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N-Terminal Pro–B-Type Natriuretic Peptide and Incident CKD

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Introduction: Serum N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels have been associated with the progression of kidney impairment among patients with chronic kidney disease (CKD), but only a few studies have investigated the association between serum NT-proBNP levels and incident CKD in general populations.

Methods: A total of 2486 Japanese community-dwelling residents ≥40 years of age without CKD at baseline were followed up by repeated annual health examinations for 10 years. Participants were divided into 4 groups according to serum NT-proBNP levels. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 or the presence of proteinuria. Cox proportional hazards models were used to estimate hazard ratios (HRs) for risk of CKD. Linear mixed models were used to compare changes in eGFR.

Results: During the follow-up period, 800 participants developed CKD. The multivariable-adjusted HRs (95% confidence intervals [CIs]) for developing CKD were 1.00 (reference), 1.32 (1.11–1.57), 1.40 (1.10–1.78), and 1.94 (1.38–2.73) for serum NT-proBNP levels of <55, 55–124, 125–299, and ≥300 pg/ml, respectively (*P* for trend <0.001). The decline of eGFR during the follow-up was significantly more rapid among participants with higher serum NT-proBNP levels (*P* for trend <0.001). Adding serum NT-proBNP to the model composed of known risk factors for CKD improved the predictive ability for developing CKD.

Conclusions: Higher serum NT-proBNP levels were associated with greater risks of developing CKD and greater decline in eGFR. Serum NT-proBNP could be a useful biomarker for assessing the future risk of CKD in a general Japanese population.

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CKD, which is characterized by decreased kidney function or persistent kidney damage, has been recognized as a significant public health problem.[1] Progression of CKD leads to end-stage kidney disease requiring kidney replacement therapy, which is an economic burden in various countries,[2] including Japan.[3] In addition, CKD has been associated with increased risks of cardiovascular disease and premature death.[4] Identification of useful risk factors for the development of CKD will help to build an effective preventive strategy for end-stage kidney disease.

B-type natriuretic peptide (BNP) is a hormone secreted into the circulating blood from cardiomyocytes in response to increasing pressure or volume load.[5] Plasma or serum concentrations of BNP and NT-proBNP, an N-terminal fragment of the prohormone of BNP, are widely used in clinical practice as biomarkers of heart failure.[6,7] On the other hand, subclinical increase in circulating NT-proBNP levels has been reported to be associated with a higher risk of the development of cardiovascular disease,[8,9] even in individuals without clinically apparent signs and symptoms of heart failure. Serum NT-proBNP levels

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have been reported to reflect the extent of systemic arteriosclerosis[10,11] and subclinical cardiac abnormalities.[12,13] Arteriosclerosis is a potential risk factor for the deterioration of kidney function,[14] and it is reasonable to conjecture that elevated serum NT-proBNP levels would be associated with a higher risk of developing CKD.

Several hospital-based studies have shown that serum NT-proBNP levels are associated with the progression of kidney impairment in patients with CKD.[15–21] However, only 3 community-based prospective studies have investigated the association of plasma BNP or serum NT-proBNP levels with the risk of CKD.[22–24] Moreover, no studies have addressed the potential use of serum NT-proBNP as a biomarker to improve the prediction of future onset of CKD. Thus, this study aimed to assess the association of serum NT-proBNP levels with the development of CKD and the ability of serum NT-proBNP to predict the development of CKD in a general Japanese population.

METHODS

Study Population and Follow-Up Survey

The Hisayama Study is an ongoing population-based prospective cohort study of cardiovascular disease and its risk factors in the town of Hisayama, located on Kyushu Island, Japan. Details of the study were described previously.[25,26] We conducted a screening survey for the residents from June 29, 2007 to August 30, 2008. A total of 3384 residents ≥40 years of age (participation rate 78.2%) underwent the baseline health examination. We excluded 8 subjects who did not consent to participate in the study, 75 subjects for whom no blood nor urine samples were obtained, 542 because of the presence of CKD, 14 who lacked data on serum NT-proBNP, and 23 who lacked baseline data on covariates. A total of 2722 participants were eligible to be followed-up by repeated annual health examinations until March 9, 2018. After excluding 236 participants who did not receive any health examinations during the follow-up period, 2486 subjects (91.3%; 1028 men and 1458 women) were included in the present analysis. During this period, 421 subjects were censored before the final follow-up survey in 2017 to 2018; this number included 137 subjects who died and 284 subjects who did not participate in the final follow-up survey. The median number of annual health examination visits during the follow-up period was 9 (interquartile range 5–10) per person.

