日本人は滋賀県住民、米国白人はペンシルバニア州ピッツバーグ市近郊住民

危険因子	日本人(N= 281)	米国白人(N= 306)	有意差
年齢(歳)	45	45	NS
LDLコレステロール(mg/dl)	134	135	NS
最大血圧(mmHg)	124	123	NS
空腹時血糖値(mg/dl)	106	101	P<0.05
喫煙率(%)	47	7	P<0.05

文献10から

表１　日米 40 歳代男性の古典的危険因子の比較

2002年～2006年に調査。日本人は滋賀県住民、米国白人はピッツバーグ近郊住民、日系米国人はハワイ在住の日系人

危険因子	日本人	日系人		米国白人	
	N= 281	N= 281	有意差 (vs. 日本人)	N= 306	有意差 (vs. 日本人)
年齢(歳)	45	46	P<0.05	45	NS
LDLコレステロール(mg/dl)	134	122	P<0.05	135	NS
高脂血症治療中(%)	3	23	P<0.05	12	P<0.05
収縮期血圧(mmHg)	124	127	P<0.05	123	NS
高血圧治療中(%)	4	20	P<0.05	8	NS
空腹時血糖値(mg/dl)	106	112	P<0.05	101	P<0.05
糖尿病治療中(%)	1	6	P<0.05	1	NS
喫煙率(%)	47	13	P<0.05	7	P<0.05

文献10から

表２　40 歳代男性の古典的危険因子の比較：ERA-JUMP 研究

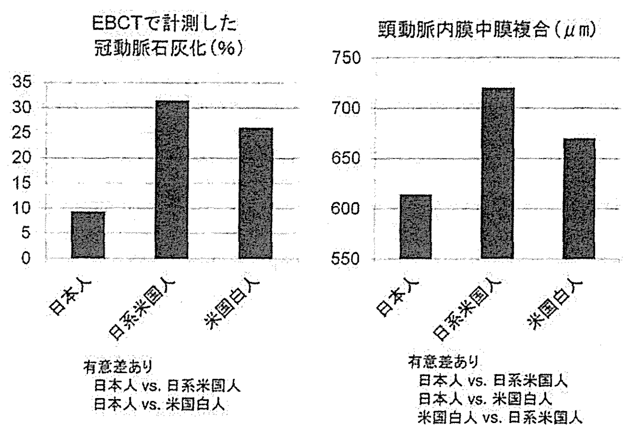
も日米差を認めなかった。要するに古典的な危険因子だけを見ると日本人のリスクプロフィールのほうが米国白人より動脈硬化を進行させやすい状態にあると考えられた。しかし両集団で動脈硬化所見を比較すると、LDL－C レベルがまったく同じこの年代でも、日本人集団のほうが米国に比して動脈硬化所見が軽度であった。例えば冠動脈石灰化の有病率は日本人 9.3 %、米国白人 26.1 %、IMT の厚さは日本人 614μm、米国白人 670μm であり有意差があった。すなわち将来的に冠動脈性疾患を発症率が米国白人集団より高くなるとは考えにくかった。

表２はハワイの日系人集団も加えて日米の古典的危険因子を比較・再掲した結果である。ハワイ日系人の喫煙率は日本人に比べて米国白人に近いレベルにまで低くなっていたが、空腹時血糖値、収縮期血圧値はハワイの集団で高かった。また LDL コレステロールはハワイ日系人で最も低かったが、高脂血症治療中の割合は最も高く、実質的にこの三集団で大きな差はなかった。表３ではその他の危険因子と肥満度（Body Mass Index, BMI）を比較している。その結果、日本人と米国白人の比較で日本人のほうが“良い”と考えられた危険因子は、High Density Lipoprotein (HDL) コレステロール、BMI、高感度 CRP、フィブリノーゲン、N－3 系脂肪酸（魚介類由来）であり、日本人のほうがずっと痩身で、炎症反応や血栓形成性が低く、魚介類の摂取が多いと考えられた。一方、ハワイの日系人ではこれらの危険因子はほぼ米国白人と同じレベルであり、“日本人”

