Table 6. Validation of the inclusion of CKD in the TC Suita Score and LDL Suita Score

6a.

Model	Log Likelihood	LR test, *p*-value	C-statistics	BIC
TC Suita Score with CKD	−1610.8	referent	0.835	3233.3
TC Suita Score without CKD	−1618.1	0.013	0.833	3238.5
LDL Suita Score with CKD	−1510.1	referent	0.831	3365.6
LDL Suita Score without CKD	−1513.6	0.032	0.829	3414.5

6b.

Model		TC Suita Score with CKD	LDL Suita Score with CKD	LDL Suita Score with CKD
Reference Model		TC Suita Score without CKD	LDL Suita Score without CKD	TC Suita Score with CKD
Cases	Reclassified Downward (%)	16.7	48.1	48.8
	Reclassified Upward (%)	83.3	51.9	51.2
Non Cases	Reclassified Downward (%)	36.7	26.1	43.8
	Reclassified Upward (%)	63.3	73.9	56.2
Category-free NRI(%)		40.0	43.9	10.1
P-value		<0.001	<0.001	0.256

6a, Comparison of the C-index , LR test and BIC results demonstrating the discrimination for CHD prediction models based on the Suita Score with and without CKD, the FRS and the FRS calibrated for the means of the Suita cohort. Log likelihoods were derived from the multivariate adjusted Cox proportional hazard model.; CKD, chronic kidney disease; FHS, Framingham Heart Study; LR test, likelihood ratio test; BIC, Bayesian information criteria

6b, Comparison of the FRS and Suita Scores and the corresponding reclassification rate for the prediction of CHD events during a 10-year period;. NRI, net reclassification improvement

and different risk factor levels were observed[32-34].

Second, the discriminatory capability of the TC Suita Score with CKD is better than those of the original and recalibrated FRS. Although recalibration with the mean value of the risk factors and baseline survival functions for the study cohort improved the discriminatory capability for various ethnic groups in the U.S., China and the CKD population[6, 12, 16], the recalibration did not improve the discriminatory capability in Japanese subjects. We believe this is probably due to the low incidence of CHD in Japan compared to Western and Chinese populations[35]. The relative risks of various factors were similar between Suita Study cohort and the Framingham cohort. Therefore, the difference between the two prediction tools heavily depends on the difference in the absolute risks between these two cohorts. Accordingly, the clinical reclassification pointed out that the FRS overestimated the risk of CHD in Japanese subjects, especially in the non-CHD group, since the baseline survival function, which was higher than that in the original FRS, affected the estimated risk in an exponential manner and the overestimation was more severe in the high risk groups.

Furthermore, we found that CKD is an independent risk factor for CHD after adjusting for other predictors of the FRS. The cohorts in the Framingham Heart Study and the Offspring study showed no significant association between the presence of kidney disease and the incidence of CVD[36] although some collaborative analyses showed positive associations[17, 37]. Our result is essentially compatible with that of Weiner's study, which reported the HRs of CKD after adjustment of the FRS for whites and blacks[38]. No previous study has dealt with this association for Asian ethnicity as an additional covariate in the prediction tool, although many cohort studies in Japan have demonstrated a significant association between CKD and cardiovascular disease[20, 25, 39].

Finally, we developed a simple prediction sheet for the estimation of CHD based on the TC and LDL Suita Score. For the exact estimation, the beta-coefficient from the TC and LDL Suita Score are preferable. However, the calculation requires computational

Table 7. A comparison of the predicted risks in models based on the Framingham risk score and Suita Score with and without CKD

7a.

Model	Log Likelihood	LR test, *p*-value	C-statistics	BIC
TC Suita Score with CKD	−1610.8	referent	0.835	3233.3
TC Suita Score without CKD	−1618.1	0.013	0.833	3238.5
Original Framingham Score	−1678.5	<0.001	0.768	3365.6
Recalibrated Framingham Score	−1702.9	<0.001	0.740	3414.5

7b.

Model		TC Suita Score with CKD	TC Suita Score with CKD	TC Suita Score without CKD	TC Suita Score without CKD
Reference Model		Original Framingham Score	Recalibrated Framingham Score	Original Framingham Score	Recalibrated Framingham Score
Cases	Reclassified Downward (%)	42.0	50.0	42.8	49.3
	Reclassified Upward (%)	58.0	50.0	57.2	50.7
Non Cases	Reclassified Downward (%)	65.4	63.1	65.4	63.2
	Reclassified Upward (%)	34.6	36.9	34.6	37.0
Category-free NRI(%)		46.8	25.4	45.3	27.5
P-value		<0.001	0.002	<0.001	0.001

7a, Comparison of the C-index, LR test and BIC results demonstrating the discrimination for CHD prediction models based on the Suita Score with and without CKD, the FRS and the FRS calibrated for the means of the Suita cohort. The log likelihoods were derived from the multivariate adjusted Cox proportional hazard model.; CKD, chronic kidney disease; FHS, Framingham Heart Study; LR test, likelihood ratio test; BIC, Bayesian information criteria

7b, A comparison of the FRS and Suita Scores and the corresponding reclassification rate for the prediction of CHD events during a 10-year period;. NRI, net reclassification improvement

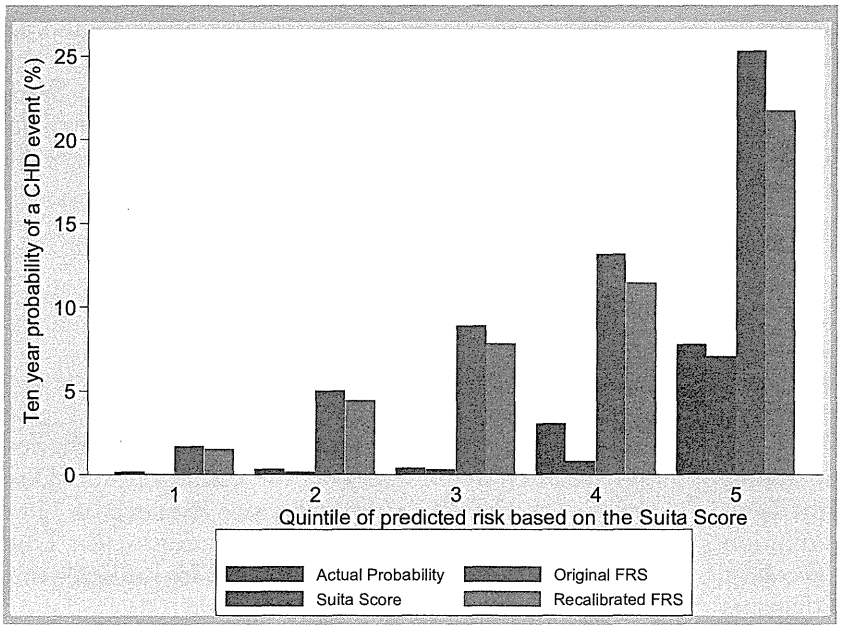

Fig. 2. The ten-year prediction of CHD events in the Suita study using the TC Suita Score with CKD

A graphical representation of the actual 10-year risk of cardiac events in the Suita cohort, along with the predicted risk and the Framingham risk function with and without recalibration for the means of the Suita cohort stratified by the quintile of predicted risk in the Suita cohort. The Suita participants were divided into quintiles of 10-year CHD risk predicted by the Suita score functions with CKD in Table 3. In each quintile, the mean predicted 10-year probabilities and actual probabilities were estimated. The Suita Score, the Suita Score with CKD shown in Table 3. FRS, Framingham risk score. CHD, coronary heart disease.

power, and the more simplified tool is as effective in the clinical setting as the original FRS, since both the models use beta coefficients and a simplified clinical score.

The incorporation of CKD yields limited improvement in the predictive capability in terms of C-statistics. However, the NRI and IDI showed marked improvement by the incorporation of CKD, which is a more clinically relevant index for prediction improvement. These two methods are becoming more popular and widely used in cardiovascular medicine[40, 41] For example, incorporating the homocysteine level into the FRS was evaluated by the NRI[42], since the inclusion of a new biomarker to the existing CHD risk score changed the predictability of events in a very marginal manner (less than 0.01 of the AUC)[43], and an enormously large odds ratio is needed for significant improvement[44, 45]. Clinicians currently do not have a tool for evaluating the CHD risk of patients with CKD but with relatively few other risk factors. These patients might be misjudged as having a very low risk.