The present study was approved by the Kyushu University Institutional Review Board for Clinical Research and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Measurement of Serum NT-proBNP

Frozen serum samples were collected at the baseline survey, and these were thawed in 2009 to measure serum NT-proBNP concentrations. Therefore, only baseline data of serum NT-proBNP were available. Serum NT-proBNP levels were measured by the Elecsys proBNP Immunoassay (Roche Diagnostics, Risch, Switzerland) in 2009.[27] Participants were divided into 4 groups based on their serum NT-proBNP levels, i.e., serum NT-proBNP<55, 55–124, 125–299, and ≥300 pg/ml, according to the guidelines of the American Heart Association and the European Society of Cardiology, and previous studies.[6,7,9]

Definition of Study Outcomes

The main outcome was the development of CKD, defined as eGFR <60 ml/min/1.73m^2 or the presence of proteinuria during the follow-up period. We also used each component of the CKD definition as a secondary outcome. eGFR levels and urinary protein were evaluated at the annual health examinations during the follow-up. eGFR was calculated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation modified by the Japanese coefficient.[28] Proteinuria was determined as urinary protein ≥1 using urinary qualitative test strips. As an alternative outcome measure, the annual change rate in eGFR was calculated as follows: annual change rate in eGFR (ml/min/1.73m^2/year) = (eGFR at each follow-up time point [ml/min/1.73m^2] − eGFR at baseline [ml/min/1.73m^2])/follow-up duration at each time point (years).

Measurement of Other Risk Factors

Self-administered questionnaires containing the baseline information on smoking habits, alcohol consumption, regular exercise, medications, and medical history were completed by each participant and confirmed by well-trained interviewers. Detailed information on measurement of other risk factors is provided in the Supplementary Methods.

Statistical Analysis

Trends in the mean values and frequencies of risk factors across serum NT-proBNP levels were tested by using a linear regression analysis and Cochran-Armitage test, respectively. The HRs and 95% CIs of serum NT-proBNP levels on the development of CKD were calculated by using a Cox proportional hazard model. The proportional hazards assumption was checked graphically using the log cumulative hazard plot. There were no violations from this assumption. Participants were censored at the latest occasion of the

follow-up survey. The time scale of the follow-up period was in years. Events occurring at the same time were dealt with by using the exact method. We also performed a competing risk analysis using the method proposed by Fine and Gray, in which all-cause death was treated as a competing event. The least-square means of the annual change rate in eGFR over time were evaluated according to the serum NT-proBNP levels by using a general linear mixed model with a random slope, including the interaction term between serum NT-proBNP levels and the number of visit years during the follow-up period. This model allows for comparisons in the annual change rate between the groups.[29] We assumed a first-order autoregressive working correlation matrix and chose the restricted maximum likelihood method for the covariance parameter estimation. To compare the accuracy of risk assessment for incident CKD between the models including known risk factors for CKD with and without serum NT-proBNP levels, the increase in Harrell's C statistics in each model was calculated and tested using a method reported by Newson.[30] The improvement of predictive ability was further investigated in 2 ways: by continuous net reclassification improvement (NRI) and by integrated discrimination improvement (IDI).[31,32] We performed the following sensitivity analyses: 1) an analysis using quintiles of serum NT-proBNP concentration; 2) an analysis using a Poisson regression analysis; 3) an analysis in which incident CKD was defined as an eGFR <60 ml/min/1.73m^2 or the presence of proteinuria at least twice during the follow-up period; 4) an analysis among subjects without apparent heart disease or serum NT-proBNP of $\geq$900 pg/ml[6]; 5) an analysis among subjects without occult hematuria; 6) an analysis among subjects with detailed information of antihypertensive medications; and 7) an analysis among subjects who visited the annual health examinations $\geq$3 times during the follow-up period. A 2-sided value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Table 1 shows the baseline characteristics of the participants according to the serum NT-proBNP level. Subjects with higher serum NT-proBNP levels were older. The mean values of systolic blood pressure, serum high-density lipoprotein cholesterol, and serum high-sensitivity C-reactive protein and the frequencies of hypertension, use of antihypertensive medication, use of lipid-modifying medication, hematuria, electrocardiogram abnormalities, heart murmur, and history of ischemic heart disease significantly increased with higher serum NT-proBNP levels. Conversely, the mean values of serum total cholesterol, serum low-density lipoprotein cholesterol, serum triglycerides, body mass index, and eGFR decreased significantly with elevating serum NT-proBNP levels. The mean values of serum uric acid and the frequency of men, dyslipidemia, current smokers, and current drinkers according to the increase in serum NT-proBNP levels appeared to have a U-shaped association, but these associations showed a statistically significant negative trend.

