厚生労働省科学研究費補助金 循環器疾患・糖尿病等生活習慣病対策総合研究事業
「特定健診・保健指導における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に関する横断・縦断研究」
分担研究報告書

ウエスト周囲長・身長比と循環器疾患発症の関連に年齢の及ぼす影響ー吹田研究ー

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研究要旨：近年、都市部のコホート研究である吹田研究においてウエスト周囲長身長比が循環器疾患のスクリーニング指標として有用であることが示されつつある。そこで、都市部住民を対象としたコホート研究であり、大規模コホート共同研究の一つとして都市部における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ウエスト周囲長身長比の循環器疾患予測マーカーとしての意義を年齢階級別・性別に検証した。50-69 歳の男性ではウエスト周囲長・身長比は循環器疾患、冠動脈疾患の発症リスク上昇と、50-69 歳の女性では脳卒中の発症リスク上昇と有意に関連していた。本研究によりウエスト周囲長・身長比は日本人の中年男女において循環器疾患発症のハイリスク者を特定するのに有用であること、また、そのカットオフ値は性別、年齢階級別に設定されるべきであることが示唆された。

A. 研究目的

ウエスト周囲長と循環器疾患の発症リスクとの関連については、吹田研究をはじめ、多くのコホート研究が報告しているが [1-3]、最近、身長の影響を考慮したウエスト周囲長の指標として、ウエスト周囲長を身長で除したウエスト周囲長身長比が循環器疾患スクリーニング指標として有用であることが広く示されつつある [4,5]。

ただ、ウエスト周囲長、身長ともに年齢・性別により大きく異なるため、本来、ウエスト周囲長身長比は年齢階級別・性別に評価することが重要であるが、これまでそのような研究はほとんどない。そこで、本年度はウエスト周囲長身長比の循環器疾患の予測マーカーとしての意義を年齢階級別・性別に検証した。

B. 研究方法

1）対象者

本研究では吹田市住民から無作為に選ばれ，国立循環器病センターでベースライン調査（1989 年 4 月から 1994 年 3 月）に参加した者で、冠動脈疾患や脳卒中、追跡不能例、データ欠損などにより除外された者をのぞく 5488 名（男性 2600 人、女性 2888）を解析対象とした。

2）ベースライン調査

ウエスト周囲長は立位時に臍レベルで測定し、ウエスト周囲長身長比はウエスト周囲長を身長で除することにより（ウエスト

周囲長(cm)/身長(cm))により計算した。既往歴・喫煙習慣及び飲酒習慣は、問診により聴取した。

3）追跡方法

吹田研究では従来の循環器疾患（脳血管障害・心筋梗塞）の発症をエンドポイントとした追跡にくわえ、冠動脈バイパス術や血管形成術（バルーンやステント留置）も含めて虚血性心疾患としてエンドポイントの拡大を行っている。

発症調査は以下の方法で行っている。①毎年、脳血管障害・心筋梗塞発症状況調査票を送付して、脳血管障害・心筋梗塞の発症を把握する。調査票が未返送の場合、電話等で確認する。②隔年の健診受診時に発症の既往を聞き取る。③人口動態統計(死因統計）から循環器疾患死亡を確認する。①～③の内容を医師研究者が確認し、同意が得られた者を対象に入院時のカルテ調査を行って確定診断を得る。なおカルテ調査が不能または人口動態統計では循環器疾患死亡が確認できるが発症歴が確認できなかったもの場合は「疑い」扱いとした。ただし発症後の同意では本人の意思表示が不可能な場合が散見されるため、今年度から健診受診時に将来発症した際のカルテ調査について予め同意を得ることとした。

4）統計解析

Cox の比例ハザードモデルにより性、年齢、喫煙習慣、飲酒習慣を調整し、循環器疾患（冠動脈疾患と脳卒中）、冠動脈疾患、脳卒中、脳梗塞の発症の多変量調整後のハザード比を算出した。

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

平均約 13.0 年間の追跡期間中に循環器疾患 428 例（冠動脈疾患 184 例、脳卒中 244 例）を認めた。

50-69 歳の男性では、第 1 四分位を基準とした場合（ウエスト周囲長・身長比 0.374-0.475)、総循環器疾患および冠動脈疾患発症での第 4 四分位（ウエスト周囲長・身長比 0.537-0.761）のハザード比は、それぞれ 1.82 倍（95%信頼区間 1.13-2.92)、2.42 倍(95%信頼区間 1.15-5.12)で、有意にリスクが上昇しており、また、ウエスト周囲長・身長比はウエスト周囲長より統計学的に予測力が高いことも示された。

50-69 歳の女性では、第 1 四分位を基準とした場合（ウエスト周囲長・身長比 0.348-0.472)、脳卒中での第 4 四分位（ウエスト周囲長・身長比 0.569-0.838）のハザード比は 2.43 倍（95%信頼区間 1.01-5.85)で、有意にリスクが上昇していた。（図）

追加解析において、第 4 四分位をさらに 2 等分して検討した。その結果、50-69 歳の男性における最も高い区分（ウエスト周囲長・身長比 0.561-0.761 以上）では 2.34(95%信頼区間 1.38-3.97)、70 歳代以上の女性における最も高い区分（ウエスト周囲長・身長比 0.647-0.812）では 2.33(95%信頼区間 1.10-4.94)であった。

D. 考察

50-69 歳代において、男性ではウエスト

周囲長・身長比 0.537 以上であることは循環器疾患、冠動脈疾患の発症リスク上昇と有意に関連しており、女性ではウエスト周囲長・身長比 0.569 以上であることは脳卒中の発症リスク上昇と有意に関連していた。また、70 歳代女性においても、ウエスト周囲長・身長比 0.647 以上と非常に高い範囲では、循環器疾患発症リスクの上昇と有意に関連していた。つまり、ウエスト周囲長・身長比のカットオフ値（基準値）は、性別・年齢階級により、異なっていることが示唆された。

また、今回の研究結果は、一般的に用いられているウエスト周囲長・身長比のカットオフ値である「0.5」は循環器疾患発症に関してハイリスクの人をスクリーニングするという観点においては低すぎる可能性を示唆している。

E. 結論

ウエスト周囲長・身長比と循環器疾患発症の関係は年齢階級により異なっており、特に日本人の中年男女において循環器疾患発症のハイリスク者を特定するのに有用であること、また、そのカットオフ値（基準値）は性別、年齢階級別に設定されるべきであることが示唆された。

