the H7700 device in 1994–2006. The participants were considered diabetic if they had a plasma glucose of ≥6.1 mmol/L in a fasted state or ≥7.8 mmol/L in a non-fasted state, or if they were being treated for diabetes mellitus. The laboratory participated in external standardization and successfully met the criteria for precision accuracy for the measurement of blood samples, as established by the Japan Medical Association, the Japanese Association of Medical Technologists, and the Japan Society of Health Evaluation and Promotion.

Blood pressure was measured on the right arm of seated participants who had rested for more than 5 min; trained observers obtained these measurements using a standard mercury sphygmomanometer in 1993–2004 and an automated sphygmomanometer in 2005–2006. When the systolic blood pressure was >150 mm Hg or the diastolic blood pressure was >90 mm Hg, a second measurement was obtained after the subject took several deep breaths. The lower values, which were almost always observed during the second measurement, were used for the analyses. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication. CVD risk factors were defined as hypertension, dyslipidemia, and diabetes.

Lastly, we conducted an interview to ascertain the number of cigarettes smoked per day, the typical weekly alcohol intake (converted to grams of ethanol per day), and the history of CVD and CKD.

Statistical analysis

The participants were classified into the following categories with regard to their BMI (kg/m^2): <18.5; 18.5–20.9; 21.0–22.9; 23.0–24.9; 25.0–26.9; 27.0–29.9; or ≥30.0. To compare the participants' physical characteristics according to the BMI categories, one-way analysis of variance was used for continuous variables, and a χ^2-test was used for categorical variables. The Cox proportional hazards regression model was used to calculate hazard ratios (HRs) and the 95% confidence intervals (CIs) of risk of development of stage ≥3 CKD relative to the BMI categories in comparison to the reference group, 21.0–22.9 kg/m^2. A BMI of 22 kg/m^2 is commonly set as the optimal body size in Japan.[16] The analyses were stratified by sex and age groups (40–59 and 60–79 years old).

We used two multivariate-adjusted models. In model one, covariates included age and the potential confounders of cigarette smoking (never, former, current [1–19 cigarettes/day or ≥20 cigarettes/day]) and typical alcohol intake (never, sometimes, everyday [<56 g/day or ≥56 g/day]). In model two, potential mediators were added to model one. Potential mediators included systolic blood pressure, the use of antihypertensive medication (yes or no), triglyceride level (log-transformed), serum total cholesterol, serum HDL cholesterol, the use of lipid medication (yes or no), blood glucose status (normal [<6.1 mmol/L in a fasted state or <7.8 mmol/L in a non-fasted state], borderline [6.1–7.0 mmol/L in a fasted state or 7.8–11.1 mmol/L in a non-fasted state], hyperglycemic [>7.0 mmol/L in a fasted state or >11.1 mmol/L in a non-fasted state]), the use of diabetes medication (yes or no), and proteinuria (yes or no). A P value <0.05 was regarded as statistically significant. The SAS System for Windows, release 9.3 (SAS Institute Inc., Cary, NC, USA), was used for all analyses.

RESULTS

Sex-stratified baseline characteristics of the cardiovascular risk factors according to our BMI categories are provided in Table 1. All of the factors, except diabetic medication use in men and lipid medication use in men and women, were associated with BMI in both sexes. A higher BMI was linked with a higher eGFR and a higher prevalence of proteinuria in both sexes.

Of the 105 611 participants (35 738 men and 69 873 women), 19 384 (18.4%) developed stage ≥3 CKD (5978 men and 13 406 women) over a mean follow-up of 5 years (4.9 years for men and 5.1 years for women). Table 2 and Figure show the sex-stratified HRs for the incidence of stage ≥3 CKD according to BMI category. In both sexes, compared to a BMI of 21.0–22.9 kg/m^2, the age- and potential confounder-adjusted HRs were higher for the higher BMI categories (model 1; P for trend <0.001; Table 2). Further, these results were similar even when adjusted for potential mediators (model 2; Figure). The HRs of BMI ≥30.0 kg/m^2 were markedly higher in men and women (HR 1.60, 95% CI 1.24–2.06 and HR 1.41, 95% CI 1.25–1.60, respectively).

Table 3 shows the sex-stratified HRs for stage ≥3 CKD by BMI categories among diabetes-free and CVD risk factor-free patients at baseline. In analyses limited to those free of either diabetes or of any CVD risk factors, the HRs were higher for the higher BMI categories (P for trend <0.001).

Table 4 shows the sex- and age-stratified HRs for the incidence of stage ≥3 CKD by BMI category compared with a BMI of 21.0–22.9 kg/m^2. In men aged 40–59 years, the multivariable HRs of BMI ≥30.0 kg/m^2 were significantly higher. In men aged 60–79 years, the multivariable HRs of BMI ≥23.0 kg/m^2 were significantly higher. In women aged 40–59 years, the multivariable HRs of the overall BMI categories were not significantly associated (P for trend = 0.291). In women aged 60–79 years, the multivariable HRs of BMI ≥27.0 kg/m^2 were significantly higher. In both sexes and age classes, except women aged 40–59 years, a significant dose-response relationship between BMI and the incidence of stage ≥3 CKD was observed.

DISCUSSION

To the best of our knowledge, this is the first cohort study to demonstrate a dose-response relationship between obesity and

Table 1. Baseline characteristics of participants by BMI categories

Gender and baseline variables	Body mass index, kg/m^2							*P* for difference
	<18.5	18.5–20.9	21.0–22.9	23.0–24.9	25.0–26.9	27.0–29.9	≥30.0	
Men (*n* = 35 738)								
Number of participants	1570	6717	9044	9097	5928	2899	483	
Age, years	65.0 (8.8)	62.5 (9.5)	60.8 (9.7)	59.8 (9.7)	59.0 (9.6)	58.9 (9.4)	57.4 (9.4)	<0.001
eGFR, mL/(min·1.73 m^2)	89.9 (18.6)	90.2 (18.4)	88.6 (17.4)	87.1 (17.3)	86.4 (16.8)	85.3 (16.5)	84.4 (16.6)	<0.001
Proteinuria, %	2.2	1.7	1.4	1.8	2.2	3.7	6.4	<0.001
Total cholesterol, mmol/L	4.67 (0.81)	4.75 (0.82)	4.94 (0.85)	5.07 (0.86)	5.17 (0.86)	5.21 (0.86)	5.26 (0.86)	<0.001
HDL cholesterol, mmol/L	1.63 (0.43)	1.52 (0.40)	1.41 (0.38)	1.30 (0.34)	1.24 (0.31)	1.18 (0.29)	1.14 (0.28)	<0.001
Triacylglycerol, mmol/L	1.06 (0.59)	1.21 (0.71)	1.50 (0.91)	1.78 (1.05)	2.05 (1.22)	2.23 (1.31)	2.32 (1.31)	<0.001
Blood glucose, mmol/L	6.41 (2.15)	6.37 (2.09)	6.35 (1.98)	6.39 (2.03)	6.45 (2.01)	6.60 (2.26)	6.70 (2.23)	<0.001
Systolic blood pressure, mm Hg	131.4 (18.2)	133.5 (17.7)	135.1 (16.9)	136.9 (16.6)	138.2 (16.2)	140.8 (16.7)	142.6 (16.2)	<0.001
Diastolic blood pressure, mm Hg	76.9 (10.6)	78.1 (10.4)	79.7 (10.3)	81.3 (10.3)	82.9 (10.3)	84.6 (10.6)	86.9 (10.9)	<0.001
Lipid medication use, %	0.4	0.7	1.2	1.6	1.5	2.0	2.3	0.289
Diabetic medication use, %	3.2	2.6	2.7	3.6	3.7	4.0	3.1	0.361
Antihypertensive medication use, %	12.5	14.5	16.6	19.7	22.4	26.5	32.1	<0.001
Smoking status, %								<0.001
Never	18.1	18.7	22.3	24.1	24.4	25.1	28.6	
Former	22.2	23.5	27.3	30.3	32.0	33.3	28.8	
Current								
<20 cigarettes/day	26.4	21.0	16.2	13.8	12.0	10.7	9.7	
≥20 cigarettes/day	33.3	36.8	34.2	31.9	31.6	31.0	32.9	
Alcohol intake, %								<0.001
Never	44.8	35.6	31.9	31.1	31.0	33.4	37.7	
Sometimes	10.4	11.1	11.9	13.8	14.6	15.7	14.9	
Everyday								
<56 g/day	41.1	47.5	49.5	49.1	47.3	42.9	38.9	
≥56 g/day	3.6	5.8	6.7	6.1	7.1	8.1	8.5	
Women (*n* = 69 873)								
Number of participants	2846	12 052	17 146	17 122	11 559	7229	1919	
Age, years	60.4 (10.3)	57.5 (9.8)	57.8 (9.3)	58.5 (8.8)	59.4 (8.6)	59.8 (8.4)	59.0 (8.5)	<0.001
eGFR, mL/(min·1.73 m^2)	94.5 (22.0)	96.1 (22.3)	94.2 (21.1)	93.4 (24.9)	91.8 (20.7)	91.4 (20.4)	91.3 (21.0)	<0.001
Proteinuria, %	0.9	0.7	0.8	0.9	1.2	1.7	3.3	<0.001
Total cholesterol, mmol/L	5.19 (0.88)	5.27 (0.87)	5.39 (0.89)	5.48 (0.89)	5.55 (0.88)	5.60 (0.91)	5.61 (0.92)	<0.001
HDL cholesterol, mmol/L	1.72 (0.40)	1.61 (0.38)	1.51 (0.36)	1.43 (0.34)	1.38 (0.33)	1.35 (0.31)	1.33 (0.31)	<0.001
Triacylglycerol, mmol/L	1.07 (0.50)	1.23 (0.65)	1.42 (0.79)	1.61 (0.90)	1.77 (0.96)	1.88 (1.04)	1.94 (0.99)	<0.001
Blood glucose, mmol/L	5.90 (1.61)	5.79 (1.40)	5.83 (1.40)	5.96 (1.50)	6.04 (1.52)	6.16 (1.71)	6.35 (2.03)	<0.001
Systolic blood pressure, mm Hg	126.5 (17.9)	127.2 (17.3)	130.1 (17.0)	132.7 (16.9)	135.4 (16.6)	138.6 (16.8)	141.7 (16.9)	<0.001
Diastolic blood pressure, mm Hg	73.5 (10.4)	74.7 (10.3)	76.4 (10.1)	78.3 (10.0)	79.9 (10.0)	82.0 (10.0)	84.1 (10.6)	<0.001
Lipid medication use, %	1.9	2.2	3.2	3.8	4.2	4.6	4.6	0.988
Diabetic medication use, %	1.3	1.5	1.5	1.9	2.3	2.7	3.2	<0.001
Antihypertensive medication use, %	8.7	10.4	13.8	19.0	23.9	30.6	38.0	<0.001
Smoking status, %								<0.001
Never	92.2	95.1	95.5	95.9	95.7	95.2	93.3	
Former	0.5	0.4	0.6	0.5	0.6	0.7	0.8	
Current								
<20 cigarettes/day	4.9	3.2	2.7	2.4	2.5	2.7	3.9	
≥20 cigarettes/day	2.3	1.3	1.1	1.3	1.3	1.5	2.1	
Alcohol intake, %								<0.001
Never	91.3	90.0	90.0	90.7	90.8	91.7	91.5	
Sometimes	4.8	5.8	6.3	5.7	5.9	5.1	4.8	
Everyday								
<56 g/day	3.9	4.1	3.6	3.5	3.2	3.1	3.4	
≥56 g/day	—	0.1	0.1	0.1	0.1	0.1	0.3	

BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; SD, standard deviation.
Showing mean (SD) for continuous variables: age, fasting and non-fasting blood glucose, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, and triglycerides.
SI conversion factors: to convert blood glucose values to mmol/L, multiply by 0.055 51; to convert cholesterols values to mmol/L, multiply by 0.025 86; to convert triglycerides values to mmol/L, multiply by 0.011 29.

the risk of stage ≥3 CKD in a Japanese population. The dose-response relationship was found in men aged 40–59 and 60–79 years and in women aged 60–79 years. In addition, this relationship was independent of diabetes and other CVD risk factors (ie hypertension and dyslipidemia). We also observed that the risk of stage ≥3 CKD was markedly higher in obese men and women with a BMI ≥30.0 kg/m^2 than in men and women with a BMI of 21.0–22.9 kg/m^2, except in women aged 40–59 years.

The significant relationship observed between BMI and the incidence of stage ≥3 CKD in our study was consistent with that observed in previous studies in Caucasian and Asian

Table 2. Sex-specific HRs and 95% CI for stage ≥3 CKD by BMI categories

Sex and body mass index category (kg/m²)	Number of participants	Number of person-years	Incidence rates per 1000 person-years	Age-adjusted HR	95% CI	Multivariate-adjusted HR[a] (model 1)	95% CI	*P* for trend
Men								
<18.5	1570	7061	20.1	0.76	0.63, 0.90	0.73	0.69, 0.61	
18.5–20.9	6717	33677	20.1	0.90	0.82, 0.99	0.89	0.87, 0.81	
21.0–22.9	9044	47022	19.9	1	(ref.)	1	(ref.)	
23.0–24.9	9097	46973	23.1	1.27	1.16, 1.38	1.27	1.09, 1.17	<0.001
25.0–26.9	5928	30170	22.9	1.38	1.25, 1.52	1.39	1.11, 1.26	
27.0–29.9	2899	14091	23.6	1.48	1.31, 1.68	1.48	1.08, 1.30	
≥30.0	483	2252	28.4	2.01	1.56, 2.59	1.98	1.24, 1.54	
Women								
<18.5	2846	14223	19.8	0.75	0.66, 0.85	0.74	0.72, 0.66	
18.5–20.9	12052	65680	17.8	0.86	0.80, 0.93	0.86	0.84, 0.80	
21.0–22.9	17146	94954	20.1	1	(ref.)	1	(ref.)	
23.0–24.9	17122	92420	22.0	1.05	0.99, 1.12	1.05	0.95, 0.99	<0.001
25.0–26.9	11559	61186	24.7	1.11	1.04, 1.19	1.11	0.96, 1.04	
27.0–29.9	7229	36348	27.9	1.23	1.14, 1.33	1.23	1.01, 1.14	
≥30.0	1919	8760	34.5	1.66	1.47, 1.87	1.64	1.25, 1.45	

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.
[a]Adjusted for age (years), smoking status (never, ex-, current <20 cigarettes/day, or ≥20 cigarettes/day), and alcohol intake (never, sometimes, <56 g/day, or ≥56 g/day).

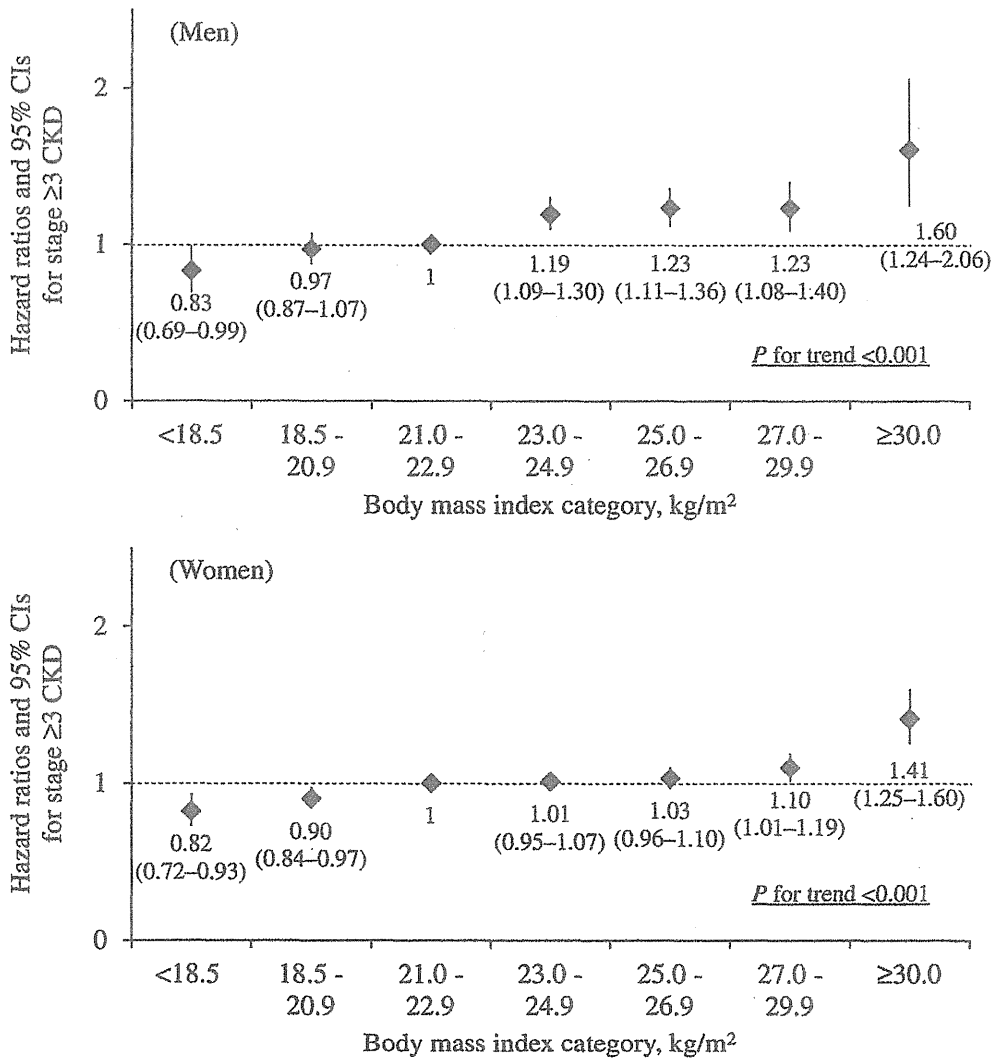

Figure. The multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the development of stage ≥3 chronic kidney disease (CKD) in men and women.

Table 3. Sex-specific HRs and 95% CIs for stage ≥3 CKD by BMI categories among diabetes-free and CVD risk factor-free at baseline

Sex and body mass index category (kg/m^2)	Number of subjects	Number of person-years	Incidence rates per 1000 person-years	Age-adjusted HR	95% CI	Multivariable HR[c]	95% CI	*P* for trend
Diabetes[a]-free								
Men								
<18.5	1207	5426	19.5	**0.73**	**0.60, 0.90**	**0.80**	**0.65, 0.99**	
18.5–20.9	5352	26978	19.4	**0.89**	**0.79, 0.99**	0.94	0.84, 1.05	
21.0–22.9	7247	38202	19.9	1	(ref.)	1	(ref.)	
23.0–24.9	7255	37952	23.1	**1.27**	**1.15, 1.40**	**1.21**	**1.09, 1.33**	<0.001
25.0–26.9	4601	23495	23.0	**1.38**	**1.24, 1.55**	**1.26**	**1.12, 1.41**	
27.0–29.9	2227	11013	22.2	**1.44**	**1.25, 1.67**	**1.24**	**1.07, 1.44**	
>30.0	359	1715	29.2	**2.02**	**1.52, 2.69**	**1.64**	**1.23, 2.19**	
Women								
<18.5	2492	12512	19.4	**0.75**	**0.65, 0.86**	**0.80**	**0.70, 0.92**	
18.5–20.9	10818	58756	17.3	**0.86**	**0.79, 0.93**	**0.89**	**0.82, 0.96**	
21.0–22.9	15336	85182	19.8	1	(ref.)	1	(ref.)	
23.0–24.9	15086	81737	21.4	1.03	0.97, 1.11	1.00	0.93, 1.06	<0.001
25.0–26.9	10024	53502	24.4	**1.11**	**1.03, 1.19**	1.04	0.96, 1.11	
27.0–29.9	6182	31475	27.2	**1.21**	**1.12, 1.32**	**1.09**	**1.00, 1.18**	
>30.0	1574	7272	33.7	**1.65**	**1.44, 1.89**	**1.41**	**1.23, 1.62**	
CVD risk factor[b]-free								
Men								
<18.5	501	2364	11.8	**0.63**	**0.42, 0.95**	**0.64**	**0.42, 0.96**	
18.5–20.9	1815	9989	12.0	0.83	0.65, 1.06	0.84	0.65, 1.08	
21.0–22.9	1945	10918	12.4	1	(ref.)	1	(ref.)	
23.0–24.9	1528	8402	13.9	**1.29**	**1.01, 1.65**	**1.30**	**1.01, 1.67**	<0.001
25.0–26.9	757	4007	12.5	1.36	0.98, 1.88	1.30	0.93, 1.81	
27.0–29.9	232	1121	16.1	**1.85**	**1.13, 3.03**	**1.78**	**1.08, 2.93**	
>30.0	29	109	9.2	2.20	0.31, 15.75	1.94	0.27, 13.92	
Women								
<18.5	1304	6802	15.1	0.90	0.72, 1.12	0.92	0.74, 1.15	
18.5–20.9	5285	29349	12.0	0.99	0.86, 1.14	1.01	0.87, 1.16	
21.0–22.9	6243	36399	11.8	1	(ref.)	1	(ref.)	
23.0–24.9	4920	27907	14.0	**1.17**	**1.02, 1.34**	**1.16**	**1.01, 1.33**	<0.001
25.0–26.9	2509	14196	16.3	**1.27**	**1.08, 1.49**	**1.21**	**1.03, 1.42**	
27.0–29.9	1126	5989	19.2	**1.57**	**1.27, 1.92**	**1.47**	**1.2, 1.81**	
>30.0	222	1111	26.1	**2.15**	**1.47, 3.13**	**1.98**	**1.35, 2.89**	

