the risk of CV events in CKD subjects. Second, the plasma BNP level has been reported as increased with progression of anemia, which is independent of the degree of cardiac dysfunction.[22,23] In this regard, an elevated plasma BNP level may indicate advanced anemia, and thus be a marker at a high risk of CV events in CKD subjects. In fact, several reports have demonstrated that the prevalence of future onset of coronary artery disease and heart failure were significantly elevated in subjects with anemia.[24–26] Third, elevated levels of plasma BNP denote impaired cardiac function, including latent structural heart diseases, cardiac volume overlord, and myocardial ischemia, and thus such patients are prone to CV disorders.

In the present study, although there were no significant differences in the levels of eGFR and blood hemoglobin between the 3rd rd and the 4th BNP quartiles, CV events were clearly prevalent in the highest quartile group. These findings indicate that the first and the second explanations are unlikely, and thus the third hypothesis may be the more possible. However, left ventricular function and morphological data were unavailable in the present cohort study, and it was unclear whether patients with structural heart disease or impaired cardiac function were more common in the 4th quartile than in the lower quartiles. In previous studies using echocardiography, a plasma level of plasma BNP >40–50 pg/ml was a useful marker with high sensitivity and specificity for identifying subjects with latent structural heart disease, including left ventricular dysfunction, valvular heart diseases, cardiomyopathy, and atrial fibrillation.[27–29] In view of these findings, a CKD subgroup with elevated plasma BNP levels tends to show subclinical structural cardiac disorders and is associated with a high risk for heart failure, ischemic stroke, and coronary artery diseases. In accordance with this hypothesis, several reports have suggested that an increased plasma BNP level in patients with renal dysfunction is mainly caused by cardiac overload and intrinsic organic heart disease rather than renal dysfunction.[30–32]

Incidentally, the present study found that CKD definition-1 using reduced GFR and/or proteinuria captured a greater number of subjects with CV events than CKD definition-2 using reduced GFR only (62 cases for definition-1 vs 43 cases for definition-2). This observation suggests that definition-1 is more useful for the definition of CKD in terms of CV risk stratification. Measurement of 2 biomarkers (GFR and urinary protein) is therefore be recommended for the selection of CKD subjects within apparent healthy populations.

Study Limitations

Although the present study with its large sample size is a prospective community-based study that included routine biochemical data, several limitations must be considered when interpreting the results. More than 35% of the CKD subjects were receiving antihypertensive agents at baseline. Several types of antihypertensive drugs, such as angiotensin-converting enzyme-inhibitors and angiotensin II receptor blockers, reduce the onset of CV events. The present study did not evaluate the effects of these drugs on the incidence of CV events. However, the percentage of subjects receiving antihypertensive drugs increased with the quartiles of plasma BNP level (Table 1), which suggests that the CKD subjects with higher plasma BNP levels were likely to receive these medications. This limitation might have underestimated the association between plasma BNP level and CV events. The urine dipstick test used in the present CKD definition is usually regarded as not being accurate for the diagnosis of persistence proteinuria. However, in a previous population-based study, trace proteinuria on dipstick test had good reproducibility and high sensitivity and specificity for detection of micro-albuminuria in an elderly population.[33] In this regard, the inclusion criterion for CKD definition-1 in the present study was a trace result for dipstick test.

In conclusion, the plasma BNP level provides strong predictive information about the future onset of CV events in subjects with mildly reduced renal function. This result implies that plasma BNP measurement is a powerful tool for stratifying CV risk in CKD subjects selected from the general population.

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Comparison of low-density lipoprotein cholesterol concentrations measured by a direct homogeneous assay and by the Friedewald formula in a large community population

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ABSTRACT

Background: We compare the direct homogeneous low-density lipoprotein cholesterol (LDL-C) assay with the Friedewald formula (FF) for determination of LDL-C in a large community-dwelling population.
Methods: A total of 21,194 apparently healthy subjects aged 40 to 79 years with triglyceride (TG) concentrations <4.52 mmol/l were enrolled. LDL-C were directly measured by the enzymatic homogeneous assay (LDL-C (D)) and also estimated by the FF (LDL-C (F)). Paired t-test, Pearson's correlation coefficient and linear regression analysis were performed and the concordances of the National Cholesterol Education Program (NCEP) risk category were estimated.
Results: Both in fasting (n = 3270) and nonfasting samples (n = 17,924), LDL-C (D) highly correlated with LDL-C (F): $r = 0.971$ and 0.955, respectively. Concordant results for NCEP categories were 84.8% for fasting samples and 80.1% for nonfasting samples. However, the bias between the 2 measurements increased in samples with TG concentrations >1.69 mmol/l, especially in nonfasting samples.
Conclusions: The results showing less variability of the direct LDL-C assay than that of the FF in nonfasting samples suggest that epidemiological studies can use LDL-C measured by the direct assay both in fasting and nonfasting samples.

1. Introduction

Many epidemiological studies and clinical trials have shown that elevated low-density lipoprotein cholesterol (LDL-C) concentrations are causally related to an increased risk of coronary artery disease (CAD) [1,2]. The findings from those studies are mainly based on LDL-C concentrations calculated by the Friedewald formula (LDL-C (F)) [3], which derives LDL-C concentrations from total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) concentrations [4–7]. The guidelines for preventing atherosclerotic disease recommend using the Friedewald formula in a fasting state (ideally a 9- to 12-h fast) [1,2]. However, it is impossible to obtain fasting samples from all patients who visit clinics, especially those who visit at night or in the afternoon. In Japan, general screenings for risk factors of cardiovascular disease (CVD) are performed under nonfasting conditions to improve the participation rates. Therefore, a convenient method for determination of LDL-C concentration that is insensitive to postprandial state has been required regardless of whether it is directly obtained or calculated.

Recently, several homogeneous assays have been used as direct measurements for determination of LDL-C concentration. They have become popular in clinics and in health check-ups. Most homogeneous assays have met the National Cholesterol Education Program (NCEP) total error goals for nondiseased individuals in a fasting state compared with β-quantification [8,9]. In addition, no significant difference in LDL-C concentrations measured by the direct homogeneous assay was seen

Abbreviations: LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; LDL-C (F), LDL-C calculated by the Friedewald formula; LDL-C (D), LDL-C measured by the enzymatic homogeneous assay; CAD, coronary artery disease; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; CVD, cardiovascular disease; NCEP, National Cholesterol Education Program; CRMLN, Cholesterol Reference Method Laboratory Network; HbA1c, glycosylated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panels III; OR, odds ratio; CI, confidence interval.

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between paired fasting and nonfasting samples in the same individuals [10,11], and postprandial changes in LDL-C concentrations measured by the homogeneous assay were similar to those measured by β-quantification [12].

On the other hand, the Friedewald formula is known to underestimate LDL-C concentrations compared with β-quantification even when TG concentrations are <4.52 mmol/l [13–15]. The calculated LDL-C concentrations also have been reported to be significantly decreased in a postprandial state [16–18]. However, in recent large-scale population-based cohort studies, CVD risk has been assessed using LDL-C concentrations calculated by the Friedewald formula in a nonfasting state because of a strong correlation between LDL-C concentrations obtained by the Friedewald formula and β-quantification [19,20] and there are only minimal changes in concentrations of LDL-C in response to normal food intake in a general population [21]. These studies suggest that LDL-C concentrations calculated by the Friedewald formula either in fasting or nonfasting samples could be used in population-based epidemiological studies.

We therefore compared the direct homogeneous LDL-C assay with the Friedewald formula for determination of LDL-C both in fasting and nonfasting samples using baseline data from a large cohort study of community-dwelling residents to clarify whether the direct homogeneous LDL-C assay can be used in population-based epidemiological studies.

2. Materials and methods

2.1. Study population

We analyzed baseline data of the Iwate-Kenpoku cohort (Iwate-KENCO) study, which was designed as a cohort study of community-dwelling residents living in the northern part of the main island of Japan. The methodology of the Iwate-KENCO study was described elsewhere [22–24]. The baseline survey was carried out between 2002 and 2005. Of 24,572 participants (8476 men and 16,096 women) aged 40 to 79 years from whom we obtained written informed consent for participation in this study, 594 subjects with missing data for serum lipids, 212 subjects with TG concentrations >4.52 mmol/l (400 mg/dl) and 54 subjects who did not have complete information were excluded from the analysis. Furthermore, 1697 subjects receiving medication for dyslipidemia and 821 subjects with a history of stroke or myocardial infarction were excluded to examine whether LDL-C concentrations measured by the direct homogeneous assay can be used as baseline data in an epidemiological study assessing the risk of first CVD events in the general community-dwelling population. Therefore, 21,194 participants (7349 men and 13,845 women) were enrolled in the present study. The study was approved by the Medical Ethics Committee of Iwate Medical University and conducted in accordance with the guidelines of the Declaration of Helsinki.

2.2. Measurements of serum lipids

Samples from participants whose last meal was ≥12 h before their blood draw were used as fasting samples (n = 3270) and samples from participants who had eaten within 12 h of their blood draw were used as nonfasting samples (n = 17,924). Both fasting and nonfasting samples were collected into vacuum tubes containing a serum separator gel. The samples were stored immediately after sampling in an icebox and were transported to a laboratory (Iwate Health Service Association) and analyzed on the same day. Serum TC, TG and HDL-C concentrations were measured by an enzymatic method. Serum LDL-C concentrations were measured by an enzymatic homogenous assay with Cholestest-LDL (Daiichi Chemicals, currently Sekisui Medical, Tokyo). LDL-C was also estimated again using the Friedewald formula. Non-HDL-C was calculated by subtracting HDL-C from TC. Measurements for TC, HDL-C and LDL-C (homogenous assay), except for the TG assay, have been standardized by the Osaka Medical Center for Health Science and Promotion, a member of the Cholesterol Reference Method Laboratory Network (CRMLN) controlled by the Centers for Disease Control and Prevention (Atlanta, USA) [25] and have met all criteria for both precision and accuracy of lipid measurement. During the period of the baseline survey, total coefficient of variations (CVs), mean biases and total errors for LDL-C assay used in this study were 0.2% to 0.4%, 0.7% to 0.8% and 1.2% to 1.5%, respectively. The corresponding values for the TC assay were −2.7% to 0.4%, 0.2% to 0.4% and 1.2% to 3.5%, and the corresponding values for the HDL-C assay were −2.2% to 3.0%, 0.6% to 1.1% and 3.0% to 4.4%. For the TG assay, total CVs at the laboratory were 0.2 to 1.9%. External quality assessment for the TG assay was performed by the Japan Association of Medical Technologists (JAMT) and the analytical performance of the TG assay has met the criteria of quality assessment in the JAMT.

