Predictive Value of Lipoprotein Indices for Residual Risk of Acute Myocardial Infarction and Sudden Death in Men With Low-Density Lipoprotein Cholesterol Levels <120 mg/dl

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Several epidemiologic studies have demonstrated that plasma low-density lipoprotein cholesterol (LDL-C) profile is a key risk indicator for coronary heart disease (CHD). However, almost half of all patients with CHD have normal LDL-C levels. A total of 7,931 male subjects aged ≥40 years from the general population with no cardiovascular history and no use of lipid-lowering agents were followed for incidence of acute myocardial infarction (AMI) and sudden death. Of the 4,827 participants with LDL-C levels <120 mg/dl, 55 subjects had a first AMI/sudden death during an average of 5.5 years of follow-up. After adjustment for confounding factors, multiadjusted hazard ratios (HRs) were increased by 1 SD for non-high-density lipoprotein cholesterol (non-HDL-C; HR = 1.36, 95% confidence interval [CI], 1.02 to 1.81), total cholesterol (TC)/HDL-C ratio (HR = 1.40, 95% CI: 1.11 to 1.78) and LDL-C/HDL-C ratio (HR = 1.32, 95% CI: 1.02 to 1.73) but not for LDL-C (HR = 1.09, 95% CI: 0.82 to 1.44) and HDL-C (HR = 0.84, 95% CI: 0.68 to 1.04). When stratified as categorical variables on the basis of points with highest accuracy on receiver operating characteristic analysis, non-HDL-C levels >126 mg/dl (HR = 1.25, 95% CI: 1.03 to 1.51), TC/HDL-C ratio above 3.5 (HR = 1.22, 95% CI: 1.01 to 1.48) and LDL-C/HDL-C ratio >1.9 (HR = 1.25, 95% CI: 1.04 to 1.51) had increased multiadjusted HRs for AMI/sudden death. In conclusion, in men with LDL-C levels <120 mg/dl, non HDL-C, TC/HDL-C, and LDL-C/HDL-C ratios have predictive value for residual risk of AMI/sudden death. **(Am J Cardiol 2013;112:1063–1068)**

Low-density lipoprotein cholesterol (LDL-C) has been identified as a key risk factor for coronary heart disease (CHD) by several epidemiological[1] and interventional[2] studies. However, almost half of all patients with CHD have normal LDL-C levels.[3] Therefore, the main question is whether there is any residual coronary risk associated with other lipid parameters even at normal LDL-C levels. High-density lipoprotein cholesterol (HDL-C) has been identified as one of the major risk factors that modify LDL-C target by the current National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines.[4] Non-HDL-C and the ratios of total cholesterol (TC) or LDL-C to HDL-C have been revealed to have predictive power for atherosclerotic cardiovascular disease[5,6] and provide incremental predictive value over TC or LDL-C levels.[7,8] Thus, these indices may be the parameters for CHD-related risk even in individuals with normal LDL-C levels; however, this remains unclear because prospective epidemiologic data are limited. The objective of the present study was to investigate whether lipid parameters including LDL-C, HDL-C, non-HDL-C, TC/HDL-C ratio, or LDL-C/HDL-C ratio are correlated with the development of CHD at LDL-C levels <120 mg/dl in the Japanese general population.

Methods

The Iwate-KENCO study cohort is a population-based prospective study of residents in the northern part of Iwate prefecture, northeast of Honsyu, Japan. Details of this cohort are provided elsewhere.[9] Participants were recruited from a government-regulated multiphasic health checkup. Of the 31,318 (11,003 men) residents aged ≥18 years who took part in the health checkup program between April 2002 and January 2005, 26,469 (9,161 men) consented to participate in this cohort study (85%). After exclusion of those with previous myocardial infarction or angina pectoris (185 men), previous stroke (328 men), use of lipid-lowering agents (249 men), or missing data (222 men) at baseline,

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This study was supported in part by grants-in-aid from the scientific research fund of the Ministry of Education, Science, and Culture of Japan (23591059), Tokyo, Japan; the Japan Arteriosclerosis Prevention Fund (JAPF), Tokyo, Japan; and the Takeda Science Foundation, Osaka, Japan.

See page 1067 for disclosure information.

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http://dx.doi.org/10.1016/j.amjcard.2013.05.049

Table 1
Baseline characteristics of total participants and those with low-density lipoprotein cholesterol <120 mg/dl

Variable	Total	LDL-C <120 mg/dL
	(n = 7,931)	(n = 4,827)
Age (yrs)	64 ± 10	65 ± 10
Body mass index (kg/m^2)	23.9 ± 3.0	23.5 ± 3.0
Total cholesterol (mg/dl)	191 ± 32	173 ± 23
LDL-C (mg/dl)	113 ± 29	95 ± 17
HDL-C (mg/dl)	56 ± 15	58 ± 17
Total/HDL-C	3.62 ± 1.06	3.20 ± 0.86
LDL-C/HDL-C	2.18 ± 0.85	1.78 ± 0.62
Non-HDL-C (mg/dl)	135 ± 33	116 ± 22
Systolic blood pressure (mm Hg)	131 ± 20	131 ± 20
Diastolic blood pressure (mm Hg)	79 ± 11	78 ± 11
Hypertension	46.6%	46.4%
eGFR (ml/min/1.73 m^2)	73 ± 15	74 ± 15
Diabetes mellitus	7.8%	7.6%
Current smoker	31.1%	31.9%

Data are presented as mean ± SD or percentage.

7,931 male subjects aged ≥40 years were recruited into the study.

Diagnosis of acute myocardial infarction (AMI) was based on the criteria of the World Health Organization-MONICA (Monitoring Trends and Determinants of Cardiovascular Disease) project, which requires evidence from suspected symptoms, an electrocardiogram, cardiac enzymes, and/or autopsy.[10] Sudden death was defined as any death after exclusion of known causes in a person who had sudden loss of ability to carry out normal activity due to serious physical impairment with death following in <24 hours.