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio.
[a]Diabetes is defined as plasma glucose ≥6.1 mmol/L in a fasted state or ≥7.8 mmol/L in a non-fasted state, or being treated for diabetes mellitus.
[b]Cardiovascular disease risk factors are hypertension, dyslipidemia, and diabetes.
[c]Adjusted for age (years), systolic blood pressure (mm Hg), total cholesterol level (mmol/liter), high-density lipoprotein cholesterol level (mmol/liter), log-transformed triglyceride level (mmol/liter), proteinuria (yes or no), smoking status (never, ex-, current <20 cigarettes/day, or ≥20 cigarettes/day), and alcohol intake (never, sometimes, <56 g/day, or ≥56 g/day).

populations.[11,17,18] The Framingham Offspring Study, which included 2585 participants (mean age, 43 years) who were followed from 1978–2001 (mean follow-up, 18.5 years), showed a strong dose-response relationship between baseline BMI and risk of CKD (defined as eGFR using the MDRD Study equation: ≤64.25 mL/[min·1.73 m^2] in men and ≤59.25 mL/[min·1.73 m^2] in women).[11] The multivariable odds ratio of CKD was 1.23 (95% CI, 1.08–1.41) per one standard deviation of approximately 4 kg.[11] A Japanese community-based study, which followed 100 753 individuals (mean age, 49 years) for 17 years, revealed that a higher BMI at baseline was associated with an increased risk of end-stage renal disease in men but not women.[18] The multivariable-adjusted odds ratios of end-stage renal disease were 1.27 (95% CI, 1.21–1.45) in men and 0.95 (95% CI, 0.83–1.09) in women for each 2 kg/m^2 increment of BMI.[18] Although these authors did not examine the association between BMI and the risk of CKD among older adults, their results in middle-aged adults are consistent with our findings.

The association between obesity and stage ≥3 CKD may be mediated through multiple biological mechanisms, including hormonal factors, inflammation, oxidative stress, and endothelial dysfunction.[19,20] In obese individuals, the rennin-angiotensin-aldosterone system is commonly activated,[21] and it is a well-coordinated hormonal system that regulates adrenal, cardiovascular, and kidney function by controlling the fluid and electrolyte balance. Activation of this system leads to the development of hypertension via the production of angiotensin 2, which causes further damage to the kidneys.[22] Estrogen, a sex hormone that is secreted more in premenopausal women compared with men and post-menopausal women, decreases the expression of angiotensin

Table 4. Age and sex-specific HRs and 95% CIs for stage ≥3 CKD by BMI categories

Sex, age group, and BMI categories (kg/m^2)	Number of participants	Number of person-years	Incidence rates per 1000 person-years	Age-adjusted HR	95% CI	Multivariable HR[a]	95% CI	*P* for trend
Men								
Age 40–59 years								
<18.5	298	1373	2.9	0.44	0.16, 1.18	0.47	0.17, 1.28	
18.5–20.9	1948	10900	4.3	**0.63**	**0.45, 0.88**	**0.71**	**0.50, 0.99**	
21.0–22.9	3310	18194	6.7	1	(ref.)	1	(ref.)	
23.0–24.9	3762	20086	9.4	**1.41**	**1.12, 1.77**	1.22	0.97, 1.54	0.001
25.0–26.9	2676	14323	8.9	**1.34**	**1.05, 1.72**	1.10	0.85, 1.42	
27.0–29.9	1384	7130	10.9	**1.57**	**1.18, 2.09**	1.21	0.90, 1.63	
≥30.0	264	1241	16.9	**2.59**	**1.63, 4.11**	**1.83**	**1.14, 2.95**	
Age 60–79 years								
<18.5	1272	5688	24.3	**0.77**	**0.64, 0.92**	0.84	0.70, 1.01	
18.5–20.9	4769	22777	27.7	0.93	0.84, 1.03	0.99	0.89, 1.10	
21.0–22.9	5734	28828	28.3	1	(ref.)	1	(ref.)	
23.0–24.9	5335	26887	33.4	**1.25**	**1.13, 1.37**	**1.18**	**1.07, 1.30**	<0.001
25.0–26.9	3252	15847	35.5	**1.39**	**1.25, 1.55**	**1.26**	**1.13, 1.41**	
27.0–29.9	1515	6961	36.6	**1.46**	**1.27, 1.68**	**1.22**	**1.06, 1.41**	
≥30.0	219	1011	42.5	**1.83**	**1.34, 2.48**	**1.47**	**1.08, 2.01**	
Women								
Age 40–59 years								
<18.5	1209	6864	6.8	0.91	0.68, 1.23	0.98	0.72, 1.33	
18.5–20.9	6611	38770	6.7	0.91	0.78, 1.07	0.96	0.82, 1.12	
21.0–22.9	9324	56401	7.7	1	(ref.)	1	(ref.)	
23.0–24.9	8808	51514	8.4	1.04	0.91, 1.19	1.00	0.88, 1.15	0.291
25.0–26.9	5436	31685	9.2	1.10	0.95, 1.28	1.02	0.87, 1.18	
27.0–29.9	3219	17926	9.5	1.17	0.98, 1.39	1.02	0.85, 1.22	
≥30.0	928	4778	11.3	**1.46**	**1.10, 1.94**	1.19	0.90, 1.59	
Age 60–79 years								
<18.5	1637	7359	31.9	**0.75**	**0.65, 0.86**	**0.81**	**0.70, 0.93**	
18.5–20.9	5441	26910	33.9	**0.86**	**0.79, 0.93**	**0.89**	**0.82, 0.97**	
21.0–22.9	7822	38553	38.3	1	(ref.)	1	(ref.)	
23.0–24.9	8314	40906	39.1	1.04	0.97, 1.12	1.00	0.93, 1.07	<0.001
25.0–26.9	6123	29501	41.4	**1.09**	**1.01, 1.18**	1.02	0.95, 1.10	
27.0–29.9	4010	18422	45.8	**1.22**	**1.12, 1.33**	**1.10**	**1.00, 1.19**	
≥30.0	991	3982	62.3	**1.67**	**1.46, 1.90**	**1.44**	**1.26, 1.65**	

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.
[a]Adjusted for age (years), smoking status (never, ex-, current <20 cigarettes/day, or ≥20 cigarettes/day), alcohol intake (never, sometimes, <56 g/day, or ≥56 g/day), fasting status (yes or no), systolic blood pressure (mm Hg), antihypertensive medication use (yes or no), total cholesterol level (mmol/liter), high-density lipoprotein cholesterol level (mmol/liter), log-transformed triglyceride level (mmol/liter), lipid medication use (yes or no), blood glucose status (normal: <6.1 mmol/l during fasting or <7.8 mmol/l during nonfasting; border: 6.1–7.0 mmol/l during fasting or 7.8–11.1 mmol/l during nonfasting; hyperglycemic: 7.0 mmol/l during fasting or 11.1 mmol/l during nonfasting), diabetes medication use (yes or no), and proteinuria (yes or no).

type 1 receptors in the vasculature and kidneys[23] and reduces the expression and activity of angiotensin-converting enzymes.[24,25] These biological mechanisms may be underlying factors for the significant relationship between obesity and the development of stage ≥3 CKD among middle-aged women in our study.

The strength of our study is that stage ≥3 CKD was defined as an eGFR level <60 mL/min/1.73 m^2 reported at more than two successive annual surveys. Further, all of the blood samples were measured by the same laboratory, which was verified using a validated quality control system.[26] However, there are several limitations. First, we only examined generalized obesity and not abdominal obesity, because the measurements of central obesity were not available during the baseline examination. Second, potential residual confounders may not have been assessed, such as fat distribution, dietary lifestyle (ie protein and salt intake), and physical activity. Third, detailed information on use of medications such as statins and omega 3-fatty acids was not collected because of the nature of the community-based health checkup.

Obesity was associated with the risk of developing stage ≥3 CKD among men and older women. Compared with participants who had a normal BMI (21.0–22.9 kg/m^2), those with a BMI ≥30.0 kg/m^2 had a markedly high risk of developing stage ≥3 CKD. Weight management may be important for preventing CKD in obese men and women.

ONLINE ONLY MATERIAL

Abstract in Japanese.

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Milk and Dairy Consumption and Risk of Dementia in an Elderly Japanese Population: The Hisayama Study

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OBJECTIVES: To determine the effect of milk and dairy intake on the development of all-cause dementia and its subtypes in an elderly Japanese population.

DESIGN: Prospective cohort study.

SETTING: The Hisayama Study, Japan.

PARTICIPANTS: Individuals aged 60 and older without dementia (N = 1,081).

MEASUREMENTS: Milk and dairy intake was estimated using a 70-item semiquantitative food frequency questionnaire grouped into quartiles. The risk estimates of milk and dairy intake on the development of all-cause dementia, Alzheimer's disease (AD), and vascular dementia (VaD) were computed using a Cox proportional hazards model.

RESULTS: Over 17 years of follow-up, 303 subjects developed all-cause dementia; 166 had AD, and 98 had VaD. The age- and sex-adjusted incidence of all-cause dementia, AD, and VaD significantly decreased as milk and dairy intake level increased (P for trend = .03 for all-cause dementia, .04 for AD, .01 for VaD). After adjusting for potential confounders, the linear relationship between milk and dairy intake and development of AD remained significant (P for trend = .03), whereas the relationships with all-cause dementia and VaD were not significant. The risk of AD was significantly lower in the second, third, and fourth quartiles of milk and dairy intake than in the first quartile.

