SPEED-DEPENDENCE OF ORTHOSTATIC SYMPATHETIC ACTIVATION IN HUMANS

A stronger orthostatic stress causes greater MSNA response during head-up tilt (HUT) and thus it is well known that orthostatic MSNA activation is amplitude-dependent (Eckberg and Sleight, 1992; Cooke et al., 1999; Fu et al., 2009). In contrast, less attention has been paid to the effects of loading speed of orthostatic stress on orthostatic sympathetic activation in humans. Our previous study (Kamiya et al., 2009) examined whether the inclining speed of HUT influences the MSNA response to passive 30° HUT, independent of the magnitude of HUT, using inclining speeds of 1, 0.1, and 0.0167°/s (RAPID, SLOW, and VERYSLOW tests, respectively), in 12 healthy subjects (**Figure 1**). Calf MSNA (averaged over every 10° tilt angle) increased during inclination from 0 to 30°, with greater increases in the RAPID test than SLOW and VERYSLOW tests. In addition, only the RAPID test caused MSNA overshoot after reaching 30° HUT, whereas the SLOW and VERYSLOW tests did not. These results indicate that slower HUT results in smaller activation of MSNA suggesting that HUT-induced sympathetic activation depends partially on the speed of inclination during HUT in humans. The speed-dependence was also found in the high frequency amplitude of R-R interval variability (an index of cardiac vagal nerve activity), that decreased to a lesser extent during the inclination and after reaching 30° in the VERYSLOW test compared to the RAPID test.

CHARACTERISTICS OF BAROREFLEX SUBSYSTEMS IN ANIMALS: NEURAL AND PERIPHERAL ARCS

Previous system identification using open-loop experiments and transfer function analysis, commonly used in engineering, have revealed that in anesthetized animals (for example, rabbits), the transfer function of the neural arc (baroreceptor pressure to SNA) approximates derivative characteristics in the frequency range below 0.8 Hz, and high-cut characteristics of frequencies above 0.8 Hz (Kamiya et al., 2005c).Therefore, the neural arc transfer function (H_N) can be modeled by using Equation A as follows:

$$H_N(f) = -K_N \frac{1 + \frac{f}{fc1} j}{\left(1 + \frac{f}{fc2}\right)^2} \exp(-2\pi f j L) \qquad (A)$$

where f and j represent the frequency (in Hz) and imaginary units, respectively; K_N is static gain (in a.u./mmHg); $fc1$ and $fc2$ ($fc_1 < fc_2$) are corner frequencies (in Hz) for derivative and high-cut characteristics, respectively; and L is pure delay (in seconds), that would represent the sum of delays in the synaptic transmission at the baroreflex central pathways and the sympathetic ganglion. The dynamic gain increases in the frequency range of fc_1 to fc_2, and decreases at frequencies above fc_2.

In addition, the transfer function of the peripheral arc (SNA to systemic AP) approximates the second-order low-pass filter with a lag time in rabbits (Kamiya et al., 2005c). Therefore, the peripheral arc transfer function (H_p) can be modeled by using Equation B as follows:

$$H_P(f) = \frac{K_P}{1 + 2\zeta \frac{f}{f_N} j + \left(\frac{f}{f_N} j\right)^2} \exp(-2\pi f j L) \qquad (B)$$

where K_P is static gain (in mmHg/a.u.); f_N and ζ indicate natural frequency (in Hz) and damping ratio, respectively; and L is

