IMT calculated from the 9 readings was used in the analysis. No measurements were taken at the discrete plaque level.

Basic Clinical Parameters

Basic clinical parameters used in this study were measured through the medical checkup program. Brachial blood pressure was measured after 5-minute resting in the sitting position (HEM-9000AI; Omron Healthcare, Kyoto, Japan). Hypertension was defined as either or both systolic blood pressure ≥140 mm Hg or diastolic BP ≥90 mm Hg, or taking antihypertensive drugs. Type 2 diabetes mellitus was defined as any or all of the following: plasma glucose ≥126 mg/dL, glycohemoblobin A1c ≥6.5%, or taking antihyperglycemic drugs.

Statistical Analysis

Differences in numeric variables were assessed by ANOVA, whereas frequency difference was assessed by a χ^2 test. Covariate adjusted analysis was performed by linear regression analysis. Factors independently associated with number or grade of cSVDs were assessed by a Poisson regression analysis, whereas a Tobit model with Weibull distribution was used in the multivariate analysis for OLST. Statistical analyses were conducted using commercially available statistical software (JMP version 9.0.2; SAS Institute Inc, Cary, NC) or the free R software (R version 3.0.2. http://www.r-project.org), with $P<0.05$ considered statistically significant.

Results

Clinical characteristics of the study subjects are shown in Table 1. Differences in the clinical parameters by the presence of cSVD are summarized in Table 2. Subjects with any cSVD tended to be older, more frequently hypertensive, and had higher carotid IMT than those without.

Frequency of short OLST, particularly OLST<20 s, increased linearly with number of lacunar infarctions ($P<0.001$), number of microbleeds ($P=0.023$), and PVH grade ($P<0.001$; Figure 1). Therefore, we used OLST 20 s as a cutoff point. Although several clinical parameters differ based on the presence of cSVD (Table 2), the associations of short OLST with lacunar infarction and microbleeds but not PVH remain significant even after adjustment for the covariates (Table 3). These associations were also found in a subanalysis with elderly subjects (≥65 years; lacunar infarction, $P=0.007$; microbleeds, $P=0.021$; PVH, $P=0.653$). However, conversely, existence of cSVD was not identified as an independent determinant for OLST (lacunar infarction, $P=0.717$; microbleeds, $P=0.737$; PVH, $P=0.347$) on Tobit regression analysis adjusted for age, sex, body mass index, current smoking, neuropsychiatric medication, hypertension, type 2 diabetes mellitus, and carotid IMT. Age and body mass index were identified as major determinants for OLST ($P<0.001$).

A significant linear correlation was noted between OLST and posturographic parameters for center of gravity movement (Table 4). However, although the posturographic parameters differed significantly based on the presence of cSVD in crude analysis, these associations disappeared in the covariates-adjusted analysis (Table 4).

Association between OLST and cognitive function is illustrated in Figure 2. Short OLST was significantly associated with lower TDAS score (Figure 2) and vice versa (ie, individuals with TDAS score <13 points had significantly shorter mean OLST than subjects with higher scores; 44.9±20.9 versus 52.4±15.9 s; $P<0.001$ [Tobit regression analysis]). Although subjects with cSVD had significantly lower TDAS scores overall (lacunar infarction, 14.0±1.5 versus 14.2±1.0; $P=0.007$; microbleeds, 14.0±1.4 versus 14.2±1.1; $P=0.038$; and PVH, 13.9±1.4 versus 14.3±1.0; $P<0.001$), the association of short OLST with TDAS score was independent of possible covariates, including cSVD (Figure 2). We included lacunar infarction, micobleeds, and PVH in a same regression model. However, no severe collinearity was detected among these factors (variation inflation factor: lacunar infarction; 1.16; microbleeds, 1.14; and PVH, 1.30).

Table 1. Clinical Characteristics of Study Subjects (n=1387)

Age, y	67±8
Sex (men/women)	546/841
Body height, cm	157.3±8.4
Body weight, kg	57.8±10.2
BMI, kg/m^2	23.2±3.1
Smoking (current, %)	5.8
Medication, %	
Antihypertensive drugs	30.4
Antihyperglycemic drugs	6.1
Neuropsychiatric drugs	11.9
SBP, mm Hg	136±19
DBP, mm Hg	77±11
Hypertension, %	53.7
Glucose, mg/dL	104±19
HbA1c, %	5.9±0.6
Type 2 diabetes mellitus, %	14.0
Carotid IMT, mm	0.79±0.14
OLST, n	
60, s	1030
<60, s	89
<40, s	120
<20, s	148
Posturography	
Eyes open	
Path length, cm	89±31
Circumferential area, cm^2	3.39±1.94
Eyes closed	
Path length, cm	144±72
Circumferential area, cm^2	5.73±4.21
cSVDs	
Lacunar infarction (n=0/1/2/>3)	1264/94/20/9
PVH (grade=0/1/2/3/4)	574/636/156/18/3
Microbleeds (n=0/1/2/>3)	1295/72/12/8

Values are mean±SD. Hypertension was defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg, or taking antihypertensive drugs. Type 2 diabetes mellitus was defined as any or all of the following: plasma glucose ≥126 mg/dL, HbA1c ≥6.5%, and taking antihyperglycemic drugs. Neuropsychiatric drugs include hypnotics, analgesics, antianxiety drugs, and antidepressants. BMI indicates body mass index; cSVDs, cerebral small-vessel disease; DBP, diastolic blood pressure; HbA1c, glycohemoglobin A1c; IMT, intima-media thickness; OLST, one-leg standing time; PVH, periventricular hyperintensity; and SBP, systolic blood pressure.

Table 2. Differences in Clinical Parameters Based on the Presence of cSVD

		Lacunar Infarction		Microbleeds		PVH	
	cSVD	Mean±SD	*P* Value	Mean±SD	*P* Value	Mean±SD	*P* Value
Age, y	+	70±7	<0.001*	70±7	<0.001*	73±6	<0.001*
	−	66±8		66±8		66±7	
Sex (male %)	+	46.3	0.097	44.6	0.291	41.2	0.584
	−	38.7		39.0		39.1	
BMI, kg/m^2	+	23.6±3.2	0.179	23.3±3.1	0.720	23.3±3.1	0.922
	−	23.2±3.0		23.2±3.1		23.2±3.0	
Neuropsychiatric drugs, %	+	15.5	0.204	13.0	0.727	19.9	0.001*
	−	11.6		11.8		10.7	
Hypertension, %	+	74.8	<0.001*	79.4	<0.001*	67.8	<0.001*
	−	51.7		51.9		51.7	
Type 2 diabetes mellitus, %	+	18.7	0.115	21.7	0.027*	18.6	0.056
	−	13.5		13.4		13.3	
Carotid IMT, mm	+	0.84±0.13	<0.001*	0.84±0.14	0.004*	0.84±0.17	<0.001*
	−	0.79±0.14		0.79±0.14		0.79±0.14	

Values are mean±SD or frequency. Differences in numeric variables were assessed by ANOVA, whereas frequency difference was assessed by a χ^2 test. cSVD was defined as presence of lacunar infarction, microbleeds, and PVH grade ≥2. BMI indicates body mass index; cSVD, cerebral small-vessel disease; IMT, intima-media thickness; and PVH, periventricular hyperintensity.

*Statistical significance.

Discussion

In the present study, we showed that short OLST (<20 s) but not posturographic parameters for center of gravity movement was significantly associated with cSVDs in an apparently healthy general population of middle-aged to elderly individuals. To our knowledge, this is the first study reporting the independent association of OLST with lacunar infarction and microbleeds, with the previously reported possible association of OLST with PVH not observed in our data set. Short OLST was also independently associated with impaired cognitive function.

The relationship between postural instability and PVH has been investigated in several studies,[10–16] with results consistently supporting the positive relationship between the 2 parameters; however, few studies have been concluded on lacunar infarction, and even fewer on microbleeds. One strength of our present study was, therefore, the concomitant evaluation of cSVDs and findings of a positive association of postural instability with lacunar infarction and microbleeds. We also evaluated cognitive function and found a cSVD-independent association of postural instability with cognitive decline. Elucidation of postural instability as a factor for not only brain histological change but also functional decline was another strength of our study.

No significant association was found between postural instability and PVH, even in the subanalysis in elderly subjects although several previous studies have reported greater severity of PVH in subjects with short OLST or low physical function.[11–14] Although reasons for the discrepancy are unclear, our results suggest that postural instability might not always be associated with PVH. Subtypes of first-ever stroke observed in both hospital-based or community-based longitudinal studies

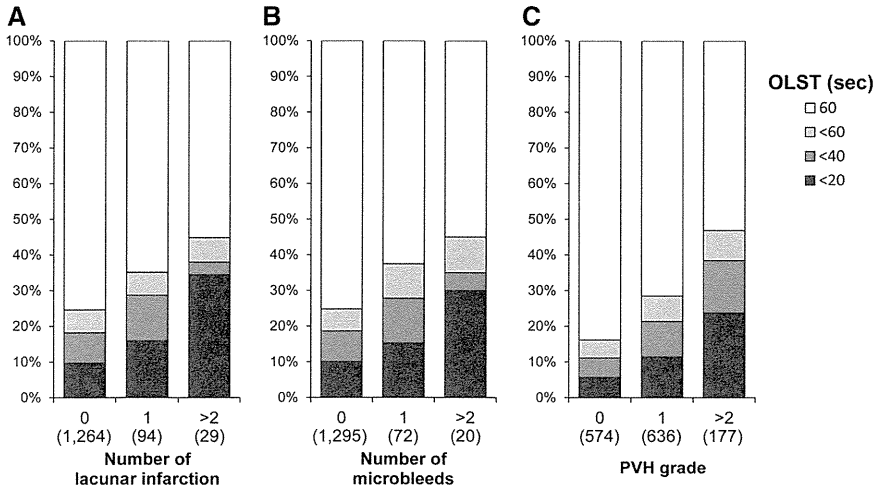

Figure 1. A–C, Association between cerebral small-vessel diseases and one-leg standing time (OLST). Number of each subgroup is shown in parentheses.