CONCLUSION: Greater milk and dairy intake reduced the risk of dementia, especially AD, in the general Japanese population. J Am Geriatr Soc 62:1224–1230, 2014.

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The increasing prevalence of dementia worldwide is a major public health concern. According to the World Health Organization and Alzheimer's Disease International, the number of people living with dementia will double by 2030 and more than triple by 2050,[1] but the causes of dementia, especially Alzheimer's disease (AD), remain unclear, and there are no disease-modifying therapies. Thus, there is an urgent need to identify factors that can prevent development of dementia to decrease the burden of this disease. Diet is one of the factors that can be modified, and it may have a protective influence against dementia. Milk and dairy intake has been reported to decrease cerebrovascular risk factors, such as hypertension,[2] diabetes mellitus,[3] and obesity,[4] which are associated with the development of dementia,[5] but a limited number of epidemiological studies have assessed the relationship between milk and dairy intake and cognitive impairment or dementia.[6–12] To this end, a community-based prospective cohort study was established to evaluate risk factors for or protective factors against dementia in the Japanese population. A feature of this study is that the subtypes of dementia have been verified using detailed neurological and morphological examination, including neuroimaging and autopsy. The purpose of this study was to elucidate the relationship between milk and dairy intake and the development of dementia and its subtypes in an elderly Japanese population.

METHODS

Study Populations

The Hisayama Study is an ongoing population-based prospective cohort study in the town of Hisayama, a suburb

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of the Fukuoka metropolitan area in the southern part of Japan.[13] This study was begun in 1961 to determine the prevalence and incidence of cerebro- and cardiovascular diseases and their risk factors in Japanese. Data from the national census and nutrition survey indicate that the age and occupational distributions and nutrient intake of the population of Hisayama are similar to those of Japan as a whole for each year from 1961 to the present.[14] Full community surveys of the health status and neurological condition of residents aged 40 and older have been repeated every 1 to 2 years since 1961. Comprehensive surveys of cognitive impairment have also been performed every 6 or 7 years in the elderly adults of the town since 1985.[15,16] In 1988, 1,228 residents aged 60 and older (participation rate 91.1%) underwent a screening examination for the present study. After excluding 35 subjects who already had dementia at baseline, 111 subjects whose dietary questionnaires were not available, and one subject with no blood sample, 1,081 subjects (457 men, 624 women) were enrolled in this study.

Follow-Up Survey

The subjects were followed prospectively for 17 years, from December 1988 to November 2005, during which time health examinations were repeated every 1 to 2 years.[13] Letters or telephone calls were used to collect the health information of subjects who did not have examinations or who had moved out of town. A daily monitoring system was also established with the study team and local physicians or members of the town's Health and Welfare Office to collect information about new events, including stroke, cognitive impairment, and dementia. Follow-up screening surveys of cognitive function, including neuropsychological tests (the Hasegawa Dementia Scale,[17] the Hasegawa Dementia Scale—Revised,[18] or the Mini-Mental State Examination[19]), were conducted in 1992, 1998, and 2005. The study physician and psychiatrist carefully evaluated any subject suspected of having new neurological symptoms, including cognitive impairment, by conducting a comprehensive investigation including interviews of the family or attending physician, physical and neurological examinations, and a review of the clinical records. Furthermore, when a subject died, all the available clinical information was reviewed, the attending physician and family of the deceased were interviewed, and an attempt was made to obtain permission for an autopsy from the family. During follow-up, 518 subjects died, 387 (74.7%) of whom underwent brain examination at autopsy. No subjects were lost to follow-up.

Diagnosis of Dementia

The guidelines of the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*, were used to define the diagnosis of dementia,[20] the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association were used to define subjects with AD,[21] and the criteria of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences were used to determine the diagnoses of vascular dementia (VaD).[22] Clinical information, including neuroimaging, was used to diagnose possible and probable dementia subtypes. Definite dementia subtypes were also determined on the basis of clinical and neuropathological information in subjects with dementia who underwent autopsy. The diagnostic procedure for autopsy cases has been previously reported.[23] A neuropathological diagnosis of AD was made following the National Institute on Aging—Reagan Institute criteria;[24] the frequency of neuritic plaques and neurofibrillary tangles was evaluated using the Consortium to Establish a Registry for Alzheimer's Disease criteria[25] and Braak stage.[26] Definite VaD cases were confirmed with causative stroke or cerebrovascular change and no neuropathological evidence of other forms of dementia. Expert stroke physicians and psychiatrists adjudicated each case of dementia.

During the 17 years of follow-up, 303 subjects (103 men, 200 women) developed dementia; 261 (86.1%) were evaluated using brain imaging, 155 (51.2%) underwent autopsy, and both were performed in 143. Thus, 273 subjects (90.0%) had some kind of morphological examination. Of subjects with dementia cases, 25 with AD and 18 with VaD had other, coexisting subtypes of dementia, 14 of which were a mixed type of AD and VaD. These cases were counted as events in the analyses for each subtype. Finally, 166 subjects had AD (77 definite AD, 68 probable AD, 21 possible AD), and 98 had VaD (63 definite VaD, 35 probable VaD).

Nutritional Survey

The dietary survey was conducted using a 70-item semiquantitative food frequency questionnaire (SFFQ) concerning food intake.[27] Average food intake per day was calculated from the weekly frequency of various foods and the amount (quantity) of each food portion. The validity of this questionnaire has been reported previously.[28] Briefly, 65 subjects were randomly selected from 981 individuals aged 40 and older who underwent a health examination in 1987. Information regarding food intake was collected for 7 successive days using a weighted food record. Similarly, information regarding food intake was collected from the same subjects using the SFFQ. As a result, the 1-day average intake of milk and dairy products based on SFFQ was 84.6 g, and that based on the weighted food record was 103.9 g. The correlation coefficient in the amount of milk and dairy intake between the SFFQ and weighted food record was 0.53 ($P < .001$); this correlation was considered moderate.

The questionnaire was administered before initiation of this study; a trained dietician or nutritionist questioned each participant in the screening examination. Nutritional intake was calculated using the *Standard Tables of Food Composition in Japan, Fourth Revision*.[29] Each food group was adjusted for energy intake using the residual method.[30]

Risk Factor Measurements

At the baseline survey, each subject was asked to complete a self-administered questionnaire covering medical history, antidiabetes and antihypertensive treatments, educational status, smoking habits, alcohol consumption, and physical

activity. History of stroke was defined as a preexisting sudden onset of nonconvulsive and focal neurological deficit persisting for longer than 24 hours on the basis of all available clinical data. Low educational level was defined as less than 7 years of formal education. Smoking habits and alcohol consumption were categorized as current use or no current use. Regular exercise was defined as engaging in sports more than three times a week during leisure time. Blood pressure was measured three times using a standard mercury sphygmomanometer in the sitting position after at least 5 minutes rest. The mean of three measurements was used for the analysis. Hypertension was defined as blood pressure of 140/90 mmHg or greater or current use of antihypertensive drugs. Body height and weight were measured in light clothing without shoes, and body mass index (kg/m^2) was calculated. Diabetes mellitus was defined as fasting plasma glucose of 7.0 mmol/L or more, 2-hour postload glucose concentrations or postprandial glucose concentrations of 11.1 mmol/L or more, or current use of insulin or oral medication for diabetes mellitus. Serum total cholesterol levels were measured enzymatically.

Statistical Analysis

Subjects were grouped into quartiles based on amount of milk and dairy intake per day, according to sex. The quartiles for milk and dairy intake were less than 45, 45 to 96, 97 to 197, and 198 g/d or more for women and less than 20, 20 to 75, 76 to 173, and 174 g/d or more for men. The trends in the mean values of risk factors for the milk and dairy intake levels were tested using linear regression and the frequencies using logistic regression analysis. Participants were censored at date of death or end of follow-up for survival analyses. The incidence of dementia was calculated using a person-year method and adjusted for age and sex using the direct method using 10-year age groups of the overall study population. The age- and sex-adjusted or multivariable-adjusted hazard ratios (HRs) with their 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model. The assumption of proportional hazards was checked graphically using log cumulative hazard plots for outcomes according to milk and dairy intake levels. In the multivariable-adjusted model, 15 covariates known to be potential risk or protective factors for dementia were selected: age; sex; low education; history of stroke; hypertension; diabetes mellitus; total cholesterol; body mass index; smoking habits; regular exercise; and energy, vegetable, fruit, fish, and meat intake.[31] Heterogeneity in the relationship between subgroups was tested by adding multiplicative interaction terms to the relevant Cox model. Two-sided $P < .05$ was considered statistically significant in all analyses. SAS version 9.3 (SAS Institute, Inc., Cary, NC) was used to perform all statistical analyses.

Ethical Considerations

This study was conducted with the approval of the Kyushu University institutional review board for clinical research. Written informed consent was obtained from participants.

RESULTS

The baseline characteristics of subjects according to milk and dairy intake levels are summarized in Table 1. Mean age and total cholesterol levels and frequencies of diabetes mellitus and regular exercise were higher with higher milk and dairy intake levels, whereas mean systolic blood pressure and frequencies of hypertension, smoking habits, and alcohol consumption were lower with higher milk and dairy intake levels. In relation to dietary factors, subjects in the fourth quartile of milk and dairy intake ate more fruit and had lower intake of fish and meat than those in the first quartile.

Figure 1 shows the age- and sex-adjusted incidence of all-cause dementia, AD, and VaD according to quartiles of milk and dairy intake levels. The age- and sex-adjusted incidence of all-cause dementia, AD, and VaD was significantly lower with higher milk and dairy intake levels (P for trend = .03 for all-cause dementia, = .04 for AD, and = .01 for VaD).

Table 2 shows the estimated HRs and 95% CIs for the development of dementia and its subtypes according to milk and dairy intake level. There was a significant inverse relationship between milk and dairy intake level and age- and sex-adjusted HR of all-cause dementia (P for trend = .03). This linear relationship did not remain significant after adjustment for age; sex; low education; diabetes mellitus; hypertension; total cholesterol; history of stroke; body mass index; smoking habits; regular exercise; and total energy, vegetable, fruit, fish, and meat intake (P for trend = .09), but the risk of all-cause dementia remained significantly lower in the third quartile than in the first quartile (adjusted HR = 0.69, 95% CI = 0.50–0.96).

