Table 1. NC Questionnaire

Daily life-1	
Q1	Do you usually travel by bus or train by yourself?
Q2	Do you go out and buy daily necessities by yourself?
Q3	Do you manage your own deposits and savings at the bank?
Q4	Do you often go out to visit your friends?
Q5	Do you consult with your family or friends about their problems?
Physical ability	
Q6	Are you able to go upstairs without holding rail or wall?
Q7	Are you able to stand up from the chair without any aids?
Q8	Are you able to keep walking for approximately 15 min?
Q9	Have you fallen during the past year?
Q10	Do you worry about falling down?
Nutrition and oral condition	
Q11	Have you lost more than 2–3 kg in the past 6 months?
Q12	Please fill out: your height (cm) and your weight (kg)
Q13	Compared with 6 months ago, do you have difficulty in eating hard food?
Q14	Do you choke when you drink tea or soup?
Q15	Do you often feel your mouth dry?
Daily life-2	
Q16	Do you go out more than once in a week?
Q17	Compared with last year, do you go out less often?
Q18	Do people around you say you repeat same thing and have become forgetful?
Q19	Do you make phone calls by yourself?
Q20	Do you find yourself not knowing today's date?
Mental status	
Q21	I don't feel any fulfillment in my life during the last 2 week.
Q22	I cannot enjoy things I used to enjoy during the last 2 weeks.
Q23	During the last 2 weeks, I am not willing to do what I could do easily before.
Q24	During the last 2 weeks, I do not feel I am useful to anyone.
Q25	During the last 2 weeks, I feel I am exhausted without any reason.

NC, nursing care.

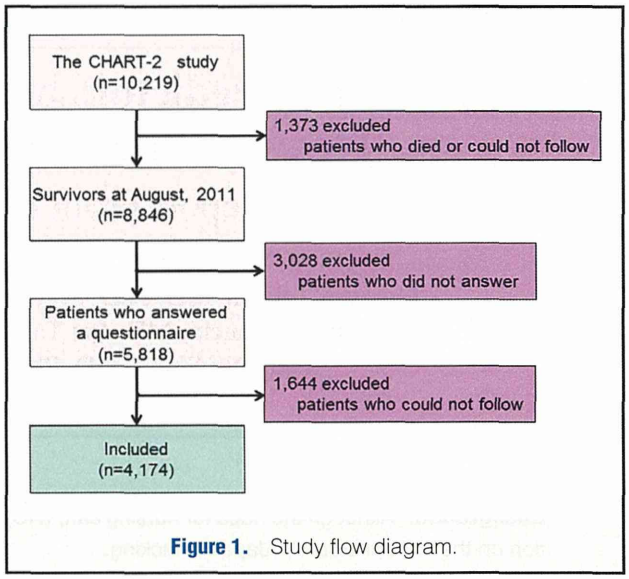

Figure 1. Study flow diagram.

the aim of the present study was to address these important issues in HF patients registered in our HF registry, the Chronic Heart Failure Analysis and Registry in the Tohoku District Study-2 (CHART-2; NCT00418041, n=10,219).[5,8–10]

Methods

Subjects and Inclusion Criteria

Details of the design, purpose and basic characteristics of the CHART-2 Study have been described previously.[5,8–10] Briefly, eligible patients were aged ≥20 years with significant coronary artery disease or in stage B, C or D defined by the American College of Cardiology/American Heart Association guidelines for the diagnosis and management of HF in adults.[11] Patients were classified as having HF by experienced cardiologists using the criteria of the Framingham Heart Study.[12] The present study was approved by the local ethics committee in each participating hospital. Eligible patients were consecutively recruited after written informed consent was obtained. The CHART-2 Study was started in October 2006 and the entry period was successfully closed in March 2010 with 10,219 patients registered from the 24 participating hospitals.[5] All data and events will be surveyed at least once a year until March 2018.[5]

