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

ウエスト周囲長またはアディポネクチンを基準とした メタボリックシンドロームの経年的検討

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研究要旨：人間ドック受診者で総アディポネクチンを経年測定した 895 例を対象とした。観察開始時、男性ではアディポネクチン判定 MS は MS なしとデータに差がなかったが、女性ではアディポネクチン判定 MS は MS なしと比し、血圧、中性脂肪、内臓脂肪面積、空腹時血糖値、IRI が有意に高値であった。男性では経年後の観察において全疾患（高血圧、糖尿病、脂質異常症、心筋梗塞、脳梗塞）の発症頻度は MS で有意に高かった。WC とアディポネクチンの組み合わせは糖尿病、動脈硬化性疾患を予防するための生活習慣介入に有用と考えた。

A.　研究目的

ウエスト周囲長またはアディポネクチンを基準としたメタボリックシンドロームにおける分布と経年的観察に差があるかどうか検討を行った。

B.　研究方法

対象は 2005 年 10 月から 2014 年 12 月の人間ドック受診者で総アディポネクチンを経年測定した 895 例（男性 498 例、女性 397 例）で、平均年齢男性 43.5±9.7 歳、女性 43.8±9.2 歳、全体 44.6±9.5 歳を対象とした。

早朝空腹時の血清脂質、血糖値、IRI、血圧値を測定した。ウエスト周囲長（WC）は臍周囲で測定した。低線量 CT で内臓脂肪面積を測定した。

総アディポネクチン値はモノクロナル抗体を用いた ELISA 法（積水化学）で測定した。

メタボリックシンドローム（MS）の判定はリスクファクターのうち 2 項目以上を保有し、腹囲、または総アディポネクチンの以下の基準を満たすものとした。

リスクファクター：血圧≧130/85 以上、FPG 110mg/dl 以上、TG 150mg/dl 以上または HDL-C 40mg/dl 未満、もしくは各々の薬物治療中

●WC を基準とした MS
　男性 85cm 以上、女性 90cm 以上

●アディポネクチンを基準とした MS
　男性総アディポネクチン 4.0 μg/ml 未満、女性 6.1 μg/ml 未満

尚、WC の基準は日本の MS 基準、総アディポネクチンの基準はアディポネクチンの MS をスクリーニングする精度を当所において検討した報告[1]から用いた。

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) 男性では WC かつアディポネクチン判定 MS 63 例、WC 判定 MS 49 例、アディポネクチン判定 MS 15 例であった（図 1）。女性ではアディポネクチン判定 MS 20 例に WC 判定 MS 6 例がすべて含まれていた（図 2）。

図1 WCとアディポネクチン基準のMS分布図 男性

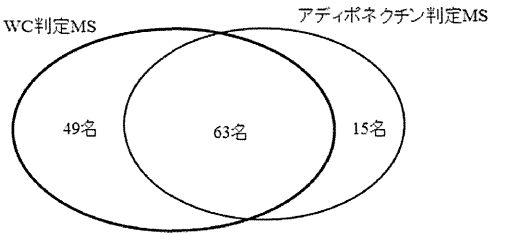
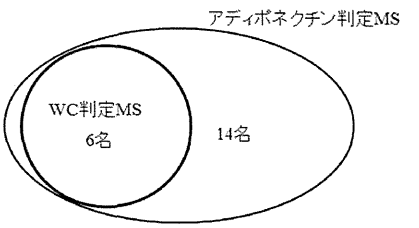


図2 WCとアディポネクチン基準のMS分布図 女性



2) 観察開始時の比較（表 1, 2）

男性ではアディポネクチン判定 MS は、MS なしとほとんど差がなかった。WC 判定 MS、WC かつアディポネクチン判定 MS は MS なし、アディポネクチン判定 MS に比し BMI、WC、内臓脂肪面積が有意に大であり、血圧、中性脂肪、空腹時血糖値、IRI が有意に高値であった。

女性では、MS なし、アディポネクチン判定 MS、WC かつアディポネクチン判定 MS の順に BMI、WC、内臓脂肪面積が有意に大であり、血圧、中性脂肪、空腹時血糖値、IRI が有意に高値であった。

3) 経年観察による比較

男性で糖尿病治療開始がアディポネクチン判定 MS 2 例、WC かつアディポネクチン判定 MS では 10 例であった。心筋梗塞が WC 判定 MS 1 例、WC かつアディポネクチン判定 MS で 1 例の発症がみられた。全疾患（高血圧、糖尿病、脂質異常症、心筋梗塞、脳梗塞）の合計は WC かつアディポネクチン判定 MS で 17 名（27.0%）、WC 判定 MS で 8 名（16.3%）、アディポネクチン判定 MS 2 名（13.3%）であり、MS なしの 29 名（7.8%）と比し有意に高かった。

女性で高血圧治療開始が WC かつアディポネクチン判定 MS で 3 例、糖尿病治療開始がアディポネクチン判定 MS 2 例であった。脳卒中が WC・アディポネクチン判定 MS で 1 例の発症がみられた。

D.考察

今回の検討では、WC またはアディポネクチンを基準とした MS における分布と経年的観察に差があるかどうか検討を行った。

まず、男性では多くが WC かつアディポネクチン判定 MS に該当した。このグループは観察開始時のデータで血圧、血清脂質、内臓脂肪面積、血糖値のすべてにおいて最も高値を示していた。一方、WC 判定 MS は、WC は大きいがアディポネクチンは低くないグループである。WC かつアディポネクチン判定 MS と比較すると観察開始時のデータでは LDL-コレステロールと IRI で有意な差を認めるのみであるが、経年後の疾患発症数は WC かつアディポネクチン判定 MS で多く認められている。WC に加えてアディポネクチンが低値による経年的変化に差があるかどうかは今後の検討が必要と考えた。アディポネクチン判定 MS は観察開始時のデータにおいて MS なしと拡張期血圧で差を認めたのみであった。経年後にはアディポネクチン判定 MS から糖尿病発症がみられたが、WC 判定 MS からの糖尿病発症は認められなかった。低アディポネクチン血症は糖尿病発症のリスクと報告されているが、この結果も従来の報告と一致するものと思われた。

女性では WC 判定 MS はアディポネクチン判定 MS にすべて含まれていた。男性ではアディポネクチン判定 MS の観察開始時データは MS なしと差がなかったが、女性では血圧、中性脂肪、内臓脂肪面積、空腹時血糖値、IRI でアディポネクチン判定 MS は MS なしと比し有意な差を認めた。この結果より、低アディポネクチン血症は女性においては男性よりも強くリスクの指標となることが考えられた。

女性での経年的データについては症例が少ないため統計学的な検討は行えなかった。今後症例を増やして検討を行いたいと考える。

今回、WC またはアディポネクチンを基準とした MS における分布と経年的観察を検討したが、男女では結果に差が認められた。これは、男性では内臓脂肪面積の蓄積が多く、女性では少ないこと、アディポネクチン値は男性より女性で高いこと、等が影響していることが推察される。

このように WC とアディポネクチンの組み合わせは糖尿病、動脈硬化性疾患を予防するための生活習慣介入に有用と考えた。

E. 結論

観察開始時、男性ではアディポネクチン判定 MS は MS なしとデータに差がなかったが、女性ではアディポネクチン判定 MS は MS なしと比し、血圧、中性脂肪、内臓脂肪面積、空腹時血糖値、IRI が有意に高値であった。