During the follow-up period, 800 participants experienced CKD, of whom 688 had kidney dysfunction and 195 had proteinuria. None of the participants developed end-stage kidney disease, which was defined as eGFR <15 ml/min/1.73m^2. As shown in Table 2, an increase in serum NT-proBNP levels was significantly associated with a higher risk of developing CKD after adjusting for potential risk factors—namely, age, sex, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, use of lipid-modifying medication, body mass index, serum uric acid, eGFR at baseline, current smoking, current drinking, regular exercise, and serum high-sensitivity C-reactive protein (P for trend <0.001). As compared with subjects with serum NT-proBNP levels <55 pg/ml, subjects with serum NT-proBNP levels of 55–124, 125–299, and $\geq$ 300 pg/ml had 1.32-, 1.40-, and 1.94-fold higher risks of incident CKD in the multivariable-adjusted analysis, respectively. There were similar upward trends in the risks of developing kidney dysfunction and proteinuria across serum NT-proBNP levels (P for trends <0.001 and 0.02, respectively). These significant associations were still present after additionally adjusting for covariates of apparent heart disease, such as electrocardiogram abnormalities, heart murmur, and history of ischemic heart disease (Table 2). In addition, the findings were not changed substantially in the analysis using quintiles of serum NT-proBNP concentration; in the analysis using the Poisson regression model; in the analysis in which CKD was defined as an eGFR <60 ml/min/1.73m^2 or the presence of proteinuria at least twice during the follow-up period; in the analysis among subjects without apparent heart disease or serum NT-proBNP of $\geq$900 pg/ml[6]; in the analysis among subjects without hematuria; in the analysis among subjects with detailed information of antihypertensive medications; or in the analysis among subjects who visited the annual health examinations $\geq$3 times during the follow-up period (Supplementary Table S1). We also investigated the association between serum NT-proBNP levels and incident CKD using the method proposed by

Table 1. Baseline characteristics of the study subjects according to the serum NT-proBNP levels, 2007–2008

	Serum NT-proBNP levels, pg/ml				
	<55 (n = 1327)	55–124 (n = 797)	125–299 (n = 286)	≥300 (n = 76)	P for trend
Age, yrs	57 (9)	64 (11)	70 (11)	72 (9)	<0.001
Male, %	48.8	31.0	32.9	52.6	<0.001
Systolic blood pressure, mm Hg	128 (18)	131 (18)	135 (19)	135 (21)	<0.001
Diastolic blood pressure, mm Hg	79 (11)	79 (11)	79 (10)	78 (12)	0.11
Hypertension, %	37.7	46.0	60.5	64.5	<0.001
Use of antihypertensive medication, %	21.3	29.5	39.5	50.0	<0.001
Use of calcium channel blockers, %[a]	19.0	23.0	32.9	32.9	<0.001
Use of ARBs or ACE inhibitors, %[a]	10.9	15.4	19.5	39.5	<0.001
Use of beta-blockers, %[a]	3.2	4.7	9.2	18.4	<0.001
Use of diuretics, %[a]	1.5	2.6	3.2	13.2	<0.001
Diabetes mellitus, %	11.1	10.0	11.2	15.8	0.64
Serum total cholesterol, mmol/l	5.5 (0.9)	5.4 (0.9)	5.3 (0.9)	5.0 (0.9)	<0.001
Serum LDL cholesterol, mmol/l	3.3 (0.8)	3.2 (0.8)	3.1 (0.8)	2.9 (0.8)	<0.001
Serum HDL cholesterol, mmol/l	1.7 (0.5)	1.8 (0.5)	1.8 (0.5)	1.7 (0.4)	0.001
Serum triglycerides, mmol/l	1.2 (0.8–1.7)	1.0 (0.8–1.5)	1.1 (0.7–1.5)	1.1 (0.8–1.7)	<0.001
Dyslipidemia, %	55.1	49.6	46.2	60.5	0.04
Use of lipid-modifying medication, %	11.3	15.2	17.8	34.2	<0.001
Body mass index, kg/m^2	23.5 (3.3)	22.7 (3.4)	22.0 (3.1)	22.5 (3.5)	<0.001
Serum uric acid, mmol/l	0.31 (0.08)	0.29 (0.08)	0.28 (0.08)	0.33 (0.08)	<0.001
eGFR, ml/min/1.73m^2	80 (8)	76 (8)	73 (8)	71 (7)	<0.001
Hematuria, %	13.9	11.3	14.0	19.7	0.002
Electrocardiogram abnormalities, %[b]	8.9	11.8	24.1	57.9	<0.001
Heart murmur, %	0.5	1.3	2.4	7.9	<0.001
History of ischemic heart disease, %	0.4	1.6	4.5	5.3	<0.001
Current smoker, %	24.3	15.6	14.0	21.1	<0.001
Current drinker, %	56.4	44.9	36.7	46.1	<0.001
Regular exercise, %	11.8	12.8	11.2	14.5	0.70
Serum hs-CRP, mg/l	0.39 (0.18–0.77)	0.37 (0.17–0.75)	0.37 (0.16–0.78)	0.69 (0.26–1.53)	0.004

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; HDL cholesterol, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein. LDL cholesterol, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro–B-type natriuretic peptide.
Values are shown as mean (standard deviation), median (interquartile range), or frequency.
[a]The 47 subjects who had missing values were excluded.
[b]Electrocardiogram abnormalities were defined as left ventricular hypertrophy (Minnesota Code, 3-1), ST depression (4-1, 4-2, or 4-3), or atrial fibrillation or atrial flutter (8-3).