Table 3. Poisson Regression Analysis for Cerebral Small-Vessel Disease

	No. of Lacunar Infarction		No. of Microbleeds		PVH Grade	
	Coefficient	*P* Value	Coefficient	*P* Value	Coefficient	*P* Value
Age, y	0.036	0.041*	0.027	0.054	0.047	<0.001*
Sex (male)	0.013	0.876	0.014	0.878	−0.027	0.424
BMI, kg/m^2	−0.011	0.675	−0.024	0.417	0.006	0.684
Current smoking	0.443	0.001*	0.203	0.241	0.061	0.391
Neuropsychiatric medication	−0.004	0.969	−0.248	0.076	0.091	0.041*
Hypertension	0.321	<0.001*	0.716	<0.001*	0.116	0.001*
Type 2 diabetes mellitus	0.019	0.858	0.021	0.853	0.028	0.535
Carotid IMT, mm	0.686	0.224	0.763	0.214	0.130	0.578
OLST (<20 s)	0.260	0.015*	0.334	0.004*	0.020	0.671

BMI indicates body mass index; IMT, intima-media thickness; OLST, one-leg standing time; and PVH, periventricular hyperintensity.

are known to differ significantly between Japanese population and whites in Western countries, with the Japanese proving more prone to hemorrhage stroke.[26] Furthermore, the proportion of lacunar stroke to total ischemic stroke in Japan was higher than that reported in Western countries.[27] Given these previous epidemiological data, some ethnic differences might be involved in the differences in relationships of physiological instability and PVH between our study population and whites.

Table 4. Associations Between cSVD and Posturographic Parameters

		Path Length, cm			Circumference Area, cm^2		
			P Value			*P* Value	
	cSVD	Mean±SD	Crude	Adjusted	Mean±SD	Crude	Adjusted
Eyes open							
OLST, s							
60		83±25	<0.001*	<0.001*	3.09±1.44	<0.001*	<0.001*
<60		101±30			3.75±1.86		
<40		102±35			4.08±2.05		
<20		115±46			4.71±3.56		
Lacunar infarction	+	99±33	0.001*	0.544	3.70±2.11	0.067	0.837
	−	89±31			3.36±1.92		
Microbleeds	+	95±33	0.070	0.644	3.66±1.92	0.174	0.989
	−	89±31			3.37±1.94		
PVH	+	100±33	<0.001*	0.540	4.07±3.27	<0.001*	0.029*
	−	88±31			3.29±1.64		
Eyes closed							
OLST, s							
60		131±56	<0.001*	<0.001*	4.97±2.98	<0.001*	<0.001*
<60		174±82			7.69±5.47		
<40		172±108			7.18±5.32		
<20		186±100			8.62±6.93		
Lacunar infarction	+	161±87	0.004*	0.768	6.38±4.72	0.069	0.818
	−	142±71			5.66±4.16		
Microbleeds	+	153±75	0.178	0.660	6.52±4.65	0.062	0.594
	−	143±72			5.67±4.18		
PVH	+	164±84	<0.001*	0.600	6.80±5.43	<0.001*	0.470
	−	141±70			5.57±3.98		

Values are mean±SD. Adjusted factors were age, sex, body mass index, current smoking, neuropsychiatric medication, hypertension, type 2 diabetes mellitus, and carotid intima-media thickness. Small-vessel disease was defined as presence of lacunar infarction, microbleeds, and PVH grade ≥2. cSVD indicates cerebral small-vessel disease; OLST, one-leg standing time; and PVH, periventricular hyperintensity.

*Statistical significance.

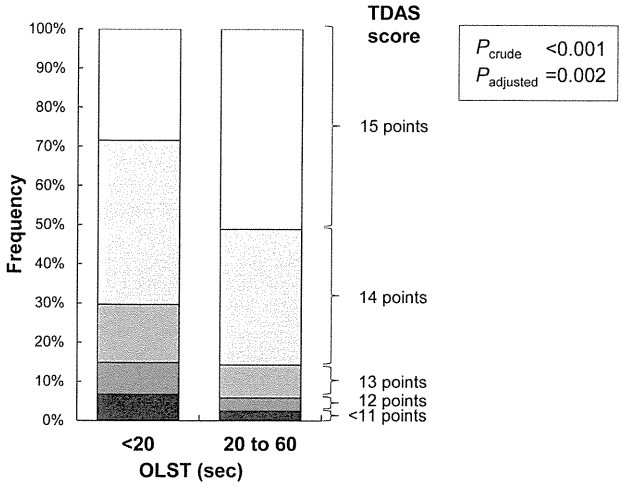

Figure 2. Association of short one-leg standing time (OLST) and cognitive function. Multiple linear regression analysis for Touch Panel-type Dementia Assessment Scale (TDAS) score was performed with adjustment for age, sex, body mass index, hypertension, type 2 diabetes mellitus, neuropsychiatric medication, carotid intima-media thickness, number of lacunar infarctions, periventricular hyperintensity grade, and number of microbleeds.

However, given the lack of supportive data, additional investigation will be required to clarify this issue.

Short OLST was independently associated with cSVDs and not vice versa. Because age and body mass index were only identified as a major significant determinant for OLST by Tobit regression analysis, OLST might be a strong function of age and anthropometric parameters and, therefore, cSVD might not be independently associated with OLST.

Marked cognitive decline was observed in subjects with short OLST. Although cSVDs was naturally associated with a relatively low TDAS score, the association between short OLST and cognitive decline was independent of the existence of cSVD. Previous studies have suggested that, in addition to the well-known risk factors, dementia increases risk of falls[28–30] and fall-related bone fractures[31] in elderly subjects, likely by impairing judgment, motor function, visual-spatial perception, and the ability to recognize and avoid hazards. Given the present findings, postural instability might also be a factor involved in the elevated incidence of falls in subjects with dementia.

OLST was strongly and inversely associated with age; as same in a previous study,[32] marked shortening of OLST occurred in subjects aged ≥60 years; it was also strongly and age-independently associated with increasing center of gravity movement; however, no significant correlation was observed between posturographic parameters and cSVD. As posturographic measurements were performed with subjects in a static upright posture, greater difficulty of postural control in one-leg standing than in an upright position with feet together might be a reason for the relevance of short OLST, but not high posturographic parameters, to cSVD. Previous studies reported that gait dysfunction was a physical marker that was associated with brain white matter lesions[14,33] and small infarction.[34] Because gait consists of 3 primary components (balance, locomotion, and adaptation to the environment),[35] the relevance of gait dysfunction to brain abnormalities further supports the importance of balance-function as a physical factor for cSVD.

Several limitations to the present study warrant mention. First, we measured postural instability using a posturograph for 60 s. Previous studies have suggested that 3 trials of 120-s measurements are needed to obtain reliable results[36]; as such, our findings for OLST may lead to underestimation. Second, we measure neither physical functions, such as gait speed or gait abnormality, nor history or incident of falls. These data would help further clarify the relationship between physical function and brain abnormalities, including impaired cognitive function. Third, the present study is a cross-sectional design. Additional longitudinal studies are, therefore, required to clarify the prognostic significance of postural instability.

Summary

Our data from community-dwelling residents identifies postural instability as a factor in early pathological changes in the brain and functional decline, even in apparently healthy subjects. In older individuals, comprehensive geriatric assessment of frailty has been reported useful in increasing hospitalized patient's survival duration.[37] Furthermore, complex intervention was reported to be useful in helping community-dwelling elderly people to live independently.[38] Comprehensive geriatric assessment is usually defined as a multidimensional diagnostic process focused on determining medical, psychological, and functional capability of a frail older patient.[39] Our findings incorporates postural instability as an important measure of comprehensive geriatric assessment, and individuals showing postural instability should subsequently receive increased attention because this instability may signal potential brain abnormalities and cognitive decline.

Acknowledgments

We thank Yoko Ochi and Hideka Fuyuki for their help in collecting clinical data.

Sources of Funding

This study was supported by Grants-in-Aid for Scientific Research from The Ministry of Education, Culture, Sports, Science and Technology of Japan; The Ministry of Health, Labour and Welfare of Japan; The Japan Arteriosclerosis Prevention Fund; and a Research Promotion Award from Ehime University.

Disclosures

None.