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G. 健康危険情報

なし

H. 研究発表

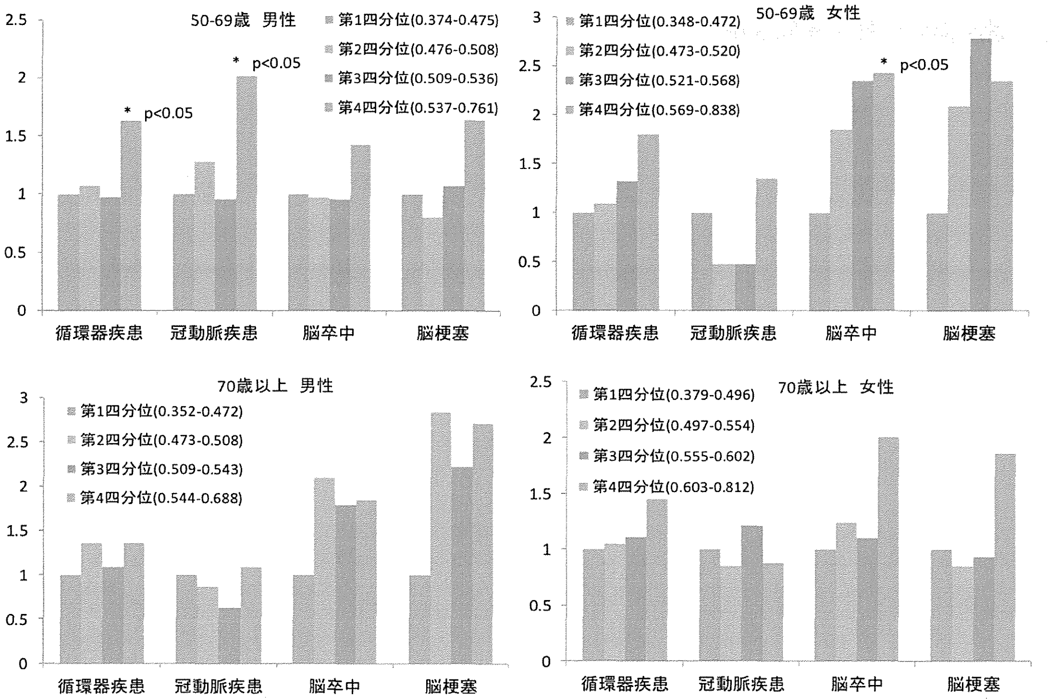
（論文公表）

1) Tatsumi Y, Watanabe M, Kokubo Y, Nishimura K, Higashiyama A, Okamura T, Okayama A, Miyamoto Y. Effect of age on the association between waist-to-height ratio and incidence

of cardiovascular disease: the Suita study. *J Epidemiol.* 2013 ;23:351-9.

H. 知的財産権の出願・登録状況

なし



*統計学的有意差あり（P値<0.05）第1四分位を基準とする

図　ウエスト周囲長身長比（四分位）と循環器疾患

別紙

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
Tatsumi Y, Watanabe M, Kokubo Y, Nishimura K, Higashiyama A, Okamura T, Okayama A, Miyamoto Y.	Effect of age on the association between waist-to-height ratio and incidence of cardiovascular disease: the Suita study.	*J Epidemiol.*	23(5)	351-9	2013

学会発表

発表者氏名	発表タイトル名	学会名	開催場所	発表年
辰巳 友佳子	5-9 年間の腹囲の変化と糖尿病発症リスク：吹田研究	第２４回日本疫学会	仙台	2014
中井　陸運	内臓脂肪蓄積と高血圧発症リスクの検討ー吹田研究	第２４回日本疫学会	仙台	2014

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Original Article

Effect of Age on the Association Between Waist-to-Height Ratio and Incidence of Cardiovascular Disease: The Suita Study

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ABSTRACT

Background: Waist-to-height ratio (WHtR) has been shown to be a useful screening tool for metabolic syndrome and cardiovascular disease (CVD). We investigated the association of WHtR with CVD incidence by age group.
Methods: We conducted a 13.0-year cohort study of Japanese adults (2600 men and 2888 women) with no history of CVD. WHtR was calculated as waist circumference (cm) (WC) divided by height (cm). We stratified participants by sex and age group (30–49, 50–69, ≥70 years). Using the Cox proportional hazards model, we calculated hazard ratios (HRs) and 95% CIs for CVD in relation to WHtR quartile for participants aged 50 to 69 years and 70 years or older.
Results: Men aged 50 to 69 years in the highest quartile had significantly increased risks of CVD and coronary heart disease as compared with the lowest quartile; the HRs (95% CI) were 1.82 (1.13–2.92) and 2.42 (1.15–5.12), respectively. Women aged 50 to 69 years in the highest quartile had a significantly increased risk of stroke (HR, 2.43; 95% CI, 1.01–5.85). No significant results were observed in men or women aged 70 years or older. The likelihood ratio test showed that the predictive value of WHtR was greater than that of WC among men aged 50 to 69 years.
Conclusions: The association between WHtR and CVD risk differed among age groups. WHtR was useful in identifying middle-aged Japanese at higher risk of CVD and was a better predictor than WC of CVD, especially in men.

Key words: waist-to-height ratio; age difference; cardiovascular disease

INTRODUCTION

Obesity and central obesity are closely tied to metabolic risks.[1,2] Waist circumference (WC) is an index of central obesity[3] and is an important component in the diagnostic criteria for metabolic syndrome.[4] Several meta-analyses have reported an association of WC with cardiovascular disease (CVD) and mortality.[5,6] Recently, waist-to-height ratio (WHtR) was shown to be a useful global clinical screening tool for cardiometabolic risk and CVD.[7,8]

WHtR is easy to measure, and the cut-off point for WHtR is subject to less ethnic variation.[7,8] However, WHtR could differ among age groups because whole-body fat distribution and WC change considerably with age[9,10] and because height differs among generations.[11] It is thus important to consider age in assessing the association between WHtR and CVD risk, but few previous studies have done so.[12,13] Therefore, in this long-term prospective cohort study of a Japanese urban population, we investigated the effect of WHtR on CVD risk among participants classified by age group.

METHODS

Study population

The Suita Study is a prospective population-based cohort study of an urban area of Japan and was established in 1989. The details of this study have been described elsewhere.[14–16] Briefly, 6407 men and women aged 30 to 83 years underwent

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a baseline survey at the National Cerebral and Cardiovascular Center between September 1989 and March 1994. Among them, a total of 919 were excluded due to past history of CVD ($n = 208$), loss to follow-up ($n = 535$), and missing data ($n = 176$). The remaining 5488 participants (2600 men and 2888 women) were included in the analysis. This cohort study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center.

Baseline examination

Blood samples were centrifuged immediately after collection, and a routine blood examination was performed, including measurement of serum levels of total cholesterol and glucose. About 96% of participants had fasted for at least 8 hours before the blood test. Well-trained physicians used a standard mercury sphygmomanometer to measure blood pressure in triplicate on the right arm after 5 minutes of rest. Hypertension was defined as systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or use of antihypertensive agents. Diabetes was defined as a fasting plasma glucose level of at least 7.0 mmol/L (126 mg/dL), a non-fasting plasma glucose level of at least 11.1 mmol/L (200 mg/dL), or use of antidiabetic agents. Hypercholesterolemia was defined as a total cholesterol level of at least 5.7 mmol/L (220 mg/dL) or use of antihyperlipidemic agents. Participants were wearing light clothing during height and weight measurement. WC was measured at the umbilical level, with the participant in a standing position. WHtR was defined as WC (cm) divided by height (cm). Body mass index (BMI) was defined as weight (kg) divided by the height (m) squared. Public-health nurses obtained information on participants' smoking, drinking, and medical histories.