2.3. Measurements of other risk factors

Plasma glucose concentrations were determined by the hexokinase method, and glycosylated hemoglobin (HbA1c) concentrations were determined by HPLC. Diabetes was defined as plasma glucose concentration being ≥7.0 mmol/l in fasting samples or ≥11.1 mmol/l in nonfasting samples, plasma HbA1c concentration being ≥6.5%, use of anti-diabetic agents or a combination of these.

Blood pressures were measured twice in the sitting position after urination and a 5-min rest by well-trained staff using an automatic device. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were each calculated as the mean of 2 measurements. Hypertension was defined as SBP being ≥140 mmHg, DBP being ≥90 mmHg or more, use of antihypertensive agents or a combination of these. Height in stockings and weight in light clothing were measured. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m).

Self-administered questionnaires for past history of stroke and myocardial infarction, medication, alcohol drinking and smoking status were used to collect individual information. To confirm whether participants had had prevalent stroke and myocardial infarction at the baseline survey, data from the Iwate Stroke Registry [26] and Northern Iwate Heart Disease Registry Consortium [27] were systematically reviewed. Smoking status was determined as current, past and never smoking by the questionnaire. Regular alcohol drinking was defined as drinking ≥5 days/week. Presence or absence of medication for dyslipidemia was determined by the answer of whether a participant had used any anti-hyperlipidemia agents.

2.4. Statistical analysis

All analyses, except for a logistic regression analysis, were separately performed in the fasting group and nonfasting group. Participants were also classified into 3 groups according to serum TG concentrations, of which cut-off points were based on the National Cholesterol Education Program Adult Treatment Panels III (NCEP-ATP III) guideline, i.e., normal: <1.69 mmol/l (150 mg/dl), moderate high: 1.69 to 2.26 mmol/l (150 to 199 mg/dl), and high: 2.26 to 4.51 mmol/l (200 to 399 mg/dl) [1]. We calculated the means and proportions of selected variables by TG group. Data for TG were expressed as geometric means. Except for TG, comparisons of selected variables between TG groups were performed using analysis of variance (ANOVA) for continuous variables and the χ^2 test for categorical variables. Concentrations of LDL-C (F) and LDL-C (D) were also compared using the paired t-test.

The correlation between LDL-C (F) and LDL-C (D) and the effect of TG concentrations on the difference in LDL-C by the 2 methods, which was calculated by subtracting LDL-C (F) from LDL-C (D) concentrations, were estimated using Pearson's correlation coefficients and linear regression analysis. To examine concordance of concentrations of

Table 1
Characteristics and serum lipid levels in fasting participants by TG groups.

	Total	TG group, mmol/L			P value[a]
		<1.69	1.69–2.26	2.26–4.51	
Number of fasting participants	3270	2906	224	140	
TG, mmol/L[b]	0.97 (1.6)	0.87 (1.4)	1.89 (1.1)	2.80 (1.2)	<0.001
Men, %	36.8	35.4	42.4	57.1	<0.001
Age, years	63.5 (9.3)	63.5 (9.4)	63.8 (8.9)	62.4 (9.4)	0.342
Body mass index, kg/m^2	24.0 (3.3)	23.8 (3.3)	25.1 (3.4)	25.6 (3.0)	<0.001
Hypertension, %	42.3	41.4	49.1	50.7	0.010
Diabetes, %	9.0	8.4	9.8	20.0	<0.001
Current smokers, %	11.2	10.4	14.3	22.1	<0.001
Regular drinkers, %	19.3	18.9	21.0	25.7	0.110
Serum lipids					
TC, mmol/L	5.31 (0.85)	5.27 (0.83)	5.53 (0.91)	5.73 (0.91)	<0.001
HDL-C, mmol/L	1.58 (0.39)	1.62 (0.39)	1.30 (0.30)	1.20 (0.29)	<0.001
non-HDL-C, mmol/L	3.73 (0.85)	3.65 (0.81)	4.23 (0.88)	4.53 (0.88)	<0.001
LDL-C (F), mmol/L	3.24 (0.77)	3.23 (0.76)	3.36 (0.87)	3.23 (0.88)	0.046
LDL-C (D), mmol/L	3.24 (0.76)	3.22 (0.75)	3.40 (0.83)	3.29 (0.83)	0.003
	$P=0.553$[c]	$P=0.232$[c]	$P=0.019$[c]	$P=0.033$[c]	

TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C (F), LDL-C calculated by the Friedewald formula; LDL-C (D), LDL-C measured by the enzymatic homogeneous assay.
Data are expressed as means (standard deviations) for continuous variables and percentages for categorical variables.
[a] *P* values for comparisons of variables between TG groups by analysis of variance or the chi-squared test.
[b] Data for triglyceride are expressed as geometric means (geometric standard deviations).
[c] *P* values for comparisons between LDL-C (F) levels and LDL-C (D) levels by the paired t-test.

LDL-C (F) and LDL-C (D), participants were classified into four groups according to concentrations of LDL-C (F) or LDL-C (D) based on the LDL-C cut-off points recommended by the NCEP-ATP III guideline, i.e., <2.58 mmol/l (100 mg/dl), 2.58 to 3.35 mmol/l (100 to 129 mg/dl), 3.36 to 4.12 mmol/l (130 to 159 mg/dl), ≥4.13 mmol/l (160 mg/dl) [1]. Cross-tables among the NCEP groups of LDL-C (F) and LDL-C (D) were presented by TG groups.

Logistic regression analysis was performed for the all participants in the fasting and nonfasting groups. In the analysis, the dependent variable was discordance of the groups between LDL-C (F) and LDL-C (D) (coded as 1 for discordance and coded as 0 for concordance) and the independent variables were logarithm-transformed TG (ln TG), age, sex, BMI, hypertension (presence or absence), diabetes (presence or absence), current smokers (or not), regular drinkers (or not) and nonfasting state (or fasting state). In all analyses, 2-sided $P<0.05$ was considered to be statistically significant. The Statistical Package for Social Science (SPSS Japan Inc. ver. 15.0J, Tokyo, Japan) was used for all analyses.

3. Results

Table 1 shows characteristics of fasting participants by TG groups. There were significant differences between TG groups in all variables except for mean age and proportion of regular drinkers: that is, mean BMI and proportions of male participants, participants with hypertension, participants with diabetes and current smokers were higher in the higher TG group. Table 1 also shows fasting serum lipid profiles by TG groups. Mean concentrations of TC, HDL-C, non-HDL-C, LDL-C (F) and LDL-C (D) were significantly different between the TG groups. There was no significant difference between mean fasting concentrations of LDL-C (D) and LDL-C (F) (3.24 mmol/l and 3.24 mmol/l, respectively). In the normal TG group, there was also no significant difference between mean fasting concentrations of LDL-C (D) and LDL-C (F): mean concentrations of LDL-C (D) and LDL-C (F) were 3.22 mmol/l and 3.23 mmol/l, respectively. In the moderate high and high TG groups, mean fasting concentrations of LDL-C (D) were

Table 2
Characteristics and serum lipid levels in nonfasting participants by TG groups.

	Total	TG group, mmol/L			P value[a]
		<1.69	1.69–2.26	2.26–4.51	
Number of nonfasting participants	17,924	13,831	2307	1786	
TG, mmol/L[b]	1.16 (1.7)	0.95 (1.4)	1.92 (1.1)	2.86 (1.2)	<0.001
Men, %	34.3	32.8	36.7	42.8	<0.001
Age, years	62.1 (9.7)	62.1 (9.8)	62.4 (9.4)	61.7 (9.6)	0.071
Body mass index, kg/m^2	24.0 (3.3)	23.7 (3.2)	25.1 (3.2)	25.5 (3.1)	<0.001
Hypertension, %	40.6	38.3	47.9	49.2	<0.001
Diabetes, %	4.9	4.4	5.8	7.8	<0.001
Current smokers, %	12.7	11.6	14.5	18.5	<0.001
Regular drinkers, %	19.0	18.7	19.0	21.8	0.007
Serum lipids					
TC, mmo/L	5.15 (0.83)	5.07 (0.81)	5.36 (0.81)	5.50 (0.84)	<0.001
HDL-C, mmol/L	1.53 (0.38)	1.60 (0.38)	1.37 (0.31)	1.26 (0.29)	<0.001
Non-HDL-C, mmol/L	3.62 (0.82)	3.47 (0.77)	3.99 (0.77)	4.24 (0.81)	<0.001
LDL-C (F), mmol/L	3.01 (0.75)	3.01 (0.73)	3.11 (0.77)	2.91 (0.82)	<0.001
LDL-C (D), mmol/L	3.08 (0.74)	3.03 (0.73)	3.28 (0.73)	3.24 (0.76)	<0.001
	$P<0.001$[c]	$P<0.001$[c]	$P<0.001$[c]	$P<0.001$[c]	

TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C (F), calculated by the Friedewald formula; LDL-C (D), LDL-C measured by the enzymatic homogeneous assay.
Data are expressed as means (standard deviations) for continuous variables and percentages for categorical variables.
[a] *P* values for comparisons of variables between TG groups by analysis of variance or the chi-squared test.
[b] Data for triglyceride are expressed as geometric means (geometric standard deviations).
[c] *P* values for comparisons between LDL-C (F) levels and LDL-C (D) levels by the paired t-test.

significantly higher than those of LDL-C (F): the differences were 0.04 mmol/l and 0.06 mmol/l, respectively.