Table 2. Risk of developing CKD and its components according to the serum NT-proBNP levels, 2007–2018

Serum NT-proBNP levels, pg/ml	Subjects at risk, n	Events, n	Age- and sex-adjusted model			Multivariable-adjusted model 1[a]			Multivariable-adjusted model 2[b]		
			HR (95% CI)	P value	P for trend	HR (95% CI)	P value	P for trend	HR (95% CI)	P value	P for trend
Chronic kidney disease[c]											
<55	1327	322	1.00 (reference)		<0.001	1.00 (reference)		<0.001	1.00 (reference)		<0.001
55–124	797	302	1.31 (1.11–1.55)	0.002		1.32 (1.11–1.57)	0.002		1.31 (1.10–1.56)	0.002	
125–299	286	129	1.35 (1.07–1.69)	0.01		1.40 (1.10–1.78)	0.006		1.39 (1.09–1.77)	0.009	
≥300	76	47	2.16 (1.57–2.99)	<0.001		1.94 (1.38–2.73)	<0.001		1.91 (1.34–2.72)	<0.001	
Kidney dysfunction[d]											
<55	1327	257	1.00 (reference)		<0.001	1.00 (reference)		<0.001	1.00 (reference)		<0.001
55–124	797	270	1.40 (1.16–1.68)	<0.001		1.38 (1.15–1.67)	<0.001		1.38 (1.14–1.66)	<0.001	
125–299	286	119	1.44 (1.13–1.83)	0.003		1.48 (1.14–1.91)	0.003		1.46 (1.12–1.90)	0.005	
≥300	76	42	2.23 (1.58–3.16)	<0.001		1.91 (1.33–2.76)	<0.001		1.92 (1.31–2.82)	<0.001	
Proteinuria[e]											
<55	1327	92	1.00 (reference)		0.04	1.00 (reference)		0.02	1.00 (reference)		0.08
55–124	797	63	1.10 (0.78–1.55)	0.59		1.17 (0.83–1.65)	0.37		1.15 (0.81–1.63)	0.43	
125–299	286	27	1.29 (0.81–2.06)	0.29		1.32 (0.81–2.15)	0.26		1.27 (0.78–2.08)	0.34	
≥300	76	13	2.47 (1.33–4.56)	0.004		2.72 (1.44–5.15)	0.002		2.43 (1.24–4.74)	0.009	

CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; NT-proBNP, N-terminal pro–B-type natriuretic peptide.
[a]Adjusted for age, sex, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, use of lipid-modifying medication, body mass index, serum uric acid, estimated glomerular filtration rate at baseline, current smoking, current drinking, regular exercise, and serum high-sensitivity C-reactive protein.
[b]Adjusted for covariates included in the multivariable-adjusted model 1 and covariates of apparent heart disease—namely, electrocardiogram abnormalities, heart murmur, and history of ischemic heart disease.
[c]Estimated glomerular filtration rate <60 ml/min/1.73m^2 and/or urinary protein ≥1+.
[d]Estimated glomerular filtration rate <60 ml/min/1.73m^2.
[e]Urinary protein ≥1+.

Table 3. Multivariable-adjusted hazard ratios for developing CKD according to the serum NT-proBNP levels in the subgroups with presence or absence of individual risk factors