危険因子	日本人 (N= 281)	日系人 (N= 281)	有意差 (vs. 日本人)	米国白人 (N= 306)	有意差 (vs. 日本人)
HDLコレステロール (mg/dl)	53.3	47.5	P<0.05	47.5	P<0.05
トリグリセライド(mg/dl)	152	184	P<0.05	151	NS
BMI (kg/㎡)	23.6	27.9	P<0.05	27.9	P<0.05
インスリン(μIU/ml)	10.2	15.2	P<0.05	15.3	P<0.05
HOMA-IR	2.67	4.19	P<0.05	3.82	P<0.05
高感度CRP(mg/L)	0.65	1.34	P<0.05	1.64	P<0.05
フィブリノーゲン(mg/dl)	254	318	P<0.05	291	P<0.05
血中脂肪酸濃度(mg/dl)	245	243	NS	237	NS
魚介類N-3系脂肪酸(%)	9.2	4.8	P<0.05	3.9	P<0.05

文献10から

表３　40 歳代男性のその他の危険因子の比較：ERA-JUMP 研究



文献10から

図３　40 歳代男性の潜在性動脈硬化所見の比較：ERA-JUMP 研究

としての危険因子上の優位性は消失していた。図３に示すように三集団の動脈硬化所見を比較すると、日系米国人の動脈硬化所見の進行度は米国白人と同等以上であり、日本人とは大きな差を認めた。

本研究からは日本と米国の冠動脈疾患の絶対リスクの差の規定要因として、肥満関連指標と魚介類由来のＮ−３系脂肪酸の摂取が大きく関与している可能性が示唆された。したがって、体型を痩身に保つことと、魚を多く食べる食生活を続けることが日本人の冠動脈疾患の絶対リスクを低く抑えるために重要と考えられた。

６．ACC/AHA ガイドラインにおける絶対リスク評価の考え方

日本でガイドライン 2012 が発表された翌年の2013 年に、米国では ACC/AHA の新しいガイドラインが公表された。そして個人の絶対リスクは New Pooled Cohort ASCVD Risk equations（以下、Pooled Risk equations）で評価されることになった[11]。このガイドラインの治療方針はスタチン治療の適否を軸に構築されている。そしてスタチンの有効性と安全性から、治療が有益と判断される対象として、（１）二次予防、（２）LDL−C が 190mg/dl 以上、（３）LDL−C が 70−189mg/dl の糖尿病患者（40 − 75 歳）、（４）LDL−C が 70 − 189mg/dl、40 − 75 歳で 10 年間の動脈硬化性疾患の絶対リスクが 7.5 ％以上の者、の４つが定義されている。このうち（１）〜（３）は現行の日本のガイドラインから見ても、管理目標値がないことは別として、少なくとも服薬治療の対象とすることに特に異論はないと思われる。ここで

どのような人が治療対象になっているのか最もわかりにくいのは（4）ということになり、「絶対リスク7.5％以上」はこのPooled Risk equationsで算出される。この計算ツールはダウンロード等で容易に入手できるが、これをアジア人に用いると絶対リスクを過剰評価する危険性があることがこのガイドラインにも明記されている。

また今回のPooled Risk equationsでは冠動脈疾患だけでなく脳卒中もエンドポイントに入っている点が日本人への適用をさらにややこしくしている。日本人の脳卒中リスクは欧米よりも高いため、これをエンドポイントに加えると絶対リスクは高くなる。ところが日本人では高コレステロール血症と脳卒中・脳梗塞の関連は弱く、これは主に脳梗塞の病型の違い（日本人ではアテローム血栓性梗塞が少ない）が関与している。そして冠動脈疾患が少ないため、日本人で冠動脈疾患と脳卒中を一つのエンドポイントにすると高コレステロール血症のリスクがほとんど描出されなくなる。一見、脳・心血管疾患を合わせて見るという考え方は合理的であるが、わが国で冠動脈疾患発症率があまり増加していない理由の一つとして、以前から積極的に脂質管理を推進してきたことも関与している。そのため冠動脈疾患発症率が低いという日本人の長所を維持するためには、今後もむしろ冠動脈疾患にターゲットを絞った脂質管理指針のほうが適切かもしれない。いずれにせよ日本人の絶対リスクは日本人集団で評価すべきであり、「借り物」の式を使うのは望ましくない。