Patients with newly diagnosed AMI and sudden death were registered from April 2002 to August 2007. Incidents of AMI were identified by accessing data from the Northern Iwate Heart Disease Registry Consortium, which has been collecting data since 2002. Registration was initially performed by attending physicians at each hospital. To ensure complete capture of all registrations, physicians or trained research nurses reviewed medical charts and/or discharge summaries at referral hospitals within the study area. Furthermore, to capture registrations of sudden death irrespective of hospital visit, we reviewed death certificates at government offices within the target district and identified sudden death (I46.1, R96) according to the *International Classification of Diseases, 10th Revision*. The study was approved by our institutional ethics committee. Women were excluded from the analysis because of the low incidence of AMI/sudden death (41 events among 14,636 women; 0.3%).

Body mass index was calculated by dividing weight (in kilograms) by the square of height (in meters). Participants completed a self-report questionnaire to document their medical history including current medications and lifestyle factors such as smoking habits. Blood pressure was measured twice using an automatic digital sphygmomanometer after 5 minutes of rest in a sitting position, and the average of these two values was used for analysis. Both fasting (n = 1,287) and nonfasting (n = 6,644) blood samples were drawn from an antecubital vein and collected

Table 2
Hazard ratios for future acute myocardial infarction/sudden death according to baseline levels of non-high-density lipoprotein cholesterol and ratios of total or low-density lipoprotein to high-density lipoprotein cholesterol as the categorical variables

Lipid Indices	Total (n = 7,931)					Lipid Indices	LDL-C <120 mg/dl (n = 4,827)				
	No. of Subjects	No. of Events	No./1,000 person-yrs	Crude HR (95% CI)	Multivariable Adjusted HR (95% CI)*		No. of Subjects	No. of Events	No./1,000 person-yrs	Crude HR (95% CI)	Multivariable Adjusted HR (95% CI)*
Non HDL-C, 131 mg/dl						Non HDL-C, 126 mg/dl					
Below	3,853	36	1.7	1	1	Below	3,345	30	1.6	1	1
Above	4,078	77	3.4	1.97 (1.33–2.93)	2.09 (1.40–3.14)	Above	1,482	25	3.1	1.86 (1.09–3.16)	2.02 (1.17–3.50)
TC/HDL-C, 3.82						TC/HDL-C, 3.47					
Below	5,024	50	1.8	1	1	Below	3,325	27	1.5	1	1
Above	2,907	63	3.9	2.17 (1.50–3.15)	2.19 (1.48–3.24)	Above	1,502	28	3.4	2.33 (1.37–3.95)	2.43 (1.39–4.26)
LDL-C/HDL-C, 2.51						LDL-C/HDL-C, 1.88					
Below	5,418	54	1.8	1	1	Below	2,904	23	1.4	1	1
Above	2,513	59	4.3	2.34 (1.62–3.39)	2.33 (1.59–3.42)	Above	1,923	32	3.1	2.14 (1.25–3.65)	2.06 (1.17–3.61)

* Hazard ratios for future AMI/sudden death in the categorical lipid variables in a multivariate Cox proportional hazards model including age, body mass index, systolic blood pressure, eGFR, presence of diabetes mellitus, and smoking habits.

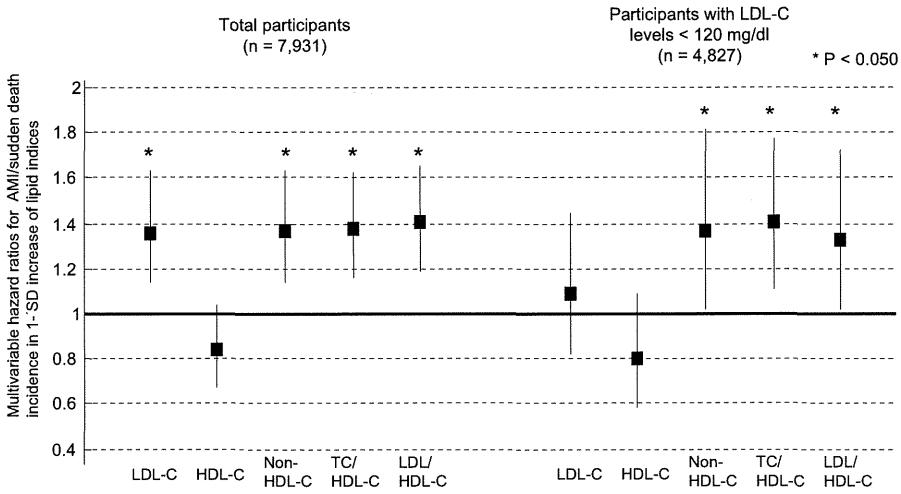

Figure 1. Adjusted relative risk for future AMI/sudden death in an increase of 1 SD of lipid indices.

into vacuum tubes containing a serum separator gel. Tubes were stored immediately after sampling in an icebox and transported to the laboratory <8 hours after collection. Glycosylated hemoglobin was measured quantitatively using high-performance liquid chromatography. Serum TC and HDL-C concentrations were measured by an enzymatic method. Serum LDL-C concentrations were measured by an enzymatic homogeneous assay Cholestest-LDL (Daiichi Chemicals Co. Ltd, Tokyo, Japan). Measurements for TC, HDL-C, and LDL-C (homogeneous assays) have been standardized by the Osaka Medical Center for Health Science and Promotion, a member of the Cholesterol Reference Method Laboratory Network (CRMLN) controlled by the CDC (Centers for Disease Control and Prevention, Atlanta, Georgia)[11] and have met all criteria for both precision and accuracy of lipid measurements.

Non-HDL-C was calculated as follows: non-HDL-C = TC to HDL-C. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive agents. Diabetes mellitus (DM) was defined as a random blood glucose level ≥200 mg/dl, a glycosylated hemoglobin value ≥6.5%, and/or current antidiabetic therapy. Estimated glomerular filtration rate (eGFR) was calculated using an equation (eGFR [ml/min/1.73m^2] = 194 × serum creatinine$^{-1.094}$ × age$^{-0.278}$) from the Modification of Diet in Renal Disease (MDRD) study.[12] Smoking habit was defined as current smoking.