Endpoint determination

The endpoint determination has been previously reported.[14–16] The endpoints of the present study were (1) date of first coronary heart disease (CHD) or stroke event; (2) date of death; (3) date of departure from Suita city; or (4) December 31, 2007. The first step in the survey of CHD and stroke was checking the health status of all participants by means of clinical visits every 2 years and a yearly questionnaire (by mail or telephone). For the second step, in-hospital medical records of participants suspected of having CHD or stroke were reviewed by registered hospital physicians, who were blinded to the baseline information. In addition, to complete the survey, we also conducted a systematic search of death certificates to identify cases of fatal CHD and stroke. In Japan, all death certificates are forwarded to the Ministry of Health, Welfare, and Labour and coded for the National Vital Statistics. The criteria for myocardial infarction were based on the World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease projects.[17] In addition to myocardial infarction, we also evaluated coronary angioplasty, coronary artery bypass grafting, and sudden cardiac death, all of which were included in the definition of CHD. Stroke was defined according to criteria from the US National Survey of Stroke and was confirmed by computed tomography.[18] Classification of stroke was based on examination of computed tomography scans, magnetic resonance images, and autopsy findings.

Statistical analysis

To assess the association between age and WHtR, we analyzed mean WC, height, and WHtR according to age in men and women. Pearson product-moment correlation coefficients between height and waist were calculated by sex and age group (30–49, 50–69, ≥70 years). Participants were categorized based on quartiles of WHtR by sex and age group. To compare baseline characteristics among WHtR quartiles, analysis of variance was used for continuous variables and the χ^2 test was used for dichotomous and categorical variables.

The Cox proportional hazards model was used to investigate the association between WHtR and CVD risk only among participants aged 50 to 69 years and 70 years or older, because there were too few CVD cases (men: 17, women: 11) for statistical analysis among those aged 30 to 49 years. Interaction terms were added to the models to assess the interaction between age and WHtR quartile for the risk of CVD. Hazard ratios (HRs) and 95% CIs were computed, and the lowest quartile of WHtR was defined as the reference group. To adjust for confounding factors, we included age, smoking status (current, quit, or never), and drinking status (current, quit, or never) in the model. Cardiometabolic risk factors such as hypertension, diabetes, and hypercholesterolemia were not included in the model because central obesity is upstream in the "metabolic domino".[19] However, in sensitivity analysis, we adjusted for hypertension, diabetes, and hypercholesterolemia to confirm that WHtR was an independent risk factor. The same analysis was performed for WC. In addition, to further assess cut-off points for WHtR, the highest quartile was dichotomized by median WHtR (ie, upper Q4 and lower Q4), and HRs and 95% CIs were estimated. The likelihood ratio test was used to compare the predictive values of WHtR with WC, as follows. First, we calculated the −2 logarithm likelihood for the model including the confounding factors, age, smoking, and drinking status ($-2\,ln[L_c]$). Second, we calculated the −2 logarithm likelihood for the model including the confounding factors plus WHtR ($-2\,ln[L_{c+WHtR}]$). The difference, ie, ($-2\,ln[L_c] - (-2\,ln[L_{c+WHtR}])$), had an approximate χ^2 distribution with 1 degree-of-freedom. The same analysis was performed for WC.

All P values were 2-tailed, and a P value less than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS (Version 20.0J; Japan IBM, Tokyo, Japan).

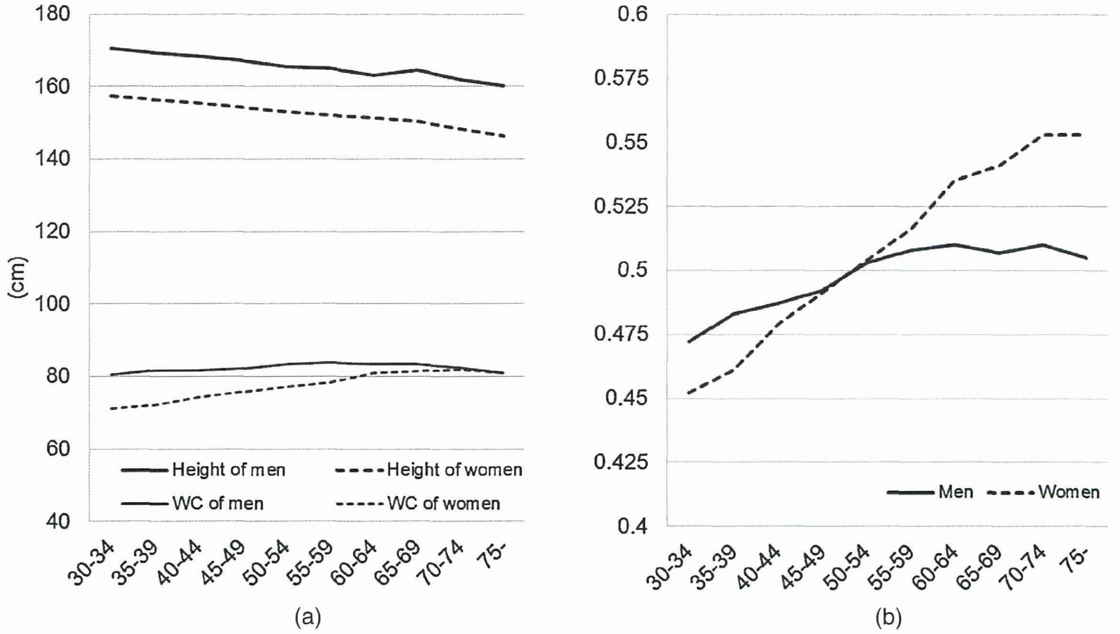

Figure. (a) Average WC (waist circumference), height, and (b) waist-to-height ratio according to age (The Suita Study, Japan)

RESULTS

During the follow-up period (mean, 13.0 years), 428 CVD events (184 CHD and 244 strokes) were observed. The Figure shows average WC, height, and WHtR by sex and age. WC in men increased up to age 50 years, remained almost unchanged from age 50 to 69 years, and decreased at age 70 years or older. WC in women younger than 75 years increased with advancing age and decreased in women aged 75 years or older, as compared with women aged 70 to 74 years. Height decreased with advancing age in both sexes. WHtR in men increased until approximately age 60 years. WHtR in women younger than 75 years increased with advancing age. The Pearson product-moment correlation coefficients (95% CI) between height and WC were 0.16 (0.09–0.22), 0.24 (0.19–0.30), and 0.13 (0.04–0.22) among men aged 30 to 49, 50 to 69, and 70 years or older, respectively, and 0.07 (0.01–0.13), 0.07 (0.02–0.13), 0.09 (−0.003–0.19) among women in the respective age groups.

