total cardiovascular disease (4.2 per 1,000 person-years).

Table 1 compares age-adjusted values and proportions of components of the metabolic syndrome and other cardiovascular risk factors between incident cases and non-cases of cardiovascular disease. Compared with non-cases, cases with ischemic heart disease were older, more hypertensive, smoked more, and had higher mean serum total cholesterol, serum triglycerides, and serum glucose levels, and lower mean HDL-cholesterol levels among both men and women. Compared with non-cases, individuals who suffered from ischemic stroke were older, more hypertensive, smoked more, and had higher mean serum triglycerides and serum glucose

Table 3. Multivariable Hazard Ratios of Ischemic Cardiovascular Disease According to the Number of Components of the Metabolic Syndrome, Stratified by the Presence of Abdominal Obesity

Metabolic syndrome	Abdominal obesity (−)			Abdominal obesity (+)		
	No. of components except abdominal obesity			No. of components except abdominal obesity		
	0	1	2+	0	1	2+
NCEP-ATP III criteria						
No. at risk	415	560	495	126	355	662
Person-years	4,392	5,801	5,145	1,354	3,785	7,001
Ischemic cardiovascular disease						
No. of cases	3	16	24	2	6	41
Multivariable HR (95% CI)	1.0	2.4 (0.7–8.4)	3.3 (1.0–11.2)	2.0 (0.3–11.9)	1.6 (0.4–6.6)	5.1 (1.6–16.9)†
AHA/NHLBI and IDF criteria						
No. at risk	378	552	540	113	336	694
Person-years	3,996	5,719	5,623	1,221	3,583	7,336
Ischemic cardiovascular disease						
No. of cases	2	16	25	1	7	41
Multivariable HR (95% CI)	1.0	3.4 (0.8–14.8)	4.3 (1.0–18.3)*	1.5 (0.1–16.3)	2.8 (0.6–13.7)	6.5 (1.6–27.5)*
Japanese criteria						
No. at risk	567	767	499	67	274	439
Person-years	5,948	8,079	5,255	725	2,830	4,639
Ischemic cardiovascular disease						
No. of cases	5	17	28	2	10	30
Multivariable HR (95% CI)	1.0	1.6 (0.6–4.5)	3.4 (1.3–8.9)*	2.4 (0.5–12.2)	2.2 (0.7–6.6)	3.4 (1.3–9.0)*

*$p<0.05$, †$p<0.01$. Multivariable HR adjusted for age, time since last meal, cigarette smoking, alcohol intake and serum total cholesterol. HR, hazard ratio; CI, confidence interval.

levels among both men and women.

The hazard ratios of the metabolic syndrome and cardiovascular disease are shown in Table 2. The metabolic syndrome based on NCEP-ATP III criteria was significantly associated with risks of ischemic heart disease, total stroke, ischemic stroke, ischemic cardiovascular disease, and total cardiovascular disease but was not associated with hemorrhagic stroke. The respective multivariable hazard ratio (95% CI) associated with the metabolic syndrome was 2.1 (1.1–4.0), 1.7 (1.0–2.7), 2.0 (1.2–3.5), 2.0 (1.3–3.1), 1.7 (1.2–2.5) and 1.1 (0.4–2.8). Based on AHA/NHLBI and IDF criteria, we found similar or weaker associations with risks of ischemic stroke, ischemic cardiovascular disease, and total cardiovascular disease, and no significant association with total stroke, hemorrhagic stroke or ischemic heart disease. Using the Japanese criteria, the metabolic syndrome was only significantly associated with risks of total and ischemic strokes; the multivariable hazard ratio (95% CI) was 1.8 (1.1–3.1) and 2.0 (1.1–3.6), respectively.

The PAFs of ischemic heart disease, total stroke, ischemic stroke, ischemic cardiovascular disease, and total cardiovascular disease were between 19% and 27% for the metabolic syndrome based on NCEP-ATP III criteria. The respective PAFs were between 18% and 23% based on AHA/NHLBI criteria and between 16% and 25% based on IDF criteria. The PAFs of total and ischemic strokes for the metabolic syndrome were between 14% and 18% based on Japanese criteria.

We also analyzed associations of the metabolic syndrome components based on the four criteria and risks of ischemic cardiovascular disease, stratified by the presence of abdominal obesity (Table 3). The multivariate hazard ratio of ischemic cardiovascular disease according to NCEP-ATP III criteria was 3.3 (1.0–11.2) in non-abdominal obese persons with at least two risk factors and 5.1 (1.6–16.9) in abdominal obese persons with at least two risk factors. The respective hazard ratios were 4.3 (1.0–18.3) and 6.5 (1.6–27.5), according to AHA/NHLBI and IDF criteria, and 3.4 (1.3–8.9) and 3.4 (1.3–9.0), according to the Japanese criteria.

Discussion

The metabolic syndrome based on NCEP-ATP III criteria was associated with 2-fold increased risks of ischemic heart disease, ischemic stroke, and total cardiovascular disease, whereas the metabolic syndrome based on AHA/NHLBI, IDF, and Japanese criteria had weaker associations with risk of cardiovascular disease, and the association with risk of ischemic heart disease was not statistically significant. The population attributable fraction of ischemic stroke was lower for the metabolic syndrome based on Japanese criteria than for that based on other criteria. Our results were consistent

with those of other prospective studies that showed that the metabolic syndrome based on NCEP-ATP III criteria was associated with risks of mortality and incidence of cardiovascular disease (*1, 2, 4–7, 13, 16–18, 27, 28*), and that the metabolic syndrome based on IDF criteria was less predictive of cardiovascular disease risk (*29–31*). The metabolic syndrome based on NCEP-ATP III, but not IDF criteria, was associated with cardiovascular disease among male diabetic patients (*14, 15*).