男性では経年後の観察において全疾患（高血圧、糖尿病、脂質異常症、心筋梗塞、脳梗塞）の発症頻度は MS 群で有意に高かった。

表1 メタボリックシンドローム判定による臨床検査データの比較
（観察開始時、男性）

	MSなし	WC判定 MS	Adipo判定 MS	WC・Adipo判定 MS
n	371	49	15	63
年齢（歳）	43.7 ± 9.3	52.3 ± 9.8*	47.8 ± 9.8	48.6 ± 8.7*
BMI (kg/m²)	23.1 ± 2.8	26.0 ± 2.6*,	23.2 ± 1.1	27.0 ± 3.2*,
WC (cm)	82.7 ± 7.5	92.0 ± 8.4*,	81.4 ± 3.2	93.4 ± 6.8*,
sBP(mmHg)	121.5 ± 12.5	136.6± 13.9*	130.0 ± 15.8	133.4 ± 14.1*
dBP (mmHg)	76.8 ± 9.1	86.1 ± 9.4*	82.1 ± 10.4*	84.4 ± 8.3*
TG (mg/dl)	121.5 ±100.5	212.7 ± 265.7*	187.3 ± 95.5	213.4 ± 119.8*
HDL-cho(mg/dl)	58.3 ±13.7	54.5 ± 12.6	50.3 ± 13.6	48.3 ± 9.9*
LDL-cho(mg/dl)	121.5 ± 30.5	123.3 ± 36.8	122.7 ± 21.4	139.0 ± 30.4*,
VFA (cm²)	70.9 ± 36.2	124.9 ± 43.7*§	83.3 ± 26.0	132.0 ± 39.3*,
FPG (mg/dl)	101.0 ± 11.5	124.3 ± 29.7*§	107.9 ± 10.8	124.9 ± 36.9*,
HbA1c (%)	5.4 ±0.4	6.1 ± 1.2*	5.5 ± 0.5	6.4 ± 1.5*,
IRI (μU/ml)	6.1 ±3.5	9.2 ±5.8*	7.1 ±2.4	13.3 ±9.6*,

*P<0.05 対 MSなし、 †P<0.05 対 腹囲判定MS、 § P<0.05対 Adipo判定MS、年齢以下は 年齢を調整した共分散分析を行った。

表2 メタボリックシンドローム判定による臨床検査データの比較
（観察開始時、女性）

	MSなし	Adipo判定 MS	WC・Adipo判定 MS
n	377	14	6
年齢（歳）	43.3 ± 8.8	55.7 ± 10.2*	47.8 ± 9.1
BMI (kg/m²)	21.2 ± 2.9	21.3 ± 3.1	29.3 ± 3.3*†
WC (cm)	77.3 ± 8.1	78.5 ± 7.1	96.3 ± 3.6*†
sBP(mmHg)	116.1 ± 14.9	130.9 ± 11.0*	146.8 ± 21.6*
dBP (mmHg)	72.4 ± 9.4	82.6 ± 7.1*	91.5 ± 13.4*
TG (mg/dl)	74.3 ± 41.7	137.5 ± 60.7*	158.2 ± 73.4*†
HDL-cho(mg/dl)	69.3 ± 14.3	64.1 ± 14.8	57.3 ± 14.2
LDL-cho(mg/dl)	113.7 ± 30.2	119.7 ± 25.6	122.8 ± 19.6
VFA (cm²)	36.2 ± 26.4	54.1 ± 20.8*	117.8 ± 43.7*†
FPG (mg/dl)	94.7 ± 7.3	110.8 ± 20.1*	119.8 ± 11.0*
HbA1c (%)	5.4 ± 0.4	5.8 ± 0.8*	6.2 ± 0.4*
IRI (μU/ml)	5.6 ± 3.2	6.3 ± 2.5*	15.4 ± 8.1*†

*P<0.05 対 MSなし、 †P<0.05 対 Adipo判定MS、年齢以下は 年齢を調整した共分散分析を行った。

G. 研究発表

1. 論文発表

1) Rumi Fujikawa, Chicako Ito, Atsuko Mitama Is possible the screening of metabolic syndrome using adiponectin? Diabetology Int. in press

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2. 学会発表

藤川るみ、三玉敦子、伊藤千賀子、吉良さくらこ、糖尿病網膜症からみた新糖尿病診断基準の妥当性に関する研究糖尿病、57:S-130, 2014

厚生労働科学研究費補助金（循環器疾患・糖尿病等生活習慣病対策総合研究事業）

分担研究報告書

空腹時・非空腹時の中性脂肪濃度と虚血性循環器疾患の発症リスクとの関連
- The Circulatory Risk in Communities Study (CIRCS)-

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研究要旨：非空腹時の中性脂肪濃度と虚血性循環器疾患の発症リスクとの関連を明らかにするため、CIRCS 研究において、40～69 歳の男女 10,659 人を対象者に、1975 年から 1986 年までにベースライン調査後、22 年間の追跡を行った。その間、284 人の虚血性心疾患と 666 人の脳梗塞が発症した。解析において、中性脂肪濃度を 4 分位にし、中性脂肪濃度の最低値群を基準にして、虚血性循環器疾患（虚血性心疾患と脳梗塞）発症のハザード比(95%信頼区間)を算出した。その結果、中性脂肪濃度の最低値群（空腹時＜0.95mmol/L、非空腹時＜0.96mmol/L）に比べ、中性脂肪濃度の最高値群（空腹時＞1.88mmol/L、非空腹時＞1.86mmol/L)での虚血性循環器疾患の多変量調整ハザード比は、空腹時で 1.71(1.14-2.59)、トレンド p 値＝0.013 であり、非空腹時で 1.60（1.25-2.05)、トレンド p 値＜0.001 であった。また、上記の関連は男性で同様に認められたが、女性では非空腹時での関連が、空腹時での関連に比べて強かった。本研究により、男性においては空腹の有無にかかわらず、女性では非空腹時の中性脂肪濃度と虚血性循環器疾患の発症リスクが関連することが示された。

A．研究目的

国外の先行研究により、非空腹時の中性脂肪濃度が空腹時の中性脂肪濃度に比べ、虚血性循環器疾患の発症リスクとの関連がより強いことが報告されている。しかしながら、日本人における非空腹時の中性脂肪濃度と虚血性循環器疾患の発症リスクとの関連についてのコホート研究は限られている。

B．研究対象と方法

本研究は、Circulatory Risk in Communities Study（CIRCS）において、秋田井川町、大阪府八尾市、高知県野市町、茨城県協和地区の 4 地域の住民を対象に、それぞれ 1975～1980、1975～1984、1975～1980 と 1981～1986 年に循環器健診の受診者でかつ脳卒中または冠動脈疾患既往者を除いた 40-69 歳の男女 10,659 人である。これらの対象者を協和地区と野市町で 2005 年末まで、井川町で 2009 年末まで、八尾市で 2008 年末までに脳卒中と虚血性心疾患の発症に関する追跡調査を行った。解析においては中性脂肪濃度を 4 分位（空腹時では＜0.95mmol/L、0.95-1.29、1.30-1.88、≥1.89mmol/L；

非空腹時では＜0.96、0.96-1.30、1.31-1.86、≥1.87mmol/L）に分けて、それぞれの最低値群を基準にし、比例ハザード比モデルを用いて、それぞれ群のハザード比(95%信頼区間)を算出した。また、上記の関連を男女別に解析した。交絡因子として、年齢、地域、肥満度（BMI）、収縮期血圧、降圧剤服薬の有無、喫煙（非喫煙、過去喫煙、現在喫煙 1－24 本/日、また≥25 本/日）・飲酒（非喫煙、過去喫煙、現在飲酒 1 合未満、1-2、2-3、3 合以上/日）、血清総コレステロール値、血糖値、食後時間（＜2、2、2-7、≥8 時間）、さらに、女性については閉経の有無を調整した。

C．研究結果

本研究により、日本人男女において中性脂肪濃度の低値群に比べ、中性脂肪濃度の高値群において空腹の有無にかかわらず虚血性循環器疾患の発症リスクが有意に高く、上記の関連が男性では同様な結果であったが、女性では非空腹時でより強く認められた（表１）。中性脂肪濃度の低値群（空腹時＜0.95mmol/L、非空腹時＜0.96mmol/L）に比べ、中性脂肪濃度の高値群（空腹時≥1.89mmol/L、非空腹時≥1.87mmol/L）での虚血性循環器疾患の多変量調整ハザード比は、空腹時で 1.71（1.14-2.59）、トレンド p 値＝0.013 であり、非空腹時で 1.60（1.25-2.05）、トレンド p 値＜0.001 であった。また、上記の関連は男性では同様に認められたが、女性では非空腹時の方がより強く認められた。多変量調整ハザード比は、男性で空腹時では 1.75（1.03-3.07）、トレンド p 値＝0.056 であり、非空腹時で 1.34（0.95-1.88）、トレンド p 値＝0.016 であった。女性で空腹時では 1.36（0.70-2.64）、トレンド p 値＝0.34 であり、非空腹時で 1.87（1.28-2.73）、トレンド p 値＜0.001 であった。

D．結論

本研究により、男性においては空腹の有無にかかわらず、女性では非空腹時の中性脂肪濃度と虚血性循環器疾患の発症リスクが関連することが示された。

E．データ管理・更新（倫理面への配慮）

対象地区からの転出は自治体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 CIRCS コホート研究全体については、大阪大学と大阪がん循環器病予防センター（旧大阪健康科学センター）の倫理審査委員会で倫理審査を受け、承認を得ている。

F. 研究の協力者

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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
Iso H, Imano H, Yamagishi K, Ohira T, Cui R, Noda H, Sato S, Kiyama M, Okada T, Hitsumoto S, Tanigawa T, Kitamura A	Fasting and non-fasting triglycerides and risk of ischemic cardiovascular disease in Japanese men and women: the Circulatory Risk in Communities Study (CIRCS).	Atherosclerosis	237	361-368	2014

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

Table 1. Multivariable hazard ratios (HR) of ischemic cardiovascular disease according to quartiles of serum triglycerides, stratified by fasting status.