Recently, an individualized risk prediction tool including more diverse risk factors increased 43% AMI and Strokes at the same cost[46]. Therefore, we believe that the inclusion of CKD in the prediction score is necessary and effective for populations at high risk for CHD. Currently, there are estimated to be more than 11 million CKD patients in Japan[47], and people have little doubt that CKD has a major impact on the population's health.

Our population had higher risks for developing CHD compared to other Japanese cohorts. The Suita cohort population was selected from an urban population, in contrast to the majority of other cohorts in Japan, which have been selected mainly from rural populations. Because approximately 66% of the Japanese population lives in urban areas according to 2006 Japanese Census[48], this is an important feature of our analysis. Interestingly, the JMS cohort and JALS reported that the crude incidence of AMI was 0.68 and 0.60 per 1000 person-years, respectively[11, 14, 15, 49]. On the contrary, the crude incidence of AMI in the Suita study was 1.40[50]. These findings may suggest that there is a large difference in the incidence of CHD between rural and urban areas in Japan. Thus, our tool is more useful for predicting the risk in urbanized populations with a higher risk of CHD.

Our study is associated with several limitations. First, the single assessment of risk factors at the baseline survey may have led to a regression dilution bias[51]. Second, the response rate of the original cohort was 53.1% (6,825/ 12,200) although the participants were randomly selected from the population of Suita city. In addition, based on the urbanized nature of the study population, it may not be possible to apply this tool in the whole Japanese population. However, since the outcome of the Suita study was the development of CHD, we believe that this tool can be a complement to the NIPPON DATA 80 risk score adopted in the JAS 2012 guidelines[11], in which the outcome was CHD mortality. The external validation of our score must be evaluated in other cohort studies, although a lack of external validation is a common problem with the existing Japanese risk prediction tools, including the NIPPON DATA 80, JALS, JMS cohort and Hisayama study. Considering the increasingly Westernized lifestyle in urban areas[52], these tools should be re-evaluated using a consortium of cohort studies, which include both urban and rural areas, such as the Epoch-Japan study group[53].

Very recently, the new AHA/ACC Guideline on the Treatment of Blood Cholesterol recommended the use of the new Pooled Cohort Equations to estimate the 10-year CHD risk in both white and black males and females, aged 40-75 years, and the FRS is no longer used for risk assessment[54]. However, this guideline is known to inaccurately estimate the CHD risk for Asians, Therefore, the value of the Suita Score for Japanese subjects and other low risk Asian populations is still superior to other systems.

Third, besides CKD, new biomarkers that can predict the CHD risk are emerging[55-57]. However, our study could not access their importance as have other existing prediction tools for Japanese subjects. For, example, the QRISK included rheumatoid arthritis, atrial fibrillation and the BMI. These relatively common, but not classic, cardiac risk factors must also be evaluated in future studies.

In conclusion, for Japanese subjects, the Suita prediction score with the CKD category resulted in better CHD prediction than the original and recalibrated FRS.

Conflict of Interest Disclosures

None.

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ORIGINAL ARTICLE

Additive Interaction of Oral Health Disorders on Risk of Hypertension in a Japanese Urban Population: The Suita Study

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BACKGROUND
This study assessed the relationship between different oral health markers—periodontitis, gingival bleeding, tooth number, and occlusal status—and hypertension in a Japanese urban population.

METHODS
A total of 1,643 participants with no prior cardiovascular disease (mean age = 66.6 years; 43.4% women) underwent comprehensive health checkups, including a lifestyle questionnaire and dental examination in the Suita Study.

RESULTS
In the multivariable-adjusted logistic model, none of the individual oral health markers, namely severe periodontitis, gingival bleeding, lowest quartile of tooth number, and malocclusion, were significantly associated with increased odds of hypertension. The additive effects of oral health markers on hypertension were examined and showed that, compared with subjects with no component of the oral health markers, the multivariale-adjusted odds ratio of hypertension in those with ≥3 components was 1.82 (95% confidence interval (CI) = 1.23–2.72; $P = 0.003$). In the subpopulation without antihypertensive medication (n = 1,148; 59.8% women), a significant graded relationship between multivariable-adjusted systolic blood pressure and the number of components was found ($P_{trend} = 0.03$), and, compared with subjects with no component of the oral health markers, having ≥3 components was related to a higher systolic blood pressure ($\beta = 5.41$; 95% CI = 1.16–9.66; $P = 0.01$).

CONCLUSIONS
There is an additive relationship between oral health disorders and risk of hypertension. Our results suggest that the existence of moderate or severe oral health disorders—that is, several concomitant oral health disorders—is associated with risk of hypertension.

Keywords: blood pressure; hypertension; life style; oral health disorder; risk factor.

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Several epidemiological surveys have suggested the existence of a positive relationship between oral health disorders and hypertension.[1–5] Among such disorders, periodontitis is a common chronic infectious disease of the adult population, characterized by an exaggerated gingival inflammatory response against pathogenic bacterial microflora. If left untreated, it leads to deterioration of the supportive tissue of the teeth and eventually to tooth loss.[6] Periodontal disease, gingival bleeding, and tooth loss have been reported to be associated with hypertension,[1–5,7,8] and the systemic inflammatory response that may accompany these conditions has been implicated as a mechanism in the development of hypertension.[9] Periodontal disease and subsequent tooth loss may lead to poor dietary habits, or vice versa, and patients with these conditions may be likely to favor soft carbohydrate foods[10] and restrict fruit intake,[11] which influences blood pressure.[12] The modification of diet that occurs with these conditions has been speculated to be another possible mechanism in the development of hypertension;[9,13] however, the clinical implication of lifestyle variables such as eating habits or physical activity in the association between oral health disorders and hypertension remains to be elucidated. Further, tooth loss could contribute to worse occlusal status or masticatory performance, which is also an important pathological condition in oral health disorders; however, the influence of worse occlusal status on hypertension is also unknown.

In an effort to enrich understanding in the emerging area of the association between oral health and hypertension, we investigated the potential interrelationship between different markers of oral health, lifestyle variables, and risk of hypertension in a Japanese urban population.

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METHODS

Study subjects

The data used in this research derive from the Suita Study, which consisted of a random sample of Japanese urban residents. The details of this study are described elsewhere.[14–16] Briefly, 6,485 men and women aged 30–79 years had a baseline survey at the National Cardiovascular Center (now the National Cerebral and Cardiovascular Center) between September 1989 and March 1994 and underwent a medical examination every 2 years. Of these, 1,797 underwent comprehensive regular health checkups and dental examinations between June 2008 and March 2012. Participants in the study population were excluded from these analyses if they had a past or present history of cardiovascular disease, including ischemic heart disease, acute coronary syndrome, congestive heart failure requiring hospitalization, valvular heart disease requiring medication, stroke, history of transient ischemic attack (n = 88), or atrial fibrillation (n = 35), or had not undergone baseline dental examination (n = 31). After applying these exclusions, a total of 1,643 participants aged 30–79 years were available for this analysis. Physicians or nurses administered the questionnaire on individual personal habits and present illnesses. Informed consent was obtained from all participants. All participants were Japanese, and this study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center (M19-062-3).

Measurement of blood pressure and covariables

Well-trained physicians measured blood pressure twice in a seated position with an automated sphygmomanometer (Colin BP-I03ill; Omron, Kyoto, Japan) and an appropriately sized cuff according to a standard protocol after at least 5 minutes of rest before the initial blood pressure reading was obtained. Systolic (SBP) and diastolic (DBP) blood pressure were considered the average of 2 measurements recorded >1 minute apart. Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg or use of antihypertensive medication.