Variables	Subjects at risk, *n*	Incident CKD, *n*	Hazard ratio (95% CI) for serum NT-proBNP levels				*P* for trend	*P* for interaction
			<55 pg/ml	55–124 pg/ml	125–299 pg/ml	≥300 pg/ml		
Age, yrs								
<65	1542	324	1.00 (reference)	1.56 (1.21–2.01)	1.66 (1.03–2.68)	3.45 (1.59–7.51)	<0.001	0.03
≥65	944	476	1.00 (reference)	1.08 (0.86–1.36)	1.07 (0.81–1.42)	1.52 (1.03–2.23)	0.11	
Sex								
Women	1458	425	1.00 (reference)	1.34 (1.06–1.71)	1.29 (0.92–1.80)	2.39 (1.43–4.00)	0.005	0.44
Men	1028	375	1.00 (reference)	1.25 (0.97–1.62)	1.60 (1.13–2.27)	1.62 (1.02–2.58)	0.003	
Hypertension								
No	1397	346	1.00 (reference)	1.32 (1.03–1.69)	1.26 (0.85–1.87)	2.91 (1.60–5.28)	0.004	0.16
Yes	1089	454	1.00 (reference)	1.39 (1.09–1.76)	1.61 (1.18–2.18)	1.82 (1.19–2.77)	<0.001	
Diabetes mellitus								
No	2215	676	1.00 (reference)	1.39 (1.16–1.68)	1.50 (1.16–1.94)	2.44 (1.69–3.52)	<0.001	<0.001
Yes	271	124	1.00 (reference)	1.09 (0.68–1.74)	0.78 (0.37–1.63)	0.67 (0.24–1.89)	0.40	
Dyslipidemia								
No	1182	341	1.00 (reference)	1.16 (0.89–1.52)	1.07 (0.74–1.55)	2.94 (1.77–4.87)	0.01	0.12
Yes	1304	459	1.00 (reference)	1.51 (1.20–1.89)	1.89 (1.37–2.60)	1.47 (0.92–2.34)	<0.001	
Obesity								
No	1864	563	1.00 (reference)	1.39 (1.13–1.70)	1.39 (1.06–1.83)	1.95 (1.29–2.95)	<0.001	0.63
Yes	622	237	1.00 (reference)	1.37 (0.99–1.88)	1.64 (0.94–2.87)	3.44 (1.77–6.67)	<0.001	
Serum uric acid, mg/dl[a]								
<4.9	1187	331	1.00 (reference)	1.52 (1.15–2.00)	1.61 (1.11–2.35)	3.07 (1.64–5.77)	<0.001	0.71
≥4.9	1299	469	1.00 (reference)	1.23 (0.98–1.54)	1.34 (0.98–1.85)	1.71 (1.13–2.60)	0.005	
Current smoking								
No	1983	665	1.00 (reference)	1.44 (1.19–1.73)	1.37 (1.05–1.78)	2.32 (1.59–3.39)	<0.001	0.57
Yes	503	135	1.00 (reference)	0.88 (0.56–1.37)	2.15 (1.18–3.91)	0.99 (0.42–2.30)	0.30	
Current drinking								
No	1240	430	1.00 (reference)	1.55 (1.22–1.97)	1.57 (1.15–2.16)	3.21 (2.01–5.13)	<0.001	0.29
Yes	1246	370	1.00 (reference)	1.14 (0.89–1.47)	1.24 (0.85–1.81)	1.15 (0.68–1.95)	0.27	
Regular exercise								
No	2184	684	1.00 (reference)	1.32 (1.10–1.60)	1.41 (1.09–1.83)	1.92 (1.33–2.77)	<0.001	0.95
Yes	302	116	1.00 (reference)	1.29 (0.80–2.07)	1.19 (0.63–2.27)	3.58 (1.30–9.89)	0.09	
Serum hs-CRP, mg/l[a]								
<0.39	1250	366	1.00 (reference)	1.33 (1.03–1.71)	1.67 (1.18–2.37)	2.56 (1.34–4.90)	<0.001	0.32
≥0.39	1236	434	1.00 (reference)	1.27 (1.01–1.61)	1.12 (0.79–1.57)	1.85 (1.23–2.79)	0.02	

CI, confidence interval; CKD, chronic kidney disease; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro–B-type natriuretic peptide.
Models were adjusted for each of age, sex, systolic blood pressure, antihypertensive medication, diabetes mellitus, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, use of lipid-modifying medication, body mass index, serum uric acid, estimated glomerular filtration rate at baseline, current smoking, current drinking, regular exercise, and serum hs-CRP, except the variable relevant to the individual subgroup.
[a]The median of each variable relevant to the individual subgroup.

Fine and Gray, in which all-cause death was treated as a competing event, because subjects with higher serum NT-proBNP levels were likely to have a greater mortality risk. As a consequence, the multivariable-adjusted risk of incident CKD was still increased significantly with elevating serum NT-proBNP levels (Supplementary Table S2).

We also performed a subgroup analysis by each risk factor (Table 3). There was no evidence of interaction in the association of serum NT-proBNP levels with the risk of CKD (all *P* for interaction >0.12), except for age and diabetes mellitus (both *P* for interaction ≤0.03). Compared with subjects <65 years of age, the magnitudes of the association between serum NT-proBNP and the development of CKD were attenuated in subjects 65 years of age, although subjects with serum NT-proBNP of ≥300 pg/ml had a significantly greater risk of CKD. A significant positive association of serum NT-proBNP with CKD was observed in subjects without diabetes, but no clear association was detected in subjects with diabetes.