Data are presented as mean ± SD or percentage. All data were analyzed using SPSS statistical software, version 11.0. We defined normal levels of LDL-C as <120 mg/dl in line with the Japan Atherosclerosis Society's suggested LDL-C levels of 120 to 139 mg/dl as borderline hyper LDL-cholesterolemia and LDL-C levels of ≥140 mg/dl as hyper LDL-cholesterolemia.[13] Baseline characteristics were shown in total participants and those with LDL-C levels <120 mg/dl.

Cox regression analysis was used to calculate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for lipid indices in relation to risk of future AMI/sudden death. A multivariate Cox proportional hazards model was constructed including lipid indices and adjusting for age, body mass index, systolic blood pressure, eGFR, presence of DM, and smoking habits. We calculated multivariable HRs for a 1 standard deviation (SD) increase in levels of LDL-C, HDL-C and non-HDL-C, and for TC/HDL-C ratio or LDL-C/HDL-C ratio in total participants and those with LDL-C levels <120 mg/dl. The SD units correspond to 29.1 mg/dl for LDL-C, 15.4 mg/dl for HDL-C, 32.7 mg/dl for non-HDL-C, 1.06 for TC/HDL-C ratio, and 0.85 for LDL-C/HDL-C ratio in total participants, and 17.5 mg/dl for LDL-C, 16.5 mg/dl for HDL-C, 21.6 mg/dl for non-HDL-C, 0.86 for TC/HDL-C ratio, and 0.62 for LDL-C/HDL-C ratio in participants with LDL-C levels <120 mg/dl. The lipid indices showing a linear correlation with risk were used to construct a receiver operating characteristic (ROC) curve with AMI/sudden death events as the outcome. The crude and multivariable adjusted HRs with corresponding 95% CIs for risk of future AMI/sudden death in the categorical variables of lipid indices on the basis of points with highest accuracy on ROC analysis were calculated for total participants and for those with LDL-C levels <120 mg/dl. To determine the HR for future AMI/sudden death, $p < 0.05$ was considered statistically significant.

Results

Of the 7,931 participants, 4,827 (60.9 %) had LDL-C levels <120 mg/dl at the baseline survey. Table 1 shows the baseline characteristics of total participants and those with LDL-C levels <120 mg/dl. During the average 5.5 years of follow-up, 113 subjects (1.4 %) had a first AMI/sudden death.

Figure 1 shows HRs for future AMI/sudden death associated with a 1-SD increase of LDL-C, HDL-C, non-HDL-C, and TC/HDL-C or LDL-C/HDL-C ratio after adjustment for age, body mass index, systolic blood pressure, eGFR, presence of DM, and smoking habits. Among all participants, adjusted HRs were increased with a 1 SD increase in LDL-C (HR = 1.36, 95% CI: 1.14 to 1.63), non-HDL-C (HR = 1.36, 95% CI: 1.13 to 1.64), TC/HDL-C ratio (HR = 1.37, 95% CI: 1.16 to 1.62), and LDL-C/HDL-C ratio (HR = 1.40, 95% CI: 1.19 to 1.65) but not HDL-C (HR = 0.84, 95% CI: 0.68 to 1.04). However,

in participants with LDL-C levels <120 mg/dl, the increased HR associated with a 1 SD increase of LDL-C was not significant (HR = 1.09, 95% CI: 0.82 to 1.44). In contrast, HRs remained increased significantly with a 1 SD increase in non-HDL-C (HR = 1.36, 95% CI: 1.02 to 1.81), TC/HDL-C ratio (HR = 1.40, 95% CI: 1.11 to 1.78) and LDL-C/HDL-C ratio (HR = 1.32, 95% CI: 1.02 to 1.73).

For categorical analysis of lipid indices showing a linear correlation with risk of future AMI/sudden death, we set the threshold of non-HDL-C, TC/HDL-C ratio, and LDL-C/HDL-C ratio as the optimal cut-off levels for prediction of AMI/sudden death from points with highest accuracy on a ROC curve. As a result, the threshold was 131 mg/dl for non-HDL-C, 3.82 for TC/HDL-C ratio, and 2.51 for LDL-C/HDL-C ratio in total participants, and 126 mg/dl for non-HDL-C, 3.47 for TC/HDL-C ratio, and 1.88 for LDL-C/HDL-C ratio in participants with LDL-C levels <120 mg/dl.

Table 2 shows the crude and multivariable adjusted HRs for risk of future AMI/sudden death with non-HDL-C, TC/HDL-C ratio or LDL-C/HDL-C ratio as the categorical variable on the basis of points with highest accuracy on ROC analysis. Among total participants, the multi-adjusted HRs for AMI/sudden death were increased in individuals with non-HDL-C levels above 131 mg/dl, TC/HDL-C ratio above 3.82, and LDL-C/HDL-C ratio above 2.51. Moreover, in participants with LDL-C levels <120 mg/dl, an increased HR remained significant in individuals with non-HDL-C levels >126 mg/dl, TC/HDL-C ratio >3.47 and LDL-C/HDL-C ratio >1.88.

Discussion

In community-dwelling men with no cardiovascular history who participated in the Iwate-KENCO study, we investigated the predictive power for future AMI/sudden death of lipid parameters including LDL-C, HDL-C, non-HDL-C, TC/HDL-C ratio, and LDL-C/HDL-C ratio. During the mean follow-up period of 5.5 years, Cox regression analysis was performed to examine the relationship between lipid indices and incidence of AMI/sudden death. Among all participants, each of the lipid indices other than HDL-C showed a linear correlation with risk of AMI/sudden death, although the event rate was low (1.4%). Even in participants with LDL-C levels <120 mg/dl, there was a linear correlation between risk of AMI/sudden death and non-HDL-C levels, TC/HDL-C ratio, and LDL-C/HDL-C ratio. Furthermore, when categorized on the basis of cut-off point obtained from ROC analysis, non-HDL-C, TC/HDL-C ratio, and LDL-C/HDL-C ratio showed an elevated risk for AMI/sudden death in participants with LDL-C levels <120 mg/dl.