We conducted a questionnaire survey, regarding daily life, physical ability, nutritional status, and mental status for the patients in the CHART-2 study in August 2011. The questionnaire consisted of 25 questions (Table 1). Questions (Q) 1–5 and 16–20 were related to daily life, Q6–10 physical ability, Q11–Q15 to nutrition and oral condition, and Q21–Q25 to mental status. These questions were based on the questionnaire of NC prevention published by the Japanese Ministry of Health, Labour and Welfare (JMHLW).[13] In Q1–8, 16, 20, if applicable, patients answered 'No'. In Q9–11, 13–15, 17, 18 and Q20–25, if applicable, patients answered 'Yes'. Need for NC, according to the JMHLW definition, was defined as follows: (1) ≥10 questions from Q1 to Q20; and (2) physical dysfunction (≥3 questions in the physical ability section; Q6–10); and (3) poor nutrition (both Q11 and body mass index [BMI] <18.5); or (4) poor oral condition (≥2 questions in the oral condition section; Q13–15).[13] According to the questionnaire results, the patients were divided into 2 groups as follows: those who needed NC (NC group) and those who did not (non-NC group). Furthermore, we considered the patients for whom at least 1 question was applicable among Q18–20 as high risk for dementia, and those for whom at least 2 questions were applicable among Q21–25 as high risk for depression according to the JMHLW definition.[13]

Figure 1 shows the study flow. Among 10,219 patients registered in the CHART-2 study, we sent the questionnaire to 8,846 patients who were alive in August 2011. At the end of 2011, we received a reply from 5,818 patients (65.8%). Among the 5,818 patients, we finally included the 4,174 patients who were eligible for the follow-up survey by the end of May 2013.

Follow-up Survey and Study Outcome

We conducted the follow-up survey for survival from January to May in 2013, and the median follow-up period was 12.7 months after the questionnaire. The outcome of this study was

Table 2. Baseline Subject Characteristics

	All patients (n=4,174)	Stage B (n=2,380)		P-value	Stage C/D (n=1,794)		P-value
		NC (n=723)	Non-NC (n=1,657)		NC (n=692)	Non-NC (n=1,102)	
Age (years)	67.1±10.9	71.3 ±10.2	65.4±10.6	<0.001	70.8±9.7	64.4±10.9	<0.001
Male	73.3	62.1	78.6	<0.001	63.0	79.1	<0.001
History of admission for HF	23.1	0.0	0.0	–	58.5	50.7	0.001
Comorbidity							
Hypertension	73.4	76.8	73.5	0.09	72.4	71.7	0.74
Diabetes	22.1	24.1	19.3	0.009	25.1	23.1	0.33
Hyperuricemia	32.9	24.6	28.2	0.07	40.6	40.6	0.99
AF	22.4	16.8	16.3	0.94	33.8	28.0	0.02
Coronary artery disease	56.5	60.3	61.8	0.49	48.0	51.3	0.17
Cerebrovascular disease	14.7	19.6	11.5	<0.001	20.7	12.5	<0.001
Clinical status							
NYHA class 3 and 4	2.8	0.1	0.3	<0.001	11.1	3.4	<0.001
BMI (kg/m^2)	24.2±3.4	24.0±3.4	24.4±3.2	0.008	23.7±3.8	24.2±3.4	0.003
SBP (mmHg)	128±18	130±18	129±17	0.86	126±19	126±17	0.91
DBP (mmHg)	74±11	74±11	75±11	<0.001	71±12	74±11	<0.001
Heart rate (beats/min)	70±13	70±12	69±13	0.16	72±15	71±14	0.12
Measurement							
LVEF (%)	62.0±13.6	66.1±11.0	65.6±11.2	0.34	57.0±15.0	57.2±14.9	0.85
Hemoglobin (g/dl)	13.7±1.8	13.3±1.6	13.9±1.6	<0.001	13.0±1.8	13.8±2.1	<0.001
BUN (mg/dl)	17.1±6.6	16.9±6.2	15.9±5.1	<0.001	19.8±8.9	17.3±6.4	<0.001
GFR (ml·min^{-1}·1.73m^{-2})	66.3±21.6	65.6±21.1	69.1±17.4	<0.001	59.9±19.9	66.5±27.1	0.001
Serum sodium (mEq/L)	141±2.5	141±2.5	141±2.2	0.23	141±2.6	141±2.6	0.86
Serum potassium (mEq/L)	4.3±0.4	4.4±0.4	4.3±0.4	0.20	4.1±0.4	4.4±0.4	0.31
BNP (pg/ml)	56†	55†	36†	<0.001	108†	72†	<0.001
Medications							
RAS inhibitor	63.0	54.1	57.2	0.16	69.7	73.2	0.10
β-blocker	42.5	34.0	34.8	0.73	52.5	53.6	0.63
Calcium channel blocker	46.6	53.8	51.2	0.25	42.5	37.4	0.03
Diuretics	29.7	19.8	11.8	<0.001	58.4	44.9	<0.001
Aldosterone inhibitor	12.2	6.5	3.2	<0.001	26.7	20.2	0.001
Statin	44.8	47.9	42.9	0.02	39.5	44.8	0.03
Digitalis	14.2	8.4	7.9	0.66	23.3	21.9	0.49