With regard to dementia subtypes, multivariable-adjusted HRs of AD were significantly lower with higher milk and dairy intake, but no such relationship was observed for VaD (P for trend = .03 for AD; P for trend = .14 for VaD). The multivariable-adjusted HR of AD was significantly lower in subjects in the second, third, and fourth quartile of milk and dairy intake than in those in the first quartile (adjusted HR = 0.64, 95% CI = 0.41–0.99 for the second quartile; adjusted HR = 0.57, 95% CI = 0.37–0.87 for the third quartile; adjusted HR = 0.63, 95% CI = 0.41–0.98 for the fourth quartile). Although the age- and sex-adjusted HR of VaD was significantly lower in subjects in the fourth quartile of milk and dairy intake than in those in the first quartile, this relationship was not significant after multivariable adjustment (adjusted HR = 0.69, 95% CI = 0.37–1.29 for the fourth quartile). There was no evidence of heterogeneity between men and women in the risk of dementia and its subtypes.

DISCUSSION

This long-term prospective study of an elderly Japanese population demonstrated a significant inverse relationship between milk and dairy intake and risk of development of all-cause dementia, AD, and probably VaD. This is, to the best of the authors' knowledge, the first prospective cohort study to investigate the protective relationship between milk and dairy intake and risk of dementia and its subtypes.

Table 1. Baseline Characteristics of Subjects According to Quartile of Milk and Dairy Consumption: The Hisayama Study, 1988

Characteristic	Q1 (Low), n = 270	Q2, n = 270	Q3, n = 271	Q4 (High), n = 270	*P* for Trend
Female, %	57.8	57.8	57.6	57.8	.99
Age, mean ± SD	68.6 ± 6.4	69.8 ± 6.4	68.9 ± 6.1	70.4 ± 6.8	.008
Education ≤6 years, %	12.0	16.8	11.2	12.0	.56
History of stroke, %	4.1	4.4	4.4	4.4	.84
Systolic blood pressure, mmHg, mean ± SD	142 ± 24	138 ± 23	139 ± 21	137 ± 21	.02
Diastolic blood pressure, mmHg, mean ± SD	77 ± 11	76 ± 11	77 ± 10	75 ± 10	.10
Hypertension, %	57.8	53.7	53.5	48.5	.04
Diabetes mellitus, %	11.5	13.7	14.4	20.0	.007
Total cholesterol, mg/dL, mean ± SD	200 ± 42	204 ± 45	213 ± 43	220 ± 43	<.001
Body mass index, kg/m^2, mean ± SD	22.3 ± 3.1	22.1 ± 3.2	22.5 ± 3.2	22.4 ± 2.7	.40
Smoking habits, %	27.4	23.7	22.9	19.3	.03
Alcohol consumption, %	30.0	26.7	27.7	20.4	.02
Regular exercise, %	13.7	10.0	13.7	21.5	.005
Dietary intake, mean ± SD					
Energy, kcal/d[a]	1,703 ± 402	1,509 ± 395	1,721 ± 400	1,605 ± 372	.44
Vegetable, g/d[a]	251 ± 118	242 ± 102	257 ± 124	256 ± 128	.30
Fruit, g/d[a]	69 ± 69	74 ± 69	91 ± 93	84 ± 64	.002
Fish, g/d[a]	43 ± 43	41 ± 28	36 ± 28	37 ± 22	.006
Meat, g/d[a]	22 ± 24	20 ± 14	19 ± 15	19 ± 15	.03

Quartiles for milk and dairy intake were <45, 45–96, 97–197, ≥198 g/d for women and <20, 20–75, 76–173, ≥174 g/d for men.
SD = standard deviation.
[a]All food groups were adjusted for energy intake using the residual method.

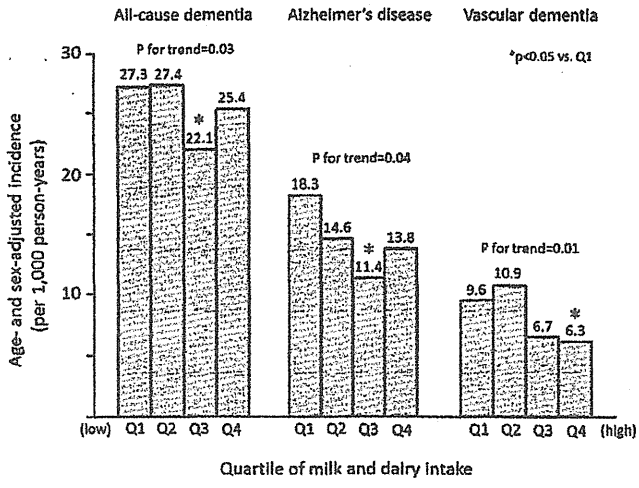

Figure 1. Age- and sex-adjusted incidence of all-cause dementia, Alzheimer's disease, and vascular dementia according to quartile of milk and dairy intake at baseline, 1988–2005.

Several epidemiological studies have investigated the relationship between milk and dairy intake and cognitive impairment or dementia.[6–12] Some cross-sectional studies have evaluated this relationship and found that higher milk and dairy intake is likely to have a protective effect against cognitive impairment.[6–8] A study in Australia demonstrated that low-fat milk and dairy consumption was associated with significantly lower likelihood of poor cognitive function but found the opposite to be true for whole-fat cream and ice cream rich in fat.[9] Similarly, a few prospective studies conducted in Western countries have reported that higher consumption of full-cream milk, milk and dairy desserts, and ice cream increased the risk of cognitive decline.[10,11] These results suggest that low-fat milk and dairy intake might have a more-favorable influence on cognitive function, especially in Western populations, although only one study has evaluated the relationship between milk intake and the risk of dementia longitudinally; the Adult Health Study with atomic bomb survivors in Japan retrospectively evaluated the relationship between milk intake, assessed 25 to 30 years earlier, and the prevalence of AD and VaD. The study concluded that subjects who consumed milk every day had significantly lower prevalence of VaD, but not of AD, than those who consumed milk twice a week or less.[12] This finding is inconsistent with that of the current study, but because the current study and the Adult Health Study had different designs (prospective vs retrospective), the heterogeneity of the methods may explain the discrepancy.

A few cohort studies in Western countries have found that it is possible that the Mediterranean dietary pattern provides protection against dementia, especially AD.[32,33] This diet recommends low to moderate consumption of milk and dairy products. Again, this is a finding that is inconsistent with that of the present study, although in a previous study of the present cohort, the greater adherence to the dietary pattern derived using a reduced rank regression analysis, which was characterized by high intake of milk and dairy products, was associated with a lower risk of dementia.[34] According to data from the Food and Agriculture Organization of the United Nations, there has consistently been a clear difference in the amount of milk and

Table 2. Likelihood of Development of All-Cause Dementia, Alzheimer's Disease, and Vascular Dementia According to Quartile of Milk and Dairy Consumption, 1988–2005

Outcome	Q1 (Low), n = 270	Q2, n = 270	Q3, n = 271	Q4 (High), n = 270	*P* for Trend
All-cause dementia					
Events, n	82	77	67	77	
HR (95% CI)[a]	1.0	0.90 (0.66–1.22)	0.66 (0.48–0.91)	0.76 (0.56–1.04)	.03
HR (95% CI)[b]	1.0	0.85 (0.62–1.18)	0.69 (0.50–0.96)	0.80 (0.57–1.11)	.09
Alzheimer's disease					
Events, n	49	38	37	42	
HR (95% CI)[a]	1.0	0.72 (0.47–1.10)	0.58 (0.38–0.89)	0.68 (0.45–1.03)	.04
HR (95% CI)[b]	1.0	0.64 (0.41–0.99)	0.57 (0.37–0.87)	0.63 (0.41–0.98)	.03
Vascular dementia					
Events, n	28	30	21	19	
HR (95% CI)[a]	1.0	1.04 (0.62–1.74)	0.65 (0.37–1.15)	0.54 (0.30–0.98)	.01
HR (95% CI)[b]	1.0	1.02 (0.59–1.77)	0.74 (0.42–1.33)	0.69 (0.37–1.29)	.14

HR = hazard ratio; CI = confidence interval.

[a]Adjusted for age and sex.

[b]Adjusted for age; sex; low education; history of stroke; hypertension; diabetes mellitus; total cholesterol; body mass index; smoking habits; regular exercise; and energy, vegetable, fruit, fish, and meat intake.

dairy consumption in Japan and Western countries; consumption in the Japanese population is historically approximately half that of Western populations.[35] This evidence, together with the findings of the present study, suggest that the difference in the amount of milk and dairy consumed in Japan and in Western countries could be the reason for the discrepancy in the influence of these foods on the risk of dementia between the populations. In populations with low intake of milk and dairy, such as the Japanese, a "high" intake of these foods is considered to reduce the risk of dementia. Further investigation is needed to clarify this in other ethnic populations.

In the present study, the age- and sex-adjusted HR of VaD was significantly lower in subjects in the fourth quartile of milk and dairy intake than in the first quartile, but this relationship was attenuated after adjustment for other covariates. This finding may have been due to the small number of VaD cases. In addition, because the frequencies of other known cerebrovascular risk factors, such as hypertension and smoking habits, were low in the fourth quartile of milk and dairy intake (Table 1), the risk of VaD may have appeared to decrease in this quartile through mediation of these risk factors.

There are presumably mechanisms for the protective influence of dairy intake against the risk of dementia. In several prospective studies, higher intake of milk and dairy was associated with lower risk of developing stroke and its risk factors, such as hypertension,[2] diabetes mellitus,[3] and obesity,[4] and these same factors were also recognized as risk factors for dementia.[5] Therefore, it is possible that milk and dairy intake decreases the risk of dementia, especially VaD, through mediating these risk factors. Another possible mechanism could be the benefits from some of the nutritional components of milk and dairy. It was previously reported that calcium and magnesium, which are components of milk and dairy, reduced the risk of development of dementia.[36] Milk and dairy consumption is also an important source of vitamin B_{12}, which is known to reduce plasma homocysteine levels. Because low serum vitamin B_{12} levels and high plasma homocysteine levels are reported risk factors for the development of dementia, especially AD,[37,38] milk and dairy consumption could decrease risk because of the influence of these nutrients.[39] Whey protein, another component of milk and dairy products, may also have favorable influence against dementia by reducing fat and improving insulin resistance.[40,41]

The strengths of the current study include its longitudinal, population-based, prospective design; the long follow-up period; perfect follow-up of subjects; and the ability to perform a morphological examination of the brains of most dementia cases using autopsy and neuroimaging, although some potential limitations should be noted. Information regarding the intake of dietary nutrients derived from a semiquantitative food frequency questionnaire may not be fully valid. In addition, the dietary assessment was performed only once, at baseline. These limitations are likely to have introduced some misclassification of food intake, and such misclassifications would weaken the relationship found in the study, biasing the results toward the null hypothesis. Finally, because dairy products are not part of traditional Japanese diets and represent a degree of westernization of lifestyle, the possibility of bias introduced by unmeasurable confounding factors cannot be eliminated.