Non-HDL-C, TC/HDL-C ratio, and LDL-C/HDL-C ratio have previously been shown to be associated with risk of cardiovascular disease.[6,14,15] In addition, primary prevention studies have revealed that non-HDL-C, cardiovascular disease/HDL-C ratio, and LDL-C/HDL-C ratio were as strong as or better predictors of CHD and cardiovascular disease mortality than LDL-C or HDL-C.[5,16–20] These reports may be related to our finding that non-HDL-C, TC/HDL-C ratio, and LDL-C/HDL-C ratio, in contrast to LDL-C and HDL-C, had a linear correlation with risk of AMI/sudden death in participants with LDL-C levels <120 mg/dl. In the Suita study in which the sample came from a Japanese urban population,[6] increased risk of AMI with serum LDL-C or non-HDL-C was similarly significant. In our study, serum LDL-C was related to risk of AMI/sudden death in all participants but not in those with LDL-C levels <120 mg/dl. The present participants with baseline LDL-C levels <120 mg/dl had lower mean LDL-C levels (95 mg/dl) than the Suita cohort (125 mg/dl). These findings suggest that, at optimal levels of LDL-C, the coronary risk associated with LDL-C is not significant.

Furthermore, the predictive value of non-HDL-C or lipid ratios for cardiovascular disease risk according to LDL-C levels also has been reported. In the Framingham heart study, higher LDL-C/HDL-C ratios were associated with elevated risk of CHD among participants in the lowest tertile of LDL-C, an average level of 113 mg/dl.[9] In EPIC-Norfolk cohorts with LDL-C levels <100 mg/dl,[8] non-HDL-C ≥130 mg/dl, or TC/HDL-C ratio ≥5 had a significantly increased HR compared with non-HDL-C <130 mg/dl or TC/HDL-C ratio <5. In the present study, non-HDL-C ≥126 mg/dl, TC/HDL-C ratio ≥3.4, and LDL-C/HDL-C ratio ≥1.8 were significantly associated with an increased risk of AMI/sudden death in participants with LDL-C levels <120 mg/dl. These findings suggest that non-HDL-C, TC/HDL-C ratio, and LDL-C/HDL-C ratio provide information about residual risk of AMI/sudden death at normal LDL-C levels.

Numerous prospective cohort studies have shown a significant correlation between HDL-C and cardiovascular risk in a primary setting.[5] In the absence of elevated TC, an inverse association between HDL-C and CHD has been shown among men without CHD.[21] In contrast, in the present study, there was no significant linear relationship between HDL-C and incidence of AMI/sudden death. This inconsistency may arise from the average age being higher in participants of our study than the other studies, given that the association between lipid levels and cardiovascular risk is weaker and more controversial in older adults than in middle-aged adults.[22] Additionally, the mean follow-up period was relatively shorter in the present study (5.5 years) compared with the other studies (7.7 years).[21] In contrast, non-HDL-C, TC/HDL-C ratio, and LDL-C/HDL-C ratio had a linear correlation with risk of AMI/sudden death in the present cohort. This finding suggests that these lipid indices have a closer correlation with coronary risk than HDL-C.

Several previous reports have shown a correlation between lipid profile and metabolic index or vascular atherosclerosis. Non-HDL-C was strongly and consistently related to subclinical carotid and coronary atherosclerosis.[23,24] Moreover, this relationship was stronger for non-HDL-C than for LDL-C or HDL-C.[24] In cross-sectional studies of individuals participating in health examinations, TC/HDL-C and LDL-C/HDL-C ratios showed a closer correlation with metabolic abnormalities such as metabolic syndrome,[25] insulin resistance[25] and carotid atherosclerosis[26] compared to LDL-C or HDL-C. In patients with CHD, LDL-C/HDL-C ratio was an independent predictor of coronary lipid-rich plaque vulnerability, but LDL-C or HDL-C was not.[27] These reports may relate to the present findings regarding risk prediction based on non-HDL-C and lipid ratios.

Our study had several limitations. First, the single cholesterol measurement at the baseline survey may have

underestimated the relationship between lipid indices and AMI/sudden death due to regression dilution bias. Second, LDL-C concentrations were directly measured by the enzymatic homogeneous assay in most nonfasting samples (84%). However, the guidelines for preventing atherosclerotic disease recommend using the Friedewald formula in a fasting state.[4] Our previous study revealed that the direct LDL-C assay has less variability in LDL-C concentrations than does the Friedwald formula in nonfasting samples and can be used in epidemiologic studies on the association of LDL-C with risk for cardiovascular disease VD in fasting and nonfasting samples.[28] Therefore, we believe that it was significant to perform a direct measurement of LDL-C concentration in large numbers of nonfasting samples. Third, sudden death could include deaths due to cause other than CHD. It makes the diagnosis of cardiac death difficult that the information about the incidence of sudden death was not necessarily provided in detail. We therefore registered sudden death as suspected coronary death to capture more AMI events, because approximately 40% of these events result in sudden death.[10] Fourth, whether non-HDL-C and lipid ratios could yield therapeutic target values remains unclear from our findings based on an epidemiological study and will require further investigation. Fifth, we were unable to assess the relationship between risk of AMI/sudden death and apolipoprotein B or A-I, markers for atherogenic lipoproteins. Although these markers could potentially provide additional information about LDL-C-related risk, unlike non-HDL-C and ratios of TC/HDL or LDL/HDL, standardized apolipoprotein B and A-I measures are not widely available in clinical practice and would add expense beyond that of routine lipoprotein analysis. Finally, the present study was conducted on relatively elderly Japanese subjects (average 64 ± 10 years), yet the cumulative incidence of AMI/sudden death was only 1.4% during the average 5.5 years of follow-up. This agrees with reports indicating lower AMI/sudden death incidence in Japan than in the United States.[29] Therefore, our results may not be easily extrapolated to other populations.

Disclosures

The authors have no conflicts of interest to disclose.

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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).