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CLINICAL INVESTIGATIONS

Tooth Loss and Atherosclerosis: The Nagahama Study

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Abstract: *Several epidemiologic studies have suggested that oral disease is a risk factor for cardiovascular disease (CVD). However, whether a clinically significant association exists between the 2 disorders remains controversial. Here, we investigated the association between tooth loss, as an indicator of oral disease, and arterial stiffness, as a marker of atherosclerosis, in Japanese adults. Cross-sectional data were collected for 8,124 persons aged 30 to 75 y with no history of tooth loss for non-inflammatory reasons, such as orthodontic treatment, malposition, and trauma. Participants received a comprehensive dental examination and extensive in-person measurements of CVD risk factors, and arterial stiffness was evaluated using the cardio-ankle vascular index (CAVI). We examined the association between CAVI and tooth loss using general linear models with adjustment for age, sex, body mass index, smoking status, hemoglobin A1c, and a history of insulin or hypoglycemic medication depending on the model. In addition, we performed an analysis that included interaction terms of the centered variables tooth loss, sex, and age. The results of the multiple regression analysis that included the interaction terms detected that the relationship between CAVI and tooth loss was dependent on sex, with only men showing a positive correlation (β for interaction = 0.04; 95% confidence interval, 0.02–0.06). The findings from this study suggest that a linear relationship exists between tooth loss and degree of arterial stiffness and that the association differed depending on sex.*

Key Words: arterial stiffness, epidemiology, inflammation, periodontal disease, cross-sectional analysis, cardiovascular diseases.

Introduction

Cardiovascular disease (CVD) is the most common cause of death and disability in industrialized nations and has a high cost to society. The coincidence of cardiovascular and oral disease is relatively high, and numerous studies have reported that a positive association exists between these 2 diseases (Beck et al. 1998; Beck et al. 2001; Hujoel et al. 2001; Desvarieux et al. 2003; Pussinen et al. 2003; Desvarieux et al. 2004; Ylostalo et al. 2006; Tonetti et al. 2007; Tu et al. 2007; Dietrich et al. 2008; Senba et al. 2008; Choe et al. 2009; de Oliveira et al. 2010; Kim et al. 2010). However, as a significant relationship was not detected in several studies (Hujoel et al. 2000; Lavelle 2002; Colhoun et al. 2008), it remains controversial whether a clinically significant association exists between the 2 diseases (Hujoel et al. 2000; Lavelle 2002; Lockhart et al. 2012).

Inflammation plays an important role in the pathogenesis of CVD. Systemic inflammation may represent the underlying mechanism that links oral and cardiovascular diseases. Oral disease, such as periodontal disease, is characterized by chronic systemic inflammation and often results in tooth loss due to the breakdown of periodontal tissue. Therefore, tooth loss is a useful proxy for the accumulated burden of inflammatory disease (Desvarieux et al. 2003; Houshmand et al. 2012).

Elderly people and men carry a disproportionate burden of CVD and oral disease. Therefore, age and sex adjustment must be performed when evaluating the potential link between oral disease and CVD. Moreover, as oral disease and CVD share common risk factors, including smoking, diabetes, hypertension, and obesity, the potential for confounding is substantial. Thus, the power for detecting effect modification is limited in small population studies.

Arterial stiffness, as assessed by the cardio-ankle vascular index (CAVI), is

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a measure of CVD (Kadota et al. 2008). CAVI was developed to overcome the dependency of pulse-wave velocity (PWV) measurements on blood pressure. The underlying principle of CAVI measurement is based on the stiffness parameter β and is calculated using the Bramwell-Hill formula, which is basically independent of blood pressure (Yambe et al. 2004; Shirai et al. 2006; Takaki et al. 2008; Shirai et al. 2011). Thus, CAVI is an easily administered arterial stiffness screening test that ensures good reproducibility as a diagnostic tool for CVD. Here, we investigated the relationship between tooth loss and arterial stiffness using baseline survey data in a population-based cohort.

Methods

Ethics Statement

This study was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee, the Ad Hoc Review Board of the Nagahama Study, and the Nagahama Municipal Review Board of Personal Information Protection. Appointments for health examinations were made by telephone by the municipal government staff, and participant registration was performed at the site of the health examinations. Written informed consent was also obtained from all participants prior to their health examination.

Study Design and Population

The Nagahama Prospective Genome Cohort for the Comprehensive Human Bioscience (the Nagahama Study) is a population-based prospective cohort study of a broad range of chronic illnesses and was conducted in Nagahama City, Shiga Prefecture, Japan (Tabara et al. 2013). The present study is a prospective study that collected data by means of questionnaires, anthropometric and physiologic measures, biochemical measurements of blood samples, genomic information, and oral examinations. The Nagahama Study participants were recruited from apparently healthy community residents living in Nagahama City, a largely rural city of approximately 125,000 inhabitants in Shiga Prefecture, which is located in central Japan. A baseline survey was conducted between fiscal years 2008 and 2010. Information on the project was provided to potential participants by newsletters, newspaper flyers, and brochures and on the homepages of the local government and citizen organizations. Information sessions for the residents were also held by researchers and city employees, who explained the project to interested residents. Residents of Nagahama City who fulfilled the following criteria were recruited for the cohort study: 1) age between 30 and 74 years old at the time of recruitment, 2) able to participate in the health examinations independently, 3) no difficulties in communication in Japanese, 4) no serious diseases/symptoms or health issues, and 5) voluntarily decided to participate in the project. We performed a complete case analysis, so only participants with complete information for subjective measures of tooth loss, CAVI, and all other examined covariates were included in the analytical sample. As no variables were missing from more than 5% of the total number of cases, and the missing data were random, the missing data are not considered to have markedly influenced the outcomes of the analysis. A total of 1,670 participants were excluded from the adjusted analyses because of missing data, and participants who reported that tooth loss was due to orthodontic treatment, malpositioned teeth, or trauma were also excluded. Therefore, the analyses reported in the present study included a total of 8,124 participants.

Risk Factor Assessment

Trained physicians and research assistants administered standardized questionnaires, performed anthropomorphic measurements, and collected fasting blood specimens using standardized protocols. Subjects were interviewed and completed a questionnaire regarding sex, age, cardiovascular risk factors, and other medical conditions.

Height and weight measurements were determined with calibrated scales. Body mass index (BMI) was calculated using the obtained height and weight data. Trained nurses measured blood pressure using a calibrated automated sphygmomanometer (HEM-9000; Omron Healthcare Co., Ltd., Kyoto, Japan). All measurements were taken at least twice in a sitting position, and the last measurement among the data measured without error was used in the analysis. Fasting blood glucose level, high-density lipoprotein (HDL) cholesterol (HDL-C), low-density lipoprotein (LDL) cholesterol (LDL-C), and hemoglobin A1c (HbA1c) were measured using the collected blood samples from all subjects. Participants were categorized as current smokers, former smokers, or never smokers based on self-report.

Hypertension was defined as a systolic blood pressure (SBP) of ≥140 mm Hg or a diastolic blood pressure (DBP) of ≥90 mm Hg, or the self-report of history of antihypertensive drug use. HbA1c values (%) are reported according to the National Glycohemoglobin Standardization Program. Diabetes mellitus was defined by a history of insulin or hypoglycemic medication, or a fasting glucose level ≥126 mg/dL or random plasma glucose level ≥200 mg/dL, or HbA1c ≥6.5 (HbA1c ≥6.1%), according to the Japan Diabetes Society criteria (Seino et al. 2010).

Measurement of CAVI

CAVI was recorded using a Vasera VS-1500 vascular screening system (Fukuda Denshi Ltd., Tokyo, Japan) with the participant resting in the supine position, as described in a previous report (Shirai et al. 2006). Briefly, electrocardiograph electrodes were placed on both wrists, a microphone for detecting heart sounds was placed on the sternum, and cuffs were wrapped around both arms and ankles. After automatic measurements, obtained data were analyzed using VSS-10 software (Fukuda Denshi Ltd.), and values of the right and left CAVI were calculated. Averages of the right and left CAVI were used for analysis.

Dental History and Oral Examination

At baseline, subjects were interviewed and underwent a complete examination of the oral cavity administered by 1 of 2

Table 1.
Characteristics of Study Participants

Variable	Men (n = 2680)	Women (n = 5444)	All Participants (N = 8124)
Age, y	56.0 (28.9–83.1)	53.3 (27.2–79.5)	54.2 (53.9–54.5)
Tooth loss	4.3 (0–18.3)	3.2 (0–14.4)	3.6 (0–15.8)
CAVI	7.9 (5.4–10.3)	7.2 (5.2–9.3)	7.4 (5.2–9.7)
Hypertension	1,066 (39.8)	1,549 (23.5)	2,420 (29.8)
Diabetes	226 (8.4)	170 (2.6)	377 (4.6)
Former smoker	1,184 (44.2)	454 (8.3)	1,638 (20.2)
Current smoker	827 (30.9)	345 (6.4)	1,172 (14.4)
BMI, kg/m^2	23.4 (17.3–29.5)	21.8 (15.3–28.3)	22.3 (15.8–28.9)
SBP, mm Hg	128.6 (91.9–160.3)	119.4 (85.6–153.3)	122.4 (88.2–156.7)
DBP, mm Hg	79.9 (58.4–101.3)	73.5 (52.1–94.9)	75.6 (53.3–97.8)
HDL-C, mg/dL	57.7 (26.2–89.2)	68.7 (36.3–101.2)	65.1 (31.3–98.8)
LDL-C, mg/dL	123.0 (60.4–185.7)	123.8 (61.36–186.2)	123.5 (61.1–181.0)
HbA1c	5.2 (3.9–6.5)	5.1 (4.2–6.0)	5.1 (4.0–6.2)
Glucose, mg/dL	94.3 (51.9–136.7)	88.8 (63.2–114.4)	90.6 (58.1–123.2)
Antihypertensive medication	598 (22.3)	843 (15.5)	1,441 (17.7)
Hypoglycemic medication	141 (5.3)	88 (1.6)	229 (2.8)
Insulin	14 (0.5)	14 (0.3)	28 (0.3)

Values are presented as the mean (reference range: mean −2 SD to mean +2 SD) or n (%).
BMI, body mass index; CAVI, cardio-ankle vascular index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

trained, calibrated dentists, who were randomly assigned to subjects. The same 2 dentists performed the dental examinations during the study period. During the oral examination, the number of missing teeth was counted. Congenitally missing and impacted teeth were excluded from the count of tooth loss. Third molars were excluded from counts of tooth loss, because third molars tend to be completely impacted or congenitally missing.