	Ischemic cardiovascular disease			
	Person years	No of events	Age and community-adjusted HR (95%CI)	Multivariable HR (95%CI)
Men				
Fasting triglycerides				
Triglyceride quartiles				
Q1(low)	5017	30	1.00	1.00
Q2	4445	35	1.36 (0.83-2.23)	1.32 (0.80-2.19)
Q3	4390	34	1.47 (0.89-2.43)	1.47 (0.87-2.49)
Q4(high)	4929	46	1.84 (1.15-2.96)*	1.75 (1.03-3.07)*
P for trend			0.015	0.056
Non-fasting triglycerides				
Triglyceride quartiles				
Q1(low)	16793	78	1.00	1.00
Q2	15764	59	0.83 (0.59-1.16)	0.77 (0.55-1.09)
Q3	15815	97	1.50 (1.10-2.04)*	1.28 (0.93-1.77)
Q4(high)	18104	110	1.73 (1.28-2.35)‡	1.34 (0.95-1.88)
P for trend			<0.001	0.016
Women				
Fasting triglycerides				
Triglyceride quartiles				
Q1(low)	8461	15	1.00	1.00
Q2	8581	24	1.14 (0.59-2.17)	1.01 (0.52-1.97)
Q3	7679	45	1.98 (1.09-3.58)*	1.81 (0.97-3.37)
Q4(high)	6930	36	1.59 (0.86-2.96)	1.36 (0.70-2.64)
P for trend			0.132	0.342
Non-fasting triglycerides				
Triglyceride quartiles				
Q1(low)	29349	50	1.00	1.00
Q2	29652	68	1.23 (0.85-1.78)	1.19 (0.82-1.73)
Q3	27576	80	1.46 (1.02-2.09)*	1.28 (0.88-1.87)
Q4(high)	23227	107	2.23 (1.57-3.17)‡	1.87 (1.28-2.73)†
P for trend			<0.001	<0.001
Total subjects				
Fasting triglycerides				
Triglyceride quartiles				
Q1(low)	13477	45	1.00	1.00
Q2	13026	59	1.29 (0.87-1.90)	1.22 (0.82-1.82)
Q3	12069	79	1.81 (1.25-2.63)†	1.73 (1.17-2.56)†
Q4(high)	11859	82	1.87 (1.29-2.72)†	1.71 (1.14-2.59)*
P for trend			<0.001	0.013
Non-fasting triglycerides				
Triglyceride quartiles				
Q1(low)	46143	128	1.00	1.00
Q2	45415	127	1.00 (0.78-1.28)	0.96 (0.75-1.23)
Q3	43391	177	1.49 (1.18-1.88)‡	1.30 (1.02-1.66)*
Q4(high)	41332	217	1.98 (1.58-2.49)‡	1.60 (1.25-2.05)‡
P for trend			<0.001	<0.001

Test for significance: * P < 0.05, † P < 0.01, ‡ P < 0.001

Multivariable hazard ratio adjusted for age, sex, community, quartiles of body mass index, systolic blood pressure, use of antihypertensive medication, serum total cholesteol, serum HDL-cholesterol, cigarette smoking status, , alcohol intake category, serum glucose category, time since last meatl and for women, menopausal status.

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Fasting and non-fasting triglycerides and risk of ischemic cardiovascular disease in Japanese men and women: The Circulatory Risk in Communities Study (CIRCS)

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ABSTRACT

Background: Non-fasting triglycerides were reported to have a greater impact on risk of ischemic cardiovascular events than fasting triglycerides. However, evidence from Asia, where the prevalence of dyslipidemia is generally lower, has been limited.
Methods: We used 1975–1986 baseline surveys to investigate cohort data of 10,659 (4264 men and 6395 women) residents aged 40–69 years, initially free from ischemic heart disease and stroke, in four Japanese communities. Serum triglyceride concentrations at baseline were obtained for 2424 fasting (≥8 h after meal) and 8235 non-fasting (<8 h after meal) participants.
Results: During the 22-year follow-up, 284 (165 men and 119 women) developed ischemic heart disease and 666 (349 men and 317 women) ischemic stroke. After adjustment for age, sex and known cardiovascular risk factors, multivariable hazard ratios (95%CI) of ischemic cardiovascular disease (ischemic heart disease and ischemic stroke) for the highest versus lowest quartiles of triglycerides were 1.71 (1.14–2.59), *P* for trend = 0.013, for fasting participants and 1.60 (1.25–2.05), *P* for trend <0.001, for non-fasting participants. The positive associations did not differ between fasting and non-fasting men, while they were strong for non-fasting women. They were stronger for ischemic heart disease than for ischemic stroke. After further adjustment for HDL-cholesterol, these associations were slightly attenuated, but remained statistically significant.
Conclusion: Non-fasting as well as fasting triglycerides are predictive of risk of ischemic cardiovascular disease for Japanese men, as are non-fasting triglycerides for women.

1. Introduction

Although the impact of total and LDL-cholesterols on ischemic cardiovascular disease has been well established [1], the impact of triglycerides has remained controversial. Large meta-analyses, primarily performed in western countries [2–4], but not all [5], have identified moderate and statistically significant associations between triglycerides and risk of ischemic heart disease, stroke, or cardiovascular events, even after adjustment for cardiovascular risk factors including body mass index, diabetes mellitus and HDL-cholesterol. The evidence for Asian populations is limited, but a previous study of ours [6,7] and a meta-analysis by Asia Pacific Cohort Studies Collaboration [8] detected an independent relationship between triglycerides and risk of coronary heart disease. Furthermore, emerging evidence from western countries supports the notion that non-fasting triglycerides, a postprandial state of lipid profile, is an even better predictor of ischemic cardiovascular disease [9–12].

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High levels of non-fasting triglycerides reflect increased residues from chylomicrons and very low density lipoproteins. These cholesterol-containing and triglyceride-rich lipoprotein residues penetrate the arterial intima and are trapped within the arterial wall, leading to the development of atherosclerosis [13–15]. It remains to be determined, however, whether populations such as Japanese, with lower levels of total- or LDL-cholesterol and triglycerides, run a similar potential risk of high postprandial triglyceride levels.

Associations between non-fasting and fasting triglycerides and risk of incident cardiovascular disease in Asian countries have not been investigated systematically in any cohort studies. We hypothesized that non-fasting triglycerides constitute a better predictor for ischemic cardiovascular disease than fasting triglycerides in Asian populations whose prevalence of dyslipidemia is lower than that in western populations. To test our hypothesis, we examined the data of the Circulatory Risk in Communities Study (CIRCS), community-based prospective study of approximately 10,000 middle-aged Japanese men and women.

2. Methods

2.1. Study population

The surveyed population comprised 11,370 residents aged 40–69 years in four communities: Ikawa town (a rural community in Akita Prefecture in northwestern Japan), the Minami-Takayasu district in Yao City (a southwestern suburb in Osaka Prefecture), Noichi town, (a rural community in Kochi Prefecture in southwestern Japan) and Kyowa town (a rural community in Ibaraki Prefecture in central Japan) [16,17]. The baseline surveys were conducted in 1975–1980, 1975–1984, 1975–1980, and 1981–1986, respectively. The total census populations aged 40–69 years old in the four communities were, respectively, 2291 in 1975, 5538 in 1980, 3599 in 1975, and 5408 in 1980. The study participation rate was 65%. After the exclusion of participants with a history of coronary heart disease and/or stroke at baseline, the data for the remaining 10,659 subjects were analyzed. This study was approved by the ethics committees of the Osaka Medical Center for Health Science and Promotion and of Osaka University.