Tables 1 and 2 summarize the baseline characteristics according to WHtR quartile (results among men and women aged 30–49 years are shown in eTable 1.) The prevalence of hypertension significantly differed by WHtR quartile, except among men aged 70 years or older. The prevalence of hypercholesterolemia and diabetes significantly differed by WHtR quartile among men and women aged 50 to 69 years.

Table 3 shows multivariable-adjusted HRs and 95% CIs for CVD and its subtypes according to WHtR quartile. A significant interaction was observed between age and WHtR for CVD among men (*P* for interaction = 0.02). Men aged 50 to 69 years in the highest quartile had significantly higher risks of CVD and CHD as compared with men in the lowest quartile; the HRs (95% CI) were 1.82 (1.13–2.92) and 2.42 (1.15–5.12), respectively. There were significant linear increases in the HRs for CVD, CHD, and ischemic stroke in men aged 50 to 69 years. After further adjustment for hypertension, diabetes, and hypercholesterolemia, the HRs (95% CI) were 1.46 (0.90–2.36) and 1.89 (0.89–4.03), respectively (eTable 3). Women aged 50 to 69 years in the highest quartile had a significantly higher risk of stroke than did those in the lowest quartile; the HR (95% CI) was 2.43 (1.01–5.85). There were significant linear increases in the HRs of CVD and stroke in women aged 50 to 69 years. After further adjustment for hypertension, diabetes, and hypercholesterolemia, the HR (95% CIs) was 2.06 (0.84–5.04) (eTable 3).

When men aged 50 to 69 years in the highest quartile were dichotomized by median WHtR (0.56), the HR (95% CI) for CVD was 1.37 (0.76–2.46) for those in the lower WHtR group and 2.34 (1.38–3.97) for those in the upper WHtR group (eTable 2). When women aged 70 years or older in the highest quartile were dichotomized by median WHtR (0.65), the HR for CVD was 1.42 (0.63–3.18) for those in the lower WHtR group and 2.33 (1.10–4.94) for those in the upper WHtR group. After adjustment for hypertension, diabetes, and hypercholesterolemia, the HRs in the upper WHtR decreased but remained significant, ie, 1.78 (1.04–3.05) among men aged 50 to 69 years and 2.16 (1.02–4.61) among women aged 70 years or older.

Table 4 shows the HRs and 95% CIs for CVD in relation to WC quartile. Among men aged 50 to 69 years in the highest quartile, the HR for CVD was 1.63 (1.03–2.59), although the HRs of CVD did not show a significant linear increase in this group. Among women aged 50 to 69 years, a significant linear

Table 1. Baseline characteristics of men, according to age group and quartile of waist-to-height ratio: The Suita Study, Japan

	Q1 (low)	Q2	Q3	Q4 (high)	*P*-value
Age 50–69 years					
No. of subjects	308	304	304	308	
Waist-to-height ratio	0.374–0.475	0.476–0.508	0.509–0.536	0.537–0.761	
Waist, cm	74.0 ± 4.3	81.2 ± 2.9	85.7 ± 3.1	92.8 ± 5.5	<0.01
Height, cm	165.0 ± 5.3	164.9 ± 5.6	164.4 ± 5.4	163.7 ± 5.3	0.01
Age, years	59.0 ± 5.3	59.1 ± 5.2	59.1 ± 5.5	59.4 ± 5.3	0.77
Body mass index, kg/m^2	20.1 ± 1.7	22.1 ± 1.5	23.7 ± 1.5	25.9 ± 2.3	<0.01
Hypertension, %	31	35	45	51	<0.01
Diabetes, %	6	7	9	11	0.045
Hypercholesterolemia, %	23	28	40	35	<0.01
Smoking status (current/quit/never), %	58/25/17	50/31/19	46/35/19	44/38/19	0.01
Drinking status (current/quit/never), %	79/2/19	74/4/22	79/4/17	76/4/21	0.58
Age ≥70 years					
No. of subjects	120	120	124	119	
Waist-to-height ratio	0.352–0.472	0.473–0.508	0.509–0.543	0.544–0.688	
Waist, cm	70.6 ± 5.0	79.8 ± 3.4	84.9 ± 3.3	92.2 ± 5.6	<0.01
Height, cm	162.5 ± 6.0	162.2 ± 5.7	161.3 ± 5.3	159.3 ± 6.0	<0.01
Age, years	74.0 ± 3.0	73.5 ± 2.7	74.1 ± 2.7	73.7 ± 2.9	0.40
Body mass index, kg/m^2	18.5 ± 1.7	21.3 ± 1.7	22.7 ± 1.4	25.6 ± 2.0	<0.01
Hypertension, %	42	44	51	57	0.07
Diabetes, %	4	7	7	8	0.70
Hypercholesterolemia, %	23	29	26	31	0.46
Smoking status (current/quit/never), %	37/48/16	42/41/18	38/47/15	30/50/19	0.66
Drinking status (current/quit/never), %	58/8/33	62/11/28	62/6/32	65/8/28	0.73

Continuous data with a normal distribution were analyzed with analysis of variance: mean ± SD.
Dichotomous and categorical data were analyzed with the χ^2 test.
Q, quartile; hypertension was defined as systolic blood pressure/diastolic blood pressure ≥ 140/90 mm Hg or current use of antihypertensive medications; diabetes was defined as a fasting plasma glucose level ≥ 7.0 mmol/L, a non-fasting plasma glucose level ≥ 11.1 mmol/L, or current use of antidiabetic medications; hypercholesterolemia was defined as a total serum cholesterol level ≥ 5.7 mmol/L or current use of antihyperlipidemic medications.

increase was observed in the HRs for CVD (*P* for trend = 0.04). However, after further adjustment for hypertension, diabetes, and hypercholesterolemia, these associations were no longer significant among men or women.

The χ^2 values for the likelihood ratio test were 6.49 ($P = 0.01$) for WHtR and 3.63 ($P = 0.06$) for WC among men aged 50 to 69 years, and 4.45 ($P = 0.03$) for WHtR and 4.54 ($P = 0.03$) for WC among women aged 50 to 69 years.

DISCUSSION

Our main findings were that WHtR was significantly positively associated with CVD and CHD risk among men aged 50 to 69 years and with stroke risk among women aged 50 to 69 years. Among men, there was a significant interaction between age and WHtR for CVD incidence. Among women aged 50 to 69 years, there was a borderline association between a WHtR in the highest quartile and increased CVD risk. In addition, among women aged 70 years or older, a WHtR in the upper level of the highest quartile was associated with significantly elevated CVD risk. These findings suggest that the association between WHtR and CVD incidence differs according to age and sex.