Statistical Analysis

Continuous variables are reported as means (reference range: mean −2 SD to mean +2 SD), and categorical variables are given as counts (percentages). The number of teeth showed right-skewed distributions and was therefore logarithmically transformed before analyses and back transformed to the original scale when presented. We examined the association between CAVI and tooth loss using general linear models with adjustment for age, sex, BMI, smoking status, HbA1c, and a history of insulin or hypoglycemic medication depending on the model, having excluded the presence of multicollinearity. In addition, the models were compared with and without interaction terms. To investigate possible effect modification with sex, age, and tooth loss, we added interaction terms using the centered variables tooth loss, sex, and age (<60 and ≥60 years). We checked the linear relationship identified in this multiple regression model by visual examination of plots of standardized residuals.

Probability values of less than 0.05 were considered indicative of statistical significance. Statistical analyses were performed using the STATA version 11 software package (Stata Corp., College Station, TX).

Results

General Characteristics

Table 1 lists demographic information of the study participants, including data for the known risk factors of arteriosclerosis and tooth loss. The mean (reference range) age of the 8124 participants was 54.2 y (27.7–80.8 y), and 67.0% were women. Men were significantly older than women (56.0 [28.9–83.1] vs. 53.3 [27.2–79.4] y) and had a high prevalence of arteriosclerosis risk factors, including hypertension, diabetes, smoking status, and obesity. CAVI values were higher for men than for women (7.9 [5.4–10.3] vs. 7.2 [5.2–9.3], respectively). The mean

Table 2.
Multivariable Linear Regression Models for CAVI and Tooth Loss Adjusted for Age, Sex, BMI, Smoking Status, Hemoglobin A1c, a History of Insulin or Hypoglycemic Medication, and Interactions

	Unadjusted Model		Adjusted Model[a]			
			Model 1		Model 2	
	β	95% CI	β	95% CI	β	95% CI
Tooth loss	0.47	(0.45 to 0.50)	0.04	(0.02 to 0.06)	0.03	(0.01 to 0.06)
Sex	−0.65	(−0.70 to −0.60)	−0.48	(−0.53 to −0.43)	−0.48	(−0.53 to −0.43)
Age	0.06	(0.06 to 0.06)	0.06	(0.05 to 0.06)	0.06	(0.05 to 0.06)
Tooth loss × sex[b]					0.05	(0.02 to 0.09)
Tooth loss × age category[c]					−0.04	(−0.08 to 0.01)

Tooth loss was logarithmically transformed.
CAVI, cardio-ankle vascular index; CI, confidence interval; BMI, body mass index.
[a]Multivariable linear regression analysis, adjusting for body mass index, smoking status, hemoglobin A1c, and a history of insulin or hypoglycemic medication.
[b]Sex (0: male, 1: female).
[c]Age category (0: <60 years, 1: ≥60 years).

(reference range) tooth loss was higher in men 4.3 (0–18.3) than in women 3.2 (0–14.3).

Association between Tooth Loss and CAVI

Table 2 shows the results of the regression modeling for the association between tooth loss and CAVI, as reported by coefficient β (β) and 95% confidence intervals (CIs). For the unadjusted analysis, a significant relationship was detected between tooth loss and CAVI (β = 0.47; 95% CI, 0.45–0.50).

Multiple regression modeling after adjustment for age, sex, BMI, smoking status, HbA1c, and a history of insulin or hypoglycemic medication was also performed (model 1, Table 2). The adjusted multiple regression analysis detected a significant positive association between CAVI and tooth loss (β = 0.04; 95% CI, 0.02–0.6). As the residuals were randomly scattered around 0 (horizontal line) and exhibited a relatively even distribution, the association between CAVI and tooth loss appeared to be linear (data not shown).

Interaction Effects of Sex, Age, and Tooth Loss

We introduced the interaction between sex, age, and tooth loss in the multiple regression analysis by examining the association between CAVI and tooth loss (model 2, Table 2). The analysis revealed that the relationship between CAVI and tooth loss differed depending on sex, with only men showing a positive correlation (β for interaction = 0.04; 95% CI, 0.02–0.6).

Discussion

The present large-scale epidemiologic study has identified that a significant positive correlation exists between tooth loss and arterial stiffness, even after adjustment for age, sex, and other confounding factors. Notably, we found an association between tooth loss and CAVI, although the association differed depending on sex. Our data provide evidence that oral disease and CVD may be positively related in men, who had higher rates of tooth loss and arterial stiffness than did women.

Previous reports examining the association between tooth loss and CVD have treated tooth loss as a nominal variable and have primarily focused on the presence or absence of CVD (Choe et al. 2009; Desvarieux et al. 2004). In contrast, here we treated both tooth loss and the primary outcome of atherosclerosis, arterial stiffness, as numeric variables. Our analysis revealed that the severity of atherosclerosis is linearly related to tooth loss, which often results from the breakdown of periodontal tissue caused by periodontal disease. As tooth loss is a marker of current and long-term cumulative effects of periodontal disease (Desvarieux et al. 2003; Houshmand et al. 2012), our findings suggest that periodontal disease may play a role in the pathogenesis of atherosclerosis progression. In this study, we excluded noninflammatory reasons for tooth loss such as traumatic or orthodontic procedures, because we considered that noninflammatory tooth loss may bias the association between tooth loss and CAVI. However, we considered that the influence of excluding noninflammatory tooth loss on the findings from this study was not significant, because the number of individuals who were excluded for noninflammatory tooth loss was small.

Several potential mechanisms have been proposed in the literature for the association between periodontal disease, including tooth loss, and CVD. The findings from animal and epidemiologic studies suggest that infectious agents, including those associated with periodontal disease, increase

inflammatory cytokine production and platelet aggregation (Herzberg and Meyer 1996), which contribute to arteriosclerosis and thrombosis. In the present study cohort, age was the most important covariate for the relationship between tooth loss and arterial stiffness. Elderly people are more likely to develop periodontal disease and ensuing tooth loss, and they have increased arterial stiffness. We detected a positive association between tooth loss and CAVI and also found that the association differed depending on sex.

We investigated the factors of sex, age, and tooth loss as potential effect modifiers and found that sex that appeared to modify the association of interest. The identified sex difference in the association between clinical periodontal disease, tooth loss, and systemic disease has several potential explanations (Desvarieux et al. 2004; Demmer et al. 2008). Findings from clinical studies and laboratory research have suggested that estrogen is associated with beneficial cardiovascular effects in women (Kannel et al. 1976; Barrett-Connor and Bush 1991) as it reduces the development of atherosclerotic plaque. However, it is also possible that oral inflammation has little or no causal relationship with arteriosclerosis in women.

Progression of atherosclerosis is closely related with increased pulse pressure (Nichols et al. 1985; Sako et al. 2009), which therefore represents an important surrogate marker of arterial stiffness. Pulse pressure is a function of SBP and DBP (pulse pressure [P] = SBP – DBP) and was incorporated into the equation used to calculate CAVI as follows: CAVI = $a\{(2\rho/\Delta P) \times \ln (SBP/DBP)PWV^2\} + b$, where ΔP = SBP – DBP, ρ is blood density, a and b are constants to match aortic PWV. Therefore, pulse pressure is an independent determinant of CAVI (Okura et al. 2007). In CAVI, the rate of increase is reportedly approximately 0.05 per year (Shirai et al. 2011). In the present study, the coefficient β of the multiple regression analysis was 0.04; the loss of 5 teeth corresponds to the amount that CAVI increases in a 4-y period. This finding suggests that the relationship between CAVI and tooth loss is clinically significant.

This study has several limitations that are inherent to cross-sectional analyses. First, the relationships reported here, while robust, should not be interpreted as causal. Our cross-sectional study design lacked information on the time sequence of events and therefore did not permit identification of causal relationships. To confirm the relationship between tooth loss and subclinical atherosclerosis, it is necessary to follow a cohort of middle-age adults until death. Second, we did not measure dietary habits. Increased tooth loss often leads to decreased masticatory performance and a change of dietary habit, which is related to risk factors of atherosclerosis, such as diabetes and hypertension. For this reason, we conducted multivariate analyses with adjustment for potential confounding factors, including hypertension and diabetes. Finally, information related to socioeconomic factors, such as education and income, were not collected in this cohort. Although previous studies have attempted to delineate the influence of socioeconomic differences on mortality, morbidity, and risk factors of disease, the Japanese population may not necessarily reflect the same pattern of relationships observed in other developed countries (Kagamimori et al. 2009). For example, an association between higher education and health is not strongly expressed among the Japanese population (Kagamimori et al. 2009; Lahelma et al. 2010). This may be partly due to the fact that a compulsory insurance system covers all people living in Japan, thereby minimizing differences in access to health care based on socioeconomic status.