At the baseline examination, routine blood tests were performed, including triglycerides, high-density lipoprotein cholesterol, glucose, and hemoglobin A1c. Height and body weight were measured, and body mass index was calculated as weight (kg) divided by the square of height (m^2). Dyslipidemia was defined according to the guidelines of the National Cholesterol Education Program Third Adult Treatment Panel.[17] Diabetes mellitus was defined according to the American Diabetes Association criteria.[18] Estimated glomerular filtration rate was calculated using the Japanese coefficient-modified Chronic Kidney Disease Epidemiology Collaboration equation in milliliters per minute per 1.73 m^2, as previously described.[19–21]

Oral examination

All participants received a complete oral examination by trained, certificated dentists. The periodontal condition was assessed using a modified Community Periodontal Index of Treatment Needs (CPITN)[22] in 8 designated molars (first and second molars) and 2 incisors (upper right and left central incisors) by applying the following scores: 0 indicates healthy periodontal tissue; 1 indicates gingival bleeding; 2 indicates calculus and/or overhanging restorations; 3 indicates pocket depth of 4–5 mm; and 4 indicates pocket depth of ≥6 mm. All periodontal examinations were performed by 4 experienced dentists, and the interobserver Cohen's kappa coefficient for grading was 0.78. The periodontal condition of every patient was reported as the worst CPITN condition. The presence or absence of gingival bleeding was also assessed by salivary occult blood test using a paper test strip (Salivaster; Showa Yakuhin, Tokyo, Japan).

The number of remaining teeth was counted in the full mouth with the exception of the third molars, which tend to be impacted, congenitally missing, or surgically removed because of anticipated pericoronitis.[23] Therefore, the maximum number of teeth was 28.

The status of occlusal support or masticatory performance was recorded by means of the Eichner index,[24] which is based on occlusal contact areas for the natural dentition in antagonist jaws, including fixed dentures. Class A contains 4 support zones; this means there is a minimum of 1 tooth in contact between the maxilla and the mandible in both the premolar and molar regions on each side. Class B contains 3, 2, or 1 support zone or support in the anterior area only. In class C, there are no antagonist contacts in the dentition.

Maximal bite force was measured by using the Dental Prescale System (GC, Tokyo, Japan), which consists of a horseshoe-shaped bite foil of pressure-sensitive film (50H, type R) and a computerized scanning system for analysis of the load.[25,26]

Lifestyle variables

Information on lifestyle was collected with a standardized questionnaire by physicians or nurses through face-to-face interviews, including demographic information such as smoking habit, dietary practices and usual frequency of food intake, exercise/sports and walking hours a day, and sleeping hours. Smoking status was defined as never smoker, former smoker, or current smoker. Alcohol consumption was categorized as none, social, or daily. Consumption of fruit and sugar-sweetened soft drinks was ascertained by questions as "fruit (citrus fruit, other fruit, and fresh fruit juice) intake ≥1 /day" and "sugar-sweetened soft drink intake ≥3 times /day," respectively. Sugar-sweetened soft drinks included all types of non-low-calorie, concentrated, carbonated, and ready-to-drink soft drinks. All low-calorie, no-added-sugar, and sugar-free types of concentrated, carbonated, and ready-to-drink soft drinks were not classified as sugar-sweetened soft drinks in this study. Physical activity was ascertained by question as"">1 hour walking or equivalent physical activity on average a day." Average sleep duration was classified into 8 categories: <4, 4–5, 5–6, 6–7, 7–8, 8–9, 9–10, and ≥10 hours per day.

Statistical analysis

Summary statistics are presented as mean (±SD) for continuous variables and as percentage for categorical

variables unless otherwise specified. First, the participants were divided into 2 groups according to the presence/absence of hypertension, and then the significance of any differences between groups was evaluated using unpaired *t* test or χ^2 test, as appropriate. Second, patients were stratified into 3 or 4 groups according to the status of oral health disorders. Differences in characteristics between groups were tested using χ^2 test for dichotomous variables and 1-way analysis of variance with Sheffe's post-test for continuous variables, as appropriate. Logistic regression analysis was used to determine the odds ratio (OR) of hypertension as a function of individual components of oral health markers, such as CPITN stage, gingival bleeding, tooth number, and Eichner index, as well as combinations of 2 oral health markers. In multivariable-adjusted models, we included variables that might confound the relationship between hypertension and oral health markers: age, body mass index, diabetes, dyslipidemia, estimated glomerular filtration rate, smoking status (3 categories), daily alcohol consumption, daily fruit intake, daily sugar-sweetened soft drink intake, physical activity, and nocturnal sleep duration.

We next divided the subjects into 4 groups according to the number of oral health disorders present (0, 1, 2, or ≥3). The relative ORs of hypertension were assessed in age and sex-adjusted or multivariable-adjusted logistic regression models and calculated using the subgroup with no component of oral health markers as a reference for each. Differences in characteristics among the 4 groups were determined by 1-way analysis of variance with Scheffe's multiple comparison post-test for continuous variables and χ^2 test for categorical variables. Multivariable linear regression analyses using SBP or DBP as the dependent variable were also performed in the subjects not taking antihypertensive medication. Mean and SE were calculated in the case of linear regression, and OR and 95% confidence interval (CI) were calculated in the case of logistic regression. All *P* values were 2-sided, and those <0.05 were considered statistically significant. All of the calculations were performed using a standard statistical package (JMP 8.0; SAS Institute, Cary, NC; and SPSS version 17.0; SPSS, Chicago, IL).

RESULTS

General characteristics

The baseline characteristics of the study subjects are shown in Table 1. Mean age was 66.6 ± 7.9 years, and 43.4% of subjects were men. We first divided the subjects into 2 groups according to the presence/absence of hypertension and found that hypertensive subjects showed a significantly worse CPITN stage, higher prevalence of gingival bleeding, lower tooth number, and worse Eichner index.

Relations among oral health markers

To examine the relationships among oral health markers, we next divided the patients into 3 or 4 groups according to the status of oral health disorders (Table 2). There were significant trends toward higher prevalence of gingival bleeding, lower remaining tooth number, and worse Eichner index with increasing stage of CPITN. Similarly, there were significant trends toward higher prevalence of gingival bleeding, worse CPITN stage, and worse Eichner index with decreasing remaining tooth number. The Eichner index C group showed significantly lower remaining tooth number and worse CPITN stage than the Eichner A group (Table 2).

Relations of oral health disorders to hypertension

Age- and sex-adjusted logistic regression analysis found that only the presence of gingival bleeding was significantly associated with risk of hypertension, and the relation between individual oral health markers (CPITN stage 4, presence of gingival bleeding, lowest quartile of remaining tooth number, and Eichner index C) and hypertension was no longer significant throughout the adjustment process (Table 3). The Nagelkerke's adjusted R^2 value of the overall multivariable-adjusted logistic regression model without including oral health markers was 0.210 and was increased in the model after adding CPITN stage 4 (adjusted R^2 = 0.230), presence of gingival bleeding (adjusted R^2 = 0.230), lowest quartile of remaining tooth number (adjusted R^2 = 0.230), or Eichner index C (adjusted R^2 = 0.229).

Combined effects of oral health markers on hypertension

We next examined the combined effects of oral health markers on hypertension—that is, CPITN stage and gingival bleeding, CPITN stage and remaining tooth number, CPITN stage and Eichner index, gingival bleeding and remaining tooth number, gingival bleeding and Eichner index, and remaining tooth number and Eichner index. In the multivariable-adjusted logistic regression model, the combination of CPITN stage and gingival bleeding, the combination of CPITN stage and Eichner index, the combination of gingival bleeding and remaining tooth number, and the combination of gingival bleeding and Eichner index, but not the combination of CPITN stage and remaining tooth number and the combination of remaining tooth number and Eichner index, were independently associated with hypertension (Table 3).

The total subjects were then divided into 4 groups by the number of components of oral health markers, including CPITN stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C (Table 4). There was a significant graded relationship between the number of components present and the corresponding prevalence of hypertension. The age- and sex-adjusted relative OR of hypertension in subjects with 0, 1, 2, and ≥3 components of oral health disorders were 1.0 (reference), 1.06 (95% CI = 0.83–1.34; *P* = 0.66), 1.19 (95% CI = 0.87–1.63; *P* = 0.28), and 1.71 (95% CI = 1.18–2.49; *P* = 0.004). In multivariable-adjusted logistic regression analysis, subjects with ≥3 components of oral health disorders had 1.82 times higher odds of hypertension compared with those with no component (Figure 1). The adjusted R^2 value of the overall model after adding the number of components of oral health markers was 0.249.