Table 2 shows characteristics and serum lipid profiles of nonfasting participants by TG groups. The differences in variables and serum lipid profiles between TG groups in nonfasting participants were similar to those in fasting participants. However, there were significant differences between concentrations of LDL-C (D) and LDL-C (F): mean concentrations of LDL-C (D) and LDL-C (F) were 3.08 and 3.01 mmol/l. A difference between them was found even in the normal TG group: mean nonfasting concentrations of LDL-C (D) and LDL-C (F) were 3.03 mmol/l and 3.01 mmol/dl, although the difference was only 0.02 mmol/l. Moreover, mean nonfasting concentrations of LDL-C (D) were significantly higher than those of LDL-C (F) in the moderate and high TG groups: the differences were 0.17 mmol/l and 0.33 mmol/l, respectively.

Both in fasting and nonfasting samples, LDL-C (D) concentrations showed strong linear correlations with LDL-C (F) concentrations: Pearson's coefficient (r) for fasting samples and that for nonfasting samples was 0.971 and 0.955, respectively (both $P<0.001$) (Fig. 1). The effect of TG concentrations on the difference between concentrations of LDL-C (D) and LDL-C (F) differed between fasting and nonfasting samples. In fasting samples, the difference in LDL-C concentrations was positively related to TG concentrations (Pearson's correlation coefficient $r=0.157$, $P<0.001$) and it increased by

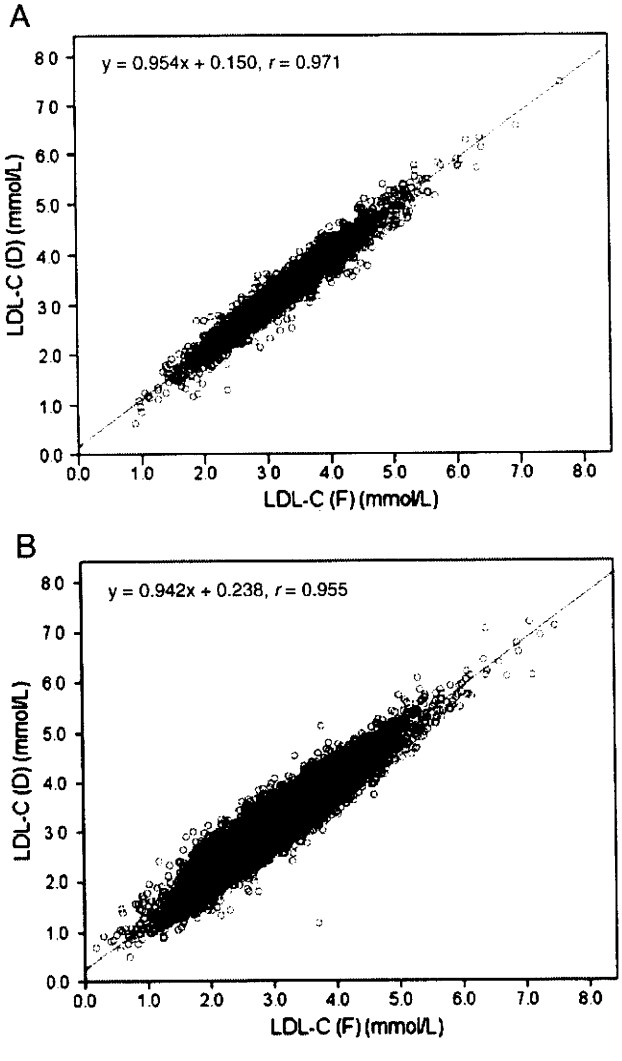

Fig. 1. Correlations between LDL-C (F) and LDL-C (D) in fasting participants (n = 3270) (A) and nonfasting participants (n = 17,294) (B). The solid lines represent regression lines.

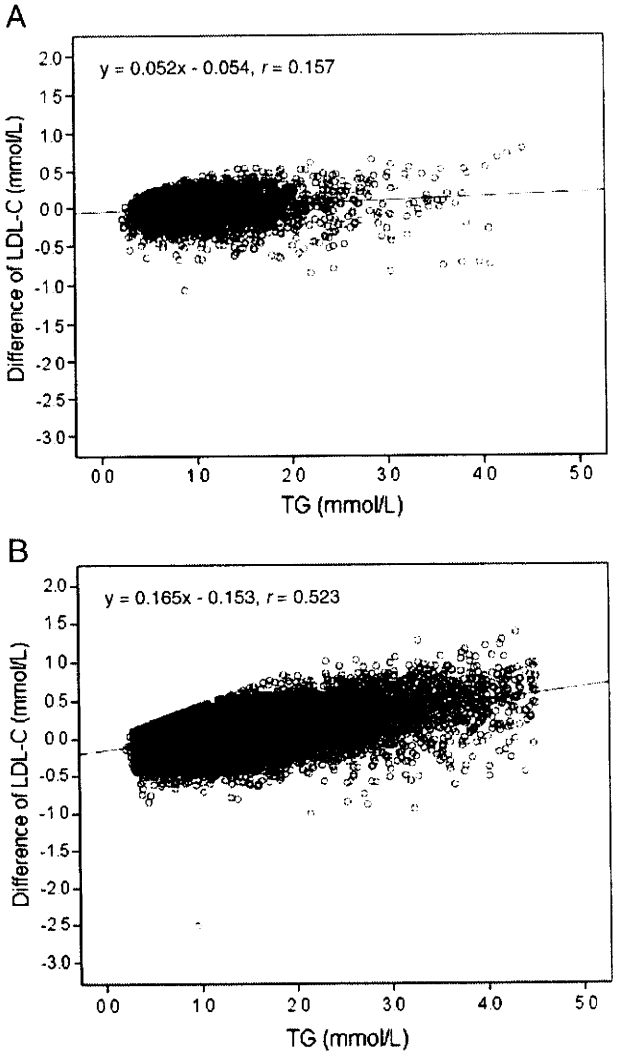

Fig. 2. Effect of increased TG concentrations on the difference in LDL-C concentrations between the homogeneous assay and the Friedewald formula in fasting participants (n = 3270) (A) and nonfasting participants (n = 17,294) (B). The difference in LDL-C, which is calculated by subtracting LDL-C concentrations by the Friedewald formula from those by the homogeneous assay, is plotted as a function of TG concentrations. The solid lines represent regression lines.

0.05 mmol/l with an increment of 1.00 mmol/l in TG concentration (Fig. 2A), whereas in nonfasting samples, the difference in LDL-C concentrations showed a relatively higher positive relation to TG concentrations compared with that in fasting samples (Pearson's correlation coefficient $r=0.523$, $P<0.001$) and increased by 0.17 mmol/l with an increment of 1.00 mmol/l in TG concentration (Fig. 2B).

Table 3 shows concordance between fasting LDL-C (F) and LDL-C (D) for classifying participants into NCEP categories of risk. Overall, 2772 (84.8%) of the 3270 participants showed concordant results. A total of 497 fasting participants (15.2%) differed by one NCEP group. Of these, the proportions of fasting participants being classified into one upper group by LDL-C (D) concentrations compared with LDL-C (F) concentrations were 54.4% (228 of 420) in the normal TG group, 59.3% (19 of 32) in the moderate high TG group and 62.2% (28 of 45) in the high TG group.

Table 4 shows concordance between nonfasting LDL-C (F) and LDL-C (D) for classifying participants into NCEP categories of risk. Overall, 14,366 (80.1%) of 17,924 participants showed concordant results. A total of 3550 nonfasting participants (19.8%) differed by one NCEP group. Of these, the proportions of nonfasting participants being

Table 3
Concordance of NCEP groups between LDL-C (F) levels and LDL-C (D) levels in fasting participants.

			LDL-C (D), mmol/L			
			<2.59	2.60–3.36	3.36–4.13	4.13+
All fasting participants (n=3270)						
LDL-C (F), mmol/L	<2.59	(n=632)	86.6	13.4	0	0
	2.60–3.36	(n=1273)	4.2	85.6	10.1	0
	3.36–4.13	(n=976)	0.1	10.5	83.2	6.3
	4.13+	(n=389)	0	0	17.0	83.0
Normal TG (<1.69 mmol/L) group (n=2906)						
LDL-C (F), mmol/L	<2.59	(n=571)	87.2	12.8	0	0
	2.60–3.36	(n=1128)	4.1	86.9	9.0	0
	3.36–4.13	(n=882)	0	10.3	83.7	6.0
	4.13+	(n=325)	0	0	16.9	83.1
Moderate high TG (1.69–2.26 mmol/L) group (n=224)						
LDL-C (F), mmol/L	<2.59	(n=33)	87.9	12.1	0	0
	2.60–3.36	(n=87)	2.3	82.8	14.9	0
	3.36–4.13	(n=60)	1.7	8.3	86.7	3.3
	4.13+	(n=44)	0	0	13.6	86.4
High TG (2.26–4.51 mmol/L) group (n=140)						
LDL-C (F), mmol/L	<2.59	(n=28)	71.4	28.6	0	0
	2.60–3.36	(n=58)	10.3	65.5	24.1	0
	3.36–4.13	(n=34)	0	17.6	64.7	17.6
	4.13+	(n=20)	0	0	25.0	75.0

TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; LDL-C (F), LDL-C calculated by the Friedewald formula; LDL-C (D), LDL-C measured by the enzymatic homogeneous assay.
Data are expressed as percentages of the number of participants being classified into each LDL-C (F) group.

classified into one upper group by LDL-C (D) concentrations compared with LDL-C (F) concentrations were 57.8% (1277 of 2210) in the normal TG group, 89.0% (541 of 608) in the moderate high TG group and 93.7% (686 of 732) in the high TG group.

