ORIGINAL ARTICLE

Risk factors for pre-heart failure or symptomatic heart failure based on NT-proBNP

Shoko Aoki[1], Kazumasa Yamagishi[1,2,3]*, Tomomi Kihara[1], Mari Tanaka[4,5], Hironori Imano[2,4,5], Isao Muraki[4], Yuji Shimizu[2], Mina Hayama-Terada[2,6], Mitsumasa Umesawa[1,7], Tomoko Sankai[8], Takeo Okada[2], Akihiko Kitamura[2,6], Masahiko Kiyama[2] and Hiroyasu Iso[1,4,9]

[1]Department of Public Health Medicine, Faculty of Medicine, and Health Services Research and Development Center, University of Tsukuba, Tsukuba, Japan; [2]Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka, Japan; [3]Ibaraki Western Medical Center, Chikusei, Japan; [4]Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Suita, Japan; [5]Department of Public Health, Kindai University, Osakasayama, Japan; [6]Yao City Public Health Center, Yao, Japan; [7]School of Medicine, Dokkyo Medical University, Mibu, Japan; [8]Department of Public Health and Nursing, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan; and [9]Institute for Global Health Policy Research Center, Bureau of International Health Cooperation, National Center for Global Health and Medicine, Tokyo, Japan

Abstract

Aims   Evidence on the risk factors for incident heart failure in Asia has been limited. We sought to identify the risk factors for pre-heart failure or symptomatic heart failure, based on N-terminal pro-B-type natriuretic peptide (NT-proBNP), in the Japanese general population.

Methods   We performed a retrospective cohort study based on the Circulatory Risk in Communities Study involving 5335 Japanese individuals whose NT-proBNP levels were measured between 2010 and 2015. Of these, 2768 people aged between 30 and 69 years who undertook annual cardiovascular risk surveys at least once between 1990 and 2000 were retrospectively eligible to be participants in this study. We performed multivariable logistic regression analyses to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of pre-heart failure or symptomatic heart failure defined as NT-proBNP >400 pg/ mL or as having a diagnosis of heart failure and taking medication for heart failure for several cardiovascular risk factors (body mass index, blood pressure, diabetes mellitus, total cholesterol, triglyceride, smoking status, drinking status).

Results   We identified 85 cases of heart failure. The multivariable ORs (95% CIs) were 5.70 (2.70–12.0) for body mass index of 27–29.9 kg/m^2 and 5.91 (2.19–16.0) for ≥30 kg/m^2 compared with 21–22.9 kg/m^2; 2.49(1.01–6.13) for systolic blood pressure of ≥160 mmHg vs. <130 mmHg; 2.87(1.23–6.68) for diastolic blood pressure of ≥100 mmHg vs. <80 mmHg; 5.16(2.14–12.4) for diabetes vs. non-diabetes; and 2.24 (0.92–5.49) for current smokers of ≥20 cigarettes/day vs. never smokers. The multivariable ORs (95% CIs) of the number of risk factors, defined as the sum of four risk factors (obesity, hypertension, diabetes, and current smoker) was 6.80 (3.69–12.5) for ≥2 risk factors vs. no risk factors.

Conclusions   The accumulation of these risk factors was associated with a graded higher risk of pre-heart failure or symptomatic heart failure.

Introduction

The prevalence and medical costs of heart failure are expected to increase along with population ageing.[1] Several risk factors for incident heart failure have been identified, including hypertension, obesity, diabetes, and smoking, but the studies evaluating the risk factors for incident heart failure were conducted mostly in Western countries,[2–16] and evidence among Asian populations has been scant. Because body composition, lifestyles,[17] and the aetiology and co-morbidities of heart failure[18] differ between Asian and Western countries, whether this relationship could apply in general Asian populations is unclear. In addition, the epidemiologic criteria for diagnosing incident heart failure

on the basis of various clinical symptoms are not established.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) has been used as a biomarker for detecting and monitoring heart failure. Ventricular dilation and cardiac overload enhance the production of pro-B-type natriuretic peptide (ProBNP) by myocardial cells. ProBNP is decomposed into NT-proBNP (inactive part) and BNP (active part), and these are then released into the bloodstream. NT-proBNP is more stable and remains in the bloodstream longer than BNP.[19] The importance of biomarkers that can be used to detect early-stage heart failure is increasing because biomarkers contribute to identification of risk and the presence of ultrastructural abnormalities in heart failure among asymptomatic patients and help to provide a treatment strategy for the prevention of symptomatic heart failure.[20]

The universal definition and classification of heart failure was launched in 2021[21] and included the concept of pre-heart failure. Individuals with pre-heart failure do not present any current or previous symptoms or signs of heart failure but do present evidence of at least one of the following: structural heart disease, abnormal cardiac function, elevated natriuretic peptide, or cardiac troponin levels.[21] We considered that NT-proBNP could be a useful and objective marker for detecting pre-heart failure and aimed to identify the risk factors for pre-heart failure or symptomatic heart failure based on NT-proBNP in a general Japanese population.