2.2. Follow-up and ascertainment of cases

Follow-up lasted until the end of 2005 for Kyowa and Noichi, 2009 for Ikawa and 2008 for Minami-Takayasu, and was terminated at the first incident of ischemic heart disease and stroke, exit from the community or death. Persons who moved out of the communities during the follow-up numbered 822 (8%), and 3597 (34%) persons died. These were censored at the date of moving out or the date of death. The median follow-up was 22.3 years for coronary heart disease and 22.2 years for ischemic stroke.

The details of endpoint determination have been described in previous CIRCS reports [16,17]. For all the residents, cardiovascular disease end points were ascertained from death certificates, national insurance claims, reports by local physicians, reports by public health nurses and health volunteers, and annual cardiovascular risk surveys. To confirm the diagnosis, all living patients were telephoned, visited or invited to take part in risk factor surveys, or a medical history was obtained from their families. In addition, medical records in the local clinics and hospitals were reviewed. In case of death with certain underlying causes of death (ICD 9 classification codes: 410–414, 428 and 429), histories were obtained from families and/or attending physicians and medical records were reviewed.

The criteria for ischemic heart disease, i.e. definite and probable myocardial infarctions, angina pectoris and sudden cardiac death within 1 h of onset were modified from those of the World Health Organization Expert Committee [1], as previously reported by us [16].

The criterion for incident stroke was a focal neurological disorder with rapid onset and persisting for at least 24 h or until death [17]. The determination of stroke subtypes was performed primarily by using CT/MRI findings, which were available for 81% of the stroke cases. Strokes that were diagnosed clinically but showed no lesion on CT/MRI films were classified based on the clinical criteria. Ischemic stroke was used as an outcome in this study. The final diagnosis for ischemic heart disease and ischemic stroke were made by a panel of 3–4 physicians participating in this study who were blinded to the data from the risk factor survey.

2.3. Baseline examination

Blood was drawn into a plain, siliconized glass tube and the serum was separated immediately after centrifugation. Fasting was not required. The time intervals since the last meal were: 0 – <1 h (3.0%), 1 – <2 h (20.7%), 2 – <3 h (43.7%), 3 – <8 h (9.9%), and ≥8 h (22.7%). Fasting was defined as ≥8 h after the last meal.

Serum triglycerides were measured with the fluorometric method using Autoanalyzer II (Technicon, Tarrytown, NY, U.S.A.) and serum total cholesterol was measured with the direct Lieberman–Burchard method using Autoanalyzer II for the period 1975–1979 and Autoanalyzer SMA-12/60 from 1979 to 1986 at the Osaka Medical Center for Cancer and Cardiovascular Diseases [6,16]. For 55% of the total sample (5880 subjects), HDL-cholesterol after heparin-manganese precipitation was measured at the same laboratory with the direct Liebermann–Burchard method. The Osaka Medical Center laboratory has been standardized by the Lipid Standardization Program, conducted by the Centers for Disease Control (Atlanta, GA), and successfully met the criteria for both reproducibility and accuracy of triglycerides and cholesterol measurements [18].

Serum total cholesterol was measured with the enzymatic method using Olympus AU 2700 at the lipid reference laboratory of the Osaka Medical Center for Health Science and Promotion, which is an international member of the US National Cholesterol Reference Method Laboratory Network. This laboratory has been certified since 1975 by the CDC-NHLBI Lipid Standardization Program conducted by the Centers for Disease Control and Prevention [18] and successfully met the performance criteria for both reproducibility and accuracy of serum triglycerides, total cholesterol and HDL-cholesterol measurements [19].

Blood pressures were measured by trained physicians using standard mercury sphygmomanometers and unified epidemiological methods [20]. Hypertension was defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg and/or use of antihypertensive medication, while normotension was defined as systolic blood pressure <140 mmHg, diastolic blood pressure <90 mmHg and no antihypertensive medication use. All others were classified as borderline hypertension. Height was measured with the subjects in stocking feet and their weight while wearing light clothing. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2).

An interview was conducted to ascertain the number of cigarettes smoked per day, usual weekly intake of ethanol measured in units of *go* (a Japanese traditional unit of volume corresponding to 23 g ethanol), and menopausal status for women.

Serum glucose values were classified into three categories (diabetic, prediabetic and normal types). Diabetic type was defined

Table 1
Baseline characteristics of subjects according to quartiles of serum triglycerides.

	Fasting (≥8 h)					Non-fasting (<8 h)				
Triglycerides quartiles	1 (low)	2	3	4 (high)	*P* for difference	1 (low)	2	3	4 (high)	*P* for difference
Range of triglycerides, mmol/L	0.33–0.94	0.95–1.29	1.30–1.88	1.89–14.29		0.26–0.95	0.96–1.30	1.31–1.86	1.87–23.71	
Range of triglycerides, mg/dL	29–83	84–114	115–166	167–1266		23–84	85–115	116–165	166–2100	
Median triglycerides, mmol/L	0.77	1.12	1.52	2.47		0.77	1.12	1.54	2.47	
Median triglycerides, mg/dL	68	99	135	219		68	99	136	219	
Men										
No. at risk	247	228	225	259		807	773	797	928	
Age, year	55.8 (0.6)	55.9 (0.6)	54.4 (0.6)	52.5 (0.6)	<0.001	54.1 (0.3)	53.6 (0.3)	52.6 (0.3)	50.8 (0.3)	<0.001
Body mass index, kg/m^2	21.5 (0.2)	22.7 (0.2)	23.4 (0.2)	24.8 (0.2)	<0.001	21.7 (0.1)	22.4 (0.1)	22.9 (0.1)	24.0 (0.1)	<0.001
Systolic blood pressure, mmHg	142 (1)	144 (1)	142 (1)	147 (1)	0.005	134 (1)	136 (1)	137 (1)	141 (1)	<0.001
Diastolic blood pressure, mmHg	82 (1)	85 (1)	85 (1)	88 (1)	<0.001	80 (0.4)	81 (0.5)	83 (0.4)	85 (0.4)	<0.001
Use of antihypertensive medication, %	15	21	22	22	0.147	8	11	12	16	<0.001
Hypertensives, %	55	60	60	74	<0.001	37	43	50	56	<0.001
Serum total cholesterol, mmol/L	4.26 (0.06)	4.50 (0.06)	4.88 (0.06)	5.17 (0.05)	<0.001	4.43 (0.03)	4.56 (0.03)	4.78 (0.03)	5.12 (0.03)	<0.001
Serum HDL-cholesterol, mmol/L	1.62 (0.04)	1.49 (0.04)	1.45 (0.04)	1.33 (0.04)	<0.001	1.59 (0.02)	1.52 (0.02)	1.43 (0.02)	1.30 (0.02)	<0.001
Diabetes mellitus, %	26	22	30	31	0.141	4	4	6	7	0.010
Current smoking, %	69	69	63	68	0.579	64	65	65	68	0.312
Ethanol intake, g/day	27.9 (1.7)	25.6 (1.7)	27.5 (1.8)	29.4 (1.6)	0.463	29.4 (1.0)	27.9 (1.0)	28.9 (0.9)	29.7 (0.9)	0.541
Women										
No. at risk	358	384	377	346		1255	1291	1280	1104	
Age, year	51.1 (0.4)	53.9 (0.4)	56.1 (0.4)	56.9 (0.5)	<0.001	50.0 (0.2)	52.1 (0.2)	53.7 (0.2)	54.8 (0.2)	<0.001
Body mass index, kg/m^2	22.8 (0.2)	23.5 (0.2)	24.4 (0.2)	25.4 (0.2)	<0.001	22.3 (0.1)	23.1 (0.1)	23.7 (0.1)	24.6 (0.1)	<0.001
Systolic blood pressure, mmHg	138 (1)	141 (1)	142 (1)	145 (1)	<0.001	130 (1)	132 (1)	135 (1)	138 (1)	<0.001
Diastolic blood pressure, mmHg	80 (1)	83 (1)	84 (1)	85 (1)	<0.001	77 (0.3)	78 (0.3)	80 (0.3)	82 (0.3)	<0.001
Use of antihypertensive medication, %	19	26	26	30	0.005	8	10	13	17	<0.001
Hypertensives, %	50	61	60	67	<0.001	32	36	40	49	<0.001
Serum total cholesterol, mmol/L	4.58 (0.05)	4.87 (0.04)	5.20 (0.04)	5.53 (0.05)	<0.001	4.71 (0.02)	4.93 (0.02)	5.12 (0.02)	5.41 (0.02)	<0.001
Serum HDL-cholesterol, mmol/L	1.64 (0.02)	1.51 (0.02)	1.42 (0.02)	1.32 (0.03)	<0.001	1.61 (0.01)	1.52 (0.01)	1.45 (0.01)	1.34 (0.01)	<0.001
Diabetes mellitus, %	17	16	17	20	0.149	2	2	4	6	<0.001
Current smoking, %	7	9	6	11	0.118	5	7	8	8	0.005
Ethanol intake, g/day	1.3 (0.4)	1.8 (0.4)	1.1 (0.4)	1.3 (0.4)	0.526	1.4 (0.2)	1.1 (0.2)	1.2 (0.2)	1.3 (0.2)	0.865
Postmenopausal, %	63	69	71	72	0.001	56	57	60	62	<0.001