Table 4
Concordance of NCEP groups between LDL-C (F) levels and LDL-C (D) levels in nonfasting participants.

			LDL-C (D), mmol/L			
			<2.59	2.60–3.36	3.36–4.13	4.13+
All nonfasting participants (n=17,924)						
LDL-C (F), mmol/L	<2.59	(n=5134)	79.2	20.7	0.1	0
	2.60–3.36	(n=7294)	5.4	79.8	14.7	0
	3.36–4.13	(n=4241)	0	10.6	80.8	8.7
	4.13+	(n=1255)	0	0	16.0	84.0
Normal TG (<1.69 mmol/L) group (n=13,831)						
LDL-C (F), mmol/L	<2.59	(n=3959)	86.0	14.0	0	0
	2.60–3.36	(n=5698)	6.5	84.2	9.2	0
	3.36–4.13	(n=3240)	0	12.2	81.7	6.0
	4.13+	(n=934)	0	0	17.6	82.4
Moderate high TG (1.69–2.26 mmol/L) group (n=2307)						
LDL-C (F), mmol/L	<2.59	(n=556)	64.2	35.8	0	0
	2.60–3.36	(n=935)	1.3	69.9	28.8	0
	3.36–4.13	(n=609)	0	5.4	82.6	12.0
	4.13+	(n=207)	0	0	10.6	89.4
High TG (2.26–4.51 mmol/L) group (n=1786)						
LDL-C (F), mmol/L	<2.59	(n=619)	49.3	49.9	0.8	0
	2.60–3.36	(n=661)	1.8	55.8	42.1	0.3
	3.36–4.13	(n=392)	0	4.8	69.9	25.3
	4.13+	(n=114)	0	0	13.2	86.8

TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; LDL-C (F), LDL-C calculated by the Friedewald formula; LDL-C (D), LDL-C measured by the enzymatic homogeneous assay.
Data are expressed as percentages of the number of participants being classified into each LDL-C (F) group.

Table 5
Odds ratios for discordance of NCEP groups between LDL-C (F) and LDL-C (D) for each factor.

	OR	(95% CI)	*P* value
ln TG (per 1-ln TG increase)	2.44	(2.26–2.63)	<0.001
Sex (men/women)	1.01	(0.92–1.11)	0.856
Age (per 1-year increase)	1.00	(0.99–1.00)	0.052
Body mass index (per 1-kg/m^2 increase)	1.00	(0.99–1.01)	0.663
Hypertension (presence/absence)	1.01	(0.93–1.09)	0.846
Diabetes (presence/absence)	1.21	(1.05–1.40)	0.009
Current smoking (yes/no)	0.96	(0.85–1.08)	0.473
Regular drinking (yes/no)	0.92	(0.82–1.02)	0.108
Nonfasting state (/fasting state)	1.18	(1.06–1.31)	0.002

LDL-C, low-density lipoprotein cholesterol; LDL-C (F), LDL-C calculated by the Friedewald formula; LDL-C (D), LDL-C measured by the enzymatic homogeneous assay; OR, odds ratio; CI, confidence interval; ln TG, logarithm-transformed triglyceride. The OR was adjusted for ln TG, sex, age, body mass index, hypertension, diabetes, current smoking, regular drinking and nonfasting state.

For all participants in the fasting and nonfasting groups, the logistic regression model revealed that the discordance of NCEP groups between LDL-C (F) and LDL-C (D) was associated with higher TG concentrations: the odds ratio (OR) (95% confidence interval (CI)) was 2.44 (2.26–2.63) with an increment of 1-ln TG. In addition, the presence of diabetes and nonfasting state was associated with the discordance between the two methods: ORs (95% CIs) were 1.21 (1.05–1.40) for the presence of diabetes and 1.18 (1.06–1.31) for the nonfasting state (Table 5).

4. Discussion

We demonstrated that LDL-C (D) concentrations had a significant correlation with LDL-C (F) concentrations and that NCEP categories of LDL-C (D) were highly coincident with those of LDL-C (F) in fasting samples. In addition, even in nonfasting samples, the correlation coefficient between LDL-C (D) and LDL-C (F) concentrations was more than 0.9 and the concordance rate of NCEP categories between the two LDL-C concentrations was approximately 80%. However, the discordance was increased in samples with higher TG concentrations, particularly in nonfasting samples.

Our findings in fasting samples are similar to results of previous studies in Western countries [28–30] and other countries [31–33] showing a strong correlation between concentrations of LDL-C (D) and LDL-C (F). Two studies have shown the concordance rate of calculated LDL-C and directly measured LDL-C for classifying participants into NCEP categories [29,30]. One of those studies used data for LDL-C concentrations measured by an immunoseparation method in 661 primary care patients who had TG concentrations less than 4.52 mmol/l (mean, 1.66 mmol/l) and who were not receiving medication for hyperlipidemia. The other study used data for LDL-C concentrations measured by an enzymatic homogeneous method in 19,777 female healthcare professionals who had TG concentrations <4.52 mmol/l (mean, 1.53 mmol/l) and no history of CVD or cancer. The concordance rates were 48.1% in the former study [29] and 79.3% in the latter study [30]. The concordance rate in the present study (84.8%) was similar to that in the latter study.

On the other hand, we showed that fasting LDL-C (D) concentrations were significantly higher than fasting LDL-C (F) concentrations when TG concentrations were ≥1.69 mmol/l, although the difference between the two LDL-C concentrations was small. Most previous studies [28,29,31–33], except for one study [30], have demonstrated that LDL-C concentrations determined by direct methods tend to be higher than those calculated by the Friedewald formula, especially in subjects with higher TG concentrations.

The Friedewald formula is known to underestimate LDL-C concentrations compared with those measured by β-quantification even in fasting samples with TG concentrations being <4.52 mmol/l [13–15].

The bias increases with increasing TG concentrations, starting at moderate high TG concentrations (1.5 or 2.0 mmol/l) [13,14]. Miller et al. simultaneously compared the Friedewald formula and the enzymatic homogeneous assay, which was the same one as that used in the present study, with β-quantification [12]. They showed that the homogeneous assay had less variability in LDL-C concentrations than did the Friedewald formula in TG concentrations between 3.39 and 6.77 mmol/l (300 and 600 mg/dl) [12]. Therefore, the reason for the higher LDL-C concentrations obtained by the direct assay in fasting samples with TG concentrations being ≥1.69 mmol/l may be due to underestimation of LDL-C concentrations by the Friedewald formula.

A recent cohort study suggested that epidemiological studies could use LDL-C concentrations calculated by the Friedewald formula in participants with nonfasting samples to assess the association of LDL-C with CVD risk [20]. However, some studies have also shown that LDL-C concentrations calculated by the Friedewald formula significantly decrease at the postprandial state [16–18] and that the LDL-C concentrations calculated by the Friedewald formula are also significantly lower than those measured by β-quantification in postprandial samples among the same individuals [16]. On the other hand, there was no significant difference in LDL-C concentrations measured by the same homogeneous assay as that used in our study between paired fasting and nonfasting samples from the same individuals [10,11]. Miller et al. showed that postprandial changes in LDL-C concentrations measured by the assay used in our study were similar to those measured by β-quantification, although LDL-C concentrations measured by the assay in postprandial samples were significantly lower than those in fasting samples [12]. Indeed, we also showed that nonfasting LDL-C concentrations calculated by the Friedewald formula were significantly lower than those measured by the homogeneous assay, particularly in samples with TG being 1.69 mmol/l or greater. The results suggest that the bias between the Friedewald formula and the direct homogeneous assay observed in our study is comparable to the bias between the Friedewald formula and β-quantification in the literature.

We also demonstrated that the discordance of NCEP categories between LDL-C (F) and LDL-C (D) was associated with diabetes as well as higher TG concentrations and nonfasting state. Some studies showed poor validity of the Friedewald formula in diabetic patients [34,35], whereas the homogeneous assay used in our study did not seem to be compromised in diabetic patients [36]. The above-mentioned findings indicate the possibility of less variability of this homogeneous assay than that of the Friedewald formula in nonfasting samples.

The present study has several limitations. First, most participants were in a nonfasting state. However, precisely because all participants were not at a fasting state, we believe that it was significant to perform a direct measurement of LDL-C concentrations. Second, we did not use β-quantification as the standard reference method. Thus, it is not clear whether the homogeneous assay overestimated the LDL-C concentration or whether the Friedewald formula underestimated the LDL-C concentration. Third, our subjects were an apparently healthy population; thus, it is unclear if our results would be applicable to diseased populations, particularly patients with hypertriglycemia or CVD. Finally, it is possible that our results may not be directly applicable to those obtained from other homogeneous assays because the present results were obtained from the direct assay by Daiichi Chemicals (currently Sekisui Medical).

In conclusion, we demonstrated a strong correlation between LDL-C concentrations measured by the direct homogeneous assay and those calculated by the Friedewald formula and high concordance rates of NCEP groups between the two LDL-C concentrations in fasting samples; however, it should be kept in mind that LDL-C concentrations measured by the direct homogeneous assay tend to be slightly higher than calculated LDL-C concentrations when TG concentrations are ≥1.69 mmol/l. We also showed less variability of the direct homogeneous assay than that of the Friedewald formula in large numbers of nonfasting samples. The bias between the Friedewald formula and the direct homogeneous assay observed in our study was comparable to the bias between the Friedewald formula and β-quantification in the literature. The findings suggest that the direct assay for LDL-C measurement can be used in epidemiological studies on the association of LDL-C with risk for CVD both in fasting and nonfasting samples. Future longitudinal studies are needed to clarify the utility of direct nonfasting LDL-C measurements as a predictor of CVD events.