Two previous studies, in the United States and China, reported that the association between WHtR and CVD risk was stronger among younger adults as compared with elderly adults.[12,13] We too observed a significantly stronger association between WHtR and CVD risk among relatively young adults (age 50–69 years) as compared with elderly adults (age ≥70 years), which supports the results of previous studies. Consequently, these findings suggest that age stratification is important in estimating the association between WHtR and CVD risk.

In this population, physical frame, eg, WC and height, differed by age group. It has been reported that WC and the ratio of abdominal fat to whole-body fat differ by age.[9,10] In addition, the National Health and Nutrition Examination Survey in Japan noted that height clearly differed by generation.[11] This generational difference in physical frame, as well as aging, could lead to age differences in the association between WHtR and CVD risk.

A recent meta-analysis reported an optimal cut-off point of 0.50 for WHtR in both sexes.[7] However, the present findings suggest that, regardless of age or sex, a cut-off of 0.50 is somewhat low for identifying individuals at higher risk for CVD. The association with CVD risk was of at least

Table 2. Baseline characteristics of women, according to age group and quartile of waist-to-height ratio: The Suita Study, Japan

	Q1 (low)	Q2	Q3	Q4 (high)	*P*-value
Age 50–69 years					
No. of subjects	337	340	335	339	
Waist-to-height ratio	0.348–0.472	0.473–0.520	0.521–0.568	0.569–0.838	
Waist, cm	67.3 ± 4.1	75.4 ± 3.3	82.7 ± 3.4	92.1 ± 6.6	<0.01
Height, cm	153.0 ± 4.7	151.8 ± 4.9	152.1 ± 5.1	150.3 ± 5.2	<0.01
Age, years	57.6 ± 5.3	58.5 ± 5.3	59.5 ± 5.2	60.5 ± 5.4	<0.01
Body mass index, kg/m^2	19.8 ± 2.0	21.7 ± 2.0	23.1 ± 2.3	25.9 ± 3.3	<0.01
Hypertension, %	21	32	36	52	<0.01
Diabetes, %	2	3	5	9	<0.01
Hypercholesterolemia, %	49	57	57	62	0.01
Smoking status (current/quit/never), %	11/2/86	11/3/86	9/3/88	12/5/84	0.43
Drinking status (current/quit/never), %	26/2/73	29/2/69	28/2/71	31/1/68	0.75
Postmenopausal, %	90	94	95	94	0.06
Age ≥70 years					
No. of subjects	103	103	103	103	
Waist-to-height ratio	0.379–0.496	0.497–0.554	0.556–0.602	0.603–0.812	
Waist, cm	68.1 ± 4.4	77.3 ± 4.1	85.6 ± 3.6	95.2 ± 6.4	<0.01
Height, cm	148.4 ± 5.5	147.7 ± 6.1	148.1 ± 5.1	145.8 ± 5.1	<0.01
Age, years	73.8 ± 2.9	73.4 ± 2.7	73.8 ± 2.7	74.0 ± 2.6	0.56
Body mass index, kg/m^2	19.1 ± 2.1	21.3 ± 2.3	23.1 ± 2.1	26.2 ± 2.9	<0.01
Hypertension, %	53	44	50	64	0.03
Diabetes, %	2	5	6	4	0.54
Hypercholesterolemia, %	42	51	53	52	0.32
Smoking status (current/quit/never), %	12/6/83	9/4/87	6/5/89	7/5/88	0.78
Drinking status (current/quit/never), %	22/5/73	18/2/81	19/1/80	19/4/77	0.62
Postmenopausal, %	100	100	100	100	1.00

Continuous data with a normal distribution were analyzed with analysis of variance: mean ± SD.
Dichotomous and categorical data were analyzed with the χ^2 test.
Q, quartile; hypertension was defined as systolic blood pressure/diastolic blood pressure ≥ 140/90 mm Hg or current use of antihypertensive medications; diabetes was defined as a fasting plasma glucose level ≥ 7.0 mmol/L, a non-fasting plasma glucose level ≥ 11.1 mmol/L, or current use of antidiabetic medications; hypercholesterolemia was defined as a total serum cholesterol level ≥ 5.7 mmol/L or current use of antihyperlipidemic medications.

borderline significance for a WHtR in the fourth quartile, except among men aged 70 years or older. Additional analyses showed that the risks markedly increased, particularly in the upper level of the fourth WHtR quartile, among men aged 50 to 69 years and women aged 70 years and older. These results suggest the presence of a threshold rather than a dose-response relation for WHtR, although the present sample was too small to confirm this hypothesis. Additionally, we think that cut-offs should be set in relation to age and sex. On the basis of our results, we propose the following cut-offs (which do not include men aged 70 years or older): 0.560 for men aged 50 to 69 years, 0.569 for women aged 50 to 69 years, and 0.647 for women aged 70 years or older.

The risk of CVD among men aged 50 to 69 years, and women aged 70 years, in the upper level of the highest quartile was significantly elevated even after adjustment for hypertension, hyperlipidemia, and diabetes. We believe that there are 2 possible explanations for this finding. First, an extremely high WHtR might actually be an independent risk factor ie, separate from classical cardiometabolic risks. It has been reported that abdominal obesity is related to increased levels of plasminogen activator inhibitor-1, which can lead to blood coagulation.[20] Such background mechanisms might be important. Second, our findings could be due to insufficient adjustment for confounders in the Cox regression model. Irrespective of the reason, men aged 50 to 69 years, and women aged 70 years or older, with extremely high WHtRs have a considerably higher risk for CVD and should be closely monitored.

We previously investigated the association between WC and CVD risk without age stratification[21] and found a significant association between WC and the risks of CVD and stroke among women but no significant association among men. However, the present age-stratified analysis of WC suggests that our previous results were substantially influenced by age. Therefore, we compared WHtR and WC in relation to CVD in analysis stratified by age group and found that the HRs associated with the highest quartile of WHtR were higher than those associated with WC among middle-aged men and that the predictive value of WHtR was greater than that of WC. Several previous studies reported similar results[12,22–24]; therefore our findings are consistent with those

Table 3. Multivariable-adjusted hazard ratios for cardiovascular disease according to sex, age group, and quartile of WHtR: The Suita Study, Japan