Table 1. Characteristics of study population

Characteristics	Total	Hypertension	
		No	Yes
No.	1,643	865	778
Age, years	66.6±7.9	64.6±7.9	68.8±7.3**
Male, %	43.4	39.9	47.3**
Body mass index, kg/m^2	22.7±3.2	21.9±2.9	23.6±3.3**
Diabetes, %	10.6	5.4	16.3**
Dyslipidemia, %	38.2	30.2	47.2**
Antihypertensive medication, %	30.1	0	36.4**
Systolic blood pressure, mm Hg	128±20	116±13	142±17**
Diastolic blood pressure, mm Hg	78±11	72±9	84±10**
Heart rate, bpm	69±11	68±10	70±12**
Triglycerides, mmol/L[a]	1.20±0.69	1.11±0.62	1.30±0.73**
HDL cholesterol, mmol/L	1.60±0.42	1.64±0.42	1.57±0.41**
Blood glucose level, mmol/L[a]	5.79±1.07	5.77±0.77	6.03±1.29**
Hemoglobin A1c, %[a]	5.47±0.64	5.37±0.52	5.58±0.73**
eGFR, ml/min/1.73 m^2	75.0±11.0	77.3±8.5	72.5±12.8**
CPITN stage, %			
0	35.4	37.8	32.8*
1	0.9	0.7	1.0
2	11.5	12.7	10.2
3	32.2	32.0	32.5
4	20.0	16.8	23.5**
Gingival bleeding +, %	35.6	32.7	38.8**
Number of remaining teeth	21.8±7.7	22.6±7.4	20.9±7.9**
Eichner index, %			
A	60.4	65.8	54.3**
B	28.1	24.9	31.8**
C	11.5	9.3	13.9**
Maximum bite force, no.	502±310	504±296	501±325
Smoking status (never/former/current), %	61.4/27.8/10.8	62.7/24.7/12.6	60.0/31.1**/8.9**
Daily alcohol intake, %	54.8	56.5	52.8
Daily fruit intake, %	53.6	53.3	53.9
Daily sugar-sweetened soft drink intake ≥3 cups/day, %	7.7	9.7	5.5**
Physical activity ≥1 hour/day, %	40.4	40.5	40.2
Nocturnal sleep duration, hours	6.55±1.10	6.46±1.04	6.66±1.15**

Values are mean ± SD or frequency (%).

Abbreviations: CPITN, Community Periodontal Index of Treatment Needs; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

[a]Values were log-transformed for analysis.

*P < 0.05 and **P < 0.01 vs. patients without hypertension.

On the other hand, except for prevalence of smoking habit or daily sugar-sweetened soft drink intake, no significant graded relationship between the number of components present and the corresponding prevalence of poor lifestyle, including smoking habit, prevalence of daily alcohol consumption, daily fruit intake, daily sugar-sweetened drink intake, physical activity, and nocturnal sleep duration, was found (Table 4).

Table 2. Associations between markers of oral health disorders

Variables	CPITN stage 0	1 or 2	3	4	P_{trend}
Gingival bleeding*, %	26.3	28.1	42.8**	45.1**	<0.01
Remaining tooth number, no.	22.6±6.4	24.7±4.8**	23.4±5.6	16.0±10.8**	<0.01
Remaining tooth number ≤18 in men, ≤21 in women, %	26.5	11.3**	20.4	48.5**	<0.01
Eichner index, %					
A	62.7	76.4**	66.4	36.6**	<0.01
B	29.4	18.7*	28.7	30.8	0.01
C	7.9	4.9	4.9	32.6**	<0.01

Variables	Remaining tooth number: 1st quartile ≤18 in men ≤21 in women	2nd quartile 19–25 in men 22–25 in women	3rd quartile 26–27 in men 22–25 in women	4th quartile 28 in men 27–28 in women	P_{trend}
Gingival bleeding*, %	37.4	40.2	33.0	30.5	0.02
CPITN stage, %					
Stage 0	34.7	33.2	37.1	37.2	0.56
Stage 1 or 2	5.2	12.9**	13.5**	19.7**	<0.01
Stage 3	24.3	34.5*	39.3**	31.1	<0.01
Stage 4	35.8	19.4**	10.1**	12.0**	<0.01
Eichner index, %					
A	5.2	51.7**	96.1**	100**	<0.01
B	52.2	48.3	3.9**	0**	<0.01
C	42.6	0**	0**	0**	<0.01

Variables	Eichner index A	B	C	P_{trend}
Gingival bleeding*, %	33.1	44.6**	27.0	<0.01
Remaining tooth number, no.	26.3±2.0	19.2±4.8**	4.5±4.4**	<0.01
Remaining tooth number ≤18 in men, ≤21 in women, %	2.3	50.2**	100.0**	<0.01
CPITN stage, %				
Stage 0	36.8	37.0	24.3**	<0.01
Stage 1 or 2	15.6	8.2**	5.3**	<0.01
Stage 3	35.5	32.9	13.8**	<0.01
Stage 4	12.1	21.9**	56.6**	<0.01

Values are mean ± SD or frequency (%).
Abbreviation: CPITN, Community Periodontal Index of Treatment Needs.
*$P < 0.05$, and **$P < 0.01$ vs. patients with CPITN stage 0, lowest quartile in remaining tooth number, or Eichner index A, respectively.

Relations of oral health disorders to blood pressure

The influence of these additive effects of oral health markers on blood pressure was examined in the subpopulation of 1,148 subjects (687 women) not taking antihypertensive medication. In the model including CPITN stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C, SBPs/DBPs (±SDs) in subjects with 0 (n = 190 men; n = 331 women), 1 (n = 142 men; n = 236 women), 2 (n = 72 men; n = 77 women), and ≥3 (n = 57 men; n = 43 women) components of oral health disorders were 123±20/76±11, 125±18/76±11, 129±20/78±12,

Table 3. Associations of markers of oral health disorders with diagnosis of hypertension

	Age- and sex-adjusted			Multivariable-adjusted[a]		
Variables, unit of increase	**Odds ratio**	**95% CI**	***P* value**	**Odds ratio**	**95% CI**	***P* value**
CPITN stage 4	1.27	0.99–1.64	0.07	1.05	0.96–1.16	0.27
Gingival bleeding +	1.25	1.01–1.54	0.04	1.17	0.94–1.47	0.16
Remaining tooth number ≤18 for men, ≤21 for women[b]	1.16	0.92–1.48	0.21	1.17	0.90–1.51	0.24
Eichner index C	1.17	0.85–1.61	0.33	1.09	0.78–1.55	0.62
CPITN stage 4 and gingival bleeding +	1.83	1.03–2.63	<0.01	1.71	1.17–2.50	<0.01
CPITN stage 4 and tooth number ≤18 for men, ≤21 for women[b]	1.34	0.95–1.91	0.10	1.34	0.92–1.94	0.13
CPITN stage 4 and Eichner index C	1.45	0.98–2.17	0.06	1.44	1.02–2.02	0.04
Gingival bleeding + and tooth number ≤18 for men, ≤21 for women[b]	1.94	1.37–2.77	<0.01	1.63	1.07–2.47	0.01
Gingival bleeding + and Eichner index C	2.26	1.22–4.40	<0.01	2.51	1.30–5.00	<0.01
Tooth number ≤18 for men, ≤21 for women[b] and Eichner index C	1.24	0.90–1.71	0.18	1.23	0.91–1.69	0.08

Abbreviation: CPITN, Community Periodontal Index of Treatment Needs.

[a]Multivariable-adjusted model included age, sex, body mass index, diabetes, dyslipidemia, estimated glomerular filtration rate, smoking status (3 categories), daily alcohol intake, daily fruit intake, daily sugar-sweetened soft drink intake, physical activity, and nocturnal sleep duration.