7．おわりに

最初に述べたように動脈硬化性疾患の予防の基本は危険因子の適切な管理である。個人が複数の危険因子を併せ持つことは珍しいことではないため、絶対リスクを総合的に判断して治療指針を決めることが重要となる。ガイドライン2012は、現時点の日本人の最良のエビデンスから構築されており、わが国の動脈硬化性疾患の実態に合致している。しかしながらよりきめ細かい予防介入を行うためには、更に大規模なコホート集団に基づいた絶対リスク評価が必要であり、今後も日本人集団における疫学研究、臨床研究によるエビデンスの蓄積が必要とされている。

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Impact of Chronic Kidney Disease on Carotid Atherosclerosis According to Blood Pressure Category
The Suita Study

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Background and Purpose—We aimed to clarify the association of chronic kidney disease (CKD) with carotid atherosclerosis and the impact of CKD on carotid atherosclerosis according to blood pressure categories in an urban general population.

Methods—We studied 3466 Japanese individuals (35–93 years old) in the Suita Study. Carotid atherosclerosis was expressed as the maximum carotid intima-media thickness and the presence of stenosis (>25%). The estimated glomerular filtration rate was calculated using the equations recommended by the Japanese Society of Nephrology. CKD was defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2. Blood pressure categories were defined by the European Society of Hypertension and European Society of Cardiology 2007 criteria.

Results—The multivariable-adjusted maximum carotid intima-media thickness and odds ratio for stenosis in subjects with estimated glomerular filtration rate <50 mL/min per 1.73 m^2 were greater than those in subjects with estimated glomerular filtration rate ≥90 mL/min per 1.73 m^2. When subjects were stratified according to blood pressure categories, the multivariable-adjusted maximum carotid intima-media thickness was significantly greater in CKD subjects than in non-CKD subjects only in subjects with hypertension. Similarly, the impact of CKD on stenosis was evident only in subjects with hypertension (multivariable-adjusted odds ratios for stenosis [95% confidence interval] were 2.21 [1.53–3.19] in non-CKD/hypertension and 3.16 [2.05–4.88] in CKD/hypertension compared with non-CKD/optimal blood pressure).

Conclusions—In a general population, the association of CKD with carotid atherosclerosis was modest, but CKD was independently associated with carotid atherosclerosis in subjects with hypertension. (***Stroke*. 2013;44:3537-3539.**)

Key Words: carotid artery diseases ■ carotid intima-media thickness ■ hypertension ■ renal insufficiency, chronic

Chronic kidney disease (CKD) has been shown to be an independent risk factor for cardiovascular disease in general populations.[1] Recently, we have shown that even slight renal dysfunction, with an estimated glomerular filtration rate (eGFR) of 50 to 59 mL/min per 1.73 m^2, results in an increased risk of cardiovascular disease in an urban general population.[2]

One possible explanation for the association of CKD with cardiovascular disease is that CKD-related nontraditional risk factors accelerate atherosclerosis independent of traditional vascular risk factors.[3] However, there is controversy as to whether CKD is independently associated with carotid intima-media thickness (IMT).[4] This may be because the impact of CKD, especially mild kidney disease, on carotid atherosclerosis is somewhat limited. CKD seems to increase the risk of carotid atherosclerosis when hypertension and impaired glucose metabolism are present.[5] We hypothesized that the impact of CKD on carotid atherosclerosis differs according to the presence of concomitant cardiovascular risk factors. Thus, we aimed to clarify the association of CKD with carotid atherosclerosis and the impact of CKD on carotid atherosclerosis according to blood pressure (BP) categories in an urban general population.

Patients and Methods

We sequentially enrolled 3,446 individuals (1,844 women and 1,602 men, 35–93 years old [62±11 years]) who underwent regular health checkups and carotid ultrasonography between April 2002 and March 2004 from the participants in the Suita Study, an epidemiological study of cerebrovascular and cardiovascular diseases. Each index of

Received July 23, 2013; accepted August 19, 2013.

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This article encompasses the doctoral dissertation of Dr Ohara.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.113.002957/-/DC1.