Participants and methods

Design and study population

The Circulatory Risk in Communities Study (CIRCS) is an ongoing dynamic community-based prospective study involving five communities in Japan. Details of the CIRCS protocol have been described elsewhere.[22] In the present study, we included two communities, Ikawa (a rural community of Akita Prefecture in north-eastern Japan) and Kyowa (a rural community of Ibaraki Prefecture in central-eastern Japan).

We performed a retrospective cohort study involving 5335 Japanese individuals whose NT-proBNP data were measured in follow-up check-ups in the Ikawa and Kyowa communities as part of annual cardiovascular risk surveys of the CIRCS from 2010 to 2015. NT-proBNP measurement was conducted once for each participant. Given that chronic kidney disease is known to increase NT-proBNP and that the usability of NT-proBNP as a criterion for diagnosing heart failure in patients with estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 was uncertain,[23] we excluded 61 people with eGFR <45 mL/min/1.73 m^2 in the follow-up check-ups.

We defined the baseline survey as the cardiovascular risk surveys conducted from 1990 to 2000 and excluded from the analysis participants who had not received this baseline survey when they were aged between 30 and 69 years. We also excluded those who met the following exclusion criteria: history of heart disease recorded on the baseline survey ($n = 101$), electrocardiogram (ECG) finding of atrial fibrillation on the baseline survey ($n = 5$), history of heart failure before the baseline survey ($n = 23$), and missing any of the variables ($n = 165$). In the end, the studied population comprised 2474 individuals (*Figure 1*). If multiple cardiovascular risk survey data were available, we used the oldest.
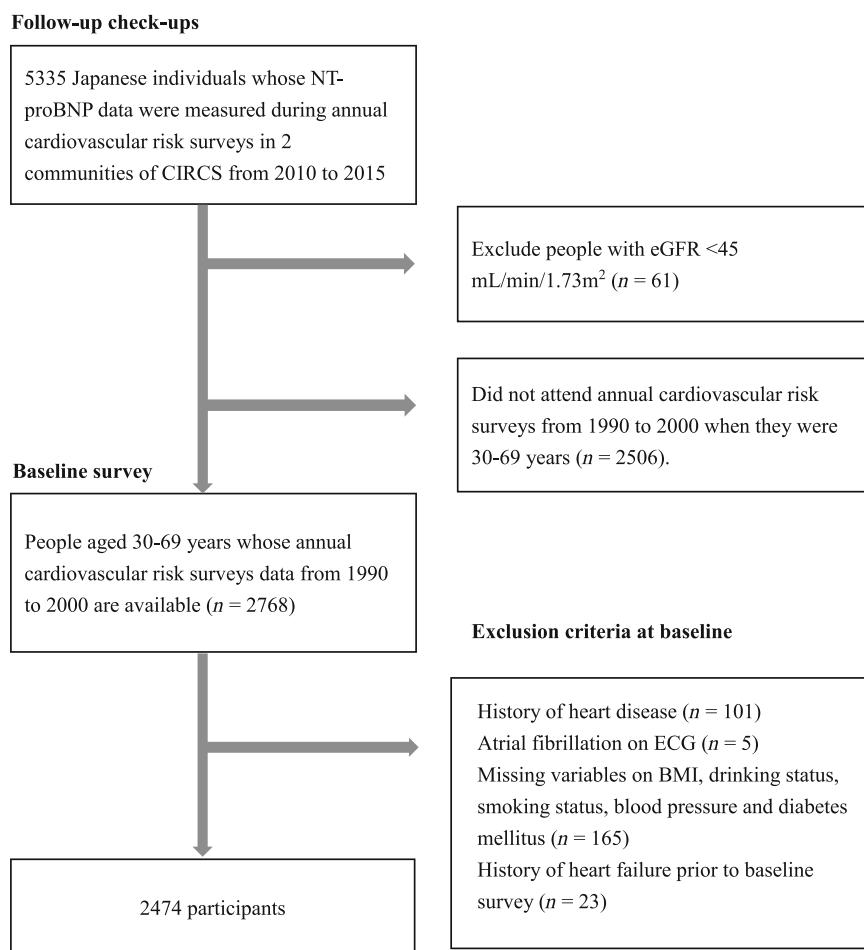
Definition of heart failure

We defined pre-heart failure or symptomatic heart failure as NT-proBNP ≥ 400 pg/mL or as having a diagnosis of heart failure and taking medication for heart failure at the follow-up check-ups, because of the National Institute for Health and Care Excellence guideline, suggesting that an NT-proBNP level <400 pg/mL in a person untreated for heart failure was unlikely to constitute a diagnosis of heart failure.[24] NT-proBNP was measured with a Cobas 8000 analyser (Roche Diagnostics Corporation, Indianapolis, USA) via electrochemiluminescence immunoassay at the Central Laboratory Tsukuba of Kotobiken Medical Laboratories, Inc (Tsukuba, Japan).