Values were presented as means ± standard errors or proportions, adjusted for age and community.
Non-fasting serum glucose values were also adjusted for time since last meal.

as a fasting glucose of 7.0 mmol/L or more, and/or a non-fasting glucose of 11.1 mmol/L or more, and/or use of medication for diabetes. Prediabetic type was defined as a fasting glucose of 6.1–6.9 mmol/L, and/or a non-fasting glucose of 7.8 mmol/L or more, without medication use for diabetes. All others were classified as normal type.

2.4. Statistical analyses

Analysis of covariance was used to test for differences in age-adjusted means and prevalence of baseline characteristics in terms of serum triglyceride categories, as well as stratification by fasting status. Person-years were calculated as the sum of individual follow-up time until the occurrence of incident ischemic heart disease, ischemic stroke, death, emigration, or the end of follow-up. Cox proportional hazards regression models were used to calculate the sex-specific and sex-adjusted hazard ratios and 95% confidence intervals (CIs) for incident ischemic cardiovascular disease using the risk for persons with the lowest category of serum triglycerides as reference. A test for trend of association between serum triglycerides and ischemic cardiovascular disease was also conducted using the median values of triglyceride levels for each category. When the assumption of proportional hazards was tested, no violation of the proportionality principle was found.

The hazard ratios were also calculated in relation to fasting status. The initial model was adjusted only for age and sex, while the variables for multivariable adjustment comprised age, sex (for total participants), community, systolic blood pressure, antihypertensive medication use, serum total cholesterol level (mg/dL), sex-specific quartiles of BMI (kg/m^2), smoking status (never, former and current 1–24 or ≥25 cigarettes per day), and alcohol intake (never, former, and current < 46, 46–68 or ≥ 69 g ethanol per day), serum glucose category (normal, impaired glucose tolerance and diabetes), time since last meal (<2, 2, 3–7 and 8 h or more), and for women menopausal status (pre- and post-menopause). Further adjustment for HDL-cholesterol (mmol/L) was conducted with a subsample for whom data on HDL-cholesterol were available. Sex interaction with the association between serum triglycerides and risk of ischemic cardiovascular disease was tested using a cross-product term of sex (0 or 1) and triglyceride levels (continuous) for the model.

All statistical analyses were performed with the SAS System for Windows (version 9.2; SAS Inc, Cary, NC). All *P*-values for statistical tests were two-tailed, and values of <0.05 were regarded as statistically significant.

3. Results

Table 1 lists sex-specific, age-adjusted mean values and prevalence of selected cardiovascular risk factors at baseline in relation to serum triglyceride quintiles and stratified by fasting status. For both fasting and non-fasting status, triglyceride levels were positively associated with body mass index, systolic and diastolic blood pressure levels, antihypertensive medication, hypertension, serum total cholesterol levels and serum glucose levels, and inversely associated with HDL-cholesterol levels for both sexes. Triglycerides levels were inversely associated with age for men, and positively with age, current smoking and postmenopausal status for women. Fasting subjects were 1–2 years younger and had lower means of body mass index and blood pressure levels, and higher prevalence of diabetes mellitus than non-fasting participants.

During the median 22-year follow-up totaling 232,947 person-years, there were 284 documented cases of incident ischemic heart diseases (165 men and 119 women) and 666 of incident ischemic strokes (349 men and 317 women).

Table 2 shows age- and community-adjusted and multivariable hazard ratios of ischemic cardiovascular disease (ischemic heart disease and ischemic stroke) by serum triglyceride quartile, per 1 mmol/L (88.6 mg/dL) increment of triglycerides, and for ≥2.26 mmol/L (200 mg/dL) and 1.69–2.25 mmol/L (150–199 mg/dL) of triglycerides compared to <1.69 mmol/L (150 mg/dL) of triglycerides. Serum triglyceride levels were positively associated with risk of ischemic cardiovascular disease for both men and women. After adjustment for conventional cardiovascular risk factors except HDL-cholesterol levels, the association with risk of ischemic cardiovascular disease weakened but remained statistically significant for both men and women. The multivariable hazard ratios (95%CIs) of ischemic cardiovascular disease for the highest versus lowest quartile of triglycerides were 1.48 (1.11–1.97); *P* for trend = 0.001 for men, 1.73 (1.24–2.40), *P* for trend < 0.001 for women and 1.65 (1.33–2.04), *P* for trend < 0.001 for total subjects. The positive association tended to be more evident for women than for men, although the sex interaction was not statistically significant (*P* for interaction = 0.535). As shown in Supplemental Table 1 the positive association with triglycerides was stronger for ischemic heart disease than for ischemic stroke for both men and women. For example, the multivariable hazard ratios (95%CIs) of ischemic heart disease for the highest versus lowest triglyceride quartile were 1.68 (1.02–2.76), *P* for trend = 0.012 for men, 2.11 (1.12–4.00), *P* for trend = 0.001 for women, and 1.93 (1.31–2.83), *P* for trend < 0.001 for total subjects, while those of ischemic stroke were 1.37 (0.98–1.92), *P* for trend = 0.025, and 1.53 (1.05–2.23), *P* for trend = 0.037, and 1.48 (1.15–1.90), *P* for trend < 0.001, respectively.

The multivariable hazard ratios associated with 1 mmol/L increment of triglycerides and for two or three other triglyceride categories showed similar results. For example, the risk after multivariable adjustment of ischemic cardiovascular disease was 11% for 1 mmol/L increment of triglycerides, 33% higher for ≥1.69 mmol/L, 45% higher for ≥2.26 mmol/L and 21% higher for 1.69–2.25 mmol/L of triglycerides, compared to <1.69 mmol/L of

Table 2
Hazard ratios (HR) of ischemic cardiovascular disease (ischemic heart disease and ischemic stroke) according to quartiles of serum triglycerides.

	Person years	No of events	Age and community-adjusted HR (95%CI)	Multivariable HR (95%CI)
Men				
Triglyceride quartiles				
Q1 (low)	21,939	108	1.00	1.00
Q2	20,185	95	0.99 (0.75–1.31)	0.94 (0.71–1.24)
Q3	20,047	129	1.48 (1.14–1.93)†	1.35 (1.03–1.77)*
Q4 (high)	23,085	157	1.77 (1.37–2.28)‡	1.48 (1.11–1.97)†
P for trend			<0.001	0.001
HR per 1 mmol/L increment	85,256	489	1.12 (1.06–1.18)‡	1.06 (0.99–1.13)
Triglycerides				
<1.69 mmol/L	57,040	301	1.00	1.00
≥1.69 mmol/L	28,216	188	1.52 (1.26–1.83)‡	1.32 (1.07–1.62)†
Triglycerides				
<1.69 mmol/L	57,040	301	1.00	1.00
1.69–2.25 mmol/L	12,181	79	1.40 (1.09–1.80)†	1.30 (1.00–1.69)*
≥2.26 mmol/L	16,035	109	1.61 (1.29–2.02)‡	1.33 (1.04–1.71)*
Women				
Triglyceride quartiles				
Q1 (low)	38,015	65	1.00	1.00
Q2	38,280	92	1.21 (0.88–1.67)	1.17 (0.85–1.62)
Q3	34,915	124	1.62 (1.19–2.20)†	1.46 (1.06–2.00)*
Q4 (high)	30,245	144	2.04 (1.51–2.77)‡	1.73 (1.24–2.40)†
P for trend			<0.001	<0.001
HR per 1 mmol/L increment	141,454	425	1.28 (1.19–1.38)‡	1.24 (1.13–1.36)‡
Triglycerides				
<1.69 mmol/L	102,716	253	1.00	1.00
≥1.69 mmol/L	38,738	172	1.47 (1.20–1.79)‡	1.27 (1.03–1.57)*
Triglycerides				
<1.69 mmol/L	102,716	253	1.00	1.00
1.69–2.25 mmol/L	20,629	72	1.19 (0.91–1.55)	1.09 (0.83–1.42)
≥2.26 mmol/L	18,109	100	1.78 (1.41–2.27)‡	1.49 (1.15–1.93)†
Total subjects				
Triglyceride quartiles				
Q1 (low)	59,954	173	1.00	1.00
Q2	58,465	187	1.09 (0.88–1.34)	1.05 (0.85–1.29)
Q3	54,962	253	1.56 (1.28–1.91)‡	1.43 (1.17–1.76)‡
Q4 (high)	53,330	301	1.94 (1.60–2.36)‡	1.65 (1.33–2.04)‡
P for trend			<0.001	<0.001
HR per 1 mmol/L increment	226,711	914	1.17 (1.12–1.21)‡	1.11 (1.06–1.17)‡
Triglycerides				
<1.69 mmol/L	159,756	554	1.00	1.00
≥1.69 mmol/L	66,955	360	1.54 (1.34–1.76)‡	1.33 (1.15–1.54)‡
Triglycerides				
<1.69 mmol/L	159,756	554	1.00	1.00
1.69–2.25 mmol/L	32,811	151	1.32 (1.10–1.59)†	1.21 (1.01–1.46)*
≥2.26 mmol/L	34,144	209	1.75 (1.49–2.06)‡	1.45 (1.21–1.73)‡