	Q1 (low)	Q2	Q3	Q4 (high)	*P* for trend
Men					
Age 50–69 years					
Person-years	4070	3069	3879	3842	
CVD, no. of cases	28	31	32	47	
HRs	1	1.14 (0.68–1.90)	1.23 (0.74–2.05)	1.82 (1.13–2.92)	0.01
CHD, no. of cases	10	16	16	23	
HRs	1	1.57 (0.71–3.47)	1.72 (0.77–3.80)	2.42 (1.15–5.12)	0.02
Stroke, no. of cases	18	15	16	24	
HRs	1	0.91 (0.46–1.81)	0.95 (0.48–1.87)	1.56 (0.84–2.89)	0.16
Ischemic stroke, no. of cases	10	9	15	18	
HRs	1	0.99 (0.40–2.43)	1.59 (0.71–3.56)	2.06 (0.94–4.49)	0.04
Age ≥70 years					
Person-years	1055	1128	1193	1155	
CVD, no. of cases	21	29	27	30	
HRs	1	1.36 (0.77–2.39)	1.09 (0.62–1.93)	1.36 (0.78–2.38)	0.45
CHD, no. of cases	13	11	10	15	
HRs	1	0.87 (0.39–1.97)	0.63 (0.28–1.45)	1.09 (0.52–2.30)	0.99
Stroke, no. of cases	8	18	17	15	
HRs	1	2.09 (0.90–4.81)	1.79 (0.77–4.15)	1.84 (0.78–4.35)	0.29
Ischemic stroke, no. of cases	4	12	10	11	
HRs	1	2.84 (0.91–8.83)	2.22 (0.69–7.07)	2.71 (0.86–8.53)	0.18
Women					
Age 50–69 years					
Person-years	4811	4863	4477	4470	
CVD, no. of cases	16	18	21	33	
HRs	1	1.09 (0.56–2.14)	1.32 (0.69–2.54)	1.80 (0.98–3.32)	0.04
CHD, no. of cases	9	4	4	13	
HRs	1	0.47 (0.14–1.51)	0.47 (0.14–1.54)	1.35 (0.56–3.22)	0.43
Stroke, no. of cases	7	14	17	20	
HRs	1	1.85 (0.75–4.60)	2.35 (0.97–5.70)	2.43 (1.01–5.85)	0.04
Ischemic stroke, no. of cases	3	7	9	10	
HRs	1	2.09 (0.54–8.10)	2.78 (0.75–10.33)	2.35 (0.63–8.77)	0.22
Age ≥70 years					
Person-years	1095	1259	1164	1094	
CVD, no. of cases	15	15	13	24	
HRs	1	1.00 (0.48–2.08)	0.91 (0.43–1.93)	1.83 (0.95–3.53)	0.08
CHD, no. of cases	6	7	5	9	
HRs	1	1.23 (0.40–3.77)	0.98 (0.29–3.32)	1.78 (0.62–5.14)	0.34
Stroke, no. of cases	9	8	8	15	
HRs	1	0.85 (0.32–2.23)	0.88 (0.34–2.29)	1.92 (0.83–4.45)	0.11
Ischemic stroke, no. of cases	5	4	4	9	
HRs	1	0.83 (0.22–3.16)	0.77 (0.21–2.91)	1.99 (0.66–6.04)	0.21

Multivariable adjustment was performed for age, smoking, and drinking status. Parentheses indicate 95% CIs for HRs.
Abbreviations: WHtR, waist-to-height ratio; Q, quartile; CVD, cardiovascular disease; CHD, coronary heart disease; HR, hazard ratio.

of previous studies. In contrast, WHtR and WC had similar predictive values for CVD among women in the present study. Many previous studies found that WHtR was similar to WC in predicting CVD risk among women.[12,22,24–26] The effect of dividing WC by height might be limited because the correlation of WC with height is weaker among women than among men. Consequently, we believe that WHtR is a better predictor than WC, particularly among middle-aged men.

The superiority of WHtR might be explained by the fact that WHtR, as measured by computed tomography, was more closely correlated than WC with intra-abdominal fat,[27] and a previous study reported that intra-abdominal fat was positively associated with number of cardiometabolic risk factors.[28] In addition, shorter adults tend to have more cardiometabolic risk factors than do taller individuals with a similar WC.[29] This suggests that WHtR, ie, dividing WC by height, is more strongly related than WC to cardiometabolic risk factors. Thus, we believe that WHtR better reflects the accumulation of cardiometabolic risks and leads to superior prediction of CVD.

BMI, along with indices of central obesity, has been an important obesity index in predicting CVD incidence,[30] although a meta-analysis reported that the predictive power of WHtR for CVD was higher than that of BMI.[7] Another report found a significant association between BMI and CVD after adjustment for WHtR[12] and suggested that WHtR and BMI are independently associated with CVD risk. Therefore, it might be better to use both BMI and WHtR to assess obesity.

Table 4. Multivariable-adjusted hazard ratios for cardiovascular disease according to sex, age group, and quartile of WC: The Suita Study, Japan

	Q1 (low)	Q2	Q3	Q4 (high)	*P* for trend
Men					
Age 50–69 years					
Person-years	4078	4004	3872	3806	
CVD, no. of cases	32	33	29	44	
HRs	1	1.07 (0.66–1.75)	0.97 (0.58–1.61)	1.63 (1.03–2.59)	0.06
CHD, no. of cases	13	17	12	23	
HRs	1	1.28 (0.62–2.63)	0.96 (0.44–2.12)	2.02 (1.02–4.02)	0.07
Stroke, no. of cases	19	16	17	21	
HRs	1	0.97 (0.50–1.88)	0.96 (0.49–1.86)	1.43 (0.76–2.67)	0.31
Ischemic stroke, no. of cases	13	9	13	17	
HRs	1	0.80 (0.34–1.87)	1.07 (0.49–2.31)	1.64 (0.79–3.41)	0.15
Age ≥70 years					
Person-years	999	1208	1200	1124	
CVD, no. of cases	25	28	27	27	
HRs	1	0.94 (0.55–1.62)	0.91 (0.53–1.58)	1.06 (0.61–1.84)	0.87
CHD, no. of cases	14	11	12	12	
HRs	1	0.67 (0.30–1.47)	0.65 (0.30–1.43)	0.82 (0.38–1.78)	0.60
Stroke, no. of cases	11	17	15	15	
HRs	1	1.29 (0.60–2.77)	1.21 (0.55–2.66)	1.36 (0.62–2.99)	0.52
Ischemic stroke, no. of cases	5	10	10	12	
HRs	1	1.70 (0.58–4.98)	1.82 (0.62–5.37)	2.26 (0.79–6.47)	0.14
Women					
Age 50–69 years					
Person-years	4669	4685	5046	4221	
CVD, no. of cases	15	18	25	30	
HRs	1	1.19 (0.60–2.36)	1.43 (0.75–2.71)	1.87 (1.00–3.51)	0.04
CHD, no. of cases	7	5	5	13	
HRs	1	0.74 (0.24–2.34)	0.65 (0.21–2.08)	1.86 (0.73–4.72)	0.18
Stroke, no. of cases	8	13	20	17	
HRs	1	1.56 (0.65–3.77)	2.06 (0.90–4.70)	1.93 (0.82–4.54)	0.11
Ischemic stroke, no. of cases	4	6	9	10	
HRs	1	1.44 (0.41–5.10)	1.70 (0.52–5.54)	2.00 (0.62–6.52)	0.23
Age ≥70 years					
Person-years	1175	1234	1046	1157	
CVD, no. of cases	16	16	15	20	
HRs	1	1.05 (0.52–2.11)	1.11 (0.54–2.25)	1.45 (0.74–2.83)	0.28
CHD, no. of cases	8	6	7	6	
HRs	1	0.85 (0.29–2.49)	1.21 (0.43–3.43)	0.88 (0.30–2.59)	0.98
Stroke, no. of cases	8	10	8	14	
HRs	1	1.24 (0.49–3.14)	1.10 (0.41–2.93)	2.00 (0.83–4.87)	0.15
Ischemic stroke, no. of cases	5	4	4	9	
HRs	1	0.85 (0.23–3.21)	0.93 (0.25–3.47)	1.86 (0.61–5.61)	0.24