In conclusion, these findings emphasize the need to consider higher intake of milk and dairy as a potentially protective factor against all-cause dementia, AD, and probably VaD in an elderly Japanese population. Further research will be necessary to clarify the relationship between milk and dairy intake and the risk of developing all-cause dementia and its subtypes in other prospective cohort studies and intervention trials.

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Non-high-density lipoprotein cholesterol and the development of coronary heart disease and stroke subtypes in a general Japanese population: The Hisayama Study

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ABSTRACT

Background and purpose: It has not been fully determined whether non-high-density lipoprotein cholesterol (non-HDLC) levels are involved in vascular events, especially stroke, in general Asian populations. We evaluated the association between non-HDLC levels and the risk of type-specific cardiovascular disease in a prospective cohort study in Japan.
Methods: A total of 2452 community-dwelling Japanese subjects aged ≥40 years were followed prospectively for 24 years.
Results: The age- and sex-adjusted incidence of coronary heart diseases (CHD) significantly increased with elevating non-HDLC levels (P for trend < 0.001), but no such association was observed for ischemic and hemorrhagic strokes. With regard to ischemic stroke subtypes, the age- and sex-adjusted incidence of lacunar infarction significantly increased with elevating non-HDLC levels (P for trend < 0.01), and such tendency was seen for atherothrombotic infarction (P for trend = 0.098), while a significant inverse association was observed for cardioembolic infarction (P for trend = 0.007). After adjustment for confounders, namely, age, sex, diabetes, body mass index, systolic blood pressure, electrocardiogram abnormalities, current drinking, current smoking, and regular exercise, the associations remained significant for CHD [adjusted hazard ratio (HR) for a 1 standard deviation of non-HDLC concentrations = 1.17, 95% confidence interval (CI) = 1.02 to 1.35], atherothrombotic infarction (adjusted HR = 1.39, 95% CI = 1.09 to 1.79), and cardioembolic infarction (adjusted HR = 0.64, 95% CI = 0.47 to 0.85).
Conclusions: Our findings suggest that elevated non-HDLC levels are a significant risk factor for the development of atherothrombotic infarction as well as CHD but reduce the risk of cardioembolic infarction in the general Japanese population.

Numerous studies have demonstrated that increased levels of low-density lipoprotein cholesterol (LDLC) are causally related to an increased risk of cardiovascular disease [1]. Aggressive LDLC lowering has therefore been the main strategy of lipid therapy. Even after achieving target LDLC levels, however, a significant number of subjects continue to have cardiovascular events. Thus, the residual risk of cardiovascular events in lipid management should be considered and identified in clinical settings. In the third report of the US National Cholesterol Education Program's Adult Treatment Panel (NCEP-ATPIII) [2], high non-high-density lipoprotein cholesterol (non-HDLC) levels were introduced as a secondary target for the prevention of coronary heart disease (CHD). Prior prospective studies have found a positive association between non-HDLC levels and the risk of CHD [1,3,4], but it has not been fully determined whether non-HDLC levels are involved in vascular events in general Asian populations, who have lower adiposity and insulin resistance than Western populations. In addition, several prospective studies have investigated the association between non-HDLC levels and the risk of stroke, and the results differed among the studies [5–7].

The purpose of this prospective study of a general Japanese population was to evaluate the association between non-HDLC

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levels and the development of CHD and total stroke and its subtypes.

1. Methods

1.1. Study population

Since 1961, we have been conducting a long-term prospective cohort study of cardiovascular disease in the town of Hisayama, a suburb of Fukuoka city in southern Japan. In 1983, a screening survey for the present study was performed in Hisayama. A detailed description of this survey was published previously [8]. Briefly, a total of 2551 residents aged ≥40 years (80.8% of the total population of this age group) consented to participate in the examination. After excluding 3 subjects who died during the screening survey and 96 subjects with a history of stroke or myocardial infarction, the remaining 2452 subjects (1046 men and 1406 women) were included in this study.

1.2. Follow-up survey

This population was followed up prospectively for 24 years, from November 1983 through October 2007, by annual health examinations. For subjects who did not undergo regular examinations or who moved out of Hisayama, health status was checked yearly by mail or telephone. We also established a daily monitoring system, which connected us with local physicians and employees of the town's Health and Welfare Office. Through this system we gathered information on new cardiovascular disease events. When stroke or CHD occurred or was suspected, physicians in the study team examined the subject and evaluated his or her detailed clinical information. The clinical diagnosis of stroke or CHD was based on the patient's history, physical and neurological findings, and ancillary laboratory examinations. When a subject died, an autopsy was performed at the Departments of Pathology of Kyushu University. During the follow-up period, one subject was lost to follow-up and 1032 subjects died; 758 of the deceased (73.5%) underwent autopsy examination.

1.3. Definition of cardiovascular events

The criteria for the diagnosis of CHD included first-ever acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 h after the onset of acute illness, coronary artery angioplasty, and bypass grafting. The diagnosis of myocardial infarction was based on detailed clinical information and at least two of the following findings: typical clinical symptoms, electrocardiographic evidence of myocardial infarction, elevated cardiac enzymes, and morphological findings including echocardiographic, scintigraphic, or angiographic abnormalities compatible with myocardial injury. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes [9]. During the follow-up period, 202 first-ever CHD events occurred.

The diagnosis and classification of stroke were determined on the basis of clinical information, including brain computed tomography and magnetic resonance imaging, cerebral angiography, echocardiography, carotid duplex imaging, or autopsy findings. In principle, stroke was defined as a sudden onset of nonconvulsive and focal neurological deficits persisting for >24 h, and was classified as either hemorrhagic or ischemic. Hemorrhagic stroke included intracranial and subarachnoid hemorrhage. Ischemic stroke was further divided into 4 clinical categories—atherothrombotic infarction, lacunar infarction, cardioembolic infarction, and undetermined subtype of ischemic stroke—based on the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke [10], as well as on the basis of the diagnostic criteria of the 'Trial of Org10172 in Acute Stroke Treatment (TOAST) Study [11] and the Cerebral Embolism Task Force [12].

Details of the diagnostic criteria for ischemic stroke subtypes have been described previously [8]. In brief, atherothrombotic infarction was diagnosed when the subjects had significant stenosis (>50%) or occlusion of a major cerebral artery with infarct size ≥1.5 cm on brain imaging or autopsy. Lacunar infarction was diagnosed as the presence of a relevant brainstem, basal ganglia, or subcortical hemispheric lesion with a diameter of <1.5 cm demonstrated on brain imaging or autopsy, and no evidence of cerebral cortical or cerebellar impairment. The diagnosis of cardioembolic infarction was made on the basis of primary and secondary clinical features suggestive of cardioembolic infarction as reported by the Cerebral Embolism Task Force [12]. The category of undetermined subtype of ischemic stroke included all ischemic stroke cases for which the subtype could not be determined because of insufficient clinical or morphologic information. We considered morphologic findings to be significant and used clinical features as reference information. Cases with cerebrovascular diseases with distinct pathology, such as collagen disease, hematological disorder, trauma, chronic subdural hematoma, or moyamoya disease, were excluded from the evaluation. During the follow-up period, 352 first-ever stroke events were identified. All of the stroke cases underwent morphological evaluation that included brain imaging and autopsy; 348 subjects (98.9%) underwent brain imaging study, and autopsy was performed on 84 of 110 deceased stroke cases (76.4%), including 4 cases who were not examined by brain imaging. On the basis of the above criteria, the stroke cases were divided into 246 ischemic strokes (64 atherothrombotic infarctions, 110 lacunar infarctions, 69 cardioembolic infarctions, and 3 undetermined subtypes of ischemic stroke) and 106 hemorrhagic strokes.

1.4. Risk factors

Blood samples from 2350 subjects were drawn after an overnight fast of at least 12 h. For the remainder of the subjects ($n = 102$), blood samples were collected in the post-prandial state. All measurements were done within 24 h after venipuncture in the central study laboratory (Japan Medical Laboratory, Fukuoka, Japan). Total cholesterol and triglyceride levels in serum were measured enzymatically. Serum HDL cholesterol concentrations were measured after the precipitation of very-low-density lipoprotein and LDL with dextran sulfate and magnesium. Serum non-HDLC concentrations were calculated by subtracting HDL cholesterol from total cholesterol values. Using the Friedewald equation [13], LDLC levels were calculated in subjects in a fasting state. Plasma glucose levels were determined by the glucose-oxidase method. Diabetes was defined as fasting glucose concentration ≥7.0 mmol/l, post-prandial glucose concentration ≥11.1 mmol/l, or taking antidiabetic medication.

Sitting blood pressure was measured three times at the right upper arm using a sphygmomanometer after at least 5 min of rest, and the average of the three measurements was used in the analysis. Hypertension was defined as blood pressure ≥140/90 mmHg or current treatment with antihypertensive agents. Electrocardiogram (ECG) abnormalities were defined as left ventricular hypertrophy (Minnesota Code, 3-1), ST depression (4-1, 2, 3), or atrial fibrillation (8-3). Body height and weight were measured in light clothing without shoes, and body mass index (kg/m^2) was calculated. Information on alcohol consumption, smoking habits, and physical activity during leisure time was obtained by the use of a

questionnaire. Alcohol consumption and smoking habits were classified as either current use or not. Those subjects engaging in sports or other forms of exertion ≥3 times a week during their leisure time made up a regular exercise group.

1.5. Statistical analysis

To analyze the data according to categorical variables, we classified the subjects into quartiles of non-HDLC levels: ≤3.14, 3.15 to 3.77, 3.78 to 4.49, and ≥4.50 mmol/l. Serum triglyceride levels were logarithmically transformed to improve the skewed distribution. Age- and sex-adjusted mean values of the possible risk factors were calculated by the analysis of covariance method, and their trends across non-HDLC levels were tested by multiple regression analysis. Frequencies of risk factors were adjusted for age and sex by the direct method and were examined for trends by the Cochran–Mantel–Haenszel test. The incidences of cardiovascular disease were calculated by the person-year method and were adjusted for age and sex by the direct method using 10-year age groupings. Differences in age- and sex-adjusted incidences between non-HDLC quartiles were tested by Cox proportional hazards regression analysis. The age- and sex-adjusted or multivariable-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were also calculated using the Cox proportional hazards model. All statistical analyses were performed with SAS version 9.3. Values of $P<0.05$ were considered statistically significant in all analyses.