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***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.113.002957**

Table 1. Adjusted Max-IMT According to eGFR Category

	eGFR, mL/min per 1.73 m²				*P* Value for Trend
	≥90	60–89	50–59	<50	
Men	236	1106	174	86	
Age adjusted	1.44±0.04	1.47±0.02	1.52±0.05	1.64±0.07*	0.078
Multivariable adjusted	1.43±0.04	1.48±0.02	1.51±0.05	1.63±0.07*	0.134
Women	436	1214	137	57	
Age adjusted	1.21±0.02	1.20±0.01	1.22±0.03	1.38±0.05†	0.014
Multivariable adjusted	1.21±0.02	1.20±0.01	1.21±0.03	1.34±0.05*	0.079

Means±SD (mm). eGFR indicates estimated glomerular filtration rate; and max-IMT, maximum carotid intima-media thickness.
**P*<0.05 and †*P*<0.01 vs eGFR≥90.

carotid atherosclerosis was defined as follows. Max-IMT was defined as the maximum IMT in the entire scanned area. Stenosis was defined as the presence of a stenotic area ≥25% on a cross-sectional scan. The eGFR was calculated using equations recommended by the Japanese Society of Nephrology.[6] The subjects were categorized into 4 groups (eGFR ≥90, 60–89, 50–59, and <50 mL/min per 1.73 m²) as in our previous study.[2] CKD was defined as an eGFR <60 mL/min per 1.73 m². BP categories (optimal, normal, high-normal BP, and hypertension) were based on the European Society of Hypertension and European Society of Cardiology 2007 criteria.[7] The association of eGFR category with carotid atherosclerosis and the association of CKD with carotid atherosclerosis according to BP categories were examined using analysis of covariance and logistic regression analysis, after adjusting for cardiovascular risk factors as covariates (see Methods in the online-only Data Supplement).

Results

CKD was identified in 16.2% (eGFR=50–59: 10.9%; eGFR<50: 5.3%) of men and in 10.5% (7.4%, 3.1%) of women (see Table I in the online-only Data Supplement.). The multivariable-adjusted max-IMT and odds ratio for stenosis in subjects with eGFR<50 were significantly greater than those in subjects with eGFR≥90; however, the max-IMT and odds ratio in subjects with eGFR=50 to 59 were not significantly different from those in subjects with eGFR≥90 (Tables 1 and 2). Consequently, the max-IMT and odds ratio for stenosis in the whole CKD sample were not significantly greater than those in the eGFR≥90 group.

When subjects were stratified according to BP categories, the multivariable-adjusted max-IMT in the hypertension category was significantly greater in both sexes. The max-IMT was significantly greater in CKD subjects than in non-CKD subjects only in subjects with hypertension (Figure [A]). The prevalence of stenosis was higher in subjects with high-normal BP and hypertension in all subjects. The impact of CKD on the prevalence of stenosis was more pronounced in subjects with hypertension (multivariable-adjusted odds ratio [95% confidence interval], 2.21 [1.53–3.19] in non-CKD/hypertension and 3.16 [2.05–4.88] in CKD/hypertension; Figure [B]). Similar trends were found in the analysis of stenosis in men.

Discussion

In our study, CKD was independently associated with carotid atherosclerosis in subjects with hypertension, but not in nonhypertensive subjects. This is the first study to show the combined impact of CKD and hypertension on carotid atherosclerosis in an urban general population.

In previous studies in general populations, only one study reported that reduced kidney function was a strong predictor of greater carotid IMT at baseline and progression of carotid atherosclerosis independent of vascular risk factors.[8] Another study found no independent association of eGFR with carotid IMT.[9] In our study, eGFR <50 mL/min per 1.73 m²

Table 2. Adjusted Odds Ratios (95% CI) for Stenosis According to eGFR Category

	eGFR, mL/min per 1.73 m²				Odds Ratio/10 mL per min eGFR Increase
	≥90	60–89	50–59	<50	
Men and women	672	2320	311	143	
Cases of stenosis	47	318	69	48	
Age adjusted	1	1.09 (0.78–1.53)	1.34 (0.87–2.06)	1.91 (1.16–3.14)	0.94 (0.88–1.01)
Multivariable adjusted	1	1.17 (0.83–1.66)	1.37 (0.88–2.13)	1.79 (1.07–2.98)	0.94 (0.88–1.01)
Men	236	1106	174	86	
Cases of stenosis	22	226	51	32	
Age adjusted	1	1.37 (0.84–2.23)	1.71 (0.96–3.04)	1.86 (0.96–3.04)	0.95 (0.87–1.03)
Multivariable adjusted	1	1.56 (0.94–2.57)	1.85 (1.02–3.36)	1.81 (0.91–3.59)	0.95 (0.87–1.04)
Women	436	1214	137	57	
Cases of stenosis	25	92	18	16	
Age adjusted	1	0.85 (0.52–1.37)	0.99 (0.50–1.96)	2.38 (1.12–5.06)	0.93 (0.84–1.04)
Multivariable adjusted	1	0.84 (0.51–1.38)	0.91 (0.45–1.84)	2.04 (0.93–4.47)	0.95 (0.85–1.06)

CI indicates confidence interval; and eGFR, estimated glomerular filtration rate.

