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.

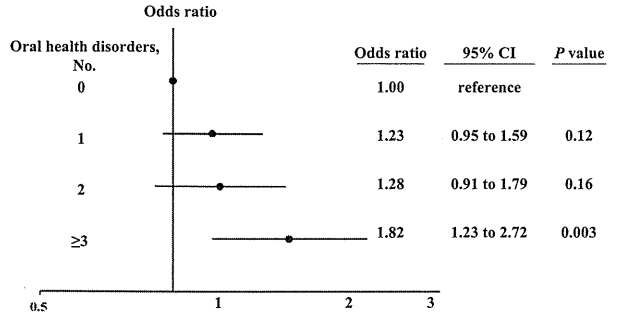

Figure 1. Odds ratios for hypertension by number of oral health disorders including Community Periodontal Index of Treatment Needs (CPITN) stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C. Data are adjusted odds ratio (95% confidence 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)

	0	1			2			≥3			
Models		β	95% CI	P value	β	95% CI	P value	β	95% CI	P trend	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.

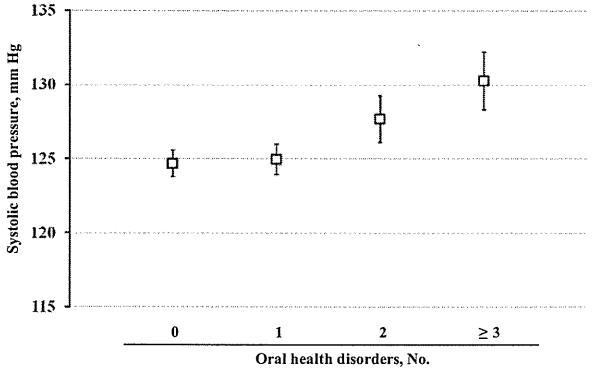

Figure 2. Adjusted mean systolic blood pressure by number of oral health disorders including Community Periodontal Index of Treatment Needs (CPITN) stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C in subjects not taking antihypertensive 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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Stroke
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Impact of Chronic Kidney Disease on Carotid Atherosclerosis According to Blood Pressure Category: The Suita Study

Tomoyuki Ohara, Yoshihiro Kokubo, Kazunori Toyoda, Makoto Watanabe, Masatoshi Koga, Satoko Nakamura, Kazuyuki Nagatsuka, Kazuo Minematsu, Masanori Nakagawa and Yoshihiro Miyamoto

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

The Suita Study

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

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

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

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

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

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

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

Patients and Methods

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

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Table 1. Adjusted Max-IMT According to eGFR Category

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

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

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

Results

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

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

Discussion

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

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

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

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

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

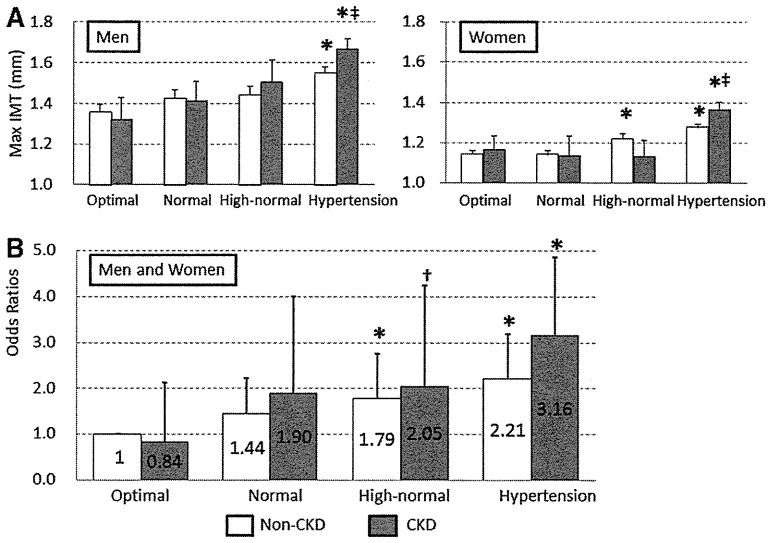

Figure. Multivariable-adjusted maximum carotid intima-media thickness (max-IMT; **A**) and odds ratios for stenosis (**B**) according to blood pressure (BP) category in subjects with and without chronic kidney disease (CKD). *P<0.05; †P=0.053 vs non-CKD/optimal BP; ‡P<0.05 vs non-CKD subjects in the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

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

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

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

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

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

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

Supplemental Methods

The Suita Study

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

Evaluation of renal function

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

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

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

Carotid Ultrasound Measurements

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

Measurement of Blood Pressure

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

Covariates

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

Statistical analysis

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

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

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

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

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

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

Supplemental References

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Original Article

Do Differences in Risk Factors Explain the Lower Rates of Coronary Heart Disease in Japanese Versus U.S. Women?