Test for significance: *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.
Q1; 0.26–0.95 mmol/L (23–84 mg/dL), Q2; 0.96–1.30 mmol/L (85–115 mg/dL), Q3; 1.31–1.86 mmol/L (116–165 mg/dL), Q4; 1.87–23.71 mmol/L (166–2100 mg/dL).
Multivariable hazard ratio adjusted for age, sex, community, quartiles of body mass index, systolic blood pressure, use of antihypertensive medication, serum total cholesterol, cigarette smoking status, alcohol intake category, serum glucose category, time since last meal and for women, menopausal status.

Table 3
Multivariable hazard ratios (HR) of ischemic cardiovascular disease (ischemic heart disease and ischemic stroke) according to quartiles of serum triglycerides, stratified by fasting status.

	Person years	No of events	Age and community-adjusted HR (95%CI)	Multivariable HR (95%CI)
Men				
Fasting triglycerides				
Quartiles				
Q1 (low)	5017	30	1.00	1.00
Q2	4445	35	1.36 (0.83–2.23)	1.32 (0.80–2.19)
Q3	4390	34	1.47 (0.89–2.43)	1.47 (0.87–2.49)
Q4 (high)	4929	46	1.84 (1.15–2.96)*	1.75 (1.03–3.07)*
P for trend			0.015	0.056
HR per 1 mmol/L increment	18,781	145	1.08 (0.96–1.23)	1.07 (0.92–1.24)
Triglycerides				
< 1.69 mmol/L	12,881	92	1.00	1.00
≥ 1.69 mmol/L	5900	53	1.39 (0.98–1.96)	1.31 (0.89–1.95)
Triglycerides				
< 1.69 mmol/L	12,881	92	1.00	1.00
1.69–2.25 mmol/L	2451	23	1.41 (0.89–2.24)	1.35 (0.83–2.19)
≥ 2.26 mmol/L	3449	30	1.37 (0.90–2.08)	1.28 (0.79–2.08)
Non-fasting triglycerides				
Quartiles				
Q1 (low)	16,793	78	1.00	1.00
Q2	15,764	59	0.83 (0.59–1.16)	0.77 (0.55–1.09)
Q3	15,815	97	1.50 (1.10–2.04)*	1.28 (0.93–1.77)
Q4 (high)	18,104	110	1.73 (1.28–2.35)‡	1.34 (0.95–1.88)
P for trend			<0.001	0.016
HR per 1 mmol/L increment	66,476	344	1.13 (1.06–1.19)‡	1.05 (0.98–1.14)
Triglycerides < 1.69 mmol/L	44,159	209	1.00	1.00
≥1.69 mmol/L	22,317	135	1.59 (1.27–1.99)‡	1.29 (1.01–1.66)*
Triglycerides < 1.69 mmol/L	44,159	209	1.00	1.00
1.69–2.25 mmol/L	9731	56	1.42 (1.05–1.91)*	1.24 (0.91–1.70)
≥2.26 mmol/L	12,586	79	1.75 (1.34–2.28)‡	1.34 (1.00–1.80)
Women				
Fasting triglycerides				
Quartiles				
Q1 (low)	8461	15	1.00	1.00
Q2	8581	24	1.14 (0.59–2.17)	1.01 (0.52–1.97)
Q3	7678	45	1.98 (1.09–3.58)*	1.81 (0.97–3.37)
Q4 (high)	6930	36	1.59 (0.86–2.96)	1.36 (0.70–2.64)
P for trend			0.132	0.342
HR per 1 mmol/L increment	31,650	120	1.10 (0.93–1.31)	1.05 (0.86–1.27)
Triglycerides				
< 1.69 mmol/L	22,924	75	1.00	1.00
≥ 1.69 mmol/L	8726	45	1.12 (0.77–1.63)	1.04 (0.67–1.50)
Triglycerides				
< 1.69 mmol/L	22,924	75	1.00	1.00
1.69–2.25 mmol/L	4277	23	1.19 (0.74–1.91)	1.11 (0.69–1.80)
≥ 2.26 mmol/L	4449	22	1.05 (0.64–1.71)	0.89 (0.53–1.50)
Non-fasting triglycerides				
Quartiles				
Q1 (low)	29,349	50	1.00	1.00
Q2	29,652	68	1.23 (0.85–1.78)	1.19 (0.82–1.73)
Q3	27,576	80	1.46 (1.02–2.09)*	1.28 (0.88–1.87)
Q4 (high)	23228	107	2.23 (1.57–3.17)‡	1.87 (1.28–2.73)†
P for trend			<0.001	<0.001
HR per 1 mmol/L increment	109,805	305	1.35 (1.25–1.47)‡	1.32 (1.20–1.47)‡
Triglycerides				
< 1.69 mmol/L	79,792	178	1.00	1.00
≥ 1.69 mmol/L	30,013	127	1.66 (1.31–2.10)‡	1.43 (1.11–1.84)†
Triglycerides				
< 1.69 mmol/L	79,792	178	1.00	1.00
1.69–2.25 mmol/L	16,353	49	1.20 (0.87–1.65)	1.09 (0.79–1.52)
≥ 2.26 mmol/L	13,660	78	2.22 (1.69–2.93)‡	1.85 (1.37–2.50)‡
Total subjects				
Fasting triglycerides				
Quartiles				
Q1 (low)	13,477	45	1.00	1.00
Q2	13,026	59	1.29 (0.87–1.90)	1.22 (0.82–1.82)
Q3	12,069	79	1.81 (1.25–2.63)†	1.73 (1.17–2.56)†
Q4 (high)	11,858	82	1.87 (1.29–2.72)†	1.71 (1.14–2.59)*
P for trend			<0.001	0.013
HR per 1 mmol/L increment	50,430	265	1.12 (1.02–1.24)*	1.08 (0.96–1.21)
Triglycerides				
< 1.69 mmol/L	35,805	167	1.00	1.00
≥ 1.69 mmol/L	14,625	98	1.34 (1.04–1.72)*	1.22 (0.93–1.62)

(*continued on next page*)

Table 3 (*continued*)

	Person years	No of events	Age and community-adjusted HR (95%CI)	Multivariable HR (95%CI)
Triglycerides				
< 1.69 mmol/L	35,805	167	1.00	1.00
1.69–2.25 mmol/L	6727	46	1.39 (1.00–1.93)	1.31 (0.93–1.84)
≥ 2.26 mmol/L	7898	52	1.30 (0.94–1.78)	1.14 (0.80–1.62)
Non-fasting triglycerides				
Quartiles				
Q1 (low)	46,143	128	1.00	1.00
Q2	45,415	127	1.00 (0.78–1.28)	0.96 (0.75–1.23)
Q3	43,391	177	1.49 (1.18–1.88)‡	1.30 (1.02–1.66)*
Q4 (high)	41,332	217	1.98 (1.58–2.49)‡	1.60 (1.25–2.05)‡
P for trend			<0.001	<0.001
HR per 1 mmol/L increment	176,281	649	1.18 (1.13–1.23)‡	1.12 (1.06–1.18)‡
Triglycerides				
< 1.69 mmol/L	123,951	387	1.00	1.00
≥ 1.69 mmol/L	52,330	262	1.65 (1.41–1.94)‡	1.38 (1.16–1.65)‡
Triglycerides				
< 1.69 mmol/L	123,951	387	1.00	1.00
1.69–2.25 mmol/L	26,084	105	1.32 (1.06–1.64)*	1.18 (0.94–1.48)
≥ 2.26 mmol/L	26,246	157	2.00 (1.65–2.42)‡	1.59 (1.29–1.96)‡

Test for significance: *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.
Q1; 0.26–0.95 mmol/L (23–84 mg/dL), Q2; 0.96–1.30 mmol/L (85–115 mg/dL), Q3; 1.31–1.86 mmol/L (116–165 mg/dL), Q4; 1.87–23.71 mmol/L (166–2100 mg/dL).
Multivariable hazard ratio adjusted for the same variables shown in Table 2.

triglycerides in all subjects. The associations with triglycerides were stronger for ischemic heart disease than for ischemic stroke (Supplemental Table 1).