Baseline survey

Potential risk factors for pre-heart failure or symptomatic heart failure were measured at the baseline survey.[22] Height without shoes and weight in light clothing were measured, and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). In brief, the arterial systolic and fifth-phase diastolic blood pressures (DBP) were measured with standard mercury sphygmomanometers on the right arm of the participants, who were quietly seated after having rested for at least 5 min. If the first systolic blood pressure (SBP) reading was ≥ 140 mmHg and/or the DBP was ≥ 90 mmHg, the blood pressure measurement was repeated. For these cases, the second reading was used in the analysis; otherwise, the first reading was used. Serum glucose, total cholesterol, and triglyceride were measured using enzymatic methods without a fasting requirement. Face-to-face interviews were conducted to determine drinking (non-current or current) and smoking (never, ex, or current) statuses; use of antihypertensive medication, cholesterol-lowering medication, and/or diabetes medication; and past medical history. Serum creatinine was measured by use of the enzymatic method. We calculated the eGFR as follows: (mL/min per 1.73 m^2) = 194 × (serum creatinine) − 1.094 × (age) − 0.287 (× 0.739 for women).[25]

BMI was categorized into six groups (<21, 21–22.9, 23–24.9, 25–26.9, 27–29.9, and ≥ 30 kg/m^2), SBP into four groups

Figure 1 Flowchart of the study population selection.

Follow-up check-ups

5335 Japanese individuals whose NT-proBNP data were measured during annual cardiovascular risk surveys in 2 communities of CIRCS from 2010 to 2015

Exclude people with eGFR <45 mL/min/1.73m^2 ($n = 61$)

Did not attend annual cardiovascular risk surveys from 1990 to 2000 when they were 30-69 years ($n = 2506$).

Baseline survey

People aged 30-69 years whose annual cardiovascular risk surveys data from 1990 to 2000 are available ($n = 2768$)

Exclusion criteria at baseline

History of heart disease ($n = 101$)
Atrial fibrillation on ECG ($n = 5$)
Missing variables on BMI, drinking status, smoking status, blood pressure and diabetes mellitus ($n = 165$)
History of heart failure prior to baseline survey ($n = 23$)

2474 participants

(<130 mmHg, 130–139 mmHg, 140–159 mmHg, ≥160 mmHg), and DBP into four groups (<80 mmHg, 80–89 mmHg, 90–99 mmHg, ≥100 mmHg) using clinical cut-off points.[26] We categorized diabetes mellitus into three groups (normal: fasting glucose <110 mg/dL or non-fasting glucose <140 mg/dL; impaired glucose tolerance: 110 mg/dL ≤ fasting glucose <126 mg/dL or 140 mg/dL ≤ non-fasting glucose <200 mg/dL; and diabetes mellitus: fasting glucose ≥126 mg/dL or non-fasting glucose ≥200 mg/dL and/or taking medication) and serum total cholesterol into four groups (<180 mg/dL, 180–199 mg/dL, 200–219 mg/dL, and ≥220 mg/dL), and we divided triglyceride into quartiles (<70 mg/dL, 70–99 mg/dL, 100–150 mg/dL, and ≥151 mg/dL), smoking status into four groups (never smoker, ex-smoker, current smoker of <20 cigarettes/day, and current smoker of ≥20 cigarettes/day), and drinking status into five groups (never drinker, ex-drinker, current drinker of <23 g/day, current drinker of 23.0–45.9 g/day, and current drinker of ≥46 g/day). We also categorized each risk factor into presence and absence of the following risk factors: overweight (BMI of ≥27 kg/m^2), hypertension (SBP of ≥140 mmHg and/or DBP of ≥90 mmHg, and/or taking antihypertensive medication), diabetes mellitus (fasting glucose of ≥126 mg/dL or non-fasting glucose of ≥200 mg/dL and/or taking medication), and current smoking, and we examined the association with risk for pre-heart failure or symptomatic heart failure. We defined the number of risk factors as the sum of the above risk factors.