Multivariable adjustment was performed for age, smoking, and drinking status. Parentheses indicate 95% CIs for HRs.
Abbreviations: WC, waist circumference; Q, quartile; CVD, cardiovascular disease; CHD, coronary heart disease; HR, hazard ratio.

Our study has several limitations. First, the number of cases of CVD among participants aged 30 to 49 years was insufficient for statistical analysis. Further study is required to confirm an association between WHtR and CVD risk among younger adults. Second, the effect of visceral fat could not be estimated because we did not use computed tomography to measure abdominal fat distribution. Third, changes in WHtR during the follow-up period were not considered in the present study. Finally, because WC was measured once, the estimated risks might have been underestimated because of regression dilution bias.[31]

In conclusion, the present findings suggest that WHtR is useful in identifying middle-aged Japanese at higher risk of CVD and is more predictable than WC in determining CVD risk, especially among men. In addition, the data indicate that WHtR cut-off points should be set according to sex and age. This study enrolled a limited Japanese population, and further studies with larger and more ethnically diverse samples are required to confirm our findings.

ONLINE ONLY MATERIALS

eTable 1. Baseline characteristics and CVD incidence among men and women aged 30–49 years according to quartile of waist-to-height ratio: the Suita Study, Japan.

eTable 2. Multivariable-adjusted hazard ratios for cardiovascular disease in the upper and lower fourth quartile of WHtR according to sex and age group: the Suita Study, Japan.

eTable 3. Multivariable-adjusted hazard ratios for cardiovascular disease according to sex, age group, and quartile of WHtR: the Suita Study, Japan.
Abstract in Japanese.

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エビデンス創出に関する横断・縦断研究」
分担研究報告書

吹田コホートにおける血圧とLDLコレステロールの脳・心血管疾患発症へのインパクト

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アジア人の地域住民集団において血圧とLDLコレステロールが重積した際の脳･心血管疾患の危険性はほとんど検討されていない。本研究では、日本人都市住民集団において血圧と脳・心血管疾患の関連におけるLDLコレステロールの交互作用の有無について検討した。対象者5,151名（30-79歳）を、LDLコレステロールカテゴリー（<140 and ≥140mg/dL / 服薬）と血圧カテゴリー（至適血圧、前高血圧、高血圧）の6グループを組み合わせて、脳・心血管疾患発症との関連を検討した。血圧 - 脳･心血管疾患の関連における高LDLコレステロール血症の交互作用の有無は、尤度比検定で検討した。13年間の観察期間中（追跡人年合計 67,287人年）、冠動脈疾患164名、脳卒中215名（うち脳梗塞126名）の発症を認めた。正常LDLコレステロール群では、冠動脈発症の多変量調整ハザード比は、前高血圧：2.01（95%信頼区間, 95% CI：0.92-4.42）、高血圧：4.71（95% CI：2.28-9.74）であった。一方、高LDLコレステロール血症群では、至適血圧： 2.09（95% CI：0.88-4.98）、前高血圧： 3.45（95%信頼区間, 95% CI.：1.59-7.51）、高血圧： 5.94（95% CI：2.28-12.27）であった。一方、脳梗塞発症の多変量調整ハザード比は、同じ血圧レベルでみると正常・高LDLコレステロール血症群の間で違いはなかった。血圧 - 脳・心血管疾患の関連における高LDLコレステロール血症の交互作用は、冠動脈疾患、脳梗塞のいずれも統計学的に有意ではなかった。

A. 研究目的

高血圧が日本人の脳・心血管疾患の最も重要な危険因子である事は、多くのコホート研究で普遍的に確認されている。これらの得られたエビデンスに基づき、血圧レベルとその他の危険因子を組み合わせ、個々人の循環器疾患のリスクの層別化が行われてきた。

1999年に発表されたWHO/ISHガイドライ[1]では、Framingham研究において45～80歳を10年間追跡した際の心血管疾患発症の絶対リスクに基づき、血圧と他の危険因子の組み合わせを用いて、低・中・高・超高の4段階のリスクに層別化している。また、ESH-ESC2007 ガイドライン[2]でも、WHO/ISHガイドラインと同様に危険因子による4段階のリスク層別化が行われている。2014年に改定された日本高血圧学会による高血圧治療ガイドラインでも[3]、高血圧の重

症度に基づいた３つの分類及び血圧以外の危険因子による３層のリスク層の組み合わせを用いて、低・中・高の３段階に分類する脳・心血管リスクの層別化評価を提唱している。

一方、脂質異常症から見ても高血圧の合併は脳・心血管疾患リスクを増大させる。動脈硬化性疾患予防ガイドライン 2012 年版 [4] では、これまでに行われてきた相対リスク評価から、NIPPON DATA80 のリスク評価チャート[5]に基づく絶対リスク評価へとシフトし、喫煙状況、収縮期血圧値、総コレステロールの組み合わせにより、性差・年齢も加味したリスク評価を行うこととされている。

しかしながらリスクチャートでバーチャルな予測を行った研究を別にすれば、日本人の地域集団で、高血圧と高コレステロール血症の組み合わせによる脳・心血管疾患発症との関連を前向きにみた研究はほとんどない。一つの理由は、日本人でも高コレステロール血症と冠動脈疾患の関連は明確であるのに対して、脳卒中、脳梗塞との関連は明確ではないことがあげられる[6]。すなわち冠動脈疾患が少なく脳卒中が多い日本人集団では、高コレステロール血症のリスクを描出しにくい。そこで地域コホートとしては冠動脈疾患発症率が高い都市集団において、血圧と LDL コレステロールの脳・心血管疾患発症へのインパクト、それらの交互作用を検証した。

B. 研究方法

１）対象とベースライン調査

吹田研究は、1989 年に吹田市の住民台帳から 30～79 歳の 12,200 名を無作為抽出し、その中で同意が得られた 6,485 名を第一次コホートとして追跡している。このうち脳・心血管疾患の既往歴がなく、空腹採血でトリグリセライド 400mg/dl 未満、データ欠損のない 5,151 名（男性 2399 名、女性 2752 名）を今回の解析対象とし、2007 年末まで追跡した。吹田研究は国立循環器病研究センターの倫理委員会の承認を得て実施されている。