Acknowledgments

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Community Dent Oral Epidemiol

COMMUNITY DENTISTRY AND ORAL EPIDEMIOLOGY

The association between neighborhood social capital and self-reported dentate status in elderly Japanese – The Ohsaki Cohort 2006 Study

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Aida J, Kuriyama S, Ohmori-Matsuda K, Hozawa A, Osaka K, Tsuji I. The association between neighborhood social capital and self-reported dentate status in elderly Japanese: The Ohsaki Cohort 2006 Study. Community Dent Oral Epidemiol 2010. © 2010 John Wiley & Sons A/S

Abstract – *Objectives:* Little is known about the influence of social capital on dental health. The aim of the present cross-sectional study was to determine the association between neighborhood social capital, individual social networks and social support and the number of remaining teeth in elderly Japanese. *Methods:* In December 2006, self-administered questionnaires were sent to 31 237 eligible community-dwelling individuals (response rate: 73.9%). Included in the analysis were 21 736 participants. Five neighborhood social capital variables were calculated from individual civic networks, sports and hobby networks, volunteer networks, friendship networks and social support variables. We used multilevel logistic regression models to estimate the odds ratio (OR) of having 20 or more teeth according to neighborhood social capital variables with adjustment for sex, age, individual social networks and social support, educational attainment, neighborhood educational level, dental health behavior, smoking status, history of diabetes and self-rated health. *Results:* The average age of the participants was 74.9 (standard deviation; 6.6) years, and 28.5% of them had 20 or more teeth. In the univariate multilevel model, there were statistically significant associations between neighborhood sports and hobby networks, friendship networks and self-reported dentate status. In the multivariable multilevel model, compared with participants living in lowest friendship network neighborhoods, those living in highest friendship network neighborhoods had an OR 1.17 (95% confidence interval, 1.04–1.30) times higher for having 20 or more teeth. *Conclusions:* There is a significant association between one network aspect of neighborhood social capital and individual dentate status regardless of individual social networks and social support.

Key words: dental status; multilevel analysis; remaining teeth; social capital; social epidemiology

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Increasing evidence suggests that a broad range of social determinants, not only biomedical factors, influence general health (1). Recent studies have revealed that social capital, a social determinant, has an important influence on health. Social capital has been defined as the features of social organization, such as civic participation, norms of reciprocity, and trust in others, that facilitate cooperation for mutual benefit (2). Social capital as a property of communities is distinguished from social capital as an attribute of individuals, which approximates the concepts of social support and

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social networks (3). It can be broadly defined as the density of trust, networks, or cooperation within a given community (4). In epidemiological studies, community-level social capital is often measured as an aggregated index of individual social networks or social support in each neighborhood (5), and a multilevel model is applied to distinguish the effects of individual- and community-level social capital on individual health (6).

Interest has also been focused on the importance of social determinants for oral health (7). However, only a few studies have examined the association between social capital and oral health. Previous cross-sectional studies examined the associations between social capital and oral health among 1302 students aged 14–15 years in Brazil: Empowerment as a social capital variable was investigated for its relationship with oral trauma (8) and dental caries (9). Another study examined the relationship between social capital and deciduous caries in 3301 3-year-old children: Multilevel analysis showed a beneficial contextual effect of social cohesion, one of the dimensions of social capital, on occurrence of deciduous caries (10). Association between the horizontal and vertical dimensions of social capital and the number of remaining teeth of 5560 elderly people was also examined, results showing a beneficial association between horizontal social capital and the number of remaining teeth (11).

Previous studies have suggested positive contextual effects on dental health. Both individual social networks and social support may mediate the association between neighborhood social capital and oral health. However, no study has simultaneously examined the association between neighborhood social capital, individual social networks and social support and oral health. These social determinants influence health status through subsequent life trajectories (12). The number of remaining teeth in elderly reflects the accumulative experience of dental caries, periodontal disease, dental injury, dental treatment and dental health behavior through their life-course. The aim of the present study was to determine the association between neighborhood social capital, individual social networks and social support and the number of remaining teeth in elderly Japanese.

Materials and methods

Setting and participants

This was a prospective cohort study, named The Ohsaki Cohort 2006 study, for which we analyzed cross-sectional data from the baseline survey of the study (13). The population and population density of Ohsaki city in 2005 were 138 141 and 173 person/km^2, respectively. The average age of the total resident population of the Ohsaki city was 44.2 years; 42.3 for men and 45.9 for women. Twenty-three percent of the population was 65 years or older. Among men, 19% were 65 years of age or older, while among women the rate was 27%. There were 69 208 workers; 19% in the manufacturing industry, 16% in the retail industry, 11% in the agricultural industry, 10% in the construction industry, and 8% in the medical and welfare industry. There were 15 hospitals, 85 clinics and 52 dental clinics.

There were two kinds of questionnaires in the Ohsaki cohort study: a questionnaire for persons aged 40–64 years and one for persons 65 years or older (13). Our study analyzed data obtained from those aged 65 years or older. The source population for the baseline survey comprised community-dwelling individuals aged 65 years or over, who were included in the Residential Registry for Ohsaki City. The Residential Registry identified 31 694 residents aged 65 years or older (12 750 men; 18 944 women) in Ohsaki city. The baseline survey was conducted from December 1 to December 15, 2006. A questionnaire was distributed by the heads of individual administrative districts to individual households and collected by mail. Of the 31 694 persons age 65 or over, 457 were found to be ineligible due to death, immigration, or hospitalization, yielding an eligible population of 31 237. The baseline questionnaires were collected from 23 394 persons, and valid responses were received from 23 091 (response rate: 73.9%, 9605 men and 13 486 women), who finally formed the study population of cohort participants. We excluded participants who did not respond to the items concerning administrative district (n = 252) and the number of remaining teeth (n = 1607). Consequently, the analyzed population consisted of 21 736 participants.

The Ohsaki city defined the municipal ordinance as administrative districts to improve efficiency of administration and citizens' welfare. The subjects were nested in 356 administrative districts, which we defined as neighborhoods. The analyzed population in each 356 administrative districts distributed as follows: 34 people = 25th percentile, 54 people = 50th percentile, 80 people = 75 percentile. The range of the response rates among the neighborhoods was relatively narrow. The distribution

of the response rates of the whole Ohsaki cohort study including the respondents aged 40–64 among the 356 administrative districts was as follows: 60.4% = 25th percentile, 67.1% = 50th percentile, 73.0% = 75 percentile.

The study protocol was reviewed and approved by the Ethics Committee of Tohoku University Graduate School of Medicine.

Baseline survey

The baseline questionnaires consisted of the following details in sequence: (i) the frailty checklist (i.e. the Kihon Checklist in Japanese) – a tool developed to screen for frailty – (14), (ii) history of diseases, (iii) health status over the last year, (iv) smoking status, (v) alcohol drinking status, (vi) dietary habits (15), (vii) past body weight, height and educational status, (viii) health status in general, (ix) pain, (x) daily activities, (xi) sports and exercise (16, 17), (xii) psychological distress (K6) (18, 19), (xiii) social support (20), (xiv) participation in community activities and (xv) dental status.

Measurement of individual-level variables

Participation in community activities was used as a source of social network variables. Four questions composed of four kinds of networks, namely, civic networks, sports and hobby networks, volunteer networks and friendship networks, were included as follows: (i) civic networks, for example, participation in civic activities, resident and neighborhood associations and so on, (ii) sports and hobby networks, for example, participation in sports activities, culture activities, lifelong learning and so on, (iii) volunteer networks, for example, participation in volunteer activities, welfare activities, sports coaching, disaster and crime prevention, environment activities and (iv) friendship networks, for example, participation in class reunions, social gatherings and so on. Choices as to the frequency of participation in each of the four kinds of network were 'never', 'several times a year', 'once a month', 'a few times a month', 'once a week', 'a few times a week' and 'more than 4 times a week'. When we included the responses in the models, they were divided into three categories as follows: (i) lowest social network (never participated), (ii) medium social network (participated several times a year) and (iii) highest social network (participated at least once a month).

The degree of social support available to each person was assessed by asking the following five questions (20): (i) Do you have someone with whom you can consult when you are in trouble?, (ii) Do you have someone with whom you can consult when your physical condition is not good?, (iii) Do you have someone who can help you with your daily housework?, (iv) Do you have someone who can take you to a hospital when you do not feel well? and (v) Do you have someone who can take care of you when you are ill in bed? This social support questionnaire consisted of five questions, each requiring a 'yes' or 'no' answer. This questionnaire was only available in Japanese. The validity and reliability of the questionnaire were not evaluated. The percentages of the respondents who answered 'no' to each five question were low: (i) 9.5%, (ii) 6.1%, (iii) 13.5%, (iv) 6.9% and (v) 12.7%. Therefore we aggregated the five questions into one social support variable, which had three categories as follows: (i) lowest social support (responding 'yes' to less than three questions), (ii) medium social support (responding 'yes' to four questions) and (iii) highest social support (responding 'yes' to five questions).

The self-reported number of remaining teeth was used as an index of the dentate status. Retention of a minimum of 20 functional teeth at age 65 years or over was an oral health goal specified in the WHO and Federation Dentaire Internationale 'Global Goals for Oral Health in the year 2000' (21). The goal set by the Japan Dental Association was retention of a minimum of 20 functional teeth at the age of 80. Therefore, the number of remaining teeth, the outcome variable of this study, was used as a dichotomous variable: either ≥20 teeth or ≤19 teeth.