[b]Sex-specific lowest quartile of remaining tooth number.

and 132±22/79±12 mm Hg, respectively (P_{trend} < 0.01, respectively). Age- and sex-adjusted SBPs (±SEs) in subjects with 0, 1, 2, and ≥3 components of oral health disorders were 124±1, 125±1, 128±2, and 131±2 mm Hg (p for trend <0.01), and DBP (±SE) was 76±1, 76±1, 78±1, and 79±1 mmHg (P_{trend} = 0.04), respectively. Multivariable linear regression analysis revealed that SBP significantly differed among groups, with the highest SBP in the subgroup with ≥3 components (130±2 mmHg) (Table 5; Figure 2).

DISCUSSION

Our study identified an additive relationship between oral health disorders and risk of hypertension. Worse occlusal status was suggested to be responsible in these relationships. Our findings were noteworthy because they were based on a large, representative sample of the Japanese general urban population. In addition, careful measures of study exposure and outcome variables allowed precise estimation of the association.

Our results showed that the associations between individual oral health markers (CPITN stage 4, presence of gingival bleeding, lowest quartile of remaining tooth number, and Eichner index C) and risk of hypertension did not remain significant after adjustment for several potential confounding factors. Although previous investigations identified that periodontal disease, as well as lower tooth number, was independently associated with risk of hypertension,[1–5,7–9] we could not confirm these associations in this study. Alternatively, we examined the combined effects of oral health markers on hypertension. Combinations of oral health markers—that is, severe periodontal disease and presence of gingival bleeding, severe periodontal disease and worse occlusal status, presence of gingival bleeding and lower tooth number, and presence of gingival bleeding and worse occlusal status—were each independently associated with risk of hypertension. Our results suggested that worse occlusal status, which was assessed by Eichner index, was responsible for the relationship between oral health disorders and hypertension. Occlusal status may better reflect chewing status than does tooth number, which may lead to alterations not only in food selection and dietary quality but also in masticatory performance. This, in turn, would affect body composition and nutritional status,[11] both of which are causal factors in the development of hypertension. Apart from masticatory performance, dental malocclusion may lead to mandibular malposition, which induces narrowing of the upper airway, resulting in obstructive breathing disorders. Mandibular position has been implicated in nocturnal oxygenation and pharyngeal collapsibility,[27] and in healthy subjects with obstructive sleep apnea, treatment with an oral jaw-positioning appliance has been reported to improve cardiac autonomic modulation.[28] Of the combinations of oral health disorders, in this study, the strongest risk of hypertension was observed with the combination of the presence of gingival bleeding and Eichner index. The mechanism by which the concomitance of gingival

Table 4. Characteristics of study population by number of oral health disorder components: Community Periodontal Index of Treatment Needs stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C

Characteristics	0	1	2	3	4	P_{trend}
No.	703	527	241	151	21	NA
Age, years	64.4±7.9	66.5±7.8**	69.7±6.7**	72.0±5.5**	69.7±7.0*	<0.01
Men, %	40.0	41.6	48.6	58.3**	38.1	<0.01
Body mass index, kg/m^2	22.4±3.0	23.0±3.2*	22.9±3.5	23.2±3.6*	22.8±3.0	<0.01
Diabetes, %	7.0	12.3	12.5	19.9**	0	<0.01
Dyslipidemia, %	34.3	38.3	41.9	48.3*	52.4	<0.01
Hypertension, %	42.7	44.6	53.9*	66.2**	61.9	<0.01
Antihypertensive medication, %	25.9	28.3	38.2*	44.4**	23.8	<0.01
Systolic blood pressure, mm Hg	126±20	128±19	132±20**	134±20**	139±19	<0.01
Diastolic blood pressure, mm Hg	77±11	78±11	79±11	80±11	83±12	<0.01
Heart rate, bpm	69±11	69±10	70±11	69±11	71±11	0.43
Triglycerides, mmol/L[a]	1.16±0.65	1.21±0.70	1.24±0.68	1.28±0.77	1.26±0.63	0.08
HDL cholesterol, mmol/L	1.68±0.43	1.58±0.40**	1.54±0.38**	1.45±0.41**	1.53±0.46	<0.01
Blood glucose level, mmol/L[a]	5.68±0.89	5.85±1.24	5.82±0.96	6.08±1.38**	5.56±0.47	<0.01
Hemoglobin A1c, %[a]	5.41±0.55	5.51±0.68	5.50±0.60	5.62±0.82**	5.25±0.67	<0.01
eGFR, ml/min/1.73m^2	76.1±10.9	76.1±10.5	72.6±11.6**	70.2±11.2**	73.9±7.8	<0.01
CPITN stage, %						
Stage 0	45.8	33.8**	29.5**	7.3**	0**	<0.01
Stage 1 or 2	18.5	11.4**	3.7**	2.7**	0	<0.01
Stage 3	35.7	40.2	21.6**	9.9**	0*	<0.01
Stage 4	0	14.6**	45.2**	80.1**	100**	<0.01
Gingival bleeding +, %	0	62.1**	71.4**	43.1**	100**	<0.01
Remaining tooth number ≤18 in men, ≤21 in women, %	0	23.3**	61.8**	100.0**	100**	<0.01
Eichner index, %						
A	85.2	60.2**	30.7**	1.3**	0**	<0.01
B	14.8	39.9**	47.7**	21.9	0	<0.01
C	0	0	21.6**	76.8**	100**	<0.01
Maximum bite force, *N*	609±297	495±298**	404±290**	229±172**	191±134**	<0.01
Smoking status (never/former/current), %	65.9/25.2/9.0	63.0/25.4/11.6	55.2/33.2/11.6	46.4**/37.8*/15.9	52.4/38.1/9.5	<0.01
Daily alcohol intake, %	52.5	57.7	51.9	59.6	57.1	0.23
Daily fruit intake, %	54.3	51.6	56.9	53.6	38.1	0.40
Daily sugar-sweetened soft drink intake ≥3 cups/day, %	6.3	7.8	9.5	8.6	28.6**	<0.01
Physical activity ≥1 hour/day, %	38.3	40.2	46.1	38.4	61.9	0.07
Nocturnal sleep duration, hours	6.5±1.1	6.5±1.1	6.7±1.2	6.7±1.3	6.6±1.2	0.11

Values are mean ± SD or frequency (%).

Abbreviations: CPITN, Community Periodontal Index of Treatment Needs; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; NA, not applicable.

[a]Values were log-transformed for analysis.

*P < 0.05 and **P < 0.01 vs. subgroup with no component.

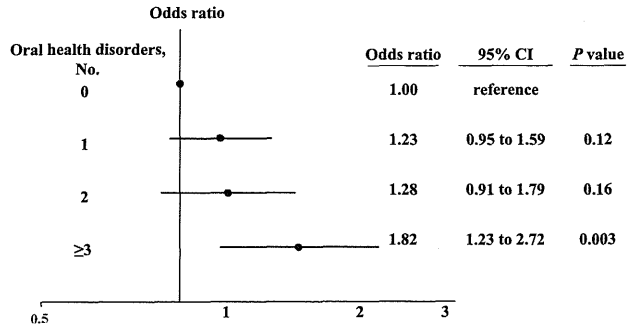

Figure 1. Odds ratios for hypertension by number of oral health disorders including Community Periodontal Index of Treatment Needs (CPITN) stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C. Data are adjusted odds ratio (95% confidence interval). Analyses were controlled for age, sex, body mass index, diabetes, dyslipidemia, estimated glomerular filtration rate, smoking status (3 categories), daily alcohol intake, daily fruit intake, physical activity, daily sugar-sweetened soft drink intake, and nocturnal sleep duration.

bleeding and malocclusion is a strong risk for hypertension remains hypothetical, but activation of inflammation, worse masticatory performance, and breathing disorders may be present and thus increase the risk of hypertension.

In this study, adjusted R^2 values in the model after adding the number of oral health components were higher than without including oral markers or after adding individual oral health markers, suggesting that the concomitance of these oral health disorders seems to jointly contribute to the risk of hypertension. The precise mechanism by which the concomitance of several oral health disorders is an independent risk for hypertension remains hypothetical but is likely multifactorial. In this study, a significant graded relationship between the number of components present and the corresponding body mass index, as well as bite force, was found. Worse masticatory performance, obstructive breathing disorders, periodontal inflammation, and obesity may be present in the case of concomitant oral health disorders and thus enhance the risk of hypertension. On the other hand, in this study, 42.6% of subjects with the lowest quartile of remaining tooth number corresponded to Eichner index C. Although these two oral health markers essentially do not mean the same thing, the remaining tooth number and Eichner index influenced each other. More generally, all of the oral health disorders examined in this study are relatively interrelated. Therefore, our results should be also interpreted as indicating that moderately or severely impaired, but not mildly impaired, oral health is associated with increased risk of hypertension.