２）追跡方法

脳・心血管疾患（脳卒中・冠動脈疾患）の発症をエンドポイントとして追跡を行った。発症の転帰は以下の方法により把握した。① 毎年、脳卒中・心筋梗塞発症状況調査票を送付して、脳卒中・心筋梗塞の発症を把握する。調査票が未返送の場合、電話等で確認する。② ２年に１回の健診受診時に発症の既往を聞き取る。③ 人口動態統計（死因統計）から循環器疾患死亡を確認する。①～③の内容を研究者が確認し、同意が得られた者を対象に入院時のカルテ調査を行い確定診断を得た。なおカルテ調査が不能または人口動態統計では循環器疾患死亡が確認できるが発症歴が確認できなかったものの場合は「疑い」扱いとした。また心筋梗塞以外の冠動脈イベントの情報も収集されており、本研究では冠動脈形成術、冠動脈バイパス術についてもエンドポイントに加えた。さらに原因不明の内因性急性死も把握した。したがって本研究の冠動脈疾患は、急性心筋梗塞、冠動脈形成術または冠動脈バイパス術の施行、24 時間以内の内因性急性死で構成されている。

３）統計解析

対象者は、至適血圧（収縮期血圧 <120 and 拡張期血圧 <80 mmHg）、前高血圧（収縮期血圧 120-139 and/or 拡張期血圧 80-90 mmHg）、高血圧（収縮期血圧 ≥ 140 and/or 拡張期血圧 ≥ 90 mmHg and/or 降圧剤服薬中）

と高LDL(low density lipoprotein)コレステロール血症（LDL コレステロール 140 mg/dl 以上または脂質低下剤服薬中）と正常LDLコレステロール（LDL コレステロール＜140mg/dl）の組み合わせで6グループに分類された。そして至適血圧かつ正常LDLコレステロールを基準とした時の各群の冠動脈疾患、脳梗塞の発症リスクをCoxの比例ハザードモデルで検討した。調整変数として年齢、HDL コレステロール、糖尿病、喫煙、飲酒を用い、ハザード比は性別をストラータに入れて算出した。

C. 研究結果

血圧とLDLコレステロールで分類した6グループ別のベースラインの危険因子等の分布を表1（男性）、表2（女性）に示した。男女とも血圧区分が高くなるに従って年齢やBMI、糖尿病の有病率も高くなっていた。また女性では同じ血圧区分であれば、高LDL コレステロール群のほうが年齢が高かった。

13 年間の観察期間中（追跡人年合計67,287 人年）、冠動脈疾患164名、脳卒中215名（うち脳梗塞126名）の発症を認めた。図1に血圧とLDLコレステロールで分類した6グループ別の冠動脈疾患および脳梗塞のハザード比を示した。

正常LDLコレステロール群では、冠動脈発症の多変量調整ハザード比は、前高血圧:2.01 (95%信頼区間, 95% CI: 0.92-4.42)、高血圧：4.71（95% CI: 2.28-9.74）であった。一方、高LDLコレステロール血症群では、至適血圧: 2.09 (95% CI: 0.88-4.98)、前高血圧： 3.45（95%信頼区間, 95% CI.: 1.59-7.51）、高血圧： 5.94（95% CI: 2.28-12.27）であった。

一方、脳梗塞発症の多変量調整ハザード比は、正常LDLコレステロール群では、前高血圧：1.69（95% CI: 0.82-3.48)、高血圧：2.70（95% CI: 1.37-5.35）であった。一方、高LDLコレステロール血症群では、至適血圧： 0.47（95% CI: 0.13-1.69），前高血圧： 1.36（95%信頼区間, 95% CI.: 0.60-3.11）、高血圧： 2.95（95% CI: 1.47-5.90）であり、同じ血圧レベルでみると正常と高LDLコレステロール群の間でリスクの違いはなかった。

なお血圧 - 循環器疾患の関連におけるLDL-C の交互作用は、冠動脈疾患、脳梗塞のいずれも統計学的に有意ではなかった。

D. 考察

脳・心血管疾患の包括的予防対策という面でもリスクの層別化は非常に重要である。特に血圧以外の危険因子を意識しながら、総合的に相対リスクや絶対リスクを判断してリスク管理を行うことができる点が有用である。先述の 2014 年度版高血圧治療ガイドラインでは[3]、血圧以外の危険因子として、65 歳以上の高齢者、喫煙、脂質異常症、肥満、メタボリックシンドローム・若年発症の心血管疾患の既往歴を示している。また各種臓器障害や心血管変の既往も評価することになっており、これらの個数あるいは組み合わせによって、同じ血圧分類でも異なったリスク評価がなされる。また血圧以外の危険因子がある場合は、血圧に対する管理・治療以外にそれぞれの危険因子に対応した管理・治療も同時に行う必要があり、このような包括管理で効果的な予防が可能である。

しかしながら他の危険因子と比べて脂質異

常、特にその根幹である高 LDL コレステロール血症のリスクを日本人の地域集団で評価することは困難であった。幾つかの研究で、日本人でも LDL コレステロールまたは総コレステロールの高値が冠動脈疾患の危険因子であることは示されているが、高血圧と合併した場合、単独の場合と比してどの程度リスクが上がるかについてはエビデンスがなかった。交互作用こそ有意ではないが、高血圧と高 LDL コレステロール血症が合併すると、至適血圧かつ正常 LDL コレステロールと比し、冠動脈疾患のリスクが約 6 倍となり、これは高血圧単独の 4.7 倍よりも大きい。また有意差はないものの正常 LDL コレステロールの前高血圧と至適血圧の高 LDL コレステロール血症の冠動脈疾患ハザード比は約 2 倍でありほぼ同じであった。一方、脳梗塞に関連するのは主に高血圧であり、高 LDL コレステロール血症はリスクの上昇にほとんど影響も与えていないことが示され、これは既存の日本のコホート研究における LDL コレステロールと脳梗塞の関連と同様であった。脳梗塞の予防のためのはまず高血圧管理が重要、しかし冠動脈疾患については高血圧と高 LDL コレステロール血症の両方の管理が必要と考えられた。

E. 結論

日本人都市住民集団のコホート研究で、高血圧と高 LDL コレステロール血症の組み合わせと冠動脈疾患、脳梗塞発症の関連を検討した。相乗的な交互作用はないものの、高血圧と高 LDL コレステロール血症があると冠動脈疾患の発症リスクはそれぞれ単独の場合よりも高くなり、このような対象者は冠動脈疾患予防のための包括的管理の対象と考えられた。一方、脳梗塞の予防にはまず高血圧管理が重要であることも示された。本研究は日本人地域住民集団で初めて高血圧と高 LDL コレステロール血症の相乗、相加作用について検証し得た。

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F. 健康危険情報

なし

G. 研究発表

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