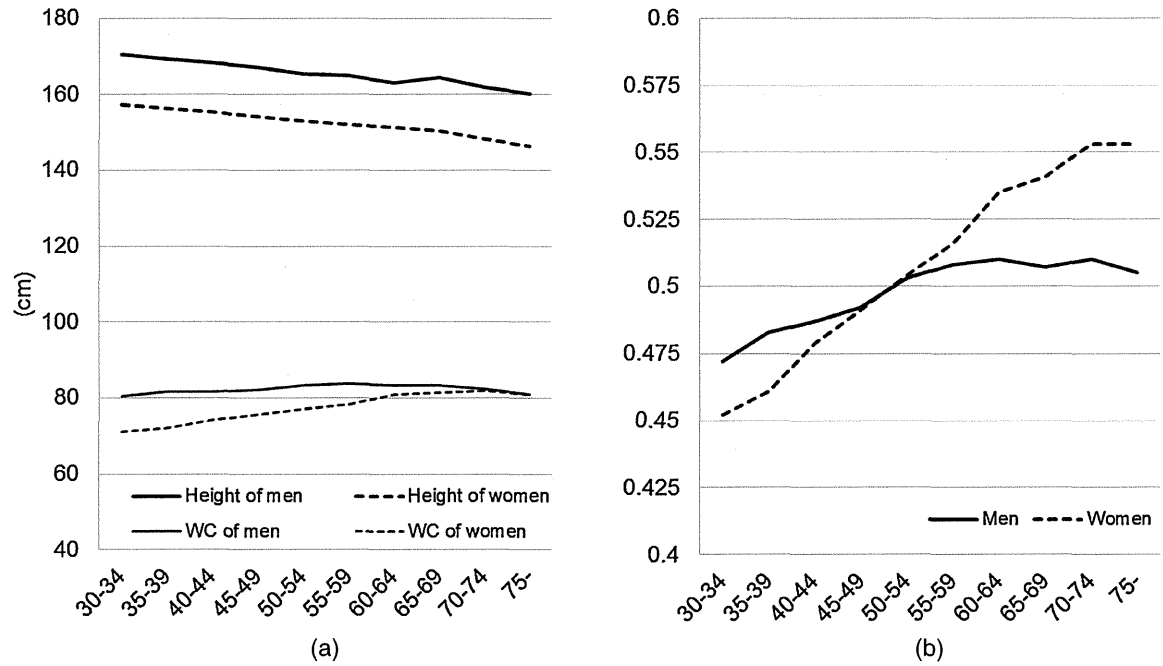

Figure. (a) Average WC (waist circumference), height, and (b) waist-to-height ratio according to age (The Suita Study, Japan)

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.

ACKNOWLEDGMENTS

The present study was supported by the Intramural Research Fund of the National Cerebral and Cardiovascular Center (22-4-5), a grant-in-aid from the Ministry of Health, Labour and Welfare (H23-Seishu-005), and a grant-in-aid for scientific research (C) from the Japan Society for the Promotion of Science (no. 24590837). We are sincerely grateful to the members of the Suita Medical Foundation and the Suita City Health Center. We also thank all researchers and co-medical staff at the Department of Preventive Cardiology, National Cerebral and Cardiovascular Center, for their excellent medical examinations and follow-up surveys. Finally, we thank the Satsuki-Junyukai, the society members of the Suita Study.

Conflicts of interest: None declared.

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J Epidemiol 2013;23(4):301-306
doi:10.2188/jea.JE20120180

Original Article

Factors Related to Tooth Loss Among Community-Dwelling Middle-aged and Elderly Japanese Men

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Received October 10, 2012; accepted March 31, 2013; released online June 29, 2013

ABSTRACT

Background: Using data from a large-scale community-based Japanese population, we attempted to identify factors associated with tooth loss in middle-aged and elderly men.

Methods: A total of 8352 men aged 40 to 79 years who lived in the north of the main island of Japan and underwent health checkups were enrolled between 2002 and 2005. Number of teeth was assessed by the question, "How many teeth do you have (0, 1–9, 10–19, or ≥20)?". On the basis of the answer to this question, participants were classified into 2 groups (≤19 teeth or ≥20 teeth). Using multivariate logistic regression, factors related to having 19 or fewer teeth were estimated.

Results: The numbers (percentages) of participants who had 0, 1 to 9, 10 to 19, and 20 or more teeth were 1764 (21.1%), 1779 (21.3%), 1836 (22.0%), and 2973 (35.6%), respectively. Among the participants overall and those aged 65 to 79 years, having 19 or fewer teeth was significantly associated with older age, smoking status (current smoking and ex-smoking), and low education level. In addition, men with 19 or fewer teeth were more likely to have a low body mass index and low serum albumin level and less likely to be current alcohol drinkers. Among men aged 40 to 64 years, but not men aged 65 to 79 years, those with 19 or fewer teeth were more likely to have a low serum high-density lipoprotein cholesterol level and high glycosylated hemoglobin (HbA1c) level.

Conclusions: Smoking, low education level, and poor nutritional status were associated with tooth loss among middle-aged and elderly Japanese men.

Key words: tooth loss; risk indicator; middle-aged men; elderly men; Japanese; cross-sectional study

INTRODUCTION

Tooth loss was found to be associated with systemic chronic diseases such as cardiovascular disease and cancer.[1,2] In addition, tooth loss affects daily activities such as speaking, smiling, chewing, and tasting.[3] Prevention of tooth loss thus helps maintain good general health and high quality of life.

Many studies in various countries have revealed factors related to tooth loss, including smoking,[4–6] nutritional status,[7–11] and educational level.[7,12–15] In Japan, numerous studies have examined the association between smoking and tooth loss at all ages.[3,16–20] There have also been several studies on the associations of tooth loss with nutritional status[21,22] and educational level.[23,24] However, because most of those studies were conducted among elderly populations, there is little information on factors related to tooth loss in middle-aged populations. Moreover, there have been few studies in Japan on the associations of tooth loss with laboratory variables.[25]

Thus, to identify factors associated with tooth loss among middle-aged and elderly men, we analyzed laboratory data and information on lifestyle and social factors from a large-scale community-dwelling Japanese population.