Based on the Japanese criteria, the excess risk of ischemic cardiovascular disease was similar in non-abdominal obese persons with at least two metabolic risk factors and abdominal obese persons with at least two risk factors. The lack of significant associations of ischemic heart disease and ischemic cardiovascular disease based on the Japanese criteria was due to the inclusion of a high-risk group of persons without abdominal obesity as a reference group. In other words, excess risk of ischemic cardiovascular disease was similar for persons with at least two metabolic risk factors, irrespective of the presence of abdominal obesity. It is controversial whether the abdominal obesity defined by waist circumference should be required for diagnosis of the metabolic syndrome (*27, 30*). Waist circumference is a valuable component of metabolic syndrome, but the requirement of an increased waist circumference may lead to reduced predictive power for cardiovascular disease (*27, 29–33*).

The strengths of the present study include the use of standardized measurements of waist circumference, serum lipids, and blood pressure levels. The stroke surveillance was almost complete, and a high percentages of the events were confirmed using imaging studies (92%).

The limitations of the present study were, first, the small number of incident cases, particularly for ischemic heart disease. However, we found a statistically significant association between the metabolic syndrome and risks of ischemic heart disease and ischemic stroke. Second, we collected non-fasting blood samples from 94% of the participants during the 1990–1993 examinations. We used non-fasting data at the baseline examination, in particular, non-fasting serum triglycerides ≥1.69 mmol/L (≥150 mg/dL) as a component of metabolic syndrome. Although the justification of the use for the same cutoff point as fasting status is under debate, the data of non-fasting triglycerides can be used because of their significant predictive power for ischemic heart disease (*34*). We used non-fasting glucose ≥7.77 mmol/L as a component of metabolic syndrome, and we may have misclassified participants with high blood glucose. However, we found no significant difference in the percentage of participants with high blood glucose in non-fasting and fasting blood samples probably because we used the different cutoff points: ≥110 mg/dL for fasting and ≥140 mg/dL for non-fasting. In men, the percentage of high blood glucose was 26% for non-fasting blood samples and 30% for fasting blood samples. In women, the respective percentages were 17% and 14%.

In summary, the metabolic syndrome based on NCEP-ATPIII criteria predicted risks of ischemic heart disease, ischemic stroke and total cardiovascular disease, whereas that based on the other three criteria predicted them to a lesser extent.

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

メタボリック症候群と喫煙都市住民における循環器疾患発症に対する予測能および寄与に関する研究- 吹田研究

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研究要旨：欧米諸国に比べアジア諸国における喫煙率は高い。同時にこの地域では肥満者の増加が著しく、肥満に伴うメタボリック症候群（MetS）の増加も懸念されている。そこで都市部住民コホートである吹田研究において、喫煙とMetSの循環器疾患発症に対する予測能および寄与を比較し、更にこれらの危険因子を併せ持った場合のリスクを明らかにした。1989～1993年の初回健診受診日をベースラインとして、循環器疾患（脳卒中及び心筋梗塞）既往のない3,911人（男性1,822人、女性,2089人）を喫煙とMetSの有無により4群に分けて追跡し、喫煙もMetSも有さない群を基準として各群の循環器疾患発症に対するハザード比を算出した(年齢、BMI、飲酒を調整)。また各群の人口寄与危険割合（PAF）も算出した。平均追跡期間は11.9年、喫煙率は男性49.5%、女性11.1%、MetSの有病率は男性18.4%、女性23.0%であった。男女とも喫煙とMetSを併せ持つ人では、どちらか片方だけの場合に比べ循環器疾患発症のリスクは大きく上昇していたが、男性では特に喫煙の影響が大きくMetSの有無に関わらず喫煙のある群でのみ有意なハザード比(HR)の上昇を認めた（喫煙のみ群；HR=1.94（95%信頼区間(CI)：1.19-3.15）、MetSのみ群；HR=1.78（95%CI：0.90-3.50）、両方あり群；HR=3.12（95%CI：1.66-5.85））。男性のPAFは喫煙のみの群で最も高かった（喫煙のみ群；21.0%、MetSのみ群；5.4%、両方；10.5%）。女性ではいずれの群でも有意なハザード比の上昇が認められ、PAFはMetSのみの群で最も高かった(23.6%)。

A. 研究目的

欧米諸国に比べアジア諸国における喫煙率は未だ高く、世界の喫煙者のうち約3分の2がアジア環太平洋地域の国民であると報告されている。同時にこの地域では肥満者の増加が著しく、これにより肥満に伴う循環器疾患危険因子の重複、所謂メタボリック症候群（MetS）の増加が懸念されている。喫煙とMetSの循環器疾患発症に対する予測能及び寄与を比較した研究や、これらの危険因子を併せ持った場合のリスクに関する報告はほとんどないため、都市部コホート研究である吹田研究において検討を行った。

B. 研究方法