Statistical analysis

The baseline characteristics were compared between the cases and the non-cases and tested for differences between the mean values and proportions by means of analysis of covariance adjusted for age, sex, and community. We used logistic regression analysis to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of pre-heart failure or symptomatic heart failure. The model for the analysis of smoking status includes age, sex, community, blood pressure, serum total cholesterol, diabetes mellitus, medication for

hypertension, and medication for hyperlipidaemia. The model for the analysis of BMI and drinking status includes age, sex, community, serum total cholesterol, BMI, drinking status, smoking status, and medication of hyperlipidaemia. For the analysis of blood pressure, diabetes mellitus, and serum total cholesterol, we further included blood pressure, medication for hypertension and diabetes mellitus. For the analysis of triglyceride, we adjusted further for postprandial time (continuous). As for the number of risk factors, we adjusted for age, sex, and community and further adjusted for serum total cholesterol, drinking status, and medication for hyperlipidaemia. The participants of this study were those who attended both the baseline and the follow-up check-ups. To evaluate follow-up bias, we compared the baseline characteristics of the participants who were followed up with those who were not, testing differences in mean values and proportions by means of analysis of covariance or logistic regression analysis with adjustments for age, sex, and communities. Furthermore, as a supplemental analysis, we defined symptomatic heart failure as those with (i) NT-proBNP ≥ 400 pg/mL and having at least one of the following symptoms: waking up at night because of dyspnoea, shortness of breath on exertion, or swollen feet; or (ii) NT-proBNP ≥400 pg/mL and having a diagnosis of heart failure; or (iii) having a diagnosis of heart failure and taking medication for heart failure regardless of NT-proBNP levels (n = 48). We also calculated the ORs and 95% CIs. All probability values for the statistical tests were two tailed, and values below 0.05 were considered significant. We used SAS 9.4 (SAS Institute, Cary, NC, USA) for the analysis.

Ethics

Individual consent was not required for the analyses of this study because we used secondary data obtained for public health practice for cardiovascular disease prevention in local municipalities. Instead, at the follow-up check-up sites, the participants were given the information on the use of the data for research as well as the opportunity to withdraw their data from the analysis. The study was conducted according to the relevant guidelines and regulations and was approved by the institutional review boards of both the Osaka Center for Cancer and Cardiovascular Disease Prevention and the University of Tsukuba.

Results

A total of 85 people were identified as having pre-heart failure or symptomatic heart failure; 27 of those people had a diagnosis of and were using medication for heart failure at the follow-up check-ups, and the remaining 58 people had a test finding of NT-proBNP ≥400 pg/mL only.

Table 1 shows the age, sex, and community-adjusted baseline characteristics according to the cases and non-cases. The proportions of men, hypertensive medication use, and diabetes mellitus and the mean values of age, BMI, SBP, and triglyceride were significantly higher in the cases than in the non-cases.

During a median follow-up of 19 years, we observed significant positive associations between obesity, blood pressure, diabetes mellitus, and risk of pre-heart failure or symptomatic heart failure. The multivariable ORs (95% CIs) for persons with a BMI of <21, 23–24.9, 25–26.9, 27–29.9, and ≥30 kg/m^2 were 1.41 (0.66–3.00), 1.67 (0.82–3.38), 1.22 (0.52–2.82), 5.70 (2.70–12.0), and 5.91 (2.19–16.0), respectively, as compared with those with a BMI of 21–22.9 kg/m^2. Of note, when we used the cut-offs for BMI according to World Health Organization standards, the multivariable ORs and 95% CIs for pre-heart failure or symptomatic heart failure were 1.43 (0.42–4.79) for persons with BMI of

Table 1 Baseline characteristics of case and non-case participants

Number of participants	Cases (n = 85)	Non-cases (n = 2389)	P for difference
Age, year[a] mean ± SD	54.2 ± 7.9	47.4 ± 8.5	<0.0001
Male sex, %[a]	49.4	37.6	0.05
Current drinker, %[b]	42.7	35.5	0.08
Current smoker, %[b]	30.3	22.5	0.55
BMI, kg/m^2 [b] mean ± SD	24.7 ± 3.7	23.2 ± 3.0	0.001
Systolic blood pressure, mmHg[b] mean ± SD	134.3 ± 16.9	126.1 ± 15.8	0.003
Diastolic blood pressure, mmHg[b] mean ± SD	82.3 ± 13.2	78.5 ± 11.0	0.09
Hypertension medication use, %[b]	18.0	7.0	0.04
Diabetes mellitus, %[b]	9.0	2.0	<0.0001
Total cholesterol, mg/dL[b] mean ± SD	196.4 ± 37.2	193.5 ± 33.4	0.44
Triglyceride, mg/dL[b] mean ± SD	152.6 ± 107.5	122.5 ± 80.1	<0.0001
Cholesterol-lowering medication use, %[b]	0	1.1	0.11
Estimated glomerular filtration rate, mL/min/1.73 m^2 [b] mean ± SD	66.6 ± 12.2	69.0 ± 11.9	0.97
History of stroke, %[b]	1.1	0.5	0.38

[a]Adjusted for communities.
[b]Adjusted for communities, age, and sex.