We also asked about dental health behavior: daily frequency of daily tooth brushing (free-answer question divided into three categories as follows: (i) less than 2 times, (ii) 2 times and (iii) 3 times or more), duration of tooth brushing at one time (<3 min, 3–5 min, 5 min or more), the use of dental floss or interdental brushes (yes, no), having a dental check-up at least once a year (yes, no), and frequency of intake of sweet foods (almost never, 1–2 times per month, 1–2 times per week, 3–4 times per week, almost every day and divided into three categories as follows: (i) 1–2 times per month or less, (ii) 1–4 times per week and (iii) almost every day). Smoking status (never, former, current) and history of diabetes (yes, no) were also investigated as risk factors of periodontal disease. As people in good health may tend to have good social networks, and people in poor health may tend to have

much social support, the questionnaire also asked about self-rated health (excellent, good, fair, poor, and very poor and divided into three categories as follows: (i) good, (ii) fair and (iii) poor) as a covariate for social networks and social support. We also investigated the number of years of educational attainment since 6 years of age as an indicator of socioeconomic status. The number of years were divided into four categories as follows: (i) ≤9 years, (ii) 10–12 years, (iii) 13–15 years and (iv) ≥16 years.

Measurement of neighborhood-level variables

Social capital can be broken down into cognitive and structural components. We used social support and social network aspects of social capital, because perceived social support is regarded as a part of cognitive social capital (5) and social network is regarded as a part of structural social capital (5).

We created neighborhood variables by aggregating individual level data. Therefore, to determine the association between neighborhood social capital and health outcome, we adjusted for individual social network and support variables (22). All neighborhood-level variables were calculated on the basis of 356 administrative districts.

We focused on the proportion of respondents who had one or more social networks. The proportions of participants in each neighborhood who answered social network questions with answers other than 'never' were calculated for each of the four kinds of networks. The proportion of participants in each neighborhood who answered 'yes' to all five social support questions was also calculated. The neighborhoods were divided into three categories (lowest, medium or highest) based on the 33rd and 66th percentiles of each of the four social network rates and one social support rate. These five variables were used as neighborhood social capital variables.

Both individual and neighborhood socioeconomic status were considered to be associated with social capital (23). Therefore, both individual and neighborhood educational variables were included in the model. Neighborhood educational level was used as an index of neighborhood socioeconomic status. The mean number of years of education was calculated for each neighborhood. The neighborhoods were divided into three categories (lowest, medium, or highest) based on the 33rd and 66th percentiles of the average number of years of education.

Within Japan, there is no community fluoridated water supply. Therefore, we did not include water fluoridation as a variable in the multilevel models.

Analysis

In our data set, individuals (first-level) were nested in communities (second-level). We applied multilevel models (24, 25) to estimate the association of neighborhood social capital, individual social networks and social support with individual dentate status, controlling for one another, the contextual effect of neighborhood educational level and the compositional effects of individual educational attainment, health behavior and self-rated health. Multilevel logistic regression models with random intercepts and fixed slopes were estimated using the MLwiN 2.10 software package (26). The number of remaining teeth (≥20 or ≤19) was used as the outcome variable. Individual and neighborhood fixed parameters were converted to odds ratios (OR) with 95% confidence intervals (95% CI). In model 1, adjustments were made for all neighborhood social capital variables simultaneously to check the fixed and random parameters. In model 2, we included sex, age, all neighborhood social capital variables, educational level, individual social networks and social support and educational attainment variables simultaneously. In model 3, adjustments were made for sex, age, and all explanatory variables simultaneously. The univariate multilevel OR and random parameter of the intercept-only model were also estimated.

Results

The average age of the 21 736 participants (9126 male and 12 610 female) in the 356 administrative neighborhoods was 74.9 (standard deviation; 6.6) years. The prevalence of respondents having 20 or more teeth and that of those having 19 or less teeth were 28.5% (95% confidence interval; 27.9–29.1) and 71.5% (95% CI; 70.9–72.1), respectively.

Table 1 shows the distribution and univariate association between explanation variables and dentate status. Univariate OR were calculated by multilevel logistic regression analyses. There were statistically significant associations between neighborhood sports and hobby networks, friendship networks, educational level and dentate status. Four individual social network variables, educational attainment, all health behavior variables,

Table 1. Distribution of characteristics of individual- and neighborhood-level variables and univariate multilevel OR for remaining teeth

Variables		No. of participants who had 20 or more teeth (%)	No. of participants who had 19 or less teeth (%)	Univariate multilevel OR (95% CI)	*P*-value
Neighborhood-level variables					
Social capital					
Civic network	Lowest	2113 (28.5)	5289 (71.5)	1.00 (referent)	
	Medium	2030 (28.5)	5090 (71.5)	1.00 (1.00–1.00)	0.964
	Highest	2054 (28.5)	5160 (71.5)	1.03 (0.93–1.14)	0.568
Sports and hobby network	Lowest	1808 (25.1)	5407 (74.9)	1.00 (referent)	
	Medium	2089 (28.8)	5160 (71.2)	1.22 (1.10–1.35)	<0.001
	Highest	2300 (31.6)	4972 (68.4)	1.37 (1.24–1.51)	<0.001
Volunteer network	Lowest	2026 (27.4)	5366 (72.6)	1.00 (referent)	
	Medium	2084 (28.9)	5134 (71.1)	1.07 (0.97–1.18)	0.181
	Highest	2087 (29.3)	5039 (70.7)	1.10 (0.99–1.22)	0.070
Friendship network	Lowest	1798 (25.0)	5394 (75.0)	1.00 (referent)	
	Medium	2074 (28.5)	5195 (71.5)	1.19 (1.08–1.31)	<0.001
	Highest	2325 (32.0)	4950 (68.0)	1.41 (1.28–1.56)	<0.001
Social support	Lowest	2079 (28.4)	5229 (71.6)	1.00 (referent)	
	Medium	2085 (28.8)	5163 (71.2)	1.04 (0.93–1.17)	0.509
	Highest	2033 (28.3)	5147 (71.7)	1.00 (1.00–1.00)	0.982
Neighborhood educational level	Lowest	1744 (24.3)	5429 (75.7)	1.00 (referent)	
	Medium	2086 (28.6)	5212 (71.4)	1.23 (1.12–1.35)	<0.001
	Highest	2367 (32.6)	4898 (67.4)	1.49 (1.36–1.64)	<0.001
Individual-level variables					
Social network					
Civic network	Lowest	2677 (25.1)	7999 (74.9)	1.00 (referent)	
	Medium	1151 (32.9)	2347 (67.1)	1.49 (1.37–1.62)	<0.001
	Highest	1717 (36.5)	2982 (63.5)	1.76 (1.63–1.90)	<0.001
Sports and hobby network	Lowest	2577 (24.0)	8154 (76.0)	1.00 (referent)	
	Medium	643 (33.6)	1270 (66.4)	1.61 (1.45–1.79)	<0.001
	Highest	2264 (38.2)	3655 (61.8)	1.93 (1.80–2.07)	<0.001
Volunteer network	Lowest	3390 (26.1)	9614 (73.9)	1.00 (referent)	
	Medium	885 (35.8)	1584 (64.2)	1.61 (1.47–1.76)	<0.001
	Highest	1057 (41.4)	1494 (58.6)	2.01 (1.84–2.20)	<0.001
Friendship network	Lowest	2383 (23.6)	7698 (76.4)	1.00 (referent)	
	Medium	2157 (36.3)	3777 (63.7)	1.84 (1.71–1.98)	<0.001
	Highest	700 (38.7)	1108 (61.3)	2.02 (1.82–2.25)	<0.001
Social support	Lowest	903 (28.3)	2290 (71.7)	1.00 (referent)	
	Medium	672 (27.3)	1792 (72.7)	0.96 (0.85–1.08)	0.493
	Highest	4558 (28.9)	11 220 (71.1)	1.04 (0.95–1.14)	0.383
Educational attainment	≤9 years	1534 (23.3)	5063 (76.7)	1.00 (referent)	
	10–12 years	2522 (30.4)	5787 (69.6)	1.41 (1.31–1.52)	<0.001
	13–15 years	1283 (34.3)	2458 (65.7)	1.69 (1.55–1.85)	<0.001
	≥16 years	474 (41.1)	680 (58.9)	2.18 (1.91–2.49)	<0.001
Age	65–69	2348 (45.3)	2834 (54.7)	1.00 (referent)	
	70–74	2088 (33.6)	4118 (66.4)	0.61 (0.57–0.66)	<0.001
	75–79	1168 (22.2)	4099 (77.8)	0.34 (0.32–0.38)	<0.001
	80–84	431 (13.8)	2687 (86.2)	0.19 (0.17–0.22)	<0.001
	≥85	162 (8.3)	1801 (91.7)	0.11 (0.09–0.13)	<0.001
Sex	Female	3309 (26.2)	9301 (73.8)	1.00 (referent)	
	Male	2888 (31.6)	6238 (68.4)	1.30 (1.22–1.38)	<0.001
Health behavior					
Daily frequency of toothbrushing	< 2 times	1986 (23.9)	6327 (76.1)	1.00 (referent)	
	2 times	2649 (34.6)	5018 (65.4)	1.65 (1.54–1.77)	<0.001
	≥3 times	1213 (31.9)	2588 (68.1)	1.45 (1.33–1.58)	<0.001
Brushing time (minutes)	<3 min	3243 (25.3)	9584 (74.7)	1.00 (referent)	
	3–5 min	2258 (37.2)	3818 (62.8)	1.74 (1.63–1.86)	<0.001
	≥5 min	599 (46.1)	700 (53.9)	2.50 (2.22–2.81)	<0.001
Use of dental floss or interdental brushes	No	4784 (25.0)	14 318 (75.0)	1.00 (referent)	
	Yes	1413 (53.6)	1221 (46.4)	3.39 (3.12–3.69)	<0.001