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METHODS

Study population

We analyzed baseline data from the Iwate-Kenpoku cohort (Iwate-KENCO) study, which was designed as a cohort study of community-dwelling residents living in the north of the main island of Japan. The methodology of the Iwate-KENCO study has been described elsewhere.[26] The baseline survey was carried out between 2002 and 2005. The original cohort members consisted of 26 469 participants aged 18 years or older who underwent annual health check-ups. Of the original cohort, we focused on 8476 men aged 40 to 79 years to identify factors associated with tooth loss. Among those 8476 male participants, we excluded 124 men with missing data on number of teeth. Ultimately, data from 8352 male participants (99% of the male participants aged 40–79 years) were used in the analysis. This study was approved by the Medical Ethics Committee of Iwate Medical University. All participants provided written informed consent.

Measurements

Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by trained nurses using an automatic device, with the participant in a sitting position after resting for at least 5 minutes. The average of 2 measurements was recorded. Casual blood samples were drawn from antecubital veins of seated participants. All samples were collected into vacuum tubes containing ethylenediaminetetraacetic acid (EDTA) or a serum separator gel. The samples were stored in an icebox immediately after collection, transported to a laboratory (Iwate Health Service Association), and analyzed on the same day. Serum levels of total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) were measured by an enzymatic method. Measurements of TC and HDL-C have been standardized by the Osaka Medical Center for Health Science and Promotion—a member of the Cholesterol Reference Method Laboratory Network (CRMLN) controlled by the Centers for Disease Control and Prevention (Atlanta, GA, USA)[27]—and have met all criteria for both precision and accuracy of lipid measurement. Plasma glucose levels were determined by the hexokinase ultraviolet method. Glycosylated hemoglobin (HbA1c) was measured by high-performance liquid chromatography as a Japan Diabetes Society (JDS) value, which was then converted to a National Glycohemoglobin Standardization Program (NGSP) value by adding 0.4%. Serum albumin level was measured by the bromocresol green method. Serum level of high-sensitivity C-reactive protein (hsCRP) was determined by the latex-enhanced immunonephelometric method (Dade Behring Diagnostics, Germany). The detection limit of the hsCRP assay is 0.1 mg/dL, and hsCRP values under the minimum detectable level were recorded as 0.1 mg/L.

Each participant completed a self-administered questionnaire that included questions on medication, smoking habits, alcohol intake, years of education, marital status, and number of teeth. Number of teeth was assessed by a single question, "How many teeth do you have (0, 1–9, 10–19, or ≥20)?". Diabetes was defined as a plasma glucose level of 200 mg/dL or higher, an HbA1c level (NGSP) of 6.5% or higher, or use of antidiabetic agents. Smoking status was classified into 3 categories: nonsmoking, ex-smoking, and current smoking. Alcohol drinking status was classified as current habitual drinking or no habitual drinking. Marital status was classified as married or single (including unmarried, divorced, and widowed). Low education level was defined as less than 10 years of education.

Statistical analysis

We calculated age-adjusted means and age-adjusted proportions of variables in each group (ie, 0, 1–9, 10–19, ≥20 teeth), using analysis of covariance (ANCOVA) for continuous variables and logistic regression for categorical variables. Data for hsCRP were expressed as age-adjusted geometric means. Linear trend across the 4 groups was examined by linear regression for continuous variables and logistic regression for categorical variables. To determine factors associated with tooth loss, we classified participants into 2 groups according to number of teeth (≤19 teeth vs ≥20 teeth). Multivariate logistic regression was performed for all participants aged 40 to 79 years, with 19 or fewer teeth as the dependent variable (coded as 1 for having ≤19 teeth and 0 for having ≥20 teeth), and age, BMI, SBP, TC, HDL-C, albumin, log-transformed hsCRP, smoking status (current smoker, ex-smoker, or non-smoker), alcohol drinking status (current drinker or not), marital status (single or not), and education level (low or not) as independent variables. In addition, similar analyses were performed after stratification by age group (40–64 years vs 65–79 years). In all analyses, a 2-sided P value of less than 0.05 was considered to indicate statistical significance. The statistical package SPSS (version 11.0J) was used for the analysis.

RESULTS

Among the 8352 men, the numbers (proportions) of men with 0, 1 to 9, 10 to 19, and 20 or more teeth were 1764 (21.1%), 1779 (21.3%), 1836 (22.0%), and 2973 (35.6%), respectively. The respective numbers (proportions) were 319 (8.8%), 570 (15.6%), 914 (25.1%), and 1840 (50.5%) among men aged 40 to 64 years and 1445 (30.7%), 1209 (25.7%), 922 (19.6%), and 1133 (24.1%) among men aged 65 to 79 years.

As shown in Table 1, mean age was higher in men with fewer teeth. After adjustment for age, number of teeth was positively associated with BMI, serum levels of TC, HDL-C, and albumin, and proportions of nonsmokers and current drinkers, and inversely associated with hsCRP and

Table 1. Age-adjusted characteristics of men aged 40–79 years, by number of teeth

Number of teeth	0	1–9	10–19	≥20	*P* for trend
Number of participants (%)	1764 (21.1)	1779 (21.3)	1836 (22.0)	2973 (35.6)	
Age (years)	69.7 (6.3)	66.7 (7.8)	63.0 (9.4)	60.0 (9.9)	<0.001
BMI (kg/m^2)	23.5 (23.3–23.6)	23.8 (23.7–24.0)	24.1 (24.0–24.3)	24.2 (24.1–24.3)	<0.001
SBP (mm Hg)	130.2 (129.4–131.1)	130.3 (129.4–131.2)	131.1 (130.2–132.0)	131.3 (131.1–132.0)	0.198
TC (mg/dL)	190.8 (189.2–192.3)	191.1 (189.6–192.6)	190.3 (188.8–191.8)	193.3 (192.1–194.5)	0.007
HDL-C (mg/dL)	55.6 (54.9–56.4)	56.3 (55.6–57.0)	55.2 (54.5–55.9)	56.7 (56.1–57.3)	0.006
HbA1c (%)	5.60 (5.56–5.63)	5.55 (5.52–5.59)	5.55 (5.51–5.58)	5.54 (5.51–5.57)	0.108
Albumin (g/dL)	4.40 (4.38–4.41)	4.38 (4.36–4.39)	4.39 (4.38–4.41)	4.42 (4.41–4.43)	<0.001
hsCRP (mg/L)	0.58 (0.55–0.61)	0.56 (0.53–0.59)	0.57 (0.54–0.60)	0.52 (0.50–0.54)	0.014
Diabetes (%)	10.8	11.0	11.0	10.0	0.658
Current smoker (%)	41.8	35.4	28.6	23.6	<0.001
Ex-smoker (%)	30.2	31.1	29.1	31.9	0.390
Nonsmoker (%)	28.2	32.3	40.3	42.9	<0.001
Current drinker (%)	55.0	61.1	64.1	65.1	<0.001
Single (%)	12.7	11.3	10.8	10.4	0.040
<10 years of education (%)	72.0	63.1	56.1	51.5	<0.001