Data given as mean±SD, % or †median.
AF, atrial fibrillation; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; DBP, diastolic blood presure; GFR, glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RAS, renin-angiotensin system; SBP, systolic blood pressure. Other abbreviation as in Table 1.

a composite of all-cause death, admission for HF, acute myocardial infarction (AMI) and stroke.

Statistical Analysis

Statistical analysis was done for both non-HF (stage B) and HF (stage C/D) patients. Comparison of data between 2 groups was done using chi-squared test and Student's t-test. Continuous data are described as mean±SD. Kaplan-Meier curves were plotted to evaluate the association between NC and composite outcome. We also constructed the following 3 Cox proportional hazard regression models: (1) unadjusted; (2) adjusted for age and sex; and (3) fully adjusted including medical treatment. In model (3) we included the following covariates that can potentially influence outcome: age, sex, New York Heart Association class, history of malignant tumor, BMI, systolic blood pressure, heart rate, serum sodium, serum albumin, estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), comorbidities (anemia defined as hemoglobin <12 g/dl in women and <13 g/dl in men, diabetes mellitus, hyperuricemia, atrial fibrillation and cerebrovascular disease), left ventricular ejection fraction (LVEF), ischemic etiology of HF, and treatment (β-blocker, renin-angiotensin system inhibitors and aldosterone antagonists). We also performed subgroup analyses based on age (<median age or ≥median age), sex, cause of HF (ischemic HF vs. non-ischemic HF) and history of cerebrovascular disease. Finally, we also constructed a logistic regression model to elucidate the predictors for NC need. We included several covariates, including age, sex, HF stage, history of malignant tumor, BMI, systolic blood pressure, heart rate, eGFR, serum albumin, comorbidities (anemia, diabetes mellitus, hyperuricemia, atrial fibrillation, and cerebrovascular disease), LVEF, ischemic etiology, and risk of dementia and that of depression.

Statistical analysis was done using SPSS Statistics 19.0 (SPSS, Chicago, IL, USA) and statistical significance was defined as 2-sided P<0.05.