Table 1. Continued

Variables		No. of participants who had 20 or more teeth (%)	No. of participants who had 19 or less teeth (%)	Univariate multilevel OR (95% CI)	*P*-value
Dental check-up at least once a year	No	3697 (25.3)	10 937 (74.7)	1.00 (referent)	<0.001
	Yes	2292 (40.6)	3355 (59.4)	2.00 (1.87–2.14)	<0.001
Frequency of intake of sweet foods	Almost every day	813 (22.8)	2747 (77.2)	1.00 (referent)	
	1–4 times/ week	2984 (29.5)	7117 (70.5)	1.41 (1.29–1.54)	<0.001
	≤1–2 times/ month	1961 (31.7)	4225 (68.3)	1.56 (1.42–1.72)	<0.001
Smoking status	Current	592 (24.1)	1861 (75.9)	1.00 (referent)	
	Past	1408 (28.3)	3574 (71.7)	1.23 (1.10–1.38)	<0.001
	Never	3453 (30.2)	7964 (69.8)	1.38 (1.25–1.53)	<0.001
History of diabetes	Yes	671 (25.7)	1943 (74.3)	1.00 (referent)	
	No	5526 (28.9)	13 596 (71.1)	1.20 (1.09–1.32)	<0.001
Self-rated health	Poor	1006 (21.6)	3655 (78.4)	1.00 (referent)	
	Fair	2985 (29.3)	7211 (70.7)	1.51 (1.39–1.64)	<0.001
	Good	2138 (32.6)	4416 (67.4)	1.75 (1.60–1.91)	<0.001

history of diabetes and self-rated health also showed significant associations.

We compared the characteristics of participants in the lowest and highest categories of neighborhood social capital, individual social networks and support variables (Table 2). We showed the percentage of participants within one category of each variable: for example, 41.6% of male participants were included in the lowest civic network category. In contrast, 59.4% (not shown in the table) of female participants were included in the lowest civic network category. There were no marked differences between the civic network aspects of social capital and the characteristics of the participants. A higher proportion of participants residing in the highest sports and hobby network neighborhoods and highest friendship network neighborhoods had 20 or more teeth, lived in the highest educational level neighborhoods, and had better oral health behavior, except for the frequency of intake of sweet foods. A higher proportion of participants residing in the highest volunteer network neighborhoods lived in the highest educational level neighborhoods. There were no marked differences between the social support aspects of social capital and the characteristics of the participants. A higher proportion of participants in the highest category of civic networks had 20 or more teeth, had a longer period of education, had better oral health behavior except for the frequency of intake of sweet foods, and had good self-rated health. A higher proportion of participants in the highest category of sports and hobby networks, volunteer networks and friendship networks was male, had 20 or more teeth, lived in neighborhoods with a higher educational level, had a longer period of education, had better oral health behavior except for the frequency of intake of sweet foods, and had good self-rated health. A higher proportion of participants in the highest category of social support had good self-rated health.

Table 3 shows the results of multivariable multilevel logistic regression analyses. Model 1 included all neighborhood social capital variables simultaneously. There were beneficial statistically significant associations between neighborhood sports and hobby networks, friendship networks and dentate status. Model 2 included sex, age, all neighborhood social capital variables, educational level, individual social networks and social support and educational attainment variables simultaneously. After adjusting for neighborhood educational level, individual social networks, social support and education attainment, neighborhood friendship network variable still had a significant association with dentate status. Model 3 adjusted for sex, age, and all explanatory variables simultaneously. Compared with the participants living in lowest friendship network neighborhoods, those living in medium friendship network neighborhoods had an OR 1.10 times higher for having 20 or more teeth and those living in highest friendship network neighborhoods had an OR 1.17 times higher for having 20 or more teeth. Compared with the participants living in the lowest educational level neighborhoods, those living in the highest educational level neighborhoods had an OR 1.17 times higher for having 20 or more teeth.

Table 2. Demographical distribution of lowest and highest categories of neighborhood social capital, individual social networks and social support variables

	Civic network		Sports and hobby network		Volunteer network		Friendship network		Social support	
	Lowest	Highest	Lowest	Highest	Lowest	Highest	Lowest	Highest	Lowest	Highest
Neighborhood social capital variables										
Number of participants	7402	7214	7215	7272	7392	7126	7192	7275	7308	7180
Age, year, mean ± SD	74.9 ± 6.6	75.1 ± 6.6	75.4 ± 6.6	74.5 ± 6.5	75.1 ± 6.6	74.7 ± 6.6	75.4 ± 6.7	74.5 ± 6.5	74.7 ± 6.5	75.2 ± 6.7
Sex, Male (%)	41.6	41.6	41.5	42.8	41.2	42.7	41.0	42.8	41.9	41.4
Number of remaining teeth, ≥20 teeth (%)	28.5	28.5	25.1	31.6	27.4	29.3	25.0	32.0	28.4	28.3
Neighborhood educational level, highest (%)	31.2	34.4	14.3	50.6	26.3	36.7	14.0	55.7	34.1	28.6
Education attainment, ≥16 years (%)	5.3	5.2	3.2	6.8	4.6	5.3	3.4	7.3	5.6	4.5
Daily frequency of toothbrushing, ≥3 times (%)	19.8	18.3	16.3	21.2	18.4	19.5	16.4	21.3	18.4	19.3
Brushing time (minutes), ≥5 minutes (%)	6.9	5.9	5.5	7.0	6.4	6.3	5.7	6.9	6.9	5.9
Use of dental floss or interdental brushes, yes (%)	13.0	11.0	9.6	14.4	11.8	11.8	10.0	14.1	12.4	11.4
Dental check-up at least once a year, yes (%)	27.9	27.5	25.5	29.6	27.6	29.2	26.0	29.8	28.5	27.0
Frequency of intake of sweet foods, 1–2 times/month	31.0	30.1	31.6	31.0	31.9	31.1	31.9	29.9	31.5	29.7
Smoking status, never, (%)	60.3	61.8	61.6	59.8	60.3	60.9	61.6	59.8	59.3	62.4
History of diabetes, no (%)	87.6	88.2	88.5	87.4	88.0	88.2	88.1	87.8	87.5	88.5
Self-rated health, good (%)	30.3	31.6	29.1	31.5	29.8	31.0	29.3	31.3	29.4	31.6
Individual social network and support variables										
Number of participants	10 676	4699	10 731	5919	13 004	2551	10 081	1808	3193	15 778
Age, year, mean ± SD	75.8 ± 7.1	73.3 ± 5.5	75.9 ± 7.1	73.1 ± 5.6	75.5 ± 6.9	72.3 ± 5	76.1 ± 7.2	73.1 ± 5.3	74.2 ± 5.9	75.1 ± 6.8
Sex, male (%)	37.8	51.4	39.0	45.2	38.2	58.6	37.3	53.3	42.8	41.4
Number of remaining teeth, ≥20 teeth (%)	25.1	36.5	24.0	38.2	26.1	41.4	23.6	38.7	28.3	28.9
Neighborhood educational level, highest (%)	33.5	33.7	31.2	39.7	33.7	37.4	31.7	41.1	34.6	33.1
Education attainment, ≥16 years (%)	4.8	7.2	3.8	9.1	4.8	10.5	3.9	11.3	5.5	5.3
Frequency of toothbrushing, ≥3 times (%)	18.2	20.2	17.0	23.9	18.0	24.4	17.0	23.2	18.3	19.4
Brushing time (minutes), ≥5 min (%)	6.2	6.5	5.7	7.9	6.1	8.2	5.7	8.0	7.7	6.2
Use of dental floss or interdental brushes, yes (%)	10.9	14.9	8.9	20.5	11.4	17.9	9.7	17.3	13.8	11.8
Dental check-up at least once a year, yes (%)	23.0	33.6	21.6	36.3	23.5	38.1	21.5	37.8	28.7	27.2
Frequency of intake of sweet foods, 1–2 times/month	32.2	28.6	32.2	28.4	31.5	28.0	32.2	25.9	38.3	29.0
Smoking status, never (%)	63.2	57.3	62.9	60.4	63.5	53.5	63.8	57.2	56.9	62.1
History of diabetes, no (%)	87.4	88.5	87.2	88.6	87.5	88.4	87.3	88.5	87.8	88.0
Self-rated health, good (%)	26.1	41.0	25.8	40.4	27.5	46.2	25.5	46.3	23.8	32.8

Table 3. Association of remaining teeth with individual- and neighborhood-level variables determined by using multivariable multilevel logistic regression models