Lifestyle changes are widely recognized to lower blood pressure or to reduce the risk of developing hypertension.[29] Of these, the lifestyle variables reported in this study have been suggested to be important factors modulating blood pressure.[29–31] Except for daily sugar-sweetened soft drink intake, we did not find a significantly worse lifestyle in the groups with a higher number of components of oral health

Table 5. Association between number of oral health disorder components—Community Periodontal Index of Treatment Needs stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C—and differences in blood pressure in subjects not taking antihypertensive medication (n = 1,148)

Models	0	1			2			≥3			P_{trend}
		β	95% CI	P value	β	95% CI	P value	β	95% CI	P trend	
Systolic blood pressure											
Age- and sex-adjusted	Reference	0.77	−1.81 to 3.34	0.56	2.79	−0.82 to 6.40	0.13	5.36	1.07 to 9.66	0.01	<0.01
Multivariable-adjusted[a]	Reference	0.24	−2.30 to 2.78	0.85	2.98	−0.55 to 6.51	0.10	5.41	1.16 to 9.66	0.01	0.03
Diastolic blood pressure											
Age- and sex- adjusted	Reference	0.16	−1.32 to 1.64	0.83	1.46	−0.62 to 3.54	0.17	2.51	0.04 to 4.98	0.047	0.04
Multivariable-adjusted[a]	Reference	−0.16	−1.61 to 1.29	0.83	1.41	−0.60 to 3.42	0.17	2.36	−0.06 to 4.78	0.06	0.046

[a]Multivariable-adjusted model included age, sex, body mass index, diabetes, dyslipidemia, estimated glomerular filtration rate, smoking status (3 categories), daily alcohol intake, daily fruit intake, daily sugar-sweetened soft drink intake, physical activity, and nocturnal sleep duration.

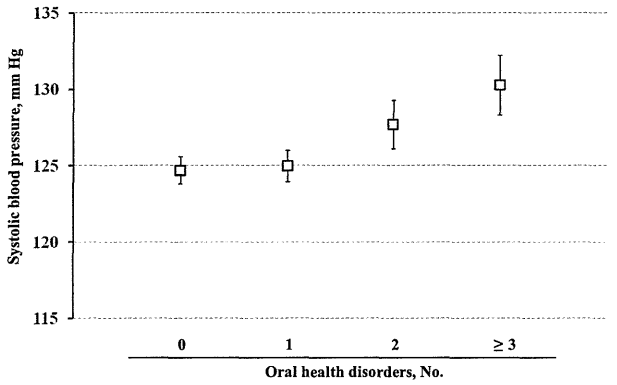

Figure 2. Adjusted mean systolic blood pressure by number of oral health disorders including Community Periodontal Index of Treatment Needs (CPITN) stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C in subjects not taking antihypertensive medication (n = 1,148). Data are adjusted mean ± SE. The *P* value for trend was 0.03. Analyses were controlled for age, sex, body mass index, diabetes, dyslipidemia, estimated glomerular filtration rate, smoking status (3 categories), daily alcohol intake, daily fruit intake, physical activity, daily sugar-sweetened soft drink intake, and nocturnal sleep duration.

disorders; rather, significantly lower prevalences of current smoking, daily sugar-sweetened soft drink intake, and longer nocturnal sleep duration were found in hypertensive subjects than in those without, suggesting that some hypertensive subjects in this study had already instituted lifestyle changes. Modification of lifestyle as a result of oral health disorders has been speculated to be another possible cause of development of hypertension;[9,13] however, our results may support the existence of a direct association of oral health disorders with hypertension.

Our analysis has several limitations. First, the design of this study does not allow us to clarify the underlying mechanism. Indeed, reverse causality whereby hypertension leads to oral health disorders cannot be excluded. Another recent study showed a negative association between periodontal disease and incident hypertension.[32] Second, several important inflammatory and metabolic markers, such as C reactive protein and insulin, were not measured in our study. Unmeasured variables, such as salt intake and sleep disorders, may affect the observed results. Nonetheless, the use of 4 oral health markers that refer to different manifestations of oral disease and cover both the presence and the extent of disease indicates that the results are not coincidental, hence limiting any bias resulting from using only 1 oral health disorder variable.

In conclusion, there is an additive relationship between oral health disorders and increased odds of hypertension and raised SBP in the Japanese urban population. Our results also suggest that moderately or severely impaired oral health—that is, several concomitant oral health disorders—is associated with risk of hypertension. Our findings emphasize that poor oral health might have a direct relationship with hypertension, and this might have important implications for public health. The next crucial step is to investigate whether oral health disorders are causally linked to hypertension in a longitudinal setting. If so, dental therapy might be used in clinical practice to reduce the development of hypertension.

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DISCLOSURE

The authors declared no conflict of interest.

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Original Article

Changes in Waist Circumference and the Incidence of Type 2 Diabetes in Community-Dwelling Men and Women: The Suita Study

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ABSTRACT

Backgrounds: The association between weight gain and the incidence of type 2 diabetes is well known. The aim of our study was to investigate the relationship between change in waist circumference (WC) and type 2 diabetes incidence.

Methods: The participants in the Suita Study, a population-based cohort study in an urban area of Japan, underwent a baseline survey between 1989 and 1994 (Exam 1) and were examined at follow-up every 2 years. We performed a 9.3-year cohort study of 946 men and 1327 women with no history of diabetes who underwent Exam 1 and Exam 2 (between 1997 and 1999). Participants were stratified by sex and median WC at Exam 1, and, in each stratum, participants were further classified into three categories by tertile of WC change per year between Exam 1 and Exam 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) for type 2 diabetes incidence were calculated by Cox proportional hazard models. The endpoints were first diagnosis of type 2 diabetes or March 2011.

Results: During follow-up, 287 participants developed type 2 diabetes. In both sexes with median WC or higher, participants in the highest tertile of WC change had a significantly higher risk of developing type 2 diabetes. Multivariable adjusted HRs were 1.84 (95% CI, 1.10–3.08) in men and 2.30 (95% CI, 1.31–4.04) in women. No significant association was observed among participants with WC below median.

Conclusions: Preventing WC gain is important in preventing type 2 diabetes in the Japanese population, especially among individuals with a relatively high WC.

Key words: waist circumference; type 2 diabetes mellitus; prospective cohort study

INTRODUCTION

The worldwide prevalence of type 2 diabetes is alarmingly high. The International Diabetes Federation (IDF) has reported that the global prevalence of diabetes has reached 8.3% (382 million people), and that the prevalence will be 10% by 2035.[1] In particular, of IDF regions, the Western pacific region, which includes China, Indonesia, and Japan, has a high prevalence of diabetes (8.6%) and is home to 36% of the total number of people with diabetes in the world.[2] At the same time, the prevalence of obesity is escalating worldwide. The mean body mass index (BMI) worldwide has increased by 0.4 kg/m^2 per decade in men and 0.5 kg/m^2 per decade in women.[3] Although the prevalence of obesity or overweight in Asia is relatively low compared with other parts of the world, the drastic increase in BMI in Asia is similar to that in other regions. Many studies have reported significant associations between weight gain and the incidence of type 2 diabetes.[4–10] Therefore, it is anticipated that this increase in obesity will lead to increased rates of type 2 diabetes.