In conclusion, our results suggest that the progression of atherosclerosis is linearly related to increased tooth loss and further strengthen the suggested association between these 2 factors. Notably, the age and sex differences in atherosclerosis prevalence seemed to be related to not only the distribution but also the differing contributions of oral inflammatory disease to atherosclerosis across sexes. These findings have profound clinical and public health implications, as they provide further evidence that implementing strategies for preventing periodontal disease, which is both preventable and treatable, might help prevent atherosclerosis. Preventable and treatable contributors of CVD would add to the existing options available to clinicians and public health practitioners for the control of CVD. Educating patients in methods for preventing periodontal disease and improving personal oral hygiene is expected to benefit not only their oral but also their systemic health.

Author Contributions

K. Asai, contributed to conception and design, performed the experiments, contributed to data analysis, drafted manuscript; M. Yamori, contributed to conception and design, performed the experiments, drafted manuscript, initially revised manuscript; T. Yamazaki, contributed to conception and design, performed the experiments, contributed to data analysis, initially revised manuscript; A. Yamaguchi, S. Kosugi, contributed to conception and design, critically revised manuscript; K. Takahashi, contributed to conception and design, performed the experiments, critically revised manuscript; A. Sekine, contributed to conception and design, contributed reagents/materials/tools for analysis, critically revised manuscript; F. Matsuda, T. Nakayama, contributed to conception and design, performed the experiments, initially revised manuscript; K. Bessho, contributed to conception and design, critically revised manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

Acknowledgments

The authors cordially thank the participants of the Nagahama Study, staff of the Nagahama City Office, and the Kohoku Medical Association, Kohoku Dental Association, Nagahama City Hospital, Nagahama Red Cross

Hospital, Nagahama Kohoku City Hospital, Non-profit Organization "Zero-ji Club for Health Promotion," and the Lion Foundation for Dental Health for providing clinical support. The Nagahama Study is in part supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan and by the Takeda Science Foundation. Finally, this study would not have been possible without the effort of all who have contributed to the establishment of the Nagahama Study project. This study was partially supported by grants-in-aid from the following organizations: Kyoto University (2006), Takeda Science Foundation (2008), the 8020 Promotion Foundation (2011), and the Ministry of Health, Labour and Welfare, Japan (2009-2013). The funding agencies had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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Original Article

Central blood pressure relates more strongly to retinal arteriolar narrowing than brachial blood pressure: the Nagahama Study

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Objectives: Although central blood pressure (BP) is considered to be more closely associated with large arterial remodeling and cardiovascular outcomes than brachial BP, few studies have investigated these associations with changes in small arteries. As morphological changes in retinal vessels might be associated with cardiovascular outcomes, we conducted a cross-sectional study to investigate the association of central BP with retinal vessel caliber.

Methods: The study included 8054 Japanese participants. Central BP was estimated by the radial arterial waveform by calibrating brachial BP. Central retinal arteriolar equivalent (CRAE) was computationally measured using fundus photography.

Results: CRAE was most strongly associated with central SBP ($r=-0.324$, $P<0.001$), followed by DBP ($r=-0.292$, $P<0.001$) and central pulse pressure (PP; $r=-0.226$, $P<0.001$). The correlation coefficient between SBP and CRAE was significantly greater in central SBP than in brachial SBP ($r=-0.300$, $P<0.001$). After adjustment for possible covariates, brachial SBP ($\beta=-0.221$, $P<0.001$) and central SBP ($\beta=-0.239$, $P<0.001$) were independently associated with CRAE. Further, higher brachial SBP ($\beta=-0.226$, $P<0.001$) and smaller PP amplification ($\beta=0.092$, $P<0.001$) were identified as independent determinants of narrowing of CRAE in the same equation, which indicated the superiority of central BP. Central BP-determined hypertensive individuals had a significantly narrower CRAE independent of brachial BP (central/brachial: hypertension/hypertension 121.4 ± 11.5, hypertension/normotension 120.9 ± 11.2, normotension/hypertension 125.1 ± 11.9, normotension/normotension $128.1\pm11.5\,\mu m$).

Conclusion: Central BP was more closely associated with the narrowing of CRAE than brachial BP. Slight increases in central BP might be involved in the morphological changes in small retinal arteries, even in individuals with optimal brachial BP.

Keywords: central blood pressure, retinal vessel caliber, small artery narrowing

Abbreviations: AIx, augmentation index; BP, blood pressure; baPWV, brachial-to-ankle pulse-wave velocity; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; MRRM, Meng–Rosenthal–Rubin method; SBP2, late SBP

INTRODUCTION

Central aortic blood pressure (BP) directly reflects the BP load on target organs and is therefore considered to be more closely associated with the cardiovascular outcomes than brachial BP. Compared with brachial BP, central BP estimated via radial arterial waveform or measured via carotid tonometry is more effective in showing the degree of association with intima–media thickness of the carotid artery in hypertensive individuals [1], the severity of coronary stenosis in patients with coronary artery diseases [2], the incidence of cardiovascular disease in the general population [3], and all-cause mortality in patients with end-stage renal disease [4]. One reason for these discrepancies is the difference in pulse pressure (PP) between the brachial artery and central aorta (PP amplification), which is largely dependent on the velocity of the reflection pressure wave. Increased pulse-wave velocity

Journal of Hypertension 2015, 33:323–329

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Received 15 March 2014 **Revised** 20 August 2014 **Accepted** 20 August 2014

DOI:10.1097/HJH.0000000000000391

(PWV) augments overlapping of the reflection pressure wave on the forward pressure wave, which strengthens the forward wave and in turn increases central aortic BP.

High BP load is also a causative factor for small-vessel diseases such as silent cerebral infarction [5]. Retinal vessels are the only visible arterioles and venules whose caliber can be easily measured by fundus photography. Retinal vessel signs, that is, the narrowing of retinal arteriolar caliber and widening of venular caliber, have been associated with cardiovascular risk factors [6,7], systemic inflammation [8], and decreased renal function [9]. Further, because of the similar anatomic features and physiological properties of retinal vessels and cerebral microvessels [10], retinal vessel caliber has been suggested to predict stroke incidence [11,12] and stroke death [13]. Recently, Ott *et al.* [14] assessed the retinal arteriolar wall-to-lumen ratio in 135 nondiabetic individuals and reported that central PP was significantly associated with retinal arteriolar remodeling, though the superiority of central BP to brachial BP was not evaluated. Muiesan *et al.* [15] also reported a significant correlation between central BP and media-to-lumen ratio of subcutaneous small resistance arteries, but again did not evaluate the superiority of central BP. Although it remains unclear whether changes in retinal vessel caliber represent structural changes in small arteries and arterioles, a strong correlation between arterial diameter and medial cross-sectional area has been observed in the subcutaneous small arteries [16]. Further, by considering a substantial number of studies that reported a clinical and prognostic significance of retinal vascular caliber measurements [17], it is promising that retinal vascular calibers represent the vascular disease risks in various kinds of populations. Given these backgrounds, it was speculated that central BP might also be more closely correlated with the pathophysiological changes in retinal vessel calibers than brachial BP, whereas a paradoxical result was reported [18].

Here, we conducted a large-scale cross-sectional study in a general population to clarify the possibility of a superior association of central BP with not only large arterial diseases, but also small-vessel properties by measuring retinal arteriolar and venular calibers. Given that the prognostic significance of retinal vessel properties on the cardiovascular and cerebrovascular outcomes has been suggested, our results might be of clinical and epidemiological significance to the possible addition of central BP measurement to conventional brachial measurement in the assessment of small arterial disease risks.

METHODS

Study participants

Participants consisted of 8054 apparently healthy middle-aged to elderly citizens who were participants of the Nagahama Prospective Cohort for Comprehensive Human Bioscience (the Nagahama Study). The Nagahama Study cohort was recruited from 2008 to 2010 from the general population living in Nagahama City, a largely suburban city of 125 000 inhabitants located in central Japan. Community residents aged 30–74 years, living independently in the community and with no physical impairment or dysfunction, were recruited for the Nagahama cohort. Of a total of 9804 participants, those meeting any of the following conditions were excluded from this study, which are as follows: unsuccessful measurement of retinal vascular caliber ($n=1521$), presence of retinal vein occlusion or collateral vessels in either eye ($n=78$), unsuccessful assessment of retinopathy ($n=45$) or clinical parameters required for this study ($n=57$), extreme deviation of renal function [estimated glomerular filtration rate $194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if women)] less than 30 ml/min per m^2 ($n=7$), and women who were pregnant ($n=42$). All study procedures were approved by the ethics committee of Kyoto University Graduate School of Medicine and the Nagahama Municipal Review Board. Written informed consent was obtained from all the participants.