As shown in Supplemental Table 2, we conducted a sub-analysis with further adjustment for HDL-cholesterol ($n = 5880$). The results were similar to those for total subjects shown in Table 2 and Supplemental Table 1, except for associations with ischemic heart disease for total subjects, which were consistent and significantly positive.

Table 3 shows the associations between triglyceride levels and risk of ischemic cardiovascular disease by fasting status. The associations were positive and did not differ substantially for fasting and non-fasting men, while they were more marked for non-fasting women and total subjects than for fasting subjects. The multivariable hazard ratios (95%CIs) of ischemic cardiovascular disease for the highest versus lowest triglyceride quartiles were 1.75 (1.03–3.07), *P* for trend = 0.056 for fasting men, and 1.34 (0.95–1.88), *P* for trend = 0.016 for non-fasting men, while that for ≥1.69 mmol/L of triglycerides versus the lower levels was 1.31 (0.89–1.95) for fasting men and 1.29 (1.01–1.66) for non-fasting men; that for ≥2.26 mmol/L of triglycerides versus <1.69 mmol/L of triglycerides was 1.28 (0.79–2.08) and 1.34 (1.00–1.80). The corresponding hazard ratios for women were 1.36 (0.70–2.64), *P* for trend = 0.342 and 1.87 (1.28–2.73), *P* for trend < 0.0001; 1.04 (0.67–1.50) and 1.43 (1.11–1.84); and 0.89 (0.53–1.50) and 1.85 (1.37–2.50), respectively, indicating that the significant positive associations were limited to non-fasting women. The corresponding hazard ratios for total subjects were 1.71 (1.14–2.59), *P* for trend = 0.013 and 1.60 (1.25–2.05), *P* for trend < 0.0001; 1.22 (0.80–1.62) and 1.38 (1.16–1.65); and 1.14 (0.80–1.62) and 1.59 (1.29–1.96), respectively. When we looked into ischemic heart disease and ischemic stroke, separately, these positive associations were more evident for non-fasitng than for fasting men, women and total subjects (Supplemental Table 3).

Further adjustment for HDL-cholesterol levels did not result in substantial changes for total subjects (Supplemental Table 4). For example, the multivariable hazard ratios (95%CIs) of ischemic cardiovascular disease for the highest versus lowest quartiles of triglycerides were 1.40 (0.70–2.81), *P* for trend = 0.517 for fasting persons, and 1.46 (1.02–2.08), *P* for trend = 0.005 for non-fasting persons; those for triglycerides ≥1.69 mmol/L versus the lower levels were 0.91 (0.55–1.49) for fasting persons and 1.49 (1.15–1.92) for non-fasting persons; and those for triglycerides ≥2.26 mmol/L and 1.69–2.25 mmol/L versus the lower levels were 0.92 (0.50–1.72) and 0.89 (0.47–1.67), respectively for fasting persons, and 1.62 (1.19–2.21) and 1.36 (0.99–1.87) for non-fasting persons.

4. Discussion

For our large, long-term prospective cohort of Japanese middle-aged residents, we found that, independent of other major cardiovascular risk factors, serum triglycerides levels were positively associated with risk of ischemic cardiovascular disease, and of either ischemic heart disease or ischemic stroke. These associations were more marked for ischemic heart disease than for ischemic stroke. When stratified by fasting status, these associations did not differ substantially between fasting and non-fasting men, but were more marked for non-fasting than for fasting women. For the subsample analysis (55% of total participants) with further adjustment for HDL-cholesterol levels, the results were similar. To the best of our knowledge, this is the first study conducted in an Asian country to examine the associations of non-fasting and fasting triglycerides with risk of cardiovascular disease for individuals who do not live in a western environment and are characterized by a lower prevalence of dyslipidemia than seen in western countries.

The stronger association between triglycerides and risk of ischemic heart disease than risk of ischemic stroke found in our study was consistent with the finding from a previous meta-analysis [5]. Further, the stronger association between triglycerides and risk of ischemic cardiovascular disease for women than for men in the present study was also consistent with the finding of a previous meta-analysis [2], but not with that of another which reported no sex difference [3]. That stronger association for women, in particular non-fasting ones, could be in part due to the smaller variability of non-fasting triglycerides in women than in men [21] because of the estrogen effect [22]. This smaller variability allowed for the representation of long-term non-fasting triglyceride values, so that the association was less attenuated.

As for the mechanisms involved in the positive association between non-fasting triglycerides and risk of ischemic cardiovascular disease, a high postprandial triglyceride level is closely linked with delayed clearance of chylomicron remnants [13,23]. These remnants with enhanced triglycerides and cholesterol esters are taken up into the arterial wall by means other than the LDL-cholesterol receptors, and they have been found to be as atherogenic as LDL-

cholesterol in animal experiments [12]. It is uncertain, however, whether postprandial increments in triglycerides levels differ for men and women. One study showed that the postprandial increment was larger for men than for women [24], while another study indicated that there was no difference in the increments did not differ when the quantity of visceral adipose tissue was equal [25].

High triglyceride levels in either the postprandial or fasting state are associated with increased small LDL particles [26], which may be more atherogenic than larger LDL particles because of increased susceptibility to oxidation [27]. High triglycerides levels are also associated with increased concentrations of factor VII and plasminogen activator inhibitor [13], as well as with enhanced insulin resistance [28] and blood leukocyte counts [29], all of which may accelerate atherosclerotic and thrombotic processes.

Our study's finding that the positive association between triglycerides and risk of ischemic heart disease was similar for fasting and non-fasting men was in agreement with the previous finding by a cohort study of American men enrolled in the Multiple Risk Factor Intervention Trial [9]. Two cohort studies of Japanese men showed a positive association between fasting triglycerides and risk of ischemic heart disease [30,31]. The positive association between triglycerides and risk of ischemic heart disease among women in our study was stronger for non-fasting than fasting status, and this was also consistent with the finding by a cohort study of American women enrolled in the trial of Women's Health Study [10]. However, our study succeeded in providing an integrated picture of potentially differential impacts of fasting and non-fasting triglycerides on risk of ischemic cardiovascular outcomes for men and women in a single cohort.

Our study has several strengths other than its large sample size, prospective design and long-term follow-up. First, we used incident cases of ischemic heart disease and ischemic stroke as the target endpoint because they may be more directly related with triglycerides than are fatal outcomes only. Second, ours was a community-based study of residents, so that our findings are likely to be able to be extrapolated to Japanese populations in general. Third, we examined sex-specific associations of triglycerides with incident ischemic cardiovascular disease stratified by fasting status, which allowed us to examine the impact of postprandial triglyceride concentrations on risk of ischemic cardiovascular disease.

There are, however, several limitations to this study. First, the study participants were not randomly assigned to fasting or non-fasting status because of the observational design. Non-fasting participants were slightly younger and had lower body mass index and blood pressure levels than their fasting counterparts, but other cardiovascular risk factors were similar, and these risk factors were adjusted for the multivariable analyses. Second, over 80 percent of the participants were non-fasting. Thus, our findings pertain primarily to postprandial triglycerides and ischemic cardiovascular disease, as in several previous studies [32–36]. This means that the findings of the investigation to detect the actual associations between fasting triglycerides and risk of ischemic cardiovascular disease were less robust, in particular for women. Third, the single measurement of triglycerides at baseline may have made the associations biased towards the null value because of their random measurement variations, so that the actual associations would be stronger.