Next, we investigated the association of serum NT-proBNP levels with the annual change rate in eGFR. Subjects with higher serum NT-proBNP levels had a significantly greater annual decline rate in eGFR across the entire follow-up period, with adjustment for the potential risk factors (*P* for trend <0.001; Figure 1).

To investigate the influence of serum NT-proBNP levels on the accuracy of risk assessment for developing CKD, we evaluated the difference in Harrell's C statistics, continuous NRI, and IDI by adding serum NT-proBNP levels to the basic model consisting of the

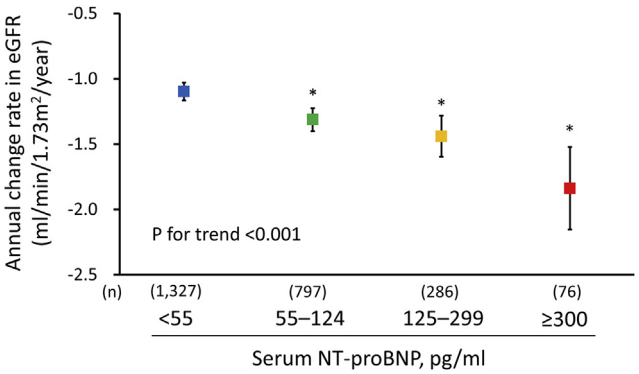

Figure 1. The annual change rates in the estimated glomerular filtration (eGFR) according to the serum N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels. The annual change rates of eGFR were adjusted for age, sex, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, use of lipid-modifying medication, body mass index, serum uric acid, estimated glomerular filtration rate at baseline, current smoking, current drinking, regular exercise, and serum high-sensitivity C-reactive protein. Boxes indicate the point estimates and bars indicate the 95% confidence intervals of the annual change rates of eGFR. *$P < 0.001$ vs. serum NT-proBNP levels of <55 pg/ml.

aforementioned potential risk factors for CKD (Table 4). The predictive performance of the model was significantly improved by adding serum NT-proBNP levels (difference in Harrell's C statistics, $P = 0.13$; continuous NRI = 0.096, $P = 0.03$; and IDI = 0.005, $P = 0.003$). The predictive performance was not altered in the analysis among the subgroups of nondiabetic subjects (Supplementary Table S3; difference in Harrell's C statistics, $P = 0.17$; continuous NRI = 0.115, $P = 0.01$; IDI = 0.008, $P < 0.001$) or in the analysis using the Kidney Failure risk equation consisting of age, sex, and eGFR as the basic model[33] (Supplementary Table S4; difference in Harrell's C statistics, $P = 0.11$; continuous NRI = 0.439, $P < 0.001$; IDI = 0.053, $P < 0.001$). We further performed an analysis in which covariates of apparent heart disease (i.e., electrocardiogram abnormalities, heart murmur, and history of ischemic heart disease) were included in the basic model; the results showed that adding serum NT-proBNP levels to the basic model including covariates of apparent heart disease also significantly improved NRI and IDI (Table 4).

DISCUSSION

This prospective cohort study of a community-dwelling Japanese population found that increasing serum NT-proBNP levels were significantly associated with higher risks of CKD. A similar association was observed for the risk of developing each component of CKD—namely, kidney dysfunction and proteinuria. The decline of eGFR during the follow-up was significantly more rapid among participants with higher serum NT-proBNP levels. The incorporation of serum NT-proBNP levels into the model consisting of potential risk factors for CKD improved the predictive ability for the development of CKD. These findings may provide insights into the clinical utility of serum NT-proBNP measurement as a useful biomarker for predicting future risk of CKD in the general population.

Two previous prospective studies targeting residents in the United States have reported that elevated serum/plasma natriuretic peptide levels were associated with an increased risk of CKD.[22,23] Fox *et al.*[22] reported that elevating plasma BNP was associated with the development of microalbuminuria.[22] The other report by Bansal *et al.*[23] showed an association between serum NT-proBNP levels and the development of decreased kidney function in a general elderly population. However, the applicability of these findings to Asian populations has not been clear, because the results from 2 population-based studies with multiethnic populations found that serum NT-proBNP levels vary among races, with a lower concentration in black and Chinese individuals compared with white individuals.[34,35] Recently, the Ohasama Study, a population-based study of 867 individuals from a Japanese community, showed that elevated serum NT-proBNP levels were associated with the development of CKD.[24] Taken together, the findings from our present study and the previous studies suggest that serum

Table 4. The predictive ability of serum NT-proBNP levels for the development of CKD, 2007–2018