Blood pressure measurements

Radial arterial waveform and brachial BP were measured simultaneously (HEM-9000AI; Omron Healthcare, Kyoto, Japan) after 5 min rest in the sitting position. Measurements were taken twice, and the mean value was used in the analysis. Absolute pressure of the late systolic peak (SBP2) of the radial arterial waveform was considered the central SBP. The radial augmentation index (AIx) was calculated from the waveform as the ratio of the late systolic peak to the first systolic peak, and the BP measurements are briefly described in the Supplemental Methods. PP amplification was calculated by subtracting central PP from brachial PP and expressed in the absolute values (mmHg). Mean BP (MBP) was calculated from SBP and DBP using the following formula: $(\text{SBP}-\text{DBP})/3+\text{DBP}$. Hypertension was defined as any or all of the following: use of antihypertensive medication, DBP greater than 90 mmHg, or brachial SBP greater than 140 mmHg or central SBP greater than 130 mmHg according to a previous report [19] that estimated central BP using the SphygmoCor system. SBP2 measured by the HEM-9000AI was almost identical to central SBP measured by the SphygmoCor system [20].

Retinal vessel caliber measurements

Fundus photographs of both eyes were taken in a shaded area using a 45-degree digital nonmydriatic camera (CR-DG10; Canon, Tokyo, Japan) at a 5-degree angle from the nasal side of the macula. A fundus photograph of the right eye was used for retinal caliber measurements. Retinal vascular caliber was measured using a semi-automated computer-based program (IVAN; University of Wisconsin, Madison, Wisconsin, USA). The measurement of central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) are briefly described in the Supplemental Methods. Intragrader and intergrader intraclass correlation coefficients for the retinal arteriolar measurements were 0.80 ± 0.06 and 0.75 ± 0.06, and for the venular caliber measurements were 0.88 ± 0.13 and 0.86 ± 0.01, respectively.

Assessment of retinopathy

Retinopathy of both eyes was independently assessed in a masked fashion by two ophthalmologists, with a third

ophthalmologist making a final decision in cases of disagreement. Retinopathy was defined by the Early Treatment Diabetic Retinopathy Study Severity Scale [21] by the presence of any of the following characteristic lesions: microaneurysms, retinal hemorrhages, cotton wool spots, hard exudates, intraretinal microvascular abnormalities, venous beading, vitreous hemorrhages, or neovascularization. Individuals having at least one characteristic lesion in either eye were diagnosed as having retinopathy.

Basic clinical parameters

Basic clinical parameters, including plasma markers, were measured at baseline. Age was calculated from the year of birth to the year of baseline measurements. Smoking, alcohol consumption, and a history of cardiovascular disease, namely symptomatic stroke or ischemic heart disease, were determined using a structured self-administered questionnaire. Daily alcohol consumption was determined using the standard Japanese alcohol unit (1 unit corresponds to 22.9 g of ethanol). Brachial-to-ankle pulse-wave velocity (baPWV) was measured as an index of arterial stiffness. The method of baPWV measurement is detailed in the Supplemental Methods. Collinearity of baPWV with a carotid-to-femoral PWV, a standard measure of arterial stiffness, has been reported elsewhere [22].

Statistical analysis

Comparison of overlapping correlation coefficients was performed using the Meng–Rosenthal–Rubin method (MRRM). Identification of the factors independently associated with retinal vessel caliber, and the assessment of differences in CRAE by hypertension status was performed using multiple regression analysis. Statistical analysis was performed using JMP 9.0.2 software (SAS Institute, Cary, North Carolina, USA) and R software. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Clinical characteristics of the study participants are shown in Table 1. Mean age was 52 ± 13 years old. There were approximately two times more female than male participants. We excluded 1750 individuals from the analysis, mostly because of the unsuccessful measurement of retinal vessel caliber. Although the excluded participants were significantly older (Figure S1), BP levels of these excluded individuals and roughly measured retinal vessel calibers in a part of the individuals ($n = 229$) were not different from those of the remaining study participants (Table S1, http://links.lww.com/HJH/A416).

Distribution of CRAE and CRVE is shown in Figure S2, http://links.lww.com/HJH/A416. There was a moderate interrelationship between CRAE and CRVE ($r = 0.352$, $P < 0.001$). CRVE was significantly larger in men than in women (183.8 ± 15.9 vs. 178.7 ± 15.1 μm, $P < 0.001$). In contrast, CRAE was only slightly different between men and women (125.7 ± 12.0 vs. 126.3 ± 11.8 μm, $P = 0.016$). Basic factors that were significantly associated with retinal vessel caliber included age (CRAE, $r = -0.210$, $P < 0.001$; CRVE, $r = -0.204$, $P < 0.001$), habitual smoking (CRAE: current smoker 128.7 ± 11.7 μm, nonsmoker 125.7 ± 11.9 μm, $P < 0.001$; CRVE: 187.3 ± 15.8, 179.2 ± 15.1 μm, $P < 0.001$), and drinking (CRAE: habitual drinker 125.2 ± 11.9 μm, nondrinker 126.6 ± 11.9 μm, $P < 0.001$; CRVE: 182.0 ± 15.8, 179.6 ± 15.3 μm, $P < 0.001$). Figure 1 shows the age-related changes in BP, baPWV, and retinal vessel caliber. Changes in CRAE and CRVE were symmetrical to those in MBP, and were predominant in middle age, whereas the progression of large arterial stiffness evaluated by baPWV was greater in older age.

TABLE 1. Participants characteristics ($n = 8054$)

Age (years old)	52 ± 13
Sex (male, %)	32.5
Body height (cm)	160.4 ± 8.4
Body weight (kg)	57.4 ± 11.0
BMI (kg/m^2)	22.2 ± 3.3
Waist circumference (cm)	80.0 ± 9.2
Smoking (current/past/never, %)	15.1/20.1/64.8
Alcohol drinking (habitual/occasional/never, %)	22.4/10.4/67.2
Daily alcohol consumption (Japanese alcohol unit)	0.60 ± 0.99
History of cardiovascular disease (%)	2.3
Brachial SBP (mmHg)	122 ± 17
Central SBP (mmHg)	113 ± 18
Brachial PP (mmHg)	47 ± 11
Central PP (mmHg)	37 ± 11
PP amplification (mmHg)	10 ± 6
DBP (mmHg)	76 ± 11
Radial AIx (%)	80 ± 14
Heart rate (beats/min)	69 ± 10
Antihypertensive medication (%)	14.6
baPWV (cm/s)	1245 ± 218
CRAE (μm)	126.1 ± 11.9
CRVE (μm)	180.4 ± 15.5
Retinopathy (%)	5.8
Axial length (mm)	24.0 ± 1.3

Values are mean ± standard deviation. Cardiovascular disease includes symptomatic stroke or ischemic heart disease. AIx, augmentation index; baPWV, brachial-to-ankle pulse-wave velocity; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; PP, pulse pressure.

The correlations of BP with CRAE and CRVE are summarized in Table 2. CRAE was strongly associated with SBP, followed by DBP, PP, radial AIx, and PP amplification. Results of MRRM analysis indicated that the correlation coefficient between BPs and CRAE was significantly larger in central BP than brachial BP even after applying the Bonferroni correction ($P = 0.05/16 = 0.003$). Approximately 6% of individuals were diagnosed with retinopathy (Table 1). These individuals were significantly older, and had higher brachial and central SBP (Table S2, http://links.lww.com/HJH/A416). However, the results of a sensitivity analysis (Table S3, http://links.lww.com/HJH/A416) indicated that the superiority of central BP in association with CRAE was independent of retinopathy (model B), as well as of antihypertensive treatment (model C), history of cardiovascular diseases (model D), and metabolic syndrome (model E).

Table 3 shows the results of multiple linear regression analysis for CRAE. After adjustment for possible covariates, brachial SBP (model 1) and central SBP (model 2) were independently associated with CRAE. Further, in the equation that included both brachial SBP and PP amplification, higher brachial SBP and smaller PP amplification were independently associated with the narrowing of CRAE

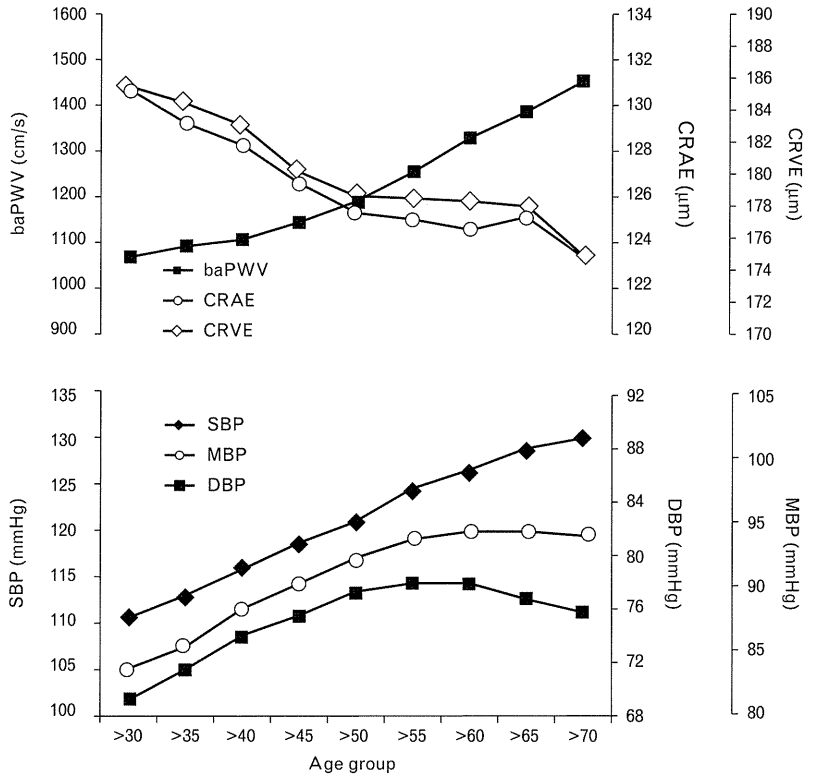

FIGURE 1 Age-related changes in retinal vessel calibers and arterial parameters. Each symbol represents the mean of individuals not taking antihypertensive drugs ($n = 6877$). baPWV, brachial-to-ankle pulse-wave velocity; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent.