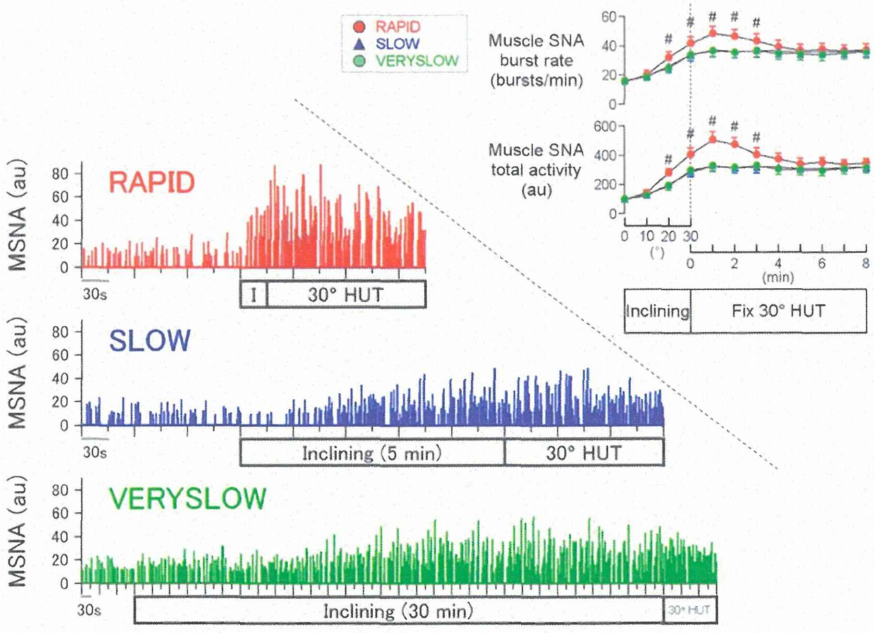

FIGURE 1 | Human MSNA responses to HUT tests with RAPID, SLOW, and VERYSLOW inclining speed. $^{\#}P < 0.05$ vs. SLOW and VERYSLOW tests. Error bars denote standard error. Modified from the study: Kamiya et al. (2009).

pure delay (in seconds), that would represent the sum of delays in the synaptic transmission at neuroeffector junction and the intracellular signal transduction in the effector organs.

NUMERICAL SIMULATION OF HUMAN MSNA RESPONSE TO HUT USING ANIMAL BAROREFLEX CHARACTERISTICS

First, a numerical simulation of the open-loop baroreflex condition was performed based on transfer functions actually identified in anesthetized animals (**Figure 2**). Since the increases in thoracic impedance averaged over tilt angle were similar in the RAPID, SLOW, and VERYSLOW HUT tests, the gravitational fluid shift directed toward the lower part of the body (such as the abdominal vascular bed and lower limbs) may be similar in all three tests at a tilt angle of 30°. Therefore, we assumed that the tilt-induced pressure perturbation was similar in the three HUT tests except for the speed. The numerical simulation indicates that in the open-loop baroreflex condition, the RAPID HUT test (1°/s) caused greater MSNA activation than SLOW (0.1°/s) and VERYSLOW (0.0167°/s) tests. This result appears to be consistent with our data observed in humans (**Figure 1**), and raises the possibility that the baroreflex control of SNA in humans also has high-pass filter characteristics.

Next, the relevance of baroreflex control of SNA to the speed-dependence in orthostatic MSNA activation was also confirmed by performing a numerical simulation mimicking the closed-loop baroreflex condition (**Figure 3**). The neural arc is arranged in series with the peripheral arc. Therefore, the total baroreflex loop is a negative-feedback control system that senses AP as baroreceptor pressure and regulates systemic AP. The simulation data indicated that the RAPID HUT test caused greater MSNA activation than the slower HUT tests, which is partially consistent with our previously observed data obtained in humans.

However, the dynamic transfer function characteristics of the neural arc cannot explain the 3-min overshoot of MSNA activation after reaching 30° HUT posture in the RAPID HUT test. In the numerical simulations, MSNA overshoot lasts less than 20 s in both baroreflex open-loop and closed-loop conditions. Accordingly, other mechanisms may be responsible for the overshoot of the orthostatic MSNA response in the faster HUT test. One possibility is a vestibulo-sympathetic response (Hammam et al., 2014; Yates et al., 2014). Another possibility is an effect of antigravity muscle contraction on SNA, since head-up suspension that removes antigravity muscle contractions caused smaller MSNA activation than HUT (Shamsuzzaman et al., 1998). Interestingly, without the numerical simulations based upon actual open-loop system identification in animals, it is difficult to predict the length of MSNA overshoot mediated by