Model	Harrell's C-statistics (95% CI)	*P* value for Harrell's C-statistics difference	Continuous NRI (95% CI)	*P* value for NRI	IDI (95% CI)	*P* value for IDI
Basic model[a]	0.832 (0.815–0.848)	0.13	0.096 (0.012–0.180)	0.03	0.005 (0.002–0.008)	0.003
Basic model[a] + log (serum NT-proBNP levels)	0.834 (0.817–0.850)					
Basic model[a] + apparent heart disease[b]	0.832 (0.816–0.848)	0.12	0.043 (0.019–0.187)	0.02	0.005 (0.002–0.008)	0.004
Basic model[a] + apparent heart disease[b] + log (serum NT-proBNP levels)	0.834 (0.817–0.850)					

CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification index; NT-proBNP, N-terminal pro–B-type natriuretic peptide.
[a]Basic model: age, sex, systolic blood pressure, antihypertensive medication, diabetes mellitus, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, use of lipid-modifying medication, body mass index, serum uric acid, estimated glomerular filtration rate at baseline, current smoking, current drinking, regular exercise, and serum high-sensitivity C-reactive protein.
[b]Electrocardiogram abnormalities, heart murmur, and history of ischemic heart disease were included in the model as covariates of apparent heart disease.

NT-proBNP levels are a significant risk factor for CKD in the general Japanese population, which has lower average NT-proBNP levels than the general population in the United States.

We performed several sensitivity analyses. Participants who met CKD criteria based on a one-time eGFR <60 ml/min/1.73m^2 or positive proteinuria might have included those with transient statuses, such as cystitis or dehydration. However, when CKD was defined as eGFR <60 ml/min/1.73 m^2 or positive proteinuria on ≥2 separate measurements, serum NT-proBNP levels were significantly associated with the incident CKD. Furthermore, to exclude the subjects with apparent heart diseases, we performed the sensitivity analysis by excluding subjects with electrocardiogram abnormalities, heart murmur, history of ischemic heart disease, and serum NT-proBNP levels ≥900 pg/ml, which resulted in no substantial change in the association between serum NT-proBNP levels and incident CKD. The other sensitivity analyses revealed the consistency of our findings. Taken together, the results of these sensitivity analyses show the robustness of the association between serum NT-proBNP levels and incident CKD, even when considering the chronicity of kidney dysfunction, the existence of apparent heart diseases, and so on.

Subjects with elevated serum NT-proBNP levels at baseline are expected to have lower eGFR—as they did in the present study—because the metabolism of NT-proBNP depends mainly on excretion by filtration from the kidneys.[36] Therefore, the excess risk of developing CKD in subjects with higher serum NT-proBNP levels may simply reflect the subjects with lower eGFR at baseline, who would be more likely to reach the criteria of CKD during follow-up. Therefore, we investigated the association between serum NT-proBNP levels and the annual decline rate of eGFR across serum NT-proBNP levels. As a result, we found that the annual decline in eGFR was increased in accordance with the elevation of serum NT-proBNP levels, suggesting that higher serum NT-proBNP levels were a significant risk factor for the progression of kidney impairment.

The present study demonstrated the additive value of serum NT-proBNP for predicting the development of CKD. There has been no previous report addressing the predictive ability of serum NT-proBNP for the development of CKD, except for a report in which a combination of biomarkers—i.e., plasma BNP, aldosterone, and homocysteine—improved the predictive ability for developing microalbuminuria.[22] In the present study, the difference in the Harrell's C statistics between the models with and without serum NT-proBNP did not achieve statistical significance. This was probably because of the insensitivity of the statistical test for the difference of C statistics, because the test describes rank order and does not take into account the magnitude of an individual's risk.[37,38] On the other hand, the addition of serum NT-proBNP to the model consisting of potential risk factors for CKD significantly improved NRI and IDI. These indices were proposed to quantify how well a new model reclassifies subjects compared with a basic model.[31,32] When serum NT-proBNP was added to the basic model, the NRI represented the sum of the percentage of participants with incident CKD reclassified into higher risk and that of participants without incident CKD reclassified into lower risk, resulting in a significant improvement in the NRI of 0.096. The IDI was the increment of the difference between the mean predicted probability for participants with CKD and without CKD when serum NT-proBNP levels were added to the basic model, and thus the IDI was significantly improved by 0.005. Furthermore, the addition of serum NT-proBNP levels to the basic models considering apparent heart disease or the model using the Kidney Failure risk equation as a basic model significantly improved NRI and IDI. Thus, we showed that adding serum NT-proBNP levels to the models improved NRI of 0.096 and IDI of 0.005, indicating that serum NT-proBNP can be a useful prognostic predictor of the development of CKD.