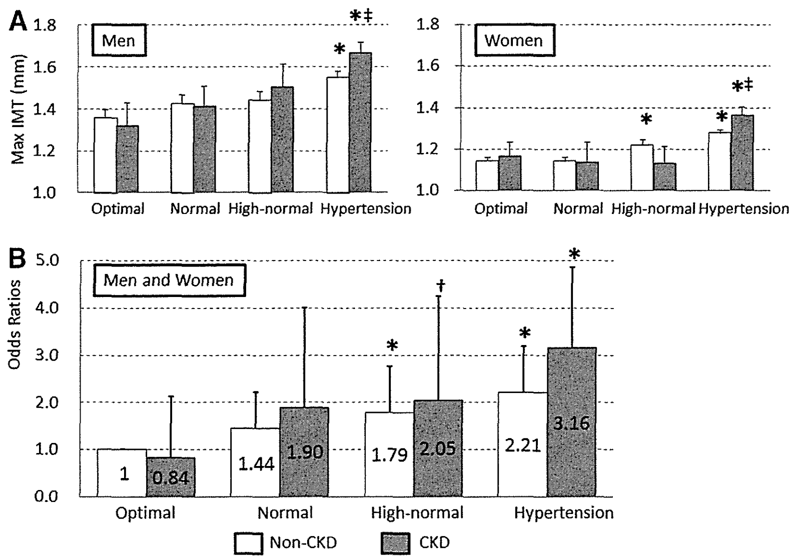

Figure. Multivariable-adjusted maximum carotid intima-media thickness (max-IMT; **A**) and odds ratios for stenosis (**B**) according to blood pressure (BP) category in subjects with and without chronic kidney disease (CKD). *$P<0.05$; †$P=0.053$ vs non-CKD/optimal BP; ‡$P<0.05$ vs non-CKD subjects in the same BP category.

was independently associated with carotid atherosclerosis, whereas CKD was not. The inconsistent results of these studies might be attributable in part to different eligibility criteria, background, or methods for evaluating renal function. An alternative explanation is that the association of CKD with carotid atherosclerosis may be somewhat limited.

In a recent Japanese study, CKD was associated with increased IMT only in subjects with hypertension.[5] Similarly, we showed that CKD was independently associated with carotid atherosclerosis in subjects with hypertension, whereas there was no significant impact of CKD in nonhypertensive subjects. Our results suggest that the impact of CKD on carotid atherosclerosis differs according to the presence of concomitant vascular risk factors. CKD may not directly contribute to early carotid atherosclerosis but may rather accelerate the development of atherosclerosis in the setting of progressive endothelial dysfunction in those with hypertension.

We could not demonstrate a causal relationship between CKD, hypertension, and carotid atherosclerosis because of the cross-sectional design of our study. However, carotid atherosclerosis reflects the cumulative effects of cardiovascular risk factors that are present over many years. In the future, we plan to determine whether the coexistence of CKD and hypertension increases the risk of carotid atherosclerosis in a prospective study.

In conclusion, the association of CKD with carotid atherosclerosis was modest, but CKD was independently associated with carotid atherosclerosis in subjects with hypertension in an urban general population. Our results suggest that the presence of hypertension should be considered for risk stratification of CKD for improved stroke prevention.

Acknowledgments

We thank Drs Masao Shinomiya and Katsuyuki Kawanishi, the president and vice-president of the Suita Medical Association, respectively, and all members of the Suita Medical Association, the Suita City Health Center, Satsuki-Junyukai, and the Division of Preventive Cardiology.

Sources of Funding

This study was supported by the Japan Heart Foundation and the Astellas/Pfizer Grant for Research on Atherosclerosis Update, the Intramural Research Fund of the National Cerebral and Cardiovascular Center (22-4-5), and Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (Grant Numbers 23390138/23591288).

Disclosures

None.