2. Results

The age- and sex-adjusted mean values or frequencies of risk factors for cardiovascular disease are listed by quartiles of non-HDLC levels at baseline in Table 1. Subjects with higher non-HDLC levels were older and were more likely to be female. The mean values of total cholesterol, triglycerides, body mass index, systolic and diastolic blood pressures, and frequencies of diabetes and hypertension significantly increased with rising non-HDLC levels, while the mean values of HDL cholesterol and the frequencies of current drinking and current smoking declined. The frequencies of ECG abnormalities and regular exercise were not different among the non-HDLC quartiles.

Table 2 shows the age- and sex-adjusted incidences of CHD and stroke according to quartiles of non-HDLC levels. The incidence of CHD significantly increased with increasing non-HDLC level (P for trend < 0.001): compared with the first quartile, the incidence was significantly higher in the third (age- and sex-adjusted HR = 1.73, 95% CI = 1.10 to 2.72, and $P = 0.02$, Table 3) and fourth (age- and sex-adjusted HR = 2.35, CI = 1.51 to 3.65, and $P < 0.001$) quartiles. No significant associations were observed between non-HDLC levels and the incidences of total stroke, whether ischemic or hemorrhagic. In regard to subtypes of ischemic stroke, the age- and sex-adjusted incidence of lacunar infarction significantly increased with increasing non-HDLC level (P for trend = 0.01), while the incidence of cardioembolic infarction significantly decreased (P for trend = 0.007). The age- and sex-adjusted incidence of atherothrombotic infarction tended to increase with higher non-HDLC level (P for trend = 0.098).

As shown in Table 3, the positive associations between non-HDLC level and risk of CHD and atherothrombotic infarction were significant even after adjustment for age, sex, diabetes, body mass index, systolic blood pressure, ECG abnormalities, current drinking, current smoking, and regular exercise (P for trend = 0.01 for CHD and 0.04 for atherothrombotic infarction), but no significant association was observed for lacunar infarction. Compared with the first quartile, the risk of CHD was significantly high in the third (multivariable-adjusted HR = 1.79, 95% CI = 1.09 to 2.95, and $P = 0.02$) and fourth (multivariable-adjusted HR = 1.96, 95% CI = 1.19 to 3.24, and $P = 0.009$) quartiles, and the risk of atherothrombotic infarction was significantly high in the fourth quartile (multivariable-adjusted HR = 2.33, 95% CI = 1.04 to 5.23, and $P = 0.04$). Similar associations were observed when non-HDLC values were examined on a continuous scale.

In the sex-specific analysis, the age-adjusted incidence of CHD significantly increased with elevating non-HDLC level in both men and women (P for trend = 0.02 for men and 0.003 for women, data not shown). After adjustment for other confounding factors, this association remained significant for women (P for trend = 0.03), but not for men (P for trend = 0.15, P for heterogeneity = 0.32). Sex-specific analysis for subtypes of ischemic stroke was not available because of the small numbers of events.

To assess whether non-HDLC levels could be beneficial for predicting the residual risk of developing cardiovascular disease beyond LDLC levels, we investigated the association between non-HDLC levels and the risk of developing cardiovascular disease defined by CHD and noncardioembolic infarction (excluding cardioembolic infarction from ischemic stroke) while taking LDLC levels into account. Subjects in a fasting state (n = 2350) were

Table 1
Age- and sex-adjusted mean values or frequencies of risk factors for cardiovascular disease according to non-HDL cholesterol quartiles at baseline.

Risk factor	Quartile of non-HDL cholesterol levels, mmol/L				P value for trend
	≤3.14 (n = 601)	3.15–3.77 (n = 620)	3.78–4.49 (n = 623)	≥4.50 (n = 608)	
Age, years	56.7 ± 11.6	57.3 ± 11.5	58.1 ± 11.5	59.0 ± 11.6	0.004
Men, %	52.7	44.8	41.0	37.4	<0.001
Total cholesterol, mmol/l	4.00 ± 0.53	4.81 ± 0.53	5.38 ± 0.53	6.46 ± 0.53	<0.001
HDL cholesterol, mmol/l	1.40 ± 0.37	1.35 ± 0.36	1.30 ± 0.36	1.27 ± 0.37	<0.001
Triglycerides, mmol/l	0.82 (0.79–0.85)	0.97 (0.94–1.01)	1.13 (1.09–1.17)	1.44 (1.39–1.49)	<0.001
Diabetes mellitus, %	4.5	4.6	5.0	8.6	0.02
Body mass index, kg/m^2	21.5 ± 3.0	22.2 ± 3.0	23.0 ± 3.0	23.9 ± 3.0	<0.001
Systolic blood pressure, mmHg	132 ± 20	133 ± 20	136 ± 20	138 ± 21	<0.001
Diastolic blood pressure, mmHg	79 ± 12	82 ± 12	82 ± 12	84 ± 12	<0.001
Hypertension, %	36.8	41.9	43.2	51.1	<0.001
Electrocardiogram abnormalities,[a] %	19.6	20.7	20.1	18.8	0.65
Current drinking, %	41.4	33.1	32.0	29.4	<0.001
Current smoking, %	30.8	27.1	29.0	28.7	<0.001
Regular exercise, %	9.2	6.3	8.7	5.2	0.06

Data are the means ± SD or percentages. The percentage of men was age-adjusted. The mean age was sex-adjusted.
Geometric mean values and 95% confidence intervals of triglycerides are shown because of the skewed distribution.
HDL: high-density lipoprotein.
[a] Minnesota codes, 3-1, 4-1, 2, 3 or 8-3.

Table 2
Age- and sex-adjusted incidence (per 1000 person-years) of cardiovascular disease according to non-HDL cholesterol quartiles.

	Quartile of non-HDL cholesterol levels				P value for trend
	≤3.14 (n = 601)	3.15–3.77 (n = 620)	3.78–4.49 (n = 623)	≥4.50 (n = 608)	
Coronary heart disease					
No. of events	29	50	55	69	
Age- sex-adjusted incidence	3.3	4.8	5.4*	6.9†	<0.001
Stroke					
No. of events	80	79	86	107	
Age- sex-adjusted incidence	9.1	8.4	8.8	11.2	0.31
Ischemic stroke					
No. of events	56	56	59	75	
Age- sex-adjusted incidence	6.2	6.1	6.2	8.2	0.37
Atherothrombotic infarction					
No. of events	12	15	14	23	
Age- sex-adjusted incidence	1.3	1.6	1.5	2.8	0.098
Lacunar infarction					
No. of events	18	24	27	41	
Age- sex-adjusted incidence	2.0	2.4	2.5	4.0*	0.01
Cardioembolic infarction					
No. of events	25	16	17	11	
Age- sex-adjusted incidence	2.7	1.9	2.1	1.4†	0.007
Hemorrhagic stroke					
No. of events	24	23	27	32	
Age- sex-adjusted incidence	2.9	2.3	2.6	3.0	0.54

HDL: high-density lipoprotein. *: $P < 0.05$, †: $P < 0.01$ vs. the lowest quartile.

Table 3
Adjusted HRs and 95% CIs for the risks of cardiovascular disease according to non-HDL cholesterol quartiles.

	Quartile of non-HDL cholesterol levels					
	≤3.14 (n = 601)	3.15–3.77 (n = 620)	3.78–4.49 (n = 623)	≥4.50 (n = 608)	P value for trend	Continuous scale
Coronary heart disease						
No. of events	29	49	55	69		
Age- and sex-adjusted HR (95%CI)	1.00	1.53 (0.97–2.42)	1.73 (1.10–2.72)*	2.35 (1.51–3.65)†	<0.001	1.28 (1.13–1.46)§
Multivariable-adjusted HR (95%CI)	1.00	1.64 (1.00–2.71)	1.79 (1.09–2.95)*	1.96 (1.19–3.24)†	0.01	1.17 (1.02–1.35)‡
Stroke						
No. of events	80	79	86	107		
Age- and sex-adjusted HR (95%CI)	1.00	0.85 (0.62–1.16)	0.89 (0.65–1.20)	1.14 (0.85–1.52)	0.31	1.02 (0.91–1.33)
Multivariable-adjusted HR (95%CI)	1.00	0.84 (0.60–1.17)	0.90 (0.65–1.24)	1.08 (0.78–1.50)	0.47	1.01 (0.90–1.13)
Ischemic stroke						
No. of events	56	56	59	75		
Age- and sex-adjusted HR (95%CI)	1.00	0.86 (0.60–1.25)	0.88 (0.61–1.27)	1.16 (0.81–1.65)	0.37	1.04 (0.92–1.18)
Multivariable-adjusted HR (95%CI)	1.00	0.83 (0.56–1.23)	0.84 (0.57–1.24)	1.05 (0.71–1.54)	0.68	1.01 (0.89–1.16)
Atherothrombotic infarction						
No. of events	12	15	14	23		
Age- and sex-adjusted HR (95%CI)	1.00	1.12 (0.53–2.40)	1.05 (0.48–2.28)	1.83 (0.90–3.73)	0.098	1.28 (1.02–1.61)‡
Multivariable-adjusted HR (95%CI)	1.00	1.36 (0.59–3.12)	1.37 (0.59–3.18)	2.33 (1.04–5.23)*	0.04	1.39 (1.09–1.79)§
Lacunar infarction						
No. of events	18	24	27	41		
Age- and sex-adjusted HR (95%CI)	1.00	1.16 (0.63–2.13)	1.24 (0.68–2.26)	1.94 (1.11–3.40)	0.01	1.18 (0.99–1.42)
Multivariable-adjusted HR (95%CI)	1.00	0.99 (0.51–1.93)	1.10 (0.58–2.10)	1.61 (0.87–2.98)	0.07	1.10 (0.90–1.34)
Cardioembolic infarction						
No. of events	25	16	17	11		
Age- and sex-adjusted HR (95%CI)	1.00	0.54 (0.29–1.01)	0.55 (0.30–1.03)	0.37 (0.18–0.76)†	0.007	0.68 (0.52–0.90)§
Multivariable-adjusted HR (95%CI)	1.00	0.52 (0.27–0.996)*	0.49 (0.25–0.94)*	0.29 (0.13–0.64)†	0.002	0.64 (0.47–0.85)§
Hemorrhagic stroke						
No. of events	24	23	27	32		
Age- and sex-adjusted HR (95%CI)	1.00	0.82 (0.46–1.46)	0.93 (0.54–1.62)	1.12 (0.66–1.92)	0.54	0.98 (0.80–1.19)
Multivariable-adjusted HR (95%CI)	1.00	0.90 (0.49–1.66)	1.07 (0.59–1.93)	1.21 (0.66–2.21)	0.43	1.02 (0.82–1.26)