Nevertheless, our findings support the usefulness of non-fasting triglyceride measurements in clinical practice and during population screening examinations because patients and participants do not need to attain fasting status, since non-fasting and fasting triglycerides have been shown to be equally predictive for ischemic cardiovascular disease for men, and even more predictive for women. Because over two-thirds of a person's life time is characterized by a non-fasting status, non-fasting triglycerides may reflect more individualized lipid profiles and metabolic status.

In conclusion, non-fasting as well as fasting serum triglycerides were found to be predictive for the risk of ischemic cardiovascular disease for middle-aged Japanese men, as were non-fasting triglycerides for women. The positive associations were stronger for ischemic heart disease than for ischemic stroke.

Author contributions

The authors made the following contributions: H.I.(first author) researched data, conducted the analyses and drafted the manuscript; H.I. (second author) researched data, contributed to the discussion and edited the manuscript; K.Y. researched data, coordinated the implementation of research at Kyowa and contributed to the discussion; T.Ohira, R.C., H.N., T.Okada, S.H., T.T. researched data and contributed to the discussion; S.S. researched data, coordinated the implementation of research at Ikawa and contributed to the discussion; M.K. researched data, coordinated the implementation of research at Minami-Takayasu and contributed to the discussion; A.K. researched data, coordinated the implementation of research at Noichi and Ikawa, and contributed to the discussion. None of the authors has any personal or financial conflict of interest to declare.

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Competing interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2014.08.028.

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分担研究報告書

都市部地域住民における腹囲の変化と2型糖尿病発症の関連：吹田研究

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研究要旨：全身性肥満の変化と2型糖尿病発症の関連についてはこれまで多くの報告があるが、中心性肥満の変化が2型糖尿病発症に及ぼす影響についてはほとんど検討されていない。そこで、都市部住民を対象としたコホート研究であり、日本人の循環器病リスクの研究をおこなっている吹田研究において、中心性肥満の変化と2型糖尿病発症とに関連があるかどうかを検証した。その結果、男女とも腹囲が比較的高い集団において、腹囲の増加は2型糖尿病発症リスクを上昇させることが明らかになり、特に女性においては全身性肥満の指標であるbody mass indexの変化の影響をのぞいても腹囲の増加は2型糖尿尿病発症リスクを上昇させた。このことより、日本人集団で中心性肥満の悪化を予防することは、特に比較的腹囲の大きい集団において、2 型糖尿病発症予防のために重要であることが示唆された。

A. 研究目的

肥満のコントロールは2型糖尿病発症予防において重要である。これまでに多くの研究より、体重増加が2型糖尿病発症リスクを上昇させることが報告されている[1-3]。近年、全身性の肥満度の指標である体重やbody mass index(BMI)よりも中心性肥満の指標である腹囲の方が2型糖尿病発症に対する予測力が高いことが報告された[4]。しかしながら、腹囲の増加が2型糖尿病発症に及ぼす影響については報告が少なく、本邦においては未だ検討されていない。

アジア人種は他の人種と比較して肥満度が低いことに加え[5]、アジア人種が多くを占める中国で行われた研究より、体重の変化と腹囲の変化は必ずしも一致しないことが報告されている[6]。従って、腹囲の増加が2型糖尿病発症に及ぼす影響をアジア人種でも検討する必要がある。そこで、本研究は日本の都市部コホート研究である吹田研究において腹囲の変化と2型糖尿病発症との関連を検討した。

B. 研究方法

1）対象者

大阪府吹田市住民台帳から無作為に抽出され、1989年9月から1994年3月（ベースライン：1 期）に国立循環器病研究センターで健診を受けた 6407 名のうち、1997-1998年度（2期）も受診した3658名を対象とした。そのうち糖尿病既往者、1期と2期の受診間隔が5年未満または9年以上の者、データに欠損値のあった者は除外し、解析対象者は2273名（男性946名、

女性1327名）であった。

2）腹囲の変化の評価とベースライン調査

腹囲は、立位時に臍レベルで測定した。腹囲の変化は、1期と2期の間の腹囲の差(cm)を1期と2期の受診間隔(年)で除した1年あたりの腹囲の変化量(cm/年)より評価した。既往歴や家族歴、生活習慣などは、問診により聴取した。BMIは式：体重(kg)÷身長(m)^{2}より算出した。

3）追跡方法

吹田研究では2年ごとに健康診断を実施しており、1997年度からHbA_{1c}の測定を開始した。健康診断は必ずしも早朝空腹時ではないため、空腹状態を食後8時間以上経過している場合と定義した。2型糖尿病発症の評価は空腹時血糖値126mg/dl以上、随時血糖値200mg/dl以上、HbA_{1c}6.5%以上、糖尿病薬物治療開始のいずれかの初回観察時点とし、2期以降2011年3月まで追跡した。

4）統計解析

性別に1期の腹囲の中央値で2群[低腹囲群、高腹囲群]に層化し、さらに1期から2期における腹囲の変化（cm/年）の3分位点で分類した。腹囲の変化が第2三分位群を基準に第1三分位群と第3三分位群の2型糖尿病発症のハザード比をCox回帰分析を用いて算出した。共変量は年齢、1期の腹囲、HbA_{1c}、糖尿病家族歴、喫煙習慣、飲酒習慣とした。

5）倫理的事項

本研究は疫学研究に関する倫理指針に従い、国立循環器病研究センター倫理委員会の承認を得ておこなった。

C. 研究結果

1期の腹囲の中央値は男性で82cm、女性で75cmだった。各群における腹囲の変化を表に示す。第3三分位群は性別、低腹囲群・高腹囲群にかかわらず、1期から2期にかけて腹囲は増加していた。第1三分位群は1期から2期にかけて腹囲は維持、もしくは減少していた。

1期と2期の平均間隔は6.8年、2期以降の平均追跡期間は9.3年、糖尿病発症者は287名であった。低腹囲群においては男女とも、腹囲の変化と2型糖尿病発症には関連がみられなかった。一方、高腹囲群においては男女とも腹囲の変化が第2三分位群と比較して、第3三分位群で2型糖尿病発症リスクが有意に上昇し、ハザード比と95%信頼区間は男性の第3三分位群では1.84（1.10-3.08）、女性の第3三分位群では2.30（1.31-4.04）であった（図）。いずれの群でも第1三分位群では2型糖尿病発症リスクの低下は見られなかった。

追加解析として、1期から2期のBMIの変化量(kg/m^2/年)を算出し、Cox回帰分析の共変量に加えた。結果、男性においては高腹囲群における第3三分位群のハザード比は1.72（0.98-3.02）、女性の高腹囲群における第3三分位群のハザード比は2.07（1.13-3.79）であり、女性ではBMIの変化量を調整しても腹囲の増加は2型糖尿病発症を有意に上昇させた。また、1期から2期の腹囲の変化とBMIの変化の相関係数は男性の低腹囲群で0.72($p<0.001$)、男性の高腹囲群で0.71($p<0.001$)、女性の低腹囲群

で 0.39($p<0.001$)、女性の高腹囲群で 0.38($p<0.001$)と、女性は男性よりも腹囲の変化と BMI の変化の相関が弱い傾向が見られた。

D. 考察

腹囲が比較的低い群では、男女ともに腹囲の変化と 2 型糖尿病発症に関連がみられなかった。腹囲が比較的高い群では、男女とも、腹囲が増加した群で 2 型糖尿病発症リスクが上昇しが、腹囲が減少した群における 2 型糖尿病発症リスクの低下は見られなかった。1 期から 2 期にかけて腹囲が減少した群は、2 期から追跡終了時までに腹囲が増加していたために腹囲の減少の効果が相殺されたと考えられた。

また、女性においては BMI の変化と独立して、腹囲の増加は 2 型糖尿病発症リスクを上昇させた。この一要因として、女性は男性よりも腹囲の変化と BMI の変化の関連が弱いことが考えられた。

E. 結論

2 型糖尿病発症予防に向けて、比較的腹囲が高い者におけるさらなる腹囲の増加を予防することが重要であり、特に女性においては体重の変化のみではなく、腹囲の変化を評価することが重要であることが示唆された。

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H. 知的財産権の出願・登録状況

なし