$<$18.5 kg/m^2, 1.90 (1.16–3.12) for persons with BMI of 25–29.9 kg/m^2, and 4.38 (1.82–10.6) for persons with BMI of 30 kg/m^2 or higher, as compared with those with BMI of 18.5–24.9 kg/m^2 (data not shown). The multivariable ORs (95% CIs) were 1.04 (0.58–1.86) for persons with SBP of 130–139 mmHg, 1.86 (1.01–3.43) for those with SBP of 140–159 mmHg, and 2.49 (1.01–6.13) for those with SBP of $\geq$160 mmHg as compared with those with SBP of $<$130 mmHg. For DBP, the multivariable ORs (95% CIs) were 0.93 (0.53–1.61) for persons with DBP of 80–90 mmHg, 0.92 (0.43–1.96) for those with DBP of 90–99 mmHg, and 2.87 (1.23–6.68) for those with DBP of $\geq$100 mmHg as compared with those with DBP of $<$100 mmHg. As for diabetes, the multivariable ORs (95% CIs) for persons with impaired glucose tolerance and diabetes mellitus were 1.48 (0.79–2.80) and 5.16 (2.14–12.4), respectively, as compared with those with normal glucose tolerance. We observed a positive, but not significant association, between smoking and risk for pre-heart failure or symptomatic heart failure. The multivariable ORs (95% CIs) for ex-smokers, current smokers of $<$20 cigarettes/day, and current smokers of $\geq$20 cigarettes/day were 0.93 (0.36–2.42), 1.37 (0.61–3.05), and 2.24 (0.92–5.49), respectively, as compared with never smokers. We did not find any associations of serum total cholesterol, triglyceride, or alcohol drinking status with risk of pre-heart failure or symptomatic heart failure. Similar positive associations were observed for overweight, hypertension diabetes mellitus, and current smoking (*Table 2*). The number of these risk factors was associated with risk of pre-heart failure or symptomatic heart failure: the multivariable ORs (95% CIs) for persons with one risk factor and two or more risk factors were 1.80 (1.01–3.20) and 6.80 (3.69–12.5), respectively, as compared with those without any risk factors.

Table 3 shows the age-adjusted, sex-adjusted, and community-adjusted baseline characteristics of participants who were followed up and of those who were not. The proportions of men, current drinkers, hypertension medication use, diabetes mellitus, history of stroke, incident coronary heart disease, and stroke and the mean values of age, SBP, diastolic blood pressure, and triglyceride were significantly higher in people who were not followed up than in those who were.

Table S1 shows the ORs and 95% CIs of symptomatic heart failure according to potential risk factors. BMI and diabetes mellitus were still associated with risk of symptomatic heart failure, whereas blood pressure and smoking status were no longer significantly associated with the risk, probably owing to the smaller number of cases. The larger the number of risk factors was, the higher the risk of symptomatic heart failure was.

Given the variation in the follow-up years ranging from 10 to 25 years, we additionally analysed risk sets involving participants with 10, 15, and 20 years of follow-up, but the results did not differ materially (data not shown).

Discussion

We found significantly positive associations of BMI, blood pressure, and diabetes mellitus with risk of pre-heart failure or symptomatic heart failure in a general Asian population. We also found a positive, but not significant, association of smoking with risk of pre-heart failure or symptomatic heart failure. The accumulation of these risk factors was associated in a stepwise manner with a higher risk of pre-heart failure or symptomatic heart failure. This is the first study to identify risk factors for pre-heart failure or symptomatic heart failure in a general Asian population.

Previous epidemiologic investigations conducted in Western countries yielded results that were generally similar to ours. A cohort study in the United States of 23 915 participants aged 55 years with over 40 years of follow-up showed that hypertension, diabetes mellitus, and obesity were associated with risk of incident heart failure.[2] The hazard ratios (95% CIs) of heart failure for non-hypertension vs. hypertension were 0.86 (0.77–0.96) in men and 0.76 (0.68–0.85) in women; for non-diabetes vs. diabetes mellitus, 0.44 (0.38–0.52) in men and 0.33 (0.28–0.38) in women; and for non-obesity vs. obesity, 0.64 (0.57–0.72) in men and 0.58 (0.52–0.65) in women. That study also showed that the absence of these three risk factors was associated with a lower risk of incident heart failure than the presence of all three risk factors: The hazard ratios (95% CIs) were 0.20 (0.15–0.25) for men and 0.14 (0.11–0.18) for women. Another cohort study of 871 687 British individuals aged 55 years or older with 5.8 years of median follow-up showed that obesity, diabetes, smoking, and hypertension were associated with an increased risk of incident heart failure.[3] The hazard ratios (95% CIs) of heart failure for BMI $\geq$ 30 kg/m^2 vs. $<$30 kg/m^2 were 1.21 (1.11–1.31) in men and 1.39 (1.25–1.54) in women; for persons with diabetes vs. non-diabetes, 1.85 (1.64–2.10) in men and 2.77 (2.36–3.24) in women; for current smokers vs. non-current smokers, 1.27 (1.14–1.40) in men and 1.33 (1.18–1.49) in women; and for persons with SBP $>$ 140 mmHg and/or use of BP-lowering medication as compared with those with SBP $\leq$ 140 mmHg and non-use of BP-lowering medication, 1.14 (1.07–1.22) in men and 1.09 (1.00–1.19) in women. The Framingham Heart Study of 8229 men and women aged 55–84 years with 25 years of follow-up showed that the lifetime risk for congestive heart failure of people with hypertension (SBP $\geq$ 160 mmHg or DBP $\geq$ 100 mmHg or undergoing treatment) was doubled for those with normal blood pressure (SBP $<$ 140 mmHg and DBP $<$ 90 mmHg).[4] Other studies showed that obesity, diabetes, smoking, and hypertension were risk factors for incident heart failure.[5–13]