HDL: high-density lipoprotein; HR: hazard ratio; CI: confidence interval.
For the continuous scale, HR is given for each 1 SD increase in non-HDL cholesterol. *: $P < 0.05$, †: $P < 0.01$ vs. the lowest quartile; ‡$P < 0.05$, §$P < 0.01$.
Multivariable adjustment was made for age, sex, diabetes, body mass index, systolic blood pressure, electrocardiogram abnormalities,current drinking, current smoking, and regular exercise.

divided into four groups based on whether their LDLC levels were above or equal to/below 3.62 mmol/l [14] and whether their non-HDLC levels were above or equal to/below 4.40 mmol/l, which was calculated by adding 0.78 mmol/l to the cutoff value of LDLC [2,15]. As shown in Table 4, compared with the reference group with low non-HDL and low LDLC levels, the multivariable-adjusted risk of developing cardiovascular disease increased significantly in the group with high non-HDL and low LDLC levels as well as in other groups with high LDLC levels (multivariable-adjusted HR = 2.09, 95%CI = 1.06 to 4.11, and $P = 0.03$ for the group with high non-HDLC and low LDLC levels; multivariable-adjusted HR = 1.61, 95%CI = 1.08 to 2.40, and $P = 0.02$ for the group with low non-HDL and high LDLC levels; and multivariable-adjusted HR = 1.47, 95% CI = 1.13 to 1.90, and $P = 0.004$ for the group with high non-HDL and high LDLC levels).

3. Discussion

In a long-term prospective study of a general Japanese population, we demonstrated positive and significant associations between serum non-HDLC levels and the risks of developing CHD and atherothrombotic infarction, as well as a significant negative association between non-HDLC levels and the risk of cardioembolic infarction. These associations were significant after adjustment for other confounding factors. In addition, our findings provided evidence that high non-HDLC levels are a risk factor for atherothrombotic cardiovascular disease (CHD and noncardioembolic infarction) in subjects without high LDLC levels.

Some prospective studies have reported a positive association between non-HDLC levels in the blood and the risk of CHD [1,3,4,6,7]. These findings are in accordance with those of the present study. A few prospective studies have also investigated the influence of non-HDLC on the development of ischemic stroke [5–7], but the results were not unanimous. One prospective investigation performed as part of the Women's Health Study in the U.S. reported a significant positive association between non-HDLC levels and the risk of ischemic stroke in women [5], but two other Japanese cohort studies found no significant association [6,7]. In the present study, there was also no significant association between non-HDLC levels and total ischemic stroke. In the analysis stratifying ischemic stroke in subtypes, however, we identified a significant positive association between non-HDLC levels and atherothrombotic infarction, as well as a significant negative association with cardioembolic infarction. To the best of our knowledge, this is the first prospective cohort study to demonstrate significant associations between non-HDLC levels and the development of subtypes of ischemic stroke. The discordance of the results of prior epidemiologic studies investigating the association between non-HDLC and ischemic stroke may be due to this heterogeneity in the associations between non-HDLC and ischemic stroke subtypes.

Non-HDLC is an assembly of atherogenic lipoproteins, including LDLC and triglyceride-rich lipoproteins such as very-low-density lipoprotein. It has been hypothesized that elevated levels of serum non-HDLC represent elevated very-low-density lipoprotein and triglyceride-rich lipoprotein, especially in subjects with low levels of LDLC [16]. In our present study, the risk of developing atherothrombotic cardiovascular disease was significantly increased even in the group with high non-HDLC and low LDLC levels. The Framingham Study [3] reported a strong positive association between non-HDLC levels and risk of CHD development in subjects with low LDLC levels. These previous and our present findings support the statement by the NCEP-ATPIII [2] and imply that, among both Japanese and US individuals with low or normal LDLC levels, increased non-HDLC levels predict the residual risk of developing cardiovascular disease.

In our subjects, there was a significant negative association between non-HDLC levels and the development of cardioembolic infarction. We also observed in our earlier studies that low total cholesterol and LDLC levels were significant risk factors for the development of this subtype of ischemic stroke [8,17]. Although the reasons for these inverse associations remain unknown, a plausible explanation is that lowered cholesterol levels might increase the risk of the occurrence of atrial fibrillation [18,19], which is a predominant risk factor for cardioembolic infarction. Further clinical and experimental evidence is needed to clarify this association and its underlying mechanism.

The strengths of our study include its longitudinal population-based design, the long duration of follow-up, the almost perfect follow-up of subjects, and the accuracy of diagnosis of cardiovascular disease including ischemic stroke subtypes. Several limitations of our study should be noted. First, our findings are based on a one-time measurement of serum lipids. Subsequent use of cholesterol-lowering agents could have altered lipid levels in some participants; however, this source of variability could not account for the association observed in the present study, because a random misclassification of this nature would tend to cause an underestimation of study findings and to bias the results toward the null hypothesis. Therefore, the true association could be stronger than that observed in our study. Second, the subgroups in the stratified analysis with or without high non-HDLC and high LDLC levels may not have been large enough to allow analysis with reliable statistical power. Additional large-scale community-based studies are needed to clarify this issue. Finally, socioeconomic factors and dietary intake may confound the association between non-HDLC and incident cardiovascular disease. However, this information was not available at baseline in the present study.

In conclusion, we showed that elevated serum non-HDLC levels were a significant risk factor for the development of CHD and atherothrombotic infarction, but were negatively associated with risk of cardioembolic infarction in a general Japanese population. Furthermore, in subjects with low or normal LDLC levels, higher non-HDLC levels were associated with the development of atherothrombotic cardiovascular disease. The estimation of non-HDLC levels may help to screen individuals at risk of cardiovascular disease in public health and clinical settings, and the decrease of lipid levels may be a potential target for the prevention of cardiovascular disease. The influence of non-HDLC levels on the risk of cardioembolic infarction should be further evaluated by other cohort studies and intervention trials.

Table 4
Adjusted HRs and 95% CIs for the risks of cardiovascular disease according to the presence or absence of high non-HDLC and high LDLC.

	Low Non-HDLC / Low LDLC	High non-HDLC / Low LDLC	Low non-HDLC / High LDLC	High non-HDLC / High LDLC
No. of subjects	1519	35	189	607
No. of events	176	9	30	115
Age- and sex-adjusted HR (95%CI)	1	2.09 (1.07–4.10)	1.44 (0.97–2.11)	1.66 (1.31–2.11)
P value		0.03	0.07	<0.0001
Multivariable-adjusted HR (95%CI)	1	2.09 (1.06–4.11)	1.61 (1.08–2.40)	1.47 (1.13–1.90)
P value		0.03	0.02	0.004

HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; HR: hazard ratio; CI: confidence interval.
Multivariable adjustment was made for age, sex, diabetes, body mass index, systolic blood pressure, electrocardiogram abnormalities, current drinking, current smoking, and regular exercise.

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Disclosures

None.

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ORIGINAL ARTICLE
Renal Disease

Serum 1,25-Dihydroxyvitamin D and the Development of Kidney Dysfunction in a Japanese Community

– The Hisayama Study –

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Background: Recent evidence indicates that vitamin D deficiency is associated with an increased risk of renal impairment, but studies addressing the influence of vitamin D deficiency on the development of chronic kidney disease (CKD) in the general Asian population have been few.

Methods and Results: A total of 2,417 community-dwelling individuals without CKD stage 3–5 aged ≥40 years were followed for 5 years (mean age, 60 years; women, 59.1%). The cumulative incidence of CKD stage 3–5, defined as estimated glomerular filtration rate (eGFR) <60 ml·min^{-1}·1.73 m^{-2}, and the rate of decline in eGFR according to quartile of serum 1,25-dihydroxyvitamin D (1,25(OH)$_2$D), were estimated. During follow-up, 378 subjects experienced CKD stage 3–5. The age- and sex-adjusted incidence of CKD stage 3–5 increased significantly with decreasing serum 1,25(OH)$_2$D (P for trend <0.001). Compared with the highest quartile, the multivariate-adjusted odds ratio for the development of CKD stage 3–5 was 1.90 in the lowest quartile and 1.74 in the second lowest quartile, after adjusting for confounding factors. Additionally, lower serum 1,25(OH)$_2$D was significantly associated with a greater change in eGFR (–0.10 ml·min^{-1}·1.73 m^{-2}·year^{-1} per 10-pg/ml decrement in serum 1,25(OH)$_2$D).

Conclusions: Lower serum 1,25(OH)$_2$D is a significant risk factor for the development of CKD stage 3–5 in the general Asian population. (*Circ J* 2014; **78:** 732–737)

Key Words: 1,25-dihydroxyvitamin D; Chronic kidney disease; Epidemiology; Glomerular filtration rate

The burden generated by the expense of dialysis has been overwhelming in several countries in which the number of dialysis patients has increased continuously over the past few decades.[1] The early stages of chronic kidney disease (CKD) are likely to progress to end-stage kidney disease requiring costly dialysis or transplantation.[2] It is also increasingly apparent that individuals with CKD are more likely to develop cardiovascular disease.[3–8] These comorbidities related to CKD produce significant socioeconomic burden for patients, families, society, and the health-care system.[9,10] Thus, the identification and treatment of risk factors for the early stages of CKD will help prevent the progression of advanced kidney disease and reduce the risk of cardiovascular events.[11]

Editorial p599

Vitamin D has been recognized for decades as a key player in the control of bone metabolism through the regulation of calcium and phosphate homeostasis.[12] Vitamin D can be obtained from the diet and by the action of sunlight on the skin. The liver and kidney are the two primary sites for producing the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH)$_2$D), which is activated mainly in the kidney after vitamin D is hydroxylated in the liver at the 25-carbon atom (25(OH)D).[13] Growing evidence suggests that 1,25(OH)$_2$D is involved in cardiovascular disease, malignant disease, infectious disease, autoimmune disease, and more.[14–17] Additionally, several prospective studies have shown that vitamin D deficiency is as-

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