It is well known that higher waist circumference (WC), as well as higher BMI, is associated with elevated risks of type 2

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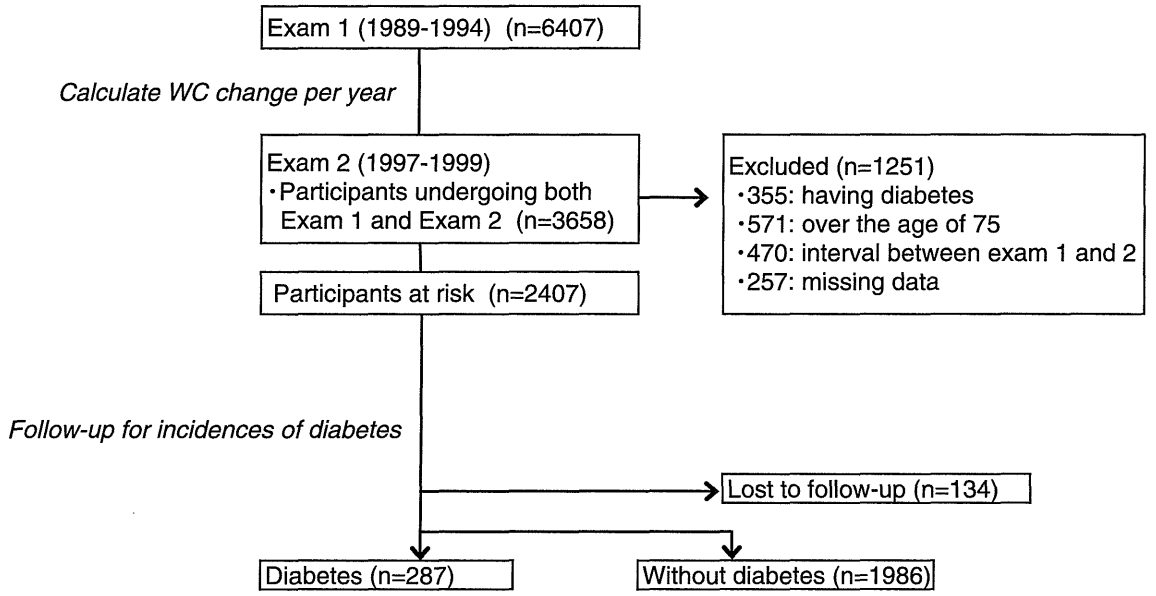

Figure 1. Process of selecting the study participants and overview of analysis of waist circumference (WC) change and the incidence of type 2 diabetes (shown in italics).

diabetes.[11] WC, an index for central obesity, is an important component in the diagnostic criteria for metabolic syndrome.[12,13] Because WC changes over the years within the same individual, in addition to assessment of the risk of type 2 diabetes based on WC at a certain point, it would be also useful to consider subsequent WC change. However, there have been just two studies on the association between WC change with the risk of type 2 diabetes, which were conducted among Iranian community residents and American health professionals.[7,14] However, percentage of visceral adipose tissue in abdominal fat is likely to differ according to race, so the impact of change in WC on type 2 diabetes could also differ from country to country.[15] This association remains unknown among the East Asians, who have a relatively low degree of obesity. In addition, it has recently also been reported that WC change does not necessarily correspond to weight change in a Chinese population.[16]

Accordingly, the purpose of this study is to investigate the association between WC change and the incidence of type 2 diabetes in an urban Japanese population, taking into consideration the influence of BMI change.

METHODS

Subjects and design

The Suita Study, a prospective population-based cohort study in an urban area of Japan, started in 1989. The details of this study have been described elsewhere.[17–19] Briefly, 6407 men and women aged 30–83 years underwent a baseline survey at the National Cerebral and Cardiovascular Center (NCVC) between September 1989 and March 1994 (examination 1 [Exam 1]) and visited the NCVC every 2 years for follow-up examinations, including blood sample testing. Of 6407 participants, 3658 underwent the follow-up examination between April 1997 and March 1999 (examination 2 [Exam 2]). Overall, 1251 participants were excluded for the following reasons: (i) having diabetes at Exam 2 ($n = 355$); (ii) age >75 years at Exam 2 ($n = 571$); (iii) the interval between Exam 1 and Exam 2 was <5 years or >9 years ($n = 470$); or (iv) missing data ($n = 257$). In addition, participants who could not be followed-up ($n = 134$) were excluded. The remaining 2273 participants were followed up from Exam 2 to the end of March 2011 (Figure 1). The Institutional Review Board of the NCVC approved this cohort study.

Data collection

Blood samples were centrifuged immediately upon collection, and a routine blood examination was performed, which included measurement of glucose levels. The Suita Study started to measure HbA_{1c} from Exam 2. The value for HbA_{1c} (%) was estimated as the National Glycohemoglobin Standardization Program equivalent value (%) calculated by the following formula: HbA_{1c} (%) = 1.02 × HbA_{1c} (Japan Diabetes Society, %) + 0.25%.[20] HbA_{1c} values are presented as percentages and SI units (mmol/mol).

Trained physicians measured blood pressure in triplicate on the right arm after 5 minutes of rest using a standard mercury sphygmomanometer. WC was measured at the umbilical level in a standing position. Participants were wearing light clothing during measurement of height and weight. BMI was calculated as weight (kg) divided by the square of height (m). Public health nurses obtained information on cigarette smoking status (current-smoker, ex-smoker, or non-smoker), alcohol drinking status (current-drinker, ex-drinker, or non-drinker) and medical histories.

Endpoint determination

Type 2 diabetes was defined as either a fasting (at least 8 hours) plasma glucose level ≥7.0 mmol/L (126 mg/dL), non-fasting plasma glucose level ≥11.1 mmol/L (200 mg/dL), HbA_{1c} ≥6.5% (48 mmol/mol),[21] or the use of antidiabetic agents. The endpoints of the present study were: (i) first diagnosis of type 2 diabetes, or (ii) March 31, 2011. Individuals not examined during follow-up were censored on the date of their last examination.

Statistical analysis

Participants were stratified by sex and median WC at Exam 1 and were additionally classified into three categories by tertile of WC change per year between Exam 1 and Exam 2. We calculated age-adjusted WC at Exam 1, Exam 2, and endpoint by sex. In addition, we assessed the correlation of changes in WC and BMI per year between Exam 1 and Exam 2.

Cox proportional hazards regression was used to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the lowest and highest tertiles, with the middle tertile as the reference group. Model 1 was adjusted for age; model 2 was adjusted for age and WC at Exam 1, HbA_{1c}, family history of diabetes, and drinking and smoking status at Exam 2; and model 3 was adjusted for model 2 variables, BMI at Exam 1, and BMI change as a continuous variable. In an additional model, HRs and 95% CIs were adjusted for model 2 variables and estimated without stratification by WC at Exam 1, with the participants falling into both the WC below median and the tertile 2 in WC change groups being set as the reference group. Interactions between WC at Exam 1 (below median or ≥median) and WC change (tertiles) were tested by adding the interaction term to the model 2. All data were analyzed using SPSS statistical software (Version 20.0J; SPSS Japan Inc., Tokyo, Japan). All reported *P*-values are two-tailed; $P < 0.05$ was considered statistically significant.

RESULTS

The median (interquartile range) WCs at Exam 1 were 82.0 (77.0–87.0) cm in men and 75.0 (69.0–82.0) cm in women. The mean (standard deviation) interval between Exam 1 and Exam 2 was 6.8 (0.9) years. Table 1 shows characteristics at Exam 2 for men and women. WC change was considerably larger in women than men (0.51 and 0.17 cm/year, respectively). Table 2 shows age-adjusted WC at Exam 1, Exam 2, and at the endpoint examination. In the lowest tertile of WC change, WC increased from Exam 2 to the endpoint examination, regardless of sex and WC strata (WC <median or WC ≥median). Conversely, the change in WC from Exam 2 to endpoint examination in the highest tertile was stable. Figure 2 shows scatter plots of WC change and BMI change between Exam 1 and Exam 2. The correlation coefficients

Table 1. Characteristics of subjects at examination 2 (*n* = 2273)

	Men	Women
n	946	1327
Age, years	58.8 (10.2)	57.6 (9.7)
WC	83.5 (7.9)	79.7 (8.6)
WC change, cm/year	0.17 (0.74)	0.51 (1.05)
BMI, kg/m^2	23.2 (2.8)	22.2 (2.9)
HbA_{1c}, %, mmol/mol	5.6 (0.3), 38 (3.3)	5.6 (0.3), 38 (3.3)
Plasma glucose level, mmol/L	5.3 (0.5)	5.1 (0.5)
Systolic blood pressure, mm Hg	126.4 (18.0)	125.3 (18.9)
Diastolic blood pressure, mm Hg	80.8 (10.7)	78.6 (10.5)
Hypertension, *n* (%)	341 (36.0)	406 (30.6)
Total cholesterol, mmol/L	5.26 (0.81)	5.60 (0.85)
Hypercholesterolemia, *n* (%)	302 (31.9)	644 (48.5)
Family history of diabetes, *n* (%)	90 (9.5)	148 (11.2)
Smoking status, *n* (%)		
Current	372 (39.3)	100 (7.5)
Former	296 (31.3)	47 (3.5)
Never	278 (29.4)	1180 (88.9)
Drinking status, *n* (%)		
Current	690 (72.9)	411 (31.0)
Former	23 (2.4)	9 (0.7)
Never	233 (24.6)	907 (68.3)

BMI, body mass index; WC, waist circumference.
Continuous data are shown as mean (standard deviation).

with a WC below the median and at the median or higher were 0.72 and 0.71 in men, respectively, and 0.39 and 0.38 in women, respectively (all $P < 0.001$).