In contrast, drinking status, total cholesterol, and triglyceride were not associated with risk of pre-heart failure or symptomatic heart failure in the present study. A meta-analysis of eight prospective studies conducted in the United States,

Table 2 Odds ratios (ORs) and 95% confidence intervals (CIs) of pre-heart failure or symptomatic heart failure according to potential risk factors

	Number of cases	Number of non-cases	Age, sex, and community adjusted OR	Multivariable OR
Body mass index (kg/m2)[a]				
<21	15	554	1.45 (0.69–3.06)	1.41 (0.66–3.00)
21–22.9	14	651	Reference	Reference
23–24.9	20	580	1.52 (0.75–3.06)	1.67 (0.82–3.38)
25–26.9	10	370	1.07 (0.47–2.46)	1.22 (0.52–2.82)
27–29.9	19	170	4.78 (2.31–9.90)	5.70 (2.70–12.0)
30 or higher	7	64	4.92 (1.87–12.9)	5.91 (2.19–16.0)
Overweight[a]				
No	59	2155	Reference	Reference
Yes	26	234	3.83 (2.33–6.29)	4.31 (2.44–7.63)
Systolic blood pressure (mmHg)				
<130	35	1444	Reference	Reference
130–139	21	585	1.16(0.67–2.03)	1.04 (0.58–1.86)
140–159	21	289	2.11 (1.19–3.73)	1.86 (1.01–3.43)
160 or higher	8	71	3.04 (1.33–6.94)	2.49 (1.01–6.13)
Diastolic blood pressure (mmHg)				
<80	37	1,288	Reference	Reference
80–89	27	735	1.08 (0.65–1.81)	0.93 (0.53–1.61)
90–99	11	277	1.10 (0.54–2.23)	0.92 (0.43–1.96)
100 or higher	10	89	3.45 (1.61–7.41)	2.87 (1.23–6.68)
Hypertension				
No	47	1816	Reference	Reference
Yes	38	578	1.79 (1.14–2.81)	1.68 (1.04–2.71)
Diabetes mellitus				
Normal	63	2112	Reference	Reference
Impaired glucose tolerance	14	233	1.58 (0.86–2.91)	1.48(0.79–2.80)
Diabetes mellitus	8	44	4.39(1.94–9.96)	5.16(2.14–12.4)
Diabetes mellitus				
No	77	2345	Reference	Reference
Yes	8	44	4.09(1.82–9.19)	4.92(2.06–11.7)
Serum total cholesterol (mg/dL)				
<180	32	861	Reference	Reference
180–199	21	603	0.72(0.41–1.28)	0.66(0.36–1.21)
200–219	12	448	0.55(0.28–1.09)	0.43(0.21–0.89)
220 or higher	20	477	0.77(0.43–1.38)	0.63(0.34–1.18)
Serum triglyceride (mg/dL)[b]				
<70	20	590	Reference	Reference
70–99	15	603	0.58(0.29–1.16)	0.53(0.26–1.09)
100–150	20	602	0.75(0.39–1.42)	0.52(0.26–1.04)
151 or higher	30	590	1.13(0.62–2.04)	0.64(0.32–1.29)
Smoking status[c]				
Never	50	1627	Reference	Reference
Ex-smoker	8	227	0.83(0.33–2.11)	0.93(0.36–2.42)
<20 cigarettes/day	15	336	1.34(0.62–2.89)	1.37(0.61–3.05)
20 cigarettes/day or more	12	199	2.26(0.95–5.38)	2.24(0.92–5.49)
Current smoking				
No	58	1854	Reference	Reference
Yes	27	535	1.73(0.96–3.13)	1.68(0.91–3.11)
Drinking status[a]				
Never	47	1495	Reference	Reference
Ex-smoker	1	50	0.38(0.05–3.02)	0.34(0.04–2.81)
<23 g/day	14	305	1.37(0.68–2.80)	1.51(0.72–3.17)
23.0–45.9 g/day	11	217	1.03(0.44–2.43)	1.18(0.49–2.85)
46 g/day or more	12	322	0.75(0.32–1.75)	0.66(0.27–1.59)
Number of risk factors[d]				
0	28	1486	Reference	Reference
1	34	743	1.68(0.94–2.98)	1.80(1.01–3.20)
2 or more	23	160	5.53(3.05–10.0)	6.80(3.69–12.5)