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Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Impact of Chronic Kidney Disease on Carotid Atherosclerosis According to Blood Pressure Category: The Suita Study

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Stroke. 2013;44:3537-3539; originally published online October 1, 2013;
doi: 10.1161/STROKEAHA.113.002957
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

SUPPLEMENTAL MATERIAL

Impact of chronic kidney disease on carotid atherosclerosis according to blood pressure: The Suita Study

Supplemental Methods

The Suita Study

Suita City is located adjacent to Osaka City, which belongs to the second largest metropolitan area in Japan. The Suita Study, an epidemiological study of cerebrovascular and cardiovascular diseases, is based on a random sampling of 12,200 Japanese urban residents.[1, 2] The participants have been visiting the National Cerebral and Cardiovascular Center every 2 years since 1989 for regular health checkups. Written informed consent was obtained from all participants. This study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center.

Evaluation of renal function

Serum creatinine (Cr) was measured by the kinetic Jaffé method. The estimated glomerular filtration rate (eGFR) was calculated from the Cr value and age, using equations recommended by the Japanese Society of Nephrology.[3]

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 194 \times \text{age}^{-0.287} \times \text{Cr}^{-1.094} \text{ (for men)}$$

$$\text{and eGFR (mL/min/1.73m}^2\text{)} = 194 \times \text{age}^{-0.287} \times \text{Cr}^{-1.094} \times 0.739 \text{ (for women).}$$

Carotid Ultrasound Measurements

Carotid atherosclerosis was evaluated by high-resolution ultrasonography with a 7.5-MHz transducer that produced an axial resolution of 0.1 mm. We measured the carotid arteries from the superior border of the collarbone to the inferior margin of the mandible. Details of the methods used for the carotid ultrasonic examination have been previously published.[4]

Measurement of Blood Pressure

Well-trained physicians measured blood pressure (BP) three times with the subject in a seated position using a mercury column sphygmomanometer, an appropriately sized cuff and a standard protocol. Before the initial BP reading was obtained, participants were seated at rest for at least 5 minutes. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken as the average of the second and third measurements, which were separated by more than 1 minute. Subjects were classified into one of four BP categories (optimal, normal, high-normal and hypertension) based on BP values according to the European Society of Hypertension and European Society of Cardiology (ESH-ESC) 2007 criteria[5]: optimal (SBP <120 mmHg and DBP <80 mmHg), normal (SBP=120~129 mmHg and DBP=80~84 mmHg), high-normal BP (SBP=130~139 mmHg and DBP=85~89 mmHg), and hypertensive (SBP ≥140 mmHg and DBP ≥90 mmHg or the use of antihypertensive drugs). If the SBP and DBP readings for a subject were in different categories, the subjects were categorized into the higher of the two BP categories.

Covariates

We performed routine blood tests that included serum total cholesterol, HDL cholesterol and glucose levels. Fasting serum glucose categories were defined as follows[6]: diabetes mellitus (DM, fasting serum glucose ≥7.0 mmol/L (126 mg/dL) or the use of medications for DM), impaired fasting glucose (fasting serum glucose levels from 5.6~6.9 mmol/L (100~125 mg/dL), and normoglycemia (fasting serum glucose levels <5.6 mmol/L (<100 mg/dL). Physicians or nurses administered questionnaires covering personal habits and present illness. Smoking and drinking status were divided into current, former and never. Body mass index (BMI) was calculated as weight (kg) divided by height $(m)^2$.

Statistical analysis

The association of GFR category with carotid atherosclerosis index was examined using analysis of covariance (ANCOVA) to compare the maximum intima-media thickness among subjects according to GFR category. In addition, logistic regression analysis was to estimate odds ratios (OR) and 95% confidence intervals (CI) for the relationship between stenosis and each GFR category, adjusting for covariates (age, smoking and drinking status, BP category, blood glucose category, total and HDL cholesterol (quartile), and body mass index). To examine the combined impact of CKD and

BP category on carotid atherosclerosis, we analyzed the association between BP category and the carotid atherosclerosis index in subjects with and without CKD, using ANCOVA and logistic regression analysis, adjusting covariates (age, smoking and drinking status, blood glucose category, total and HDL cholesterol and body mass index). A P value <0.05 was considered significant for all comparisons. All analyses were performed with SAS statistical software (version 8.2; SAS Institute, Cary, NC, USA).