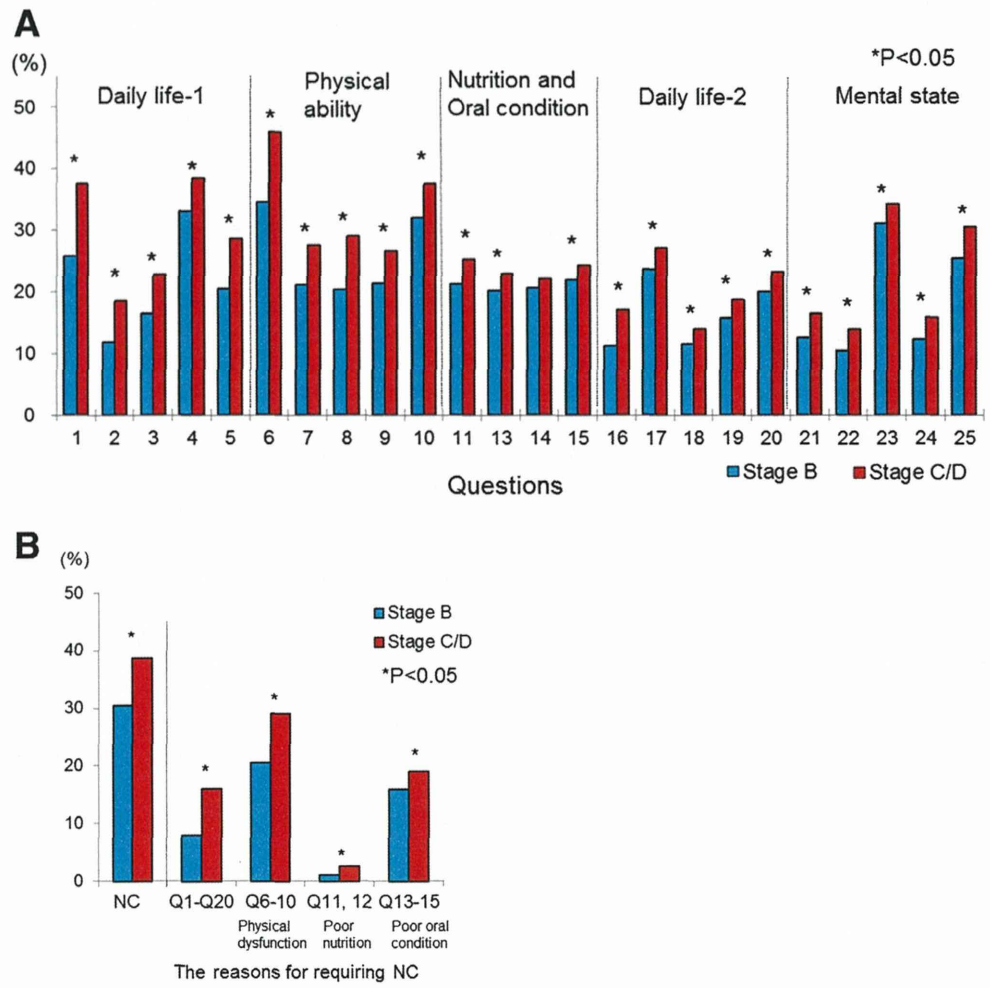

Figure 2. (**A**) Questionnaire results: stage B vs. stage C/D. Q1–8, 16, 20 are answered 'No'. Q9–11, 13–15, 17, 18, 20–25 are answered 'Yes'. (**B**) Prevalence of and reasons for nursing care (NC) need in stage B vs. stage C/D. Q11, Q12: 'Yes' and body mass index <18.5, respectively. *P<0.05.

Results

Prevalence of NC and Baseline Patient Characteristics

Mean age was 67.1±10.9 years and male patients accounted for 73.3% of the subjects. Female patients were older than male patients (68.3±11.5 vs. 66.6±10.6 years, P<0.001). Coronary artery disease was noted in 56.5% and mean LVEF in 62.0±13.6%. The prevalence of cerebrovascular disease was 14.7%. The prevalence of NC was significantly higher in stage C/D (38.6%) than in stage B (30.4%; P<0.001; **Table 2**; **Figure 2B**).

More than 30% of the patients in stage C/D did not go out by themselves using bus or train (Q1), did not visit their friend's house (Q4), could not go upstairs without holding onto the railing (Q6), and had serious concerns and/or fears for falling (Q10; **Figure 2A**). Furthermore, approximately one-quarter of the patients in both stage B and C/D had an experience of falling (Q9).

Among the reasons for requiring NC, physical dysfunction (Q6–10) was the most prevalent in both stage B and C/D (**Figure 2B**). Female patients had a higher prevalence of impaired physical activity (female 38.3% vs. male 19.1%, P<0.001), and impaired oral condition (female 20.6% vs. male 15.9%, P<0.001). The baseline characteristics of the NC patients are listed in **Table 2**. In both stage B and C/D, the patients who needed NC were characterized by older age, higher prevalence of female gender and history of cerebrovascular disease, lower BMI and hemoglobin, and higher BUN and B-type natriuretic peptide. In both stage B and C/D, the patients who needed NC were more frequently treated with diuretics.