Variables		Model 1		Model 2		Model 3	
		OR (95% CI)[a]	*P*-value	OR (95% CI)[b]	*P*-value	OR (95% CI)[c]	*P*-value
Neighborhood-level variables							
Social capital							
Civic network	Lowest	1.00 (referent)		1.00 (referent)		1.00 (referent)	
	Medium	0.94 (0.85–1.04)	0.224	0.94 (0.85–1.03)	0.180	0.96 (0.87–1.06)	0.399
	Highest	0.87 (0.77–0.98)	0.020	0.94 (0.84–1.04)	0.236	0.99 (0.89–1.10)	0.824
Sports and hobby network	Lowest	1.00 (referent)		1.00 (referent)		1.00 (referent)	
	Medium	1.16 (1.05–1.28)	0.004	1.03 (0.94–1.14)	0.523	1.02 (0.93–1.12)	0.687
	Highest	1.29 (1.16–1.44)	$P < 0.001$	1.06 (0.95–1.18)	0.280	1.04 (0.94–1.16)	0.436
Volunteer network	Lowest	1.00 (referent)		1.00 (referent)		1.00 (referent)	
	Medium	0.95 (0.85–1.06)	0.365	0.95 (0.86–1.05)	0.350	0.96 (0.87–1.06)	0.372
	Highest	0.92 (0.81–1.05)	0.212	0.92 (0.82–1.03)	0.142	0.92 (0.82–1.03)	0.129
Friendship network	Lowest	1.00 (referent)		1.00 (referent)		1.00 (referent)	
	Medium	1.2 (1.08–1.33)	0.001	1.10 (1.00–1.22)	0.061	1.10 (1.00–1.21)	0.057
	Highest	1.37 (1.22–1.54)	$P < 0.001$	1.17 (1.04–1.31)	0.008	1.17 (1.04–1.30)	0.007
Social support	Lowest	1.00 (referent)		1.00 (referent)		1.00 (referent)	
	Medium	1.06 (0.97–1.16)	0.217	1.03 (0.94–1.12)	0.573	1.01 (0.93–1.10)	0.833
	Highest	1.01 (0.86–1.19)	0.904	1.02 (0.93–1.12)	0.657	1.01 (0.92–1.10)	0.885
Neighborhood educational level	Lowest			1.00 (referent)		1.00 (referent)	
	Medium			1.10 (1.01–1.21)	0.039	1.07 (0.98–1.17)	0.132
	Highest			1.22 (1.10–1.35)	$P < 0.001$	1.17 (1.06–1.29)	0.002
Individual-level variables							
Social network							
Civic network	Lowest			1.00 (referent)		1.00 (referent)	
	Medium			1.05 (0.95–1.16)	0.310	1.01 (0.91–1.12)	0.907
	Highest			1.08 (0.98–1.20)	0.123	1.07 (0.97–1.19)	0.187
Sports and hobby network	Lowest			1.00 (referent)		1.00 (referent)	
	Medium			1.07 (0.95–1.20)	0.284	0.99 (0.87–1.12)	0.862
	Highest			1.32 (1.21–1.44)	$P < 0.001$	1.12 (1.02–1.22)	0.019
Volunteer network	Lowest			1.00 (referent)		1.00 (referent)	
	Medium			1.00 (0.90–1.12)	0.930	0.98 (0.88–1.10)	0.788
	Highest			1.13 (1.01–1.27)	0.034	1.09 (0.97–1.23)	0.146
Friendship network	Lowest			1.00 (referent)		1.00 (referent)	
	Medium			1.23 (1.13–1.34)	$P < 0.001$	1.14 (1.04–1.25)	0.004
	Highest			1.23 (1.09–1.40)	0.001	1.14 (0.99–1.30)	0.060
Social support	Lowest			1.00 (referent)		1.00 (referent)	
	Medium			0.93 (0.82–1.05)	0.219	0.93 (0.82–1.05)	0.256
	Highest			1.03 (0.94–1.12)	0.542	1.03 (0.94–1.13)	0.542
Educational attainment	≤9 years			1.00 (referent)		1.00 (referent)	
	10–12 years			1.06 (0.98–1.14)	0.170	0.99 (0.91–1.08)	0.840
	13–15 years			1.14 (1.03–1.26)	0.009	1.04 (0.94–1.15)	0.482
	≥16 years			1.31 (1.14–1.51)	$P < 0.001$	1.12 (0.97–1.30)	0.136
Health behavior							
Daily frequency of toothbrushing	<2 times					1.00 (referent)	
	2 times					1.23 (1.14–1.33)	$P < 0.001$
	3 times≥					0.95 (0.86–1.05)	0.289
Brushing time (minutes)	<3 min					1.00 (referent)	
	3–5 min					1.44 (1.34–1.55)	$P < 0.001$
	5 min ≥					1.81 (1.59–2.05)	$P < 0.001$
Use of dental floss or interdental brushes	No					1.00 (referent)	
	Yes					2.07 (1.88–2.27)	$P < 0.001$
Dental check-up at least once a year	No					1.00 (referent)	
	Yes					1.41 (1.31–1.52)	$P < 0.001$

Table 3. Continued

Variables		Model 1 OR (95% CI)[a]	Model 1 *P*-value	Model 2 OR (95% CI)[b]	Model 2 *P*-value	Model 3 OR (95% CI)[c]	Model 3 *P*-value
Frequency of intake of sweet foods	Almost every day					1.00 (referent)	
	1–4 times/week					1.28 (1.16–1.41)	$P < 0.001$
	≤1–2 times/month					1.45 (1.31–1.61)	$P < 0.001$
Smoking status	Current					1.00 (referent)	
	Past					1.42 (1.26–1.60)	$P < 0.001$
	Never					2.40 (2.12–2.72)	$P < 0.001$
History of diabetes	Yes					1.00 (referent)	
	No					1.16 (1.04–1.28)	0.006
Self-rated health	Poor					1.00 (referent)	
	Fair					1.16 (1.06–1.27)	0.002
	Good					1.37 (1.24–1.51)	$P < 0.001$

[a]Adjust for all neighborhood social capital variables simultaneously.
[b]Adjust for sex, age, all neighborhood social capital, educational level, individual social networks and social support and educational attainment variables simultaneously.
[c]Adjust for sex, age, and all explanatory variables simultaneously.

Individual- and community-level social support variables did not show any significant associations. The result of the intercept-only multilevel model showed significant neighborhood level variance ($\sigma^2_{\mu 0}$ (standard error) = 0.075 (0.012), $P < 0.001$). This means that dentate status significantly differed between neighborhoods. Since the neighborhood social capital variables explained the neighborhood level variance, neighborhood level variance in model 1 was decreased ($\sigma^2_{\mu 0}$ (SD) = 0.044 (0.009), $P < 0.001$). The neighborhood level variance in the model 2 was 0.023 (SD = 0.008, $P = 0.004$). The neighborhood level variance in the model 3 was 0.012 (SD = 0.007, $P = 0.093$).

Discussion

To our knowledge, this large-scale cross-sectional study is the first to have simultaneously examined the association between neighborhood social capital, individual social networks, and individual social support and oral health. After adjustment for individual- and neighborhood-level covariables, one aspect of neighborhood-level high social capital was found to be significantly associated with having 20 or more teeth. This result suggests that one aspect of neighborhood social capital has a contextual effect on the self-reported dentate status of elderly people. In addition, neither individual nor neighborhood social support variables showed any significant association. It was suggested that the network aspect of social capital has a more important effect on dentate status than the social support aspect of social capital. Only the friendship network neighborhoods had a statistically significant but small OR (1.17). However, because neighborhood social capital has an influence on all the residents in each area, this result was meaningful.

There were several plausible pathways linking social capital to health outcomes. At first, social capital may affect individual health by influencing health-related behavior through promotion of more rapid diffusion of health information and by exerting social control over deviant health-related behavior (27). For example, cigarette smoking by peers is among the best predictors of smoking in adolescents (28). Second, social capital may affect health by influencing access to local service and amenities (27). Access to service such as transportation, dental clinics and community health centers could affect dental health. Third, there are associations between social capital and psychological distress (29). Psychological distress is a risk indicator of periodontal disease (30, 31). In addition, psychological distress can lead to an increase in smoking and/or consumption of 'comfort foods' such as confectionary (12). These behaviors may increase the risk of periodontal disease and dental caries respectively. In addition, neighborhoods with higher social capital are less violent (32) with fewer dental injuries (8). In our results, only friendship-network-based social capital showed a significant beneficial association, while other kinds of network variables did not. This may suggest that access to dental clinics as well as dental health behavior and stress are influenced mainly by close friends.

A multilevel approach enables demonstration of whether social capital has an independent 'contextual' effect on individual health outcomes, regardless of individual characteristics, including individual-level social networks and social support (6). Our results emphasize the importance of community actions or governmental investment to establish amenities that promote the building of social capital, especially that based on friendship networks. In addition, our results showed a significant neighborhood level variation of dentate status. Approaches for influencing not only individual risk factors but also the underlying social determinants of oral health through upstream public health interventions, such as water fluoridation or a tobacco tax policy, are needed to reduce neighborhood level variation on dentate status by improving the dental health of the population (7).

Broadly speaking, there are two ways of measuring neighborhood variables: (i) aggregating individual level data and (ii) directly measuring the properties of groups (22). However, it is difficult to separate collective explanation about the neighborhood effect from the contextual explanation (33). Aggregating collective measurements have been generally used to estimate the neighborhood contextual effect (6). We determined the association between neighborhood level collective variables and health outcome with adjustment for individual level variables (22).

Our study had some limitations. First, although it demonstrated an association between one aspect of social capital and dentate health, a cross-sectional study showed no causal inference, and therefore prospective follow-up studies are required. Second, it could be argued that the questionnaire used in this study did not provide a full picture of social capital. There is still debate about the definition and measurement of social capital (6). Various types of social capital such as bonding, bridging and linking should be measured. Third, it could be argued that the questionnaire used in this study did not provide a full picture of the differences in quantity and quality of dental health behavior and dentate status. Because of our measure of remaining teeth was discrete variable, it could not describe the full picture of dental health status. In addition, we could not consider occlusal pairs of the teeth of respondents. Although we used many covariables pertaining to dental health behavior, more detailed variables, such as use of fluoride toothpaste, are needed. Additionally, variation of dental health behavior and dentate status were needed. Although previous studies in other countries have shown that the general population can provide accurate self-reported estimates of the number of remaining teeth (34), validation among Japanese elderly was needed. This study could not include other measurements of neighborhood and individual social capital or dental health variables. Therefore, there may be residual bias. Our study had some strength. Because dental health has an important influence on personal appearance and speaking ability, people with a poor dentate health status might have a less well developed social network. Our multilevel study showed that regardless of individual social networks, dental health behavior and self-rated health, neighborhood friendship networks were significantly associated with individual dentate status. This result was reliable because our study had a large number of participants and a sufficient response rate.

The present study has demonstrated a significant association between one aspect of neighborhood social capital and individual dentate status in the elderly population. In addition, only the network aspect of social capital, and not the social support aspect, was found to have a significant association with dentate status.

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