Supplemental Table I. Characteristics of study subjects according to eGFR category

	GFR in men, mL/min/1.73m^2 (n = 1602)				GFR in women, mL/min/1.73m^2 (n = 1844)			
	≤90	60-89	50-59	<50	≤90	60-89	50-59	<50
Patients, n	236	1106	174	86	436	1214	137	57
Age, y	57±11	67±11	72±8	78±7	59±9	64±11	71±9	74±8
BP category								
Optimal BP, %	31	20	14	8	35	31	21	9
Normal BP, %	18	19	19	11	18	19	10	5
High normal BP, %	13	17	12	11	15	13	14	11
Hypertension, %	38	44	55	70	32	37	55	75
Diabetes mellitus, %	14	11	13	15	7	5	8	9
Total cholesterol, mg/dL	199±33	199±31	200±30	196±35	215±32	217±31	216±32	207±33

HDL cholesterol, mg/dL	59±16	55±14	52±13	51±13	66±16	65±15	61±13	63±16
Body mass index, kg/m^2	23±3	23±3	23±3	23±3	22±3	22±3	23±3	22±4
Current smoking, %	43	29	20	17	8	6	6	4
Current drinking, %	74	68	58	50	32	27	20	16

Values are the means±standard deviation or percent.
GFR, glomerular filtration rate; BP, blood pressure; HDL, high-density lipoprotein

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J Epidemiol 2013;23(5):351-359
doi:10.2188/jea.JE20130004

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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Received January 18, 2013; accepted April 18, 2013; released online June 29, 2013

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

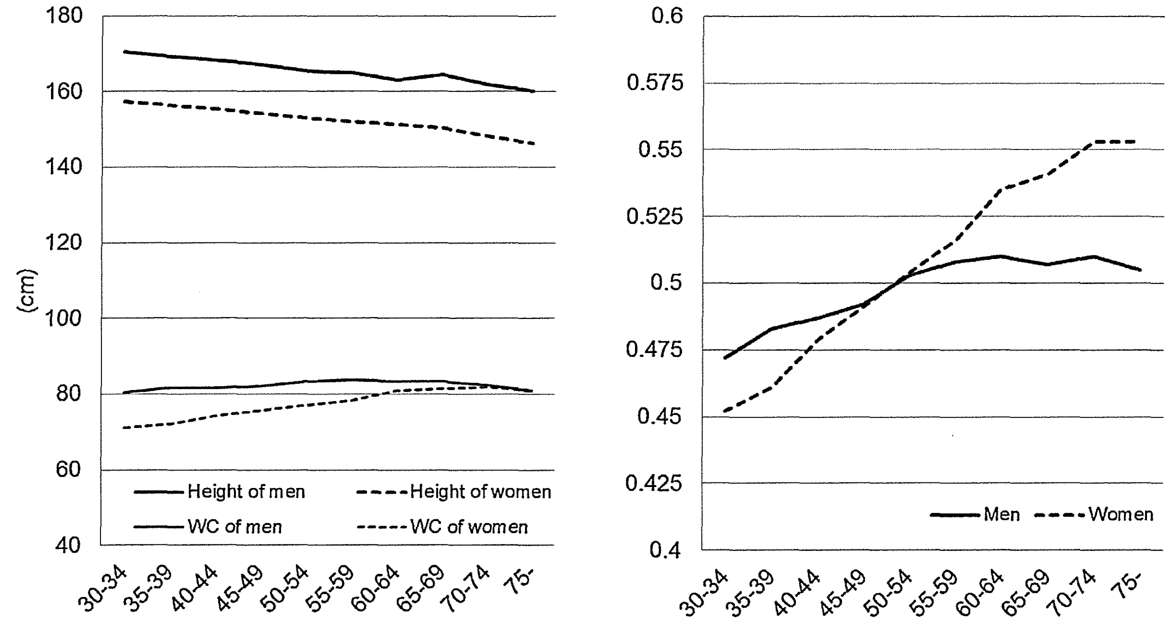
The endpoint determination has been previously reported.[14–16] The endpoints of the present study were (1) date of first coronary heart disease (CHD) or stroke event; (2) date of death; (3) date of departure from Suita city; or (4) December 31, 2007. The first step in the survey of CHD and stroke was 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).



(a) (b)

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.