Data are expressed as age-adjusted means (95% CIs) for continuous variables, except for age and hsCRP, and age-adjusted proportions for categorical variables. Data for age are expressed as means (SD), and data for hsCRP are expressed as age-adjusted geometric means (95% CI). Age-adjusted means and proportions were estimated, with the exception of missing data: the number of missing values was 11 for BMI, 2 for SBP, 2 for TC, 2 for HDL-C, 3 for HbA1c, 184 for hsCRP, 2374 for albumin, 286 for marital status, and 145 for years of education.
P values for linear trend tests across the 4 groups were estimated using linear regression for continuous variables and logistic regression for categorical variables. BMI, body mass index; SBP, systolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; hsCRP, high-sensitivity C-reactive protein.

Table 2. Adjusted odds ratios (ORs) and 95% CIs for having ≤19 teeth among men aged 40–79 years

		OR	95% CI	*P* value
Age	(per 10-year increase)	2.05	(1.90–2.21)	<0.001
BMI	(per 1-kg/m^2 increase)	0.96	(0.94–0.99)	0.001
SBP	(per 10-mm Hg increase)	1.00	(0.97–1.03)	0.938
TC	(per 10-mg/dL increase)	1.00	(0.98–1.02)	0.852
HDL-C	(per 10-mg/dL increase)	0.97	(0.93–1.01)	0.144
HbA1c	(per 1% increase)	1.01	(0.94–1.09)	0.774
Albumin	(per 1-g/dL increase)	0.70	(0.55–0.88)	0.002
hsCRP	(per log(1)-mg/L increase)	1.05	(0.99–1.11)	0.084
Current smoker	(vs. nonsmoker)	1.66	(1.42–1.93)	<0.001
Ex-smoker	(vs. nonsmoker)	1.19	(1.03–1.37)	0.019
Current drinker	(vs. other)	0.77	(0.68–0.88)	0.000
Single	(vs. marriage)	0.97	(0.81–1.17)	0.748
<10 years of education	(vs. ≥10 yrs)	1.57	(1.39–1.78)	<0.001

Logistic regression analysis was performed using data from 5706 participants with complete data.
BMI, body mass index; SBP, systolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; hsCRP, high-sensitivity C-reactive protein.

Table 3. Adjusted odds ratios (ORs) and 95% CIs for having ≤19 teeth among men aged 40–64 years

		OR	95% CI	*P* value
Age	(per 10-year increase)	1.82	(1.58–2.09)	<0.001
BMI	(per 1-kg/m^2 increase)	0.96	(0.93–0.99)	0.012
SBP	(per 10-mm Hg increase)	1.02	(0.97–1.07)	0.445
TC	(per 10-mg/dL increase)	1.00	(0.98–1.03)	0.879
HDL-C	(per 10-mg/dL increase)	0.94	(0.88–1.00)	0.042
HbA1c	(per 1% increase)	1.13	(1.01–1.27)	0.030
Albumin	(per 1-g/dL increase)	0.78	(0.56–1.07)	0.128
hsCRP	(per log(1)-mg/L increase)	1.07	(0.98–1.16)	0.114
Current smoker	(vs. nonsmoker)	1.42	(1.16–1.73)	0.001
Ex-smoker	(vs. nonsmoker)	1.04	(0.84–1.30)	0.706
Current drinker	(vs. other)	0.93	(0.77–1.12)	0.443
Single	(vs. marriage)	1.00	(0.78–1.27)	0.978
<10 years of education	(vs. ≥10 yrs)	1.52	(1.29–1.81)	<0.001

Logistic regression analysis was performed using data from 2523 participants with complete data.
BMI, body mass index; SBP, systolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; hsCRP, high-sensitivity C-reactive protein.

proportions of current smokers, single men, and men with low education level.

Table 2 shows adjusted odd ratios (ORs) and their 95% CIs for having 19 or fewer teeth among men aged 40 to 79 years. Older men, current smokers, and men with a low education level had a significantly higher risk of having 19 or fewer teeth. In contrast, men with high BMI, men with high serum albumin, and current drinkers had a significantly lower risk of having 19 or fewer teeth. Among men aged 40 to 64 years (Table 3), older men, men with a high HbA1c level, current smokers, and men with a low education level had a significantly higher risk of having 19 or fewer teeth, whereas men with a high BMI and high HDL-C had a significantly lower risk of having 19 or fewer teeth. Among men aged 65 to 79 years (Table 4), older men, current smokers, ex-smokers, and men with a low education level had a significantly higher risk of having 19 or fewer teeth, whereas men with a high BMI, men with a high albumin level, and current drinkers had a significantly lower risk of having 19 or fewer teeth.