Impact of NC on Composite Outcome

During the median follow-up period of 12.7 months after the questionnaire, the composite outcome occurred in 234 patients (5.6%). In stage B patients, 90 composite outcomes occurred, including all-cause death in 38 (42.2%), AMI in 7 (7.8%), admission for HF in 25 (27.8%), and stroke in 20 (22.2%). In stage C/D patients, 144 composite outcomes occurred, including all-cause death in 68 (47.2%), AMI in 5 (3.4%), admission for HF in 55 (38.2%), and stroke in 17 (11.8%).

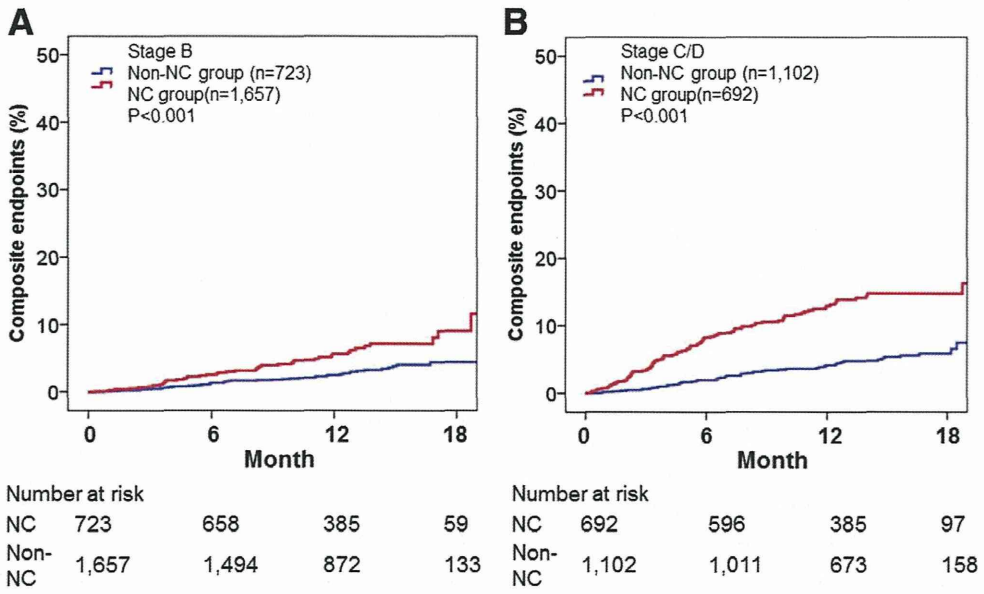

Figure 3. Kaplan-Meier curves for composite outcome in (**A**) stage B and (**B**) stage C/D. NC, nursing care.

Table 3. Risk of Need for NC

HR categories	Stage B		Stage C/D	
	Non-NC group (reference)	NC group	Non-NC group (reference)	NC group
n	1,656	722	1,102	692
(1) Unadjusted				
HR	1.00	2.17	1.00	3.00
95% CI		1.44–3.28		2.13–4.21
P-value		<0.001		<0.001
(2) Adjusted for age and sex				
HR	1.00	1.73	1.00	2.59
95% CI		1.11–2.69		1.82–3.69
P-value		0.015		<0.001
(3) Fully adjusted				
HR	1.00	1.62	1.00	2.31
95% CI		1.01–2.59		1.57–3.39
P-value		0.045		<0.001

Model (3) was adjusted for age, sex, NYHA class, SBP, heart rate, diabetes mellitus, hyperulicemia, BMI, anemia, estimated GFR, BUN, serum sodium, ischemic etiology, AF, LVEF, history of cerebrovascular disease and medication (RAS inhibitor, β-blocker, and aldosterone blocker).
CI, confidence interval; HR, hazard ratio. Other abbreviations as in Tables 1,2.

Kaplan-Meier curves showed that the NC group had significantly higher occurrence of the composite outcome in both stage B and C/D (**Figure 3**). **Table 3** lists the results of multivariate Cox proportional hazard regression analysis for composite outcome. In the unadjusted model (1), as compared with the non-NC group (reference), the NC group had more than 2-fold increase in risk for composite outcome in both stage B and C/D (all P<0.001). In model (2), as compared with the non-NC group, the hazard ratios (HR) and 95% confidence interval (95% CI) for the composite outcome of the NC group in stage B and C/D was 1.73 (1.11–2.6) and 2.59 (1.82–3.69), respectively. Importantly, the significance of HR for the composite outcome of the NC group in stage B and C/D remained robust even after the adjustment in model (3).