The present study showed that subclinical levels of serum NT-proBNP for heart failure (e.g., 55–124 pg/ml) were significantly associated with increased risk of developing CKD and a greater annual decline in eGFR. Progression of kidney impairment in patients with chronic heart failure has been given the name cardiorenal syndrome type 2.[39] The mechanism linking chronic heart failure and the progression of kidney dysfunction is considered to involve increased activity of the renin-angiotensin system, increased venous pressure, decreased cardiac output, etc. However, it has not been fully clarified how subclinically elevated levels of serum NT-proBNP in subjects without heart failure are involved in the development of CKD. Since several epidemiologic studies found that serum NT-proBNP levels, even within a subclinical range, are associated with the development of arteriosclerotic disease,[9,10,40] serum NT-proBNP levels may be a biomarker reflecting the accumulation of risk factors for arteriosclerosis in individuals without chronic heart failure. There may be unmeasured residual confounders that cannot be adequately explained by an accumulation of risk factors alone because the association remained significant even after adjusting for known potential risk factors.

We found that the magnitude of the association between serum NT-proBNP levels and CKD risk was

heterogeneous between age and diabetic status; i.e., no significant linear association was observed in subjects ≥65 years of age or in subjects with diabetes. The exact reason for the heterogeneous findings is unclear. The lack of a significant linear association between serum NT-proBNP levels and the risk of developing CKD among older people and diabetic subjects may merely reflect an influence of aging or diabetes mellitus itself, because aging and diabetes mellitus are known as strong risk factors for the development of CKD. Especially in patients with diabetes mellitus, previous studies have reported disparate results in regard to the association between NT-proBNP levels and the development of CKD.[41,42] One possible explanation is that diabetes mellitus contributed to incident CKD as a risk factor for not only arteriosclerosis but also diabetic nephropathy, and these contributions in turn may have contributed to the nonsignificant association between serum NT-proBNP levels and incident CKD among diabetic subjects. The influence of older age and diabetes mellitus on the association between serum NT-proBNP levels and incident CKD should be examined in other cohorts.

The strengths of the present study were its community-based prospective cohort study design and the high rate of participation in the annual health examinations. However, there were also some limitations. First, the serum NT-proBNP levels were based on a single measurement at baseline health examination. Serum NT-proBNP levels and other risk factors may have changed during follow-up, leading to misclassification, which may have attenuated the association between serum NT-proBNP levels and incident CKD found in the present study. Second, interval censoring caused by the inclusion of subjects with a small number of visits may have affected the results. However, when we performed a sensitivity analysis that excluded subjects with <3 follow-up visits, our results were not altered substantially, suggesting that this limitation did not appreciably affect our conclusions. Third, urinary protein was evaluated by urinary test strips, which a qualitative measure. In a future study, it would be useful to adopt a more quantitative measure of microalbuminuria. Fourth, we could not estimate the influence of proteinuria on the association between serum NT-proBNP levels and eGFR decline, because the number of subjects with proteinuria at baseline was small ($n = 102$) in this study. Fifth, there is possibility that residual confounding (e.g., the severity of hypertension and arteriosclerosis) may affect the present findings even after adjusting for potential confounders. Serum NT-proBNP is considered to be a biomarker reflecting sustained uncontrolled hypertension and subsequent hypertension-mediated organ damage and arterial sclerosis. However, we did not have available data on morphologic or functional cardiac information at baseline, such as echocardiography. Finally, it is unclear whether the conclusions of this Japanese community-based study can be generalized to other ethnic groups.

In conclusion, increased serum NT-proBNP levels were significantly associated with higher risks of CKD and greater annual decline rates in eGFR in a general Japanese population. Serum NT-proBNP significantly improved the predictive ability of the risk assessment model for CKD. These findings suggest that serum NT-proBNP could serve as a useful biomarker for predicting future risk of CKD in the general population.

DISCLOSURE

All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

Study concept and design: TS and TNi. Data collection: EO, SS, SC, YF, TH, DY, and JH. Data interpretation: TS, EO, TNa, SS, SC, YF, TH, DY, JH, and TNi. Statistical analysis: TS. Study coordination and performance: TNi. All authors contributed relevant intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions on the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods. Measurement of other risk factors.

Table S1. Sensitivity analyses for the association of serum N-terminal pro–B-type natriuretic peptide levels with the risk of developing chronic kidney disease, 2007 to 2018.

Table S2. Hazard ratios for developing chronic kidney disease according to the serum N-terminal pro–B-type natriuretic peptide levels using the method proposed by Fine and Gray, 2007 to 2018.

Table S3. The predictive ability of serum N-terminal pro–B-type natriuretic peptide levels for the development of chronic kidney disease among the participants without diabetes mellitus, 2007 to 2018.

Table S4. The predictive ability of serum N-terminal pro–B-type natriuretic peptide levels for the development of chronic kidney disease using Kidney Failure risk equation as the basic model, 2007 to 2018.

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