DISCUSSION

In this study of 8532 community-dwelling men aged 40 to 79 years, having 19 or fewer teeth was significantly associated with older age, smoking status (current smoking and ex-smoking), and low education level. In addition, men with 19

Table 4. Adjusted odds ratios (ORs) and 95% CIs for having ≤19 teeth among men aged 65–79 years

		OR	95% CI	*P* value
Age	(per 10-year increase)	2.53	(2.01–3.18)	<0.001
BMI	(per 1-kg/m^2 increase)	0.97	(0.94–1.00)	0.039
SBP	(per 10-mm Hg increase)	0.98	(0.94–1.03)	0.385
TC	(per 10-mg/dL increase)	0.99	(0.96–1.02)	0.602
HDL-C	(per 10-mg/dL increase)	1.00	(0.94–1.06)	0.995
HbA1c	(per 1% increase)	0.92	(0.83–1.02)	0.116
Albumin	(per 1-g/dL increase)	0.63	(0.45–0.87)	0.006
hsCRP	(per log(1)-mg/L increase)	1.03	(0.95–1.12)	0.439
Current smoker	(vs. nonsmoker)	1.91	(1.51–2.42)	<0.001
Ex-smoker	(vs. nonsmoker)	1.28	(1.05–1.55)	0.014
Current drinker	(vs. other)	0.66	(0.55–0.80)	<0.001
Single	(vs. marriage)	0.84	(0.63–1.13)	0.245
<10 years of education	(vs. ≥10 yrs)	1.68	(1.40–2.02)	<0.001

Logistic regression analysis was performed using data from 3138 participants with complete data.
BMI, body mass index; SBP, systolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; hsCRP, high-sensitivity C-reactive protein.

or fewer teeth were more likely to have a low BMI and low serum albumin level and less likely to be current alcohol drinkers. In addition, among men aged 40 to 64 years, men with 19 or fewer teeth were more likely to have a low serum HDL-C level and a high HbA1c level.

Studies have shown that tooth loss is associated with smoking in middle-aged and elderly populations,[4–6] as was observed in the present study. In Japan, a nationwide study of 3999 adults aged 40 years or older showed that, as compared with nonsmokers, current smokers had a significant 2.22-fold risk of having 19 or fewer teeth and that the difference in risk for ex-smokers was not significant.[18] A retrospective cohort study of 547 men aged 55 to 75 years showed that current smokers and ex-smokers had significant 1.96-fold and 1.86-fold risks of having more than 8 missing teeth, respectively.[16] That study also showed that ex-smokers who had smoked for 21 years or longer had a significantly higher risk of having more than 8 missing teeth, as compared with never smokers, and that the risk of having more than 8 missing teeth among ex-smokers who had stopped smoking for more than 21 years was equal to that of never smokers.[16] The present study showed that, as compared with never smokers, male ex-smokers aged 65 to 79 years, but not those aged 40 to 64 years, had a significantly higher risk of having 19 or fewer teeth. Mean number of smoking years was higher in men aged 65 to 79 years (29.3 years) than in men aged 40 to 64 years (20.8 years). The longer duration of smoking among elderly men may increase the risk of having 19 or fewer teeth among ex-smokers.

In this study, low education level was significantly associated with tooth loss among men aged 40 to 64 years and men aged 65 to 79 years. This finding is consistent with the results of previous studies in various populations.[7,12–15] Low education level was found to be associated with less utilization of dental care[28] and unfavorable oral health-related behaviors,[29] which could lead to tooth loss. In Japan, a study of 1201 community residents aged 55 to 75 years showed that those with higher educational levels had a greater likelihood of having 20 or more teeth.[23] Another study, of elderly Japanese aged 65 years or older, showed that subjects with 9 years of education or less had a significantly higher risk of having 19 or fewer teeth than did those with at least 13 years of education.[24] These present and past findings suggest a significant association between low education level and tooth loss among both the elderly and middle-aged populations in Japan.

We found that having 19 or fewer teeth was significantly associated with low BMI (among the participants overall) and with low serum albumin (among men aged 65–79 years). These findings are consistent with the results of previous studies[7,8,11] and suggest that people with fewer teeth, particularly elderly adults, may have poor nutritional status. People with fewer teeth may also have impaired masticatory function that limits their dietary choices and affects their nutritional status.[10] A study of 6985 US adults found that those with fewer than 28 teeth had significantly lower intakes of carrots, tossed salads, and dietary fiber and lower serum levels of beta carotene, folate, and vitamin C than did fully dentate adults.[9] In Japan, a study of 20 366 dentists showed a decreasing trend in intakes of carotene and vitamins A and C with increasing number of teeth lost. That study also showed similar trends for consumption of milk and dairy products and green-yellow vegetables, whereas consumption of rice and confectioneries was inversely associated with number of remaining teeth.[21]

In this study, having 19 or fewer teeth was associated with low serum HDL-C and high HbA1c among men aged 40 to 64 years but not among those aged 65 to 79 years. Diabetes is a major risk factor for periodontal disease,[30] and periodontal disease was found to be associated with the development of glucose intolerance.[31] In addition, several studies found that people with periodontal disease have low HDL-C levels.[32,33] Therefore, the significant associations of tooth loss with HDL-C and HbA1c among the middle-aged men in this study may reflect associations of periodontal disease with HDL-C and HbA1c, although we had no information on the causes of tooth loss. In contrast, as mentioned above, tooth loss in elderly adults may reflect poor nutritional status, expressed as low BMI and low albumin level, rather than the presence of periodontal disease.

There were several limitations in this study. First, the cross-sectional design of the present study does not allow identification of casual relationships. Second, number of teeth was assessed by a self-administered questionnaire, without clinical examination. However, self-reported number of teeth was found to be highly correlated with actual number of teeth at a clinical examination in a general population.[34] Third, our subjects were middle-aged and elderly Japanese men living in the north of the main island of Japan, which limits the generalizability of the present results.

In conclusion, we found that smoking, low education level, and poor nutritional status were associated with tooth loss among middle-aged and elderly men. These risk indicators should be considered when planning oral health programs for both elderly and middle-aged adults.

ONLINE ONLY MATERIALS

Abstract in Japanese.

ACKNOWLEDGMENTS

The Iwate-KENKO study was supported by grants from the Japan Arteriosclerosis Prevention Fund and the Japanese Ministry of Health, Labor and Welfare, Health and Labor Sciences Research Grants (Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H23-Junkankitou [Seishuu]-Ippan-005). We are grateful to the staff of the Iwate Health Service Association and the staffs in all the relevant municipalities (Iwate Prefecture, Ninohe City, Ichinohe Town, Karumai Town, Kunohe Village, Yamada Town, Kawai Village, Miyako City, Niisato Village, Taro Town, Iwaizumi Town, Tanohata Village, Kuji City, Yamagata Village, Fudai Village, Ohno Village, Noda Village, and Taneichi Town).

Conflicts of interest: None declared.

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