Figure 4 shows subgroup analyses for composite outcome. In the stage B patients, there were no interactions between age, sex, etiology of the HF or history of cerebrovascular disease. In contrast, there was an interaction between age and etiology of HF in stage C/D patients. Older patients and those with ischemic heart disease had higher HR for composite endpoints.

Predictors for NC Need

Figure 5 shows the predictors for NC need. According to the

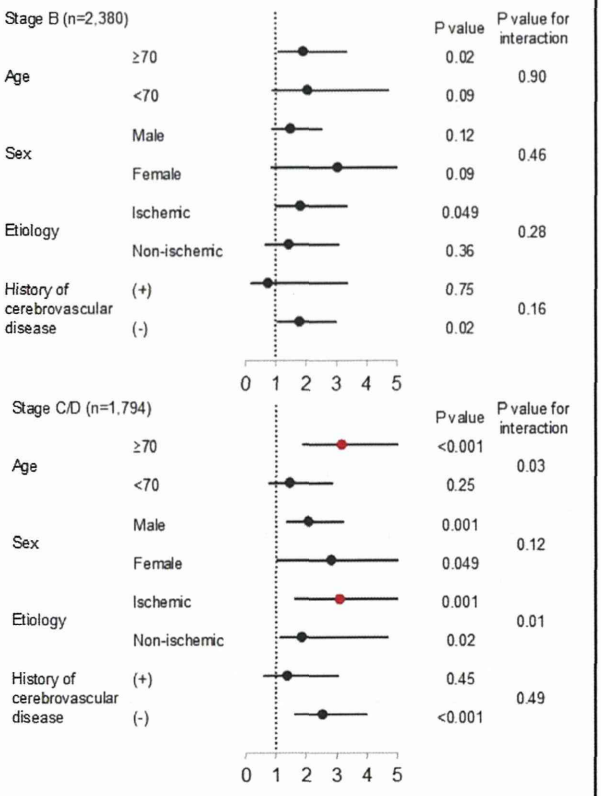

Figure 4. Subgroup analysis for the patients in stage B and in stage C/D.

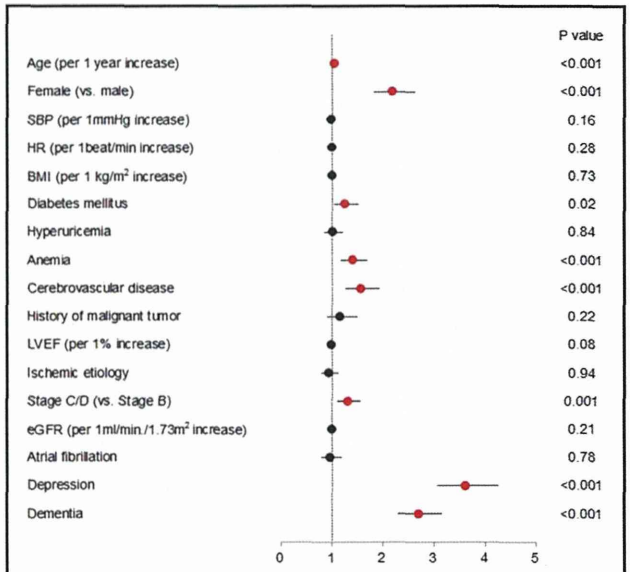

Figure 5. Predictors of nursing care (NC) need. BMI, body mass index; eGFR, estimated glomerular filtration rate; HR, heart rate; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

analysis, older age, female gender, diabetes mellitus, cerebrovascular disease and stage C/D were significantly associated with NC need. Particularly, HR for NC need for depression and dementia were 3.61 (95% CI: 3.06–4.25, P<0.001) and 2.70 (95% CI: 2.30–3.16, P<0.001), respectively.

Discussion

The novel findings of the present study are that (1) >30% of HF patients needed NC regardless of HF stage; (2) NC patients had worse prognosis compared with non-NC patients regardless of HF stage; and (3) the predictors of NC need included older age, female gender, greater severity of HF status, history of cerebrovascular disease, diabetes, depression and dementia. To the best of our knowledge, this is the first study to describe the prevalence, baseline characteristics and clinical outcome of HF patients requiring NC in Japan. Indeed, the present study underlines the importance of NC in the management of HF.