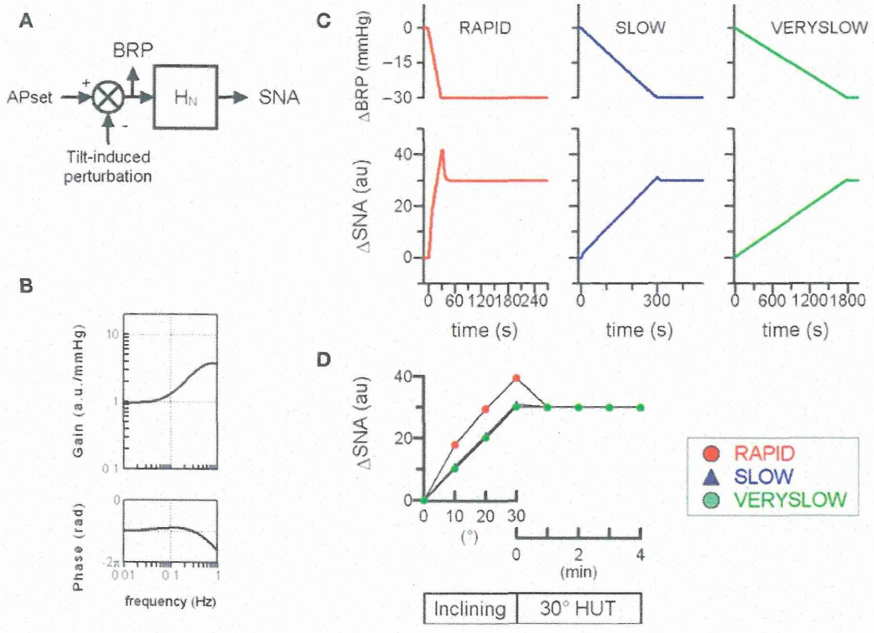

FIGURE 2 | Simulation of orthostatic activation of SNA in response to HUT at different inclining speeds in the baroreflex open-loop condition. **(A)** A block diagram of baroreflex control of SNA containing the neural arc transfer function (H_N). We assigned maximum tilt-induced perturbation of −30 mmHg in the simulations, equivalent to −1, −0.1, and −0.0167 mmHg/s in RAPID, SLOW and VERYSLOW HUT tests, respectively. We set APset at 100 mmHg. BRP; baroreceptor pressure. **(B)** The gain and phase function of H_N. The gains K_N are set at 1 au/mmHg. The fc_1, fc_2, and L are set at 0.1, 0.8, and 0.2, respectively, based on animal experimental data. **(C)** Simulated time series changes in BRP and SNA at conditions set in **(A,B)**. The RAPID test resulted in greater activation and an overshoot of SNA, compared with SLOW and VERYSLOW tests. **(D)** Simulated SNA data (same as **C**) of the RAPID (open circle), SLOW (closed triangle), and VERYSLOW (closed circle) HUT tests plotted on the same axes. Upper X-axis indicates that data are averaged over every 10° tilt angle during inclination from 0° supine to 30° HUT, while the lower X-axis indicates that data are averaged over every 1 min after reaching 30° HUT. Modified from the study: Kamiya et al. (2009).