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Abstract

Background: Mortality from coronary heart disease (CHD) in women in Japan is one of the lowest in developed countries. In an attempt to shed some light on possible reasons of lower CHD in women in Japan compared with the United States, we extensively reviewed and analyzed existing national data and recent literature.
Methods: We searched recent epidemiological studies that reported incidence of acute myocardial infarction (AMI) and examined risk factors for CHD in women in Japan. Then, we compared trends in risk factors between women currently aged 50–69 years in Japan and the United States, using national statistics and other available resources.
Results: Recent epidemiological studies have clearly shown that AMI incidence in women in Japan is lower than that reported from other countries, and that lipids, blood pressure (BP), diabetes, smoking, and early menopause are independent risk factors. Comparing trends in risk factors between women in Japan and the United States, current levels of serum total cholesterol are higher in women in Japan and levels have been similar at least since 1990. Levels of BP have been higher in in Japan for the past 3 decades. Prevalence of type 2 diabetes has been similar in Japanese and white women currently aged 60–69 for the past 2 decades. In contrast, rates of cigarette smoking, although low in women in both countries, have been lower in women in Japan.
Conclusions: Differences in risk factors and their trends are unlikely to explain the difference in CHD rates in women in Japan and the United States. Determining the currently unknown factors responsible for low CHD mortality in women in Japan may lead to new strategy for CHD prevention.

Introduction

JAPANESE WOMEN IN JAPAN HAVE EXPERIENCED the greatest longevity for the past 25 years.[1] This is partly due to a constant decline in mortality from coronary heart disease (CHD) since the 1960s, although CHD mortality in women in Japan was one of the lowest in developed countries.[2] Low CHD mortality in Japan in the 1960s was attributed to low dietary intake of saturated fat and cholesterol, resulting in low serum levels of total cholesterol (e.g., 160 mg/dL in Japan and 240 mg/dL in the United States).[3] The hypothesis at that time was that with Western acculturation, CHD rates in Japan would increase. In fact, CHD mortality in Asian countries has increased with concomitant rise in serum total cholesterol except for Japan.[4,5] Between 1960 and 1990, dietary intake of both total fat and animal protein almost tripled,[6,7] and the current dietary intake of cholesterol in women in Japan is higher than in the United States (i.e.,199 vs. 128 mg/1,000 kcal).[8] The current levels of total cholesterol in women aged 50–69 years in Japan are higher than those in the United States.[9] The absence of increase in CHD is unusual, given that during this period, dietary-related diseases (e.g., colon and breast cancer in women and colon and prostate cancer in men increased substantially).[10] It is important to note that low CHD mortality in women in Japan is not a function of high mortality from other causes (e.g., stroke, cancer).[1]

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Low CHD mortality in Japanese in Japan does not appear to be due primarily to genetics or host susceptibility because CHD incidence and mortality increased substantially in Japanese migrants to the United States within one to two generations.[11] Additionally, we have recently documented that levels of atherosclerosis assessed as calcification of the coronary artery and aorta and intima-media thickness (IMT) of the carotid artery in Japanese American men are not only higher than those in Japanese men in Japan, but are also higher compared with white Americans.[12,13] We have previously reported that low CHD mortality in middle-aged men in Japan compared with the United States is very unlikely due to misclassification of cause of death,[14] difference in risk factors,[15,16] or cohort effect.[16] In an attempt to shed some light on possible reasons of lower CHD in women in Japan compared to the United States, we extensively reviewed and analyzed existing national data and recent literature.

Materials and Methods

Data on CHD mortality were obtained from the World Health Organization (WHO) Statistical Information System (www.who.int/whosis). For age-adjusted mortality from CHD, a new WHO standard was used.[17] To define CHD we used codes I20–25 in the International Statistical Classification of Diseases and Related Health Problem 10th Revision (ICD-10) and codes 410–414 in ICD-9. To depict the international trend in CHD mortality from 1995 to 2004, we chose Canada, France, Greece, Japan, Spain, the United Kingdom, and the United States.