(model 3), suggesting that a relatively high central PP is a risk for the narrowing of CRAE. Radial AIx was significantly associated with CRAE in a model that included brachial SBP (model 4), but not central SBP (model 5). In contrast, central SBP was not an important determinant for CRVE (central SBP, $\beta = -0.031$, $P = 0.026$).

Multiple linear regression analysis for retinal vessel caliber (Table 4) indicated that CRAE was strongly associated with BP. In contrast, CRVE was affected by various factors, namely body fluid parameters including hematocrit and white blood cell count, body weight, and smoking, and had only a weak association with MBP. Metabolic and hematological characteristics of the study participants are summarized in Tables S4 and S5, http://links.lww.com/HJH/A416.

Figure 2a shows the differences in mean CRAE by hypertension status defined by central and brachial BP. Central BP-determined hypertensive individuals had a significantly narrower CRAE that was independent of brachial BP. Further, CRAE was linearly decreased with increasing central BP even within the same brachial BP levels (Fig. 2b). By a simple correlation analysis, central SBP corresponded to an approximately 10 mmHg lower brachial SBP (central SBP $= -7.15 + 0.98 \times$ brachial SBP). Individuals exhibiting a relatively lower central SBP, that is, whose central SBP was more than 10 mmHg lower than brachial SBP, had a wider CRAE than those whose central SBP was at a similar level to brachial SBP. In contrast, individuals exhibiting a relatively higher central SBP showed a narrower CRAE.

TABLE 2. Correlation between BP and retinal vessel caliber

	CRAE				CRVE			
	Simple correlation		MRRM		Simple correlation		MRRM	
	r	*P*	*z*	*P*	*r*	*P*	*z*	*P*
Brachial SBP (mmHg)	−0.300	<0.001	6.85	<0.001	−0.107	<0.001	11.65	<0.001
Central SBP (mmHg)	−0.324	<0.001			−0.149	<0.001		
Brachial PP (mmHg)	−0.181	<0.001	7.87	<0.001	−0.108	<0.001	11.65	<0.001
Central PP (mmHg)	−0.226	<0.001			−0.176	<0.001		
DBP (mmHg)	−0.292	<0.001			−0.064	<0.001		
Radial AIx (%)	−0.163	<0.001			−0.175	<0.001		
PP amplification (mmHg)	−0.105	<0.001			0.142	<0.001		

Overlapping correlation coefficients were compared with the Meng–Rosenthal–Rubin method (MRRM). AIx, augmentation index; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; PP, pulse pressure.

TABLE 3. Multiple linear regression analysis for CRAE

	Model 1		Model 2		Model 3		Model 4		Model 5	
	β (VIF)	P	β (VIF)	P	β (VIF)	P	β (VIF)	P	β (VIF)	P
Brachial SBP (mmHg)	−0.221 (1.90)	<0.001			−0.226 (1.91)	<0.001	−0.206 (1.98)	<0.001		
Central SBP (mmHg)			−0.239 (1.84)	<0.001					−0.244 (2.46)	<0.001
PP amplification (mmHg)					0.092 (1.50)	<0.001				
AIx (%)							−0.072 (1.86)	<0.001	0.009 (2.40)	0.545

Adjusted factors were as follows: age, sex, body height, body weight, current smoking, daily alcohol consumption, history of cardiovascular diseases, antihypertensive medication, heart rate, brachial-to-ankle pulse-wave velocity, axial length, retinopathy, and fellow retinal vessel caliber. β, standardized regression coefficient; AIx, augmentation index; CRAE, central retinal arteriolar equivalent; PP, pulse pressure; VIF, variance inflation factor.

DISCUSSION

In this study of an apparently healthy general population, we observed that central BP was more closely associated with the narrowing of CRAE than brachial BP. Even in individuals diagnosed as normotensive by brachial BP, slight increases in central SBP might be a risk factor for the narrowing of CRAE.

We clarified the stronger association of central SBP with the morphological changes in small arterioles, though close associations between central BPs and pathophysiological changes in large arteries [1,2] and cardiovascular morbidity [3] have already been demonstrated. In contrast, central SBP was not a major determinant for venular caliber. Given the strong correlation between BPs and CRAE but not CRVE, changes in arteriolar caliber might more accurately reflect the pressure load of the central aorta. Previous cross-sectional population-based studies have suggested that the associations of retinal vessel caliber with the cardiovascular risk factors largely differs between CRAE and CRVE, with most observing a strong association between brachial BP and the narrowing of CRAE rather than the widening of CRVE [6,7,23,24]. The wide range of covariates for CRVE (Table 4) might also be a reason for the weak association between BPs and CRVE.

Correlation coefficient between central SBP and CRAE was stronger than that of the brachial SBP (Table 2). As a result of the strong collinearity between brachial and central SBP, we could not directly compare the superiority by including both SBPs in a same regression model. However, in the model that included brachial SBP and PP amplification (Table 3, model 3), both the parameters were identified as independent determinant for CRAE. As central SBP is a function of brachial SBP and PP amplification, the results indirectly support the superiority of central SBP in association with CRAE. Further, radial AIx was independently associated with CRAE in a model that included brachial SBP (Table 3, model 4). However, when central SBP was exchanged for brachial SBP (model 5), the association between AIx and CRAE became insignificant. These results suggest that the absolute value of central aortic pressure rather than the ratio of forward and reflection pressure waves may be important for retinal arteriolar narrowing.

A recent longitudinal study of cardiovascular mortality [19] reported that a central BP of 130/90 mmHg has the best discriminatory power in the prediction of cardiovascular outcomes. In addition, a cross-sectional study based on 10 756 Japanese participants reported a central SBP of 129 mmHg as a reference value of normal BP [25]. Here, we found a significantly narrower CRAE in individuals whose central SBP exceeded 130 mmHg independent of the brachial BP levels. Further, the narrowing of CRAE was observed in cases with even lower central SBP. Small arteries may be adversely impacted by even minor increases in central BP load, even in those within the normal limits.

Results from the Strong Heart Study of Native Americans showed that PP measured at the central aorta or brachial artery was more strongly associated than SBP at any artery with large arterial remodeling, namely increased carotid intima–media thickness, vascular mass, and plaque score

TABLE 4. Multiple linear regression analysis for retinal vessel caliber

	CRAE		CRVE	
	β	P	β	P
Body height (cm)	0.079	<0.001	−0.023	0.184
Body weight (kg)	−0.017	0.255	0.136	<0.001
Currently smoking	0.048	<0.001	0.068	<0.001
Hyperglycemia	0.012	0.226	−0.017	0.106
Dyslipidemia	0.010	0.360	0.018	0.103
White blood cell count ($\times 10^2/\mu l$)	−0.008	0.436	0.073	<0.001
Hematocrit (%)	−0.042	0.001	0.115	<0.001
Mean BP (mmHg)	−0.249	<0.001	−0.056	<0.001
baPWV (cm/s)	−0.017	0.259	−0.008	0.596

Metabolic and hematological characteristics of patients are shown in Tables S4 and S5, http://links.lww.com/HJH/A416, respectively. Hyperglycemia was defined as either or both of plasma glucose greater than 126 mg/dl (fasting) or 200 mg/dl (nonfasting), or the use of hypoglycemic treatment, including insulin therapy. Individuals who met any of the following criteria were diagnosed with dyslipidemia: LDL-cholesterol greater than 140 mg/dl, HDL-cholesterol lower than 40 mg/dl, triglyceride greater than 150 mg/dl, or the use of lipid-lowering drugs. Adjustment factors were as follows: age, sex, daily alcohol consumption, history of cardiovascular disease, antihypertensive medication, heart rate, axial length, retinopathy, fellow retinal vessel caliber, and fasting time. β, standardized regression coefficient; baPWV, brachial-to-ankle pulse-wave velocity; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent.