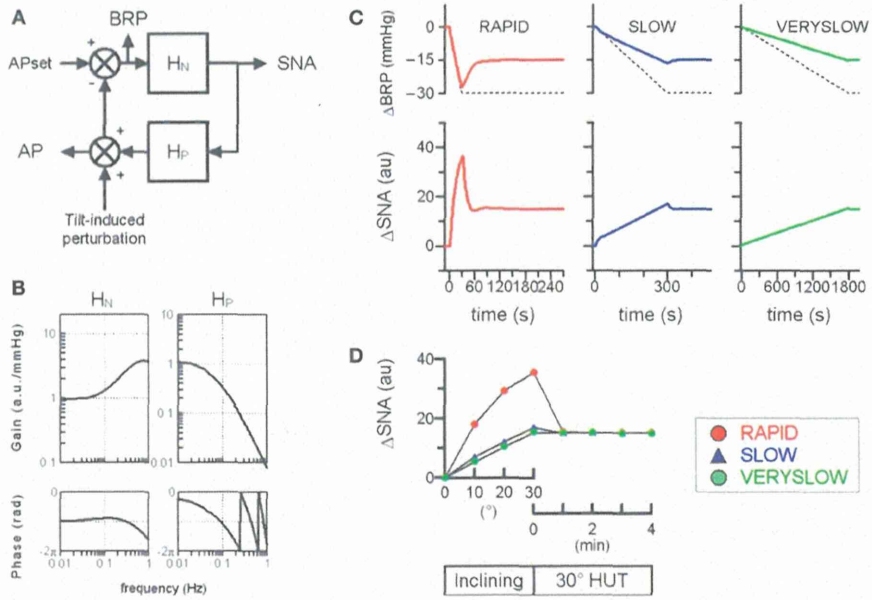

FIGURE 3 | Simulation of orthostatic activation of SNA in response to HUT at different inclining speeds in the baroreflex closed-loop condition. **(A)** A block diagram of total arc baroreflex system that contains the neural arc transfer function (H_N) and theperipheral arc transfer function (H_P). We assigned maximum tilt-induced perturbation of −30 mmHg in the simulations, equivalent to −1, −0.1, and −0.0167 mmHg/s in RAPID, SLOW and VERYSLOW HUT tests, respectively. We set APset at 100 mmHg. BRP; baroreceptor pressure. **(B)** The gain and phase function of H_N and H_P. In the model of H_N, the gain (K_N) is set at 1 au/mmHg, while the remaining parameters are set similarly in **Figure 2**. In the model of H_P, the K_P, f_N, ζ and L are set at 1, 0.07, 1.4, and 1, respectively, based on observation in animals. **(C)** Simulated time series changes in BRP (solid lines, upper panels) and SNA (lower panels) at conditions set in **(A)** and **(B)**. The dotted lines in upper panels indicate the tilt-induced perturbations. The RAPID test results in greater activation and an overshoot of SNA compared to SLOW and VERYSLOW tests. **(D)** Simulated SNA data (same as **C**) of the RAPID (open circle), SLOW (closed triangle), and VERYSLOW (closed circle) HUT tests plotted on the same axes. Upper X-axis indicates that data are averaged over every 10° tilt angle during inclination from 0° supine to 30° HUT, while the lower X-axis indicates that data are averaged over every 1 min after reaching 30° HUT.

the baroreflex and the potential involvement of mechanisms other than the baroreflex.

BAROREFLEX DYNAMIC TRANSFER CHARACTERISTICS AND BASIC CLASSIC DATA OF BARORECEPTOR AFFERENT

The baroreflex dynamic transfer function identified by a white-noise and open-loop method (Kamiya et al., 2011) is a transfer characteristics from baroreceptor pressure input to SNA in the baroreflex neural arc and that from SNA input to systemic AP in the baroreflex peripheral arc. The dynamic transfer function shows a linear component of the system, and is able to predict a time-series SNA response to randomly drug-induced (phenylephrine and nitroprusside infusions) AP changes in closed-loop condition with a high degree-of accuracy (r^2 of 0.9 ± 0.1) (Kamiya et al., 2011). However, the baroreflex dynamic transfer function is limited to address basic classic data of baroreceptor afferent, in particular the contrasting effects of static and pulsatile pressure on carotid baroreceptor activity in dogs (Chapleau and Abboud, 1987). For example, although the single unit baroreceptor afferent nerve activity increased in response to an increase in baroreceptor pressure, the pulsatile baroreceptor pressure resulted in lower threshold as compared with static (ramp-like) baroreceptor pressure. Another example is a baroreceptor afferent response to a shift from static to pulsatile pressure. A pulsatility increased afferent nerve activity at low mean arterial pressures, whereas it decreased afferent nerve activity at high mean arterial pressures. These interesting observations may relate with a non-linear component of baroreflex system.

CONCLUSION

System identification can be a powerful tool in the research of complex biosystems. However, its application for human research is often difficult since it requires open-loop surgical operation when the system is a closed-loop biosystem, which applies to the baroreflex. As a helpful challenge, I show the possibility that system identification based analysis and numerical simulation using baroreflex subsystem characteristics identified in animals can contribute to our understanding of human sympathetic physiology under orthostasis (Kamiya et al., 2005a, 2009).

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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				P_{trend}
	0	1 or 2	3	4	
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				P_{trend}
	1st quartile	2nd quartile	3rd quartile	4th quartile	
	≤18 in men	19–25 in men	26–27 in men	28 in men	
	≤21 in women	22–25 in women	22–25 in women	27–28 in women	
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			P_{trend}
	A	B	C	
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