Multivariable model adjusted for age, sex, community, serum total cholesterol, blood pressure, diabetes mellitus, body mass index, drinking status, smoking status, medication for hypertension, and medication for hyperlipidaemia. Categories of each risk factor in the two groups as follows: Overweight: BMI ≥ 27 kg/m^2. Hypertension: SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or taking medication. Diabetes mellitus: fasting glucose ≥126 mg/dL or non-fasting glucose ≥200 mg/dL and/or taking medication. The number of risk factors is the sum of the following risk factors: current smoking, overweight, hypertension, and diabetes mellitus.

[a]Multivariable model of BMI and drinking status adjusted for age, sex, community, serum total cholesterol, body mass index, drinking status, smoking status, and medication for hyperlipidaemia.

[b]Multivariable model of serum triglyceride adjusted for age, sex, community, serum total cholesterol, blood pressure diabetes mellitus body mass index, drinking status, smoking status, medication for hypertension, medication for hyperlipidaemia, and postprandial time.
[c]Multivariable model of smoking status adjusted for age, sex, community, serum total cholesterol, blood pressure, diabetes mellitus, medication for hypertension, and medication for hyperlipidaemia.
[d]Multivariable model of number of risk factors adjusted for age, sex, community, serum total cholesterol, drinking status, and medication for hyperlipidaemia.

Table 3 Baseline characteristics of followed-up and non-followed-up participants

	Those who were followed up	Those who were not followed up	*P* for difference
Number of participants	(*n* = 2474)	(*n* = 3719)	
Age, year[a] mean ± SD	47.6 ± 8.6	53.2 ± 11.1	<0.0001
Male sex, %[a]	38.0	43.2	<0.0001
Current drinker, %[b]	35.7	38.5	<0.0001
Current smoker, %[b]	22.7	31.2	0.13
BMI, kg/m^2 [b] mean ± SD	23.3 ± 3.1	23.5 ± 3.3	0.17
Systolic blood pressure, mmHg[b] mean ± SD	126.4 ± 15.9	131.8 ± 18.2	<0.0001
Diastolic blood pressure, mmHg[b] mean ± SD	78.7 ± 11.1	80.4 ± 11.4	0.0004
Hypertension medication use, %[b]	7.4	15.1	<0.0001
Diabetes mellitus, %[b]	2.3	7.2	<0.0001
Total cholesterol, mg/dL[b] mean ± SD	193.6 ± 33.5	195.7 ± 36.5	0.40
Triglyceride, mg/dL[b] mean ± SD	123.6 ± 81.3	136.9 ± 94.3	<0.0001
Cholesterol-lowering medication use, %[b]	1.1	1.6	0.73
Estimated glomerular filtration rate, mL/min/ 1.73 m^2 [b] mean ± SD	68.9 ± 11.9	66.6 ± 12.4	0.23
History of stroke, %[b]	0.5	1.6	0.02
Incident coronary heart disease, %[c]	0.5	1.6	0.03
Incident stroke, % [c]	1.3	5.3	<0.0001

[a]Adjusted for communities.
[b]Adjusted for communities, age, and sex.
[c]*P* for difference was calculated by logistic regression model adjusted for communities, age, and sex.

Sweden, and Finland demonstrated that light-to-moderate alcohol consumption was associated with a lower risk of heart failure. The multivariable hazards ratios (95% CIs) were 0.90 (0.84–0.96) for 36 g/week, 0.83 (0.73–0.95) for 84 g/week, 0.90 (0.73–1.10) for 168 g/week, and 1.07 (0.77–1.48) for 252 g/week as compared with those in non-drinkers.[14] This discrepancy may be partly due to the difference in the underlying comorbidity in heart failure, that is, mainly coronary heart disease in Western countries and mainly hypertensive disease and atrial fibrillation in Eastern countries. In the present study, only 14 people developed coronary heart disease during the follow-up years; in 10 of them, pre-heart failure or symptomatic heart failure was identified. A study involving 21 601 American participants showed no association between alcohol consumption and heart failure without antecedent myocardial infarction and coronary artery disease.[15] As for total or low-density lipoprotein cholesterol and triglyceride, the results of previous studies have been inconsistent. Most of the previous studies showed no association between higher total or low-density lipoprotein cholesterol levels and risk of incident heart failure,[3,6,16,27] whereas another study of 84 740 Swedish middle-aged men and women with 11.8 years of follow-up reported that total and non-high-density lipoprotein cholesterol levels were associated with an increased risk of heart failure.[28] For triglyceride, some

previous studies conducted in Denmark and Sweden showed an association between higher triglyceride and risk of incident heart failure,[27,28] although another study involving 5688 American individuals aged 45–84 years with 8.5 years of median follow-up observed such an association only in patients with diabetes mellitus, and the association was attenuated when adjusted for history of myocardial infarction.[29] However, a study of 871 687 British individuals aged 55 years or older with 5.8 years of median follow-up did not show such an association.[3]