During the follow-up periods (mean 9.3 [3.5] years), 287 participants developed type 2 diabetes (Figure 1). Table 3 shows multivariable adjusted HRs for incidences of type 2 diabetes according to WC change tertile. Among participants with the median WC or higher, the highest tertile had significantly higher risk for the incidence of type 2 diabetes in both sexes in model 2 (HR 1.84; 95% CI, 1.10–3.08 in men and HR 2.30; 95% CI, 1.31–4.04 in women). The lowest tertile did not have a significantly lower risk for the incidence of type 2 diabetes in either sex (HR 1.27; 95% CI, 0.73–2.21 in men and HR 1.13; 95% CI, 0.59–2.18 in women). Among participants with WC below the median, there was no significant association between WC change and the incidence of type 2 diabetes in either sex. Interactions between WC at Exam 1 (below median or ≥median) and WC change (tertiles) was not significant in men ($P = 0.395$) but was significant in women ($P = 0.011$).

Even after adjustment of BMI at Exam 1 and BMI change (model 3), these results did not change much, although the HR of the highest tertile of WC change among men with WC median or higher was borderline significant (HR 1.72; 95% CI, 0.98–3.02). In model 3, the HRs for BMI change (per 1.0 kg/m^2/year) were 2.11 (95% CI, 0.49–9.16) in men with the median WC or higher and the highest tertile of WC change and 0.93 (95% CI, 0.31–2.82) in women. In the additional model, HRs of the highest tertile of WC change significantly increased among both men and women with the median WC at Exam 1 or higher.

Table 2. Waist circumference and BMI adjusted by age at Exam 1, Exam 2, and endpoint examination (n = 2273)

	WC change		
	tertile 1	tertile 2	tertile 3
Men with WC <median[a]			
Range of WC change, cm/year	−2.556 to 0.000	0.117 to 0.552	0.558 to 2.648
Age at examination 2	59.2 (10.6)	57.0 (10.0)	57.1 (10.6)
WC, Exam 1/Exam 2/endpoint	76.9/74.2/77.6	76.3/78.4/80.2	75.9/82.9/83.9
BMI, Exam 1/Exam 2/endpoint	20.9/20.5/20.8	21.3/21.7/21.7	21.2/22.6/22.7
Men with WC ≥median[a]			
Range of WC change, cm/year	−3.598 to −0.265	−0.263 to 0.296	0.304 to 2.454
Age at examination 2	60.9 (10.4)	60.0 (8.8)	58.2 (10.1)
WC, Exam 1/Exam 2/endpoint	90.1/84.7/87.4	88.3/88.6/89.4	87.3/92.1/92.6
BMI, Exam 1/Exam 2/endpoint	24.8/23.8/23.8	24.6/24.8/24.6	24.7/25.8/25.7
Women with WC <median[a]			
Range of WC change, cm/year	−2.023 to 0.506	0.509 to 1.378	1.380 to 3.820
Age at examination 2	53.5 (9.8)	55.0 (10.3)	56.9 (8.9)
WC, Exam 1/Exam 2/endpoint	69.5/69.3/73.3	67.7/74.4/77.3	67.5/81.7/81.7
BMI, Exam 1/Exam 2/endpoint	19.7/20.3/21.2	19.6/20.7/22.2	19.7/20.8/21.9
Women with WC ≥median[a]			
Range of WC change, cm/year	−2.363 to −0.341	−0.334 to 0.463	0.472 to 3.160
Age at examination 2	60.0 (9.6)	59.5 (9.3)	60.1 (8.7)
WC, Exam 1/Exam 2/endpoint	85.3/79.4/82.9	83.4/83.8/84.8	80.8/88.4/88.5
BMI, Exam 1/Exam 2/endpoint	23.0/23.4/23.9	22.5/23.5/24.6	22.6/23.1/24.2

BMI, body mass index; WC, waist circumference.
[a]Medians of waist circumference at examination 1 were 82.0 cm in men and 75.0 cm in women. Ages are shown as mean (standard deviation).

Table 3. Multivariable adjusted hazard ratios for the incidence of type 2 diabetes according to change in waist circumference (n = 2273)

	Cases/n	IR[a]	HRs (95% CIs)			
			Model 1	Model 2	Model 3	Additional model
Men with WC <median[b]						
tertile 1	25/169	16.6	1.06 (0.59–1.90)	1.19 (0.66–2.16)	1.01 (0.52–1.96)	1.25 (0.69–2.25)
tertile 2	21/148	15.5	ref	ref	ref	ref
tertile 3	32/158	22.3	1.44 (0.83–2.49)	1.25 (0.71–2.22)	1.34 (0.73–2.46)	1.36 (0.77–2.38)
Men with WC ≥median[b]						
tertile 1	29/157	20.0	1.16 (0.68–1.99)	1.27 (0.73–2.21)	1.40 (0.75–2.58)	1.50 (0.84–2.68)
tertile 2	24/157	16.8	ref	ref	ref	1.18 (0.65–2.15)
tertile 3	39/157	29.3	1.80 (1.08–3.01)	1.84 (1.10–3.08)	1.72 (0.98–3.02)	2.22 (1.28–3.83)
Women with WC <median[b]						
tertile 1	16/213	7.9	1.70 (0.77–3.75)	1.38 (0.60–3.20)	1.98 (0.80–4.91)	1.67 (0.75–3.69)
tertile 2	10/213	4.7	ref	ref	ref	ref
tertile 3	10/213	4.7	0.93 (0.39–2.25)	0.70 (0.28–1.74)	0.52 (0.20–1.38)	0.83 (0.35–2.23)
Women with WC ≥median[b]						
tertile 1	19/229	8.6	0.90 (0.48–1.69)	1.13 (0.59–2.18)	1.24 (0.63–2.44)	1.56 (0.72–3.39)
tertile 2	20/229	9.4	ref	ref	ref	1.24 (0.57–2.69)
tertile 3	42/230	19.9	2.14 (1.26–3.65)	2.30 (1.31–4.04)	2.07 (1.13–3.79)	2.45 (1.22–4.94)

CI, confidence interval; HR, hazard ratio; Ref, reference group; WC, waist circumference.
Model 1: Adjusted by age; Model 2: Adjusted by age, HbA1c, family history of diabetes, smoking and drinking status at examination 2, and WC at examination 1; Model 3: Adjusted by model 2 variables, body mass index at examination 1, and change in body mass index as continuous variables; Additional Model: Without stratification by median of WC at exam 1 and adjusted by model 2 variables except for WC at examination 1;
[a]Incidence rates/1000 person-years; [b]Medians of waist circumference were 82.0 cm in men and 75.0 cm in women at examination 1.

DISCUSSION

The present study demonstrates that, among participants with relatively high WC and regardless of sex, WC gain for 5–9 years was significantly associated with an elevated risk of incidence of type 2 diabetes for almost 10 years following WC gain, after adjustment for baseline HbA_{1c}. On the other hand, WC loss was not associated with a decreased risk of incidence of type 2 diabetes. No significant association between WC change and the incidence of type 2 diabetes was observed among individuals with relatively low WC.