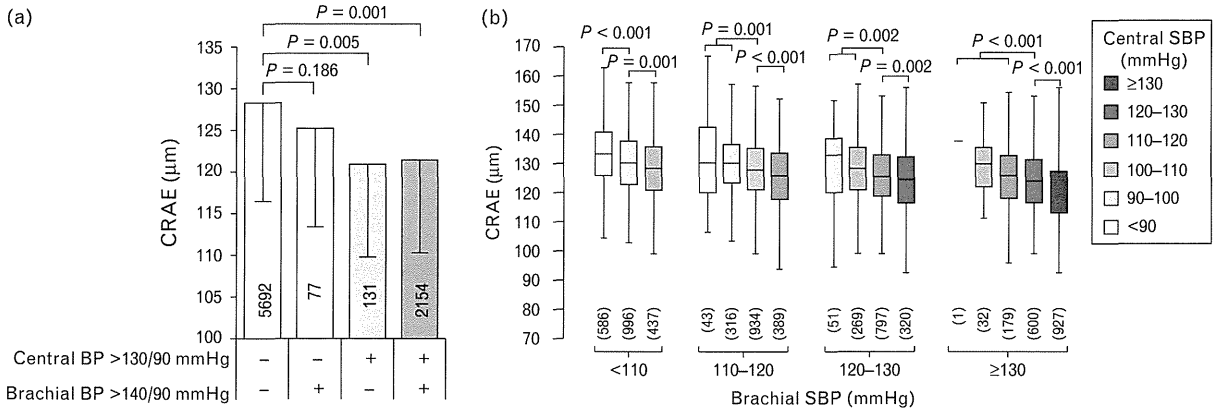

FIGURE 2 Differences in mean CRAE by central and brachial BP levels. (a) Values are mean ± standard deviation. Participants were classified into four groups according to the hypertension status as defined by central BP (any or all of central SBP ≥130 mmHg, DBP ≥90 mmHg, or use of antihypertensive medications) or brachial BP (any or all of brachial SBP ≥140 mmHg, DBP ≥90 mmHg, or use of antihypertensive medications). (b) Box plot of mean CRAE in patients not prescribed antihypertensive drugs ($n = 6877$) by various brachial and central BP levels. Statistical significance was assessed by a multiple linear regression analysis adjusted for age, sex, body height, body weight, current smoking, daily alcohol consumption, history of cardiovascular diseases, heart rate, brachial-to-ankle pulse-wave velocity, axial length, retinopathy, and CRVE. The number of patients in each subgroup is shown in the figure. CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent.

[3]. The superiority of PP in prognosis for all-cause mortality was also reported from a longitudinal study based on patients with end-stage renal disease [4]. In contrast, we observed a close association between CRAE and SBPs rather than PPs. Remodeling of large arteries decreases the Windkessel function of the aorta, which increases the SBP, decreases DBP, and consequently increases PP. In contrast, systemic remodeling of small arteries increases both SBP and DBP. The different pathophysiological features of large and small arterial remodeling in association with BPs might be a factor that explains the stronger association of SBP with the narrowing of CRAEs.

Several limitations of our study warrant mention. First, we estimated central SBP using radial arterial waveform analysis, that is, late systolic peak of the radial arterial waveform (SBP2) was considered equivalent to central SBP. SBP2 was recently reported to not always represent central SBP accurately, particularly in cases with a type C aortic pressure waveform, in which peak SBP precedes an inflection point [26]. The type C waveform is observed in young individuals [27]. Therefore, misestimation of central SBP, if any, might have had no substantial impact on the present findings which were obtained from individuals aged 30 years or older. Second, we excluded a considerable number of potential individuals from analysis, mostly because of the unsuccessful measurement of retinal vessel caliber as a result of an increased frequency of cataracts, small pupils, and difficulties with ocular fixation. However, our ungradable rate 15.5% (1521 of 9804) was not too high compared with that of other large-scale epidemiological studies using the same semi-automated computer system to measure retinal vascular calibers: Atherosclerosis Risk In Communities study, 19% [28]; Beaver Dam Eye Study, 13.8% [29]; and Rotterdam study, 16.3% [30]. Further, as BP level and retinal vessel caliber of the excluded individuals did not differ from those of the included participants, the findings are unlikely confounded by the selection bias. Third, as this study was a cross-sectional setting, further longitudinal studies are needed to clarify the prognostic significance of central hemodynamics in retinal vessel morphological change.

In summary, we have clarified for the first time that central BP is strongly associated with the narrowing of retinal arteriolar caliber in a large-scale general population. As narrowing of the retinal artery is suggested to represent a subclinical cardiovascular and cerebrovascular risk and has been associated with poor prognosis, our study supports the importance of evaluating central BP in the assessment of small arterial disease risks.

ACKNOWLEDGEMENTS

The authors thank Dr Yoshihiko Kotoura, Dr Miyaki Koichi, and Dr Ishizaki Tatsuro for their help regarding clinical measurements, Nagahama City Office, and the Zeoji Club, a non-profit organization, for their assistance in conducting this study. The authors thank the editors of DMC Corporation for their help in the preparation of this manuscript.

Financial support: This study was supported by a University Grant, and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science & Technology in Japan, and a research grant from the Takeda Science Foundation.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Reviewers' Summary Evaluations

Reviewer 2

In a cross-sectional analysis of over 8000 middle-aged to older Japanese adults, the authors report that central SBP as measured by radial artery waveform is more strongly related to retinal arteriolar narrowing than brachial artery SBP. The cohort size is impressive and the findings are seemingly novel in relating retinal arteriolar narrowing to central pressures as opposed to brachial pressures, as has been in prior studies. Study limitations include its observational design and exclusion of large number of enrolled subjects (>1500) because of having been unable to successfully measure retinal arteriolar diameter.

Reviewer 3

In this large cohort study central blood pressure has been found to be associated with retinal arteriolar narrowing independently of brachial blood pressure. The paper focuses the attention on a topic of marked interest employing an outstanding methodology.

pii: sp-00854-13 http://dx.doi.org/10.5665/sleep.4176

Gastroesophageal Reflux Disease Symptoms and Dietary Behaviors are Significant Correlates of Short Sleep Duration in the General Population: The Nagahama Study

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Study Objectives: To examine relationships among gastroesophageal reflux disease (GERD) symptoms, dietary behaviors, and sleep duration in the general population.

Design: Cross-sectional.

Setting: Community-based.

Participants: There were 9,643 participants selected from the general population (54 ± 13 y).

Interventions: None.

Measurements and Results: Sleep duration, sleep habits, and unfavorable dietary behaviors of each participant were assessed with a structured questionnaire. Participants were categorized into five groups according to their sleep duration: less than 5 h, 5 to less than 6 h, 6 to less than 7 h, 7 to less than 8 h, and 8 or more h per day. GERD was evaluated using the Frequency Scale for the Symptoms of GERD (FSSG) and participants having an FSSG score of 8 or more or those under treatment of GERD were defined as having GERD. Trend analysis showed that both the FSSG score and the number of unfavorable dietary habits increased with decreasing sleep duration. Further, multiple logistic regression analysis showed that both the presence of GERD (odds ratio = 1.19, 95% confidence interval (CI) = 1.07–1.32) and the number of unfavorable dietary behaviors (odds ratio = 1.19, 95% CI = 1.13–1.26) were independent and potent factors to identify participants with short sleep duration even after controlling for other confounding factors.

Conclusion: The current study showed that both GERD symptoms and unfavorable dietary behaviors were significant correlates of short sleep duration independently of each other in a large sample from the general population.

Keywords: dietary behavior, gastroesophageal reflux disease, general population, sleep duration

Citation: Murase K, Tabara Y, Takahashi Y, Muro S, Yamada R, Setoh K, Kawaguchi T, Kadotani H, Kosugi S, Sekine A, Nakayama T, Mishima M, Chiba T, Chin K, Matsuda F. Gastroesophageal reflux disease symptoms and dietary behaviors are significant correlates of short sleep duration in the general population: the Nagahama Study. *SLEEP* 2014;37(11):1809-1815.

INTRODUCTION

Amid mounting interest over the effect of sleep on health concerns, many previous studies have suggested that short sleep duration causes a number of conditions such as obesity, insulin resistance, hypertension, and cardiovascular diseases from results of large general populations.[1-6] However, relatively little interest has been paid to determining what factors predict or influence an individual's sleep duration.

Gastroesophageal reflux disease (GERD) is a chronic condition that develops when reflux of gastric contents into the esophagus causes troublesome symptoms or complications.[7] Acid regurgitation and heartburn are the major complaints of GERD and approximately 10% to 25% of the general population was reported to complain of these symptoms.[8–10] Patients with symptoms of GERD commonly report poor sleep, and previous epidemiologic studies have established a link between nighttime heartburn and sleep disturbances.[11–13] However, these studies did not focus on sleep duration but rather on subjective sleep quality. The relationship between sleep duration and GERD symptoms has been investigated in very few studies and their results were discrepant. Matsuki et al. examined lifestyle factors associated with GERD in participants who underwent gastroscopy and showed that the subjects with GERD symptoms were more likely to report short sleep duration than those without such symptoms.[14] However, Chen et al. performed a similar study and showed that symptoms of GERD were not associated with sleep duration.[15] Furthermore, the 800 and 3,000 subjects, respectively, of those studies were recruited during routine health examinations in the hospital and it is possible that these studies did not reflect situations in the general population. A general population survey with a larger sample size is warranted.

In addition, some unfavorable dietary behaviors such as late eating time and snacking after dinner may affect both GERD

Submitted for publication December, 2013
Submitted in final revised form March, 2014
Accepted for publication April, 2014
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