In Japan, statins were approved as medication for hyperlipidaemia in 1989. Thus, cholesterol-lowering medication was not widely prescribed at the baseline survey (from 1990 to 2000), as shown in *Table 1*. The association between total cholesterol and risk of pre-heart failure or symptomatic heart failure did not change when not adjusted for use of cholesterol-lowering medication (data not shown).

The present study suggested that Asian and Western populations generally shared common risk factors for heart failure. In addition, risk factors for pre-heart failure or symptomatic heart failure based on NT-proBNP in the present study were basically the same as for those in the previous studies mentioned above, which defined heart failure on the basis of the clinical symptoms.

Experimental studies showed physiologic mechanisms for the relationship of these risk factors with heart failure.

Among 2754 participants who underwent echocardiographic screening, diabetes mellitus was correlated with higher left ventricular mass and wall thickness and with lower left ventricular systolic chamber and myocardial function.[30] In a follow-up study involving 30 920 participants with 3.2 years of average follow-up, obesity was positively associated with risk of left ventricular geometric abnormalities such as left ventricular hypertrophy and concentric remodelling.[31] An intervention study involving 12 healthy volunteers showed that brief active smoking increased circulating endothelial progenitor cell levels, which suggested that smoking injured the vascular walls.[32] Another clinical trial of 1111 patients with hypertension followed up for 2 years showed that control of SBP (target of less than 130 mmHg) reduced the risk of electrocardiographic left ventricular hypertrophy.[33]

The strengths of the present study are its long follow-up (17.5 years on average) and its study population derived from community-based middle-aged individuals (aged 47.6 years on average). All adults aged ≥30 years in Ikawa were eligible to participate in the annual cardiovascular risk survey. For Kyowa, many employees were not included in the participants. However, a study in Japan reported that participants of health examinations had a more favourable lifestyle profiles than those of non-participants.[34] Therefore, we should note the possibility of healthy participant effects to some extent. Another strength is that we evaluated the risk of heart failure among an Asian general population whose aetiology and co-morbidities of heart failure may differ from those of a Western population (e.g., low incidence of and mortality from coronary heart disease in Asia). As for BMI, Asian populations have lower BMI than those of Western populations. Most studies conducted in Western countries demonstrated a risk of heart failure for persons with BMI of ≥30 kg/m^2 as compared with those with BMI of <30 kg/m^2,[2,3,5,7,12] whereas we observed that persons with BMI of 27–29.9 kg/m^2 and ≥30 kg/m^2 had a higher risk of pre-heart failure or symptomatic heart failure than those with BMI of 21–22.9 kg/m^2.

Several limitations of this study should be noted. First, the participants were required to attend both the baseline survey and the follow-up check-ups. Because people who died or had difficulties in participating in the follow-up check-ups owing to serious health problems were probably not included, the participants of this study were healthier than those who attended the baseline survey but not the follow-up check-ups (*Table 3*). Second, we did not have NT-proBNP data at the baseline survey. Instead, our study design involved a long follow-up (17.5 years on average) and exclusion criteria to remove people with a high probability of heart failure at the baseline survey. Third, the year of the baseline survey differed for each participant, which led to variation in the number of follow-up years ranging from 10 to 25 years. We analysed risk sets involving participants with 10, 15, and 20 years of follow-up, but the results did not differ materially (data not shown). Lastly, we defined pre-heart failure or symptomatic heart failure as finding of NT-proBNP ≥400 pg/mL, which may over-diagnose those without heart failure. Among individuals with NT-proBNP ≥400 pg/mL, 29% of them were not reported as having a diagnosis of heart failure.[35] However, when we analysed for symptomatic heart failure only, the results were similar, although the number of cases was small (*Table S1*).

In conclusion, high BMI, current smoking, diabetes mellitus, and hypertension in a general Japanese population were positively associated with risk of pre-heart failure or symptomatic heart failure, and the accumulation of these four risk factors was associated with a graded higher risk of pre-heart failure or symptomatic heart failure.

Conflict of interest

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Odds ratios (ORs) and 95% confidence intervals (CIs) of symptomatic heart failure according to potential risk factors.

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