Prevalence and Clinical Characteristics of Non-HF Patients Needing NC

In the present study, we found that >30% of HF patients needed NC. Furthermore, the patients in stage C/D had higher prevalence of NC need compared with the stage B patients. Gure et al reported that HF patients were more likely to have impaired activity of daily living (ADL) or instrumental activities of daily living (IADL) compared with those without HF.[7] Their ADL and IADL instruments were almost identical to the questionnaire on daily life and physical ability used in the present study. Furthermore, the present questionnaire covered a broad spectrum of daily life, not only physical activity but also nutrition, oral condition and depression. Thus, the present results may reflect the real situation of NC need in HF patients more comprehensively than the previous reports.

NC need was mostly likely due to physical dysfunction in both stage B and C/D patients. The questionnaire on physical ability found that >40% of the stage C/D patients were unable to go upstairs without holding onto the railing. Furthermore, >20% of the patients in both stage B and C/D experienced falling down, and >30% had serious concerns and/or fears about falling. This suggests the presence of serious physical dysfunction in HF patients in the present study. Given that it has been reported that higher physical activity is associated with better prognosis[14] and that exercise training is associated with improved physical function, a heightened sense of quality of life (QOL) may be important to improve ADL and prognosis, regarding ventilatory parameters, muscle function, endothelial function and neurohumoral factors and cardiac rehabilitation.[15,16] Furthermore, neurological rehabilitation in addition to cardiac rehabilitation may be beneficial in HF patients with a history of cerebrovascular disease.

In the present study, poor nutritional status was one of the reasons for NC need. We previously reported that poor nutritional status was associated with increased incidence of death in stage B patients.[7] The present results also indicate that poor nutritional status may influence the prognosis of stage C/D patients. In addition, oral condition was one of the reasons for requiring NC, possibly in association with poor nutritional status. Taken together, these results underlie the importance of dietary life in the management of HF patients.

Prognosis of Patients Who Need NC

In the present study, the patients who needed NC had worse prognosis regardless of severity of HF. It was reported that nurse educator-delivered teaching session at the time of hospital discharge resulted in improved clinical outcome, increased

self-care measure adherence, and reduced cost of care in hospitalized patients with systolic HF.[17] Furthermore, home-based intervention that consisted of a single home visit by a nurse and a pharmacist was associated with reduced frequency of unplanned readmission and mortality in HF patients,[18] and nurse-led follow-up in HF clinic improved survival and self-care behavior in HF patients.[19] Thus, education and implementation of home-based intervention for self-care in HF patients who need NC may be important to improve prognosis.

Predictors of NC Need in HF Patients

In the present study, predictors of NC need in HF patients included older age, female gender, diabetes, anemia, cerebrovascular disease, severe HF status, depression and dementia. Several studies reported that female patients with HF had a better prognosis and longer survival after diagnosis compared with male patients.[20,21] We also reported that female chronic HF patients had better survival than male patients after adjustment for baseline differences.[8] The crude mortality rate, however, was similar between female and male patients.[8] The clinical manifestations of HF appeared to be more severe in women compared with men,[8] which may be associated with NC need. In the present study, we found that female patients were older than male patients. Older patients may have exercise intolerance as a strong determinant of decreased QOL, an independent negative predictor of survival and thus a key therapeutic target.[22] Furthermore, older HF patients tend to have more comorbidities than young HF patients.[23] Indeed, in the present study, female patients had higher prevalence of impaired physical activity and impaired oral condition. Thus, older patients and/or female patients may have physical disability or comorbidities that lead to NC need.

In the present study, several comorbidities (diabetes, anemia and cerebrovascular disease) were associated with NC need in HF patients. Diabetes and anemia were risk factors for the cardiovascular events causing severe HF status.[23] Furthermore, patients with cerebrovascular disease usually have neurological dysfunction associated with physical dysfunction. Thus, secondary prevention for these lifestyle diseases is important for avoiding NC need in HF patients.