To compare trends in risk factors between women in Japan and the United States, data were obtained from the National Health and Nutrition Examination Surveys (NHANES) in the United States,[18,19] the National Health and Nutrition Survey and the National Survey of Cardiovascular Diseases in Japan[6,7,20] as well as published articles (Table 1).[21–23] Prevalence of diabetes in white women in 2007–2010 in the United States was estimated using the NHANES dataset available at a web site of the Centers for Disease Control and Prevention.[19]

For incidence of acute myocardial infarction (AMI) and the association of risk factors with CHD in women in Japan, we identified epidemiological studies published after 2001 that reported the data in women and men separately, because no previous epidemiological studies in Japan reported the association only in women. We identified these studies using review papers we and others published in 2008,[24,25] articles citing these review papers, a website listing cardiovascular epidemiology studies conducted in Japan with their publications,[26] and PubMed.

Table 1. Sources of Information Used in Comparing Statistics Between Japan and the United States

	Japan	*United States*
Mortality	WHO Statistics	WHO Statistics
Trend in total cholesterol	NHNS/NSCD	NHANES
Trend in blood pressure	NHNS/NSCD	NHANES
Trend in smoking	NHNS/NSCD	NHANES
Diabetes	Published literature	NHANES
Incidence of AMI	Published literature	Published literature

AMI, acute myocardial infarction; NHANES, National Health and Nutrition Examination Survey; NHNS, National Health and Nutrition Survey; NSCD: National Survey of Cardiovascular Diseases; WHO, World Health Organization.,

Results

Between 1995 and 2004, age-adjusted CHD mortality in women was declining in each country (Fig. 1). During this period, women in France and Japan had the lowest and women in the United Kingdom and the United States had the highest CHD mortality. A five-fold difference existed in aged-adjusted CHD mortality (per 100,000) in 2004 between Japan and the United States: 13.5 in Japan verses 65.6 in the United States.

AMI incidence in women in Japan, evaluated using the protocol of the WHO MONICA Project (Monitoring of Trends and Determinants in Cardiovascular Disease)[27] was much lower compared to other countries. The Takashima AMI Registry covering about 55,000 individuals reported that age-adjusted incidence of AMI in women aged 25–74 years was 18.0/100,000[28] and that the incidence was the lowest as compared to the incidence in registries from the WHO MONICA Project.[27] Age-adjusted incidence of AMI in women aged 35–64 in Takashima was 9.1/100,000, which was less than a tenth of that in the United Kingdom (256/100,000), the United States (139/100.000), and Finland (86–165/100,000) and even less than a half of that in France (37–77/100,000), and China(37/100,000).[28] AMI incidence in women in other registries in Japan was reported and similarly low.[24,29]

Additionally, there is little evidence that AMI incidence in women in Japan has increased recently. The MIYAGI-AMI registry study, which covers more than 2 million individuals, the largest AMI registry in Japan, reported AMI incidence in women between 1979 and 2009.[30] Age-adjusted incidence of AMI in women remained similar or appeared to be slightly decreasing between 1987 and 2008, although it increased between 1979 and 1986. The Circulatory Risk in Communities Study (CIRCS) which covers more than 30,000 individuals reported that age-adjusted incidence of sudden cardiac death in women in Japan significantly decreased from 1981 to 2005.[31] Age-adjusted incidence of sudden cardiac death (per 100,000) was 50.6, 39.5, 27.1, 16.7, and 18.2 during 1981–1985, 1986–1990, 1991–1995, 1996–2000, and 2001–2005 respectively. Although the Takashima AMI registry reported a significant increase in AMI incidence in women from 1990–1992 to 1993–1995, there was no increase since 1993–1995 to 1999–2001.[32] Several other studies reported trends in AMI incidence in women in Japan but the number of cases was too small to examine the trend.[33–36]

Up until 2009, epidemiological studies did not show significant independent associations of lipids with CHD in women in Japan (Table 2).[37–42] Japan Atherosclerosis Longitudinal Study-Existing Cohorts Combine (JALS-ECC), a project pooling the data from cohort studies in Japan examined the association of total cholesterol and non-high-density lipoprotein cholesterol (non-HDL-C) with AMI incidence in 13,477 women and 8,953 men aged 40–89 years at baseline with an average follow-up of 7.6years.[38] The study reported that among women incidence rate ratio for one standard