In the present study, depression and dementia were also important predictors of NC need in HF patients. Kato et al reported that depressive symptoms were strongly associated with impaired QOL, independently of disease severity.[22] Furthermore, Hjelm et al reported that HF patients had a significantly higher prevalence of dementia compared with those without HF.[24] Considering that patients with dementia usually have a high prevalence of depressive symptoms[25] and that physical ability intervention was effective for both depression and dementia,[26] cardiac rehabilitation may be useful for patients with depression and/or dementia to prevent NC need.

Study Limitations

Several limitations should be mentioned for the present study. First, we used the JMHLW questionnaire, the relevance of which has been reported for the Japanese population,[27] but although the questionnaire covers a broad range of QOL, the present results should be extrapolated with caution to other cohorts or populations. Second, the follow-up period was relatively short. Although we obtained several positive findings that should be useful for daily practice, further study with a longer follow-up period is needed to examine the influencing factors on NC need and the prognostic impact on HF patients. Third, the collection rate of the questionnaire was 65.8% (5,818/8,846 patients). Furthermore, in the present study, we were unable to follow up 28.2% of the patients after the questionnaire. In addition, the patients included in the present study were characterized by younger age and relatively mild status compared with the patients excluded (**Table S1**). Thus, caution is needed when interpreting the present results in this regard.

Conclusions

One-third of the present HF patients required NC associated with increased mortality, indicating that NC for HF patients is an emerging issue in the health-care system and that earlier intervention is needed to improve QOL and mortality.

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Disclosures

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Supplementary Files

Supplementary File 1

Table S1. Baseline subject characteristics vs. study exclusion

Organization of the CHART-2 Study

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Cardiorespiratory fitness and the incidence of type 2 diabetes: a cohort study of Japanese male athletes

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Abstract

Background: In Japan, although the incidence of overweight (BMI ≥ 25) is still low compared with that in Europe and the United States, the prevalence of type 2 diabetes has increased over the last 15 years,. In both Japanese and Caucasian populations it has been reported that a high level of cardiorespiratory fitness protects against the development of type 2 diabetes. However, there are no reports focused specifically on athletes that investigate whether high cardiorespiratory fitness at a young age can prevent disease later in life. We examined the relationship between cardiorespiratory fitness at a young age and the development of type 2 diabetes in Japanese athletes using a cohort study.

Methods: The cardiorespiratory fitness of male alumni of the physical education department of Juntendo University, as measured by stored data of a 1,500-m endurance run in college (1971–1991) was compared with their incidence of type 2 diabetes as determined by follow-up questionnaires (2007–2009). This study used Cox's proportional hazards models and adjusted for age, year of graduation, BMI, smoking, and sports club participation at college age.

Results: We collected data on cardiorespiratory fitness at college age and medical history survey data during 2007–2009 from 570 male alumni. The median follow-up period was 26 years (IQR: 23–29 years), and 22 men had developed type 2 diabetes. An inverse relationship was observed between incidence of type 2 diabetes and level of cardiorespiratory fitness at time of college after adjustment for age, year of graduation, BMI, smoking, and sports participation. The adjusted hazards ratio and 95% CI by category (low, medium, and high) were 1.00 (reference), 0.40 (0.14–1.13) and 0.26 (0.07–1.00) ($p = 0.03$ for trend).

Conclusions: A high level of cardiorespiratory fitness at a young age can help prevent type 2 diabetes later in life.

Keywords: Cardiorespiratory fitness, Type 2 diabetes, Japanese, Athletes, Cohort study

Background

Worldwide, more than 371 million people over age 20 have type 2 diabetes [1]. In Japan, although the prevalence of overweight (BMI ≥ 25), the strongest predisposing factor for type 2 diabetes, is low compared with that in Europe and the United States, the prevalence of type 2 diabetes has increased [2]. The National Health and Nutrition Survey reported that type 2 diabetes incidence in Japan increased by 30% between 1997 and 2007 [2,3]. In addition, the International Diabetes Federation reported in 2012 that Japan had the ninth-highest rate of type 2 diabetes in the world [1]. In epidemiological studies conducted in Western countries, a high level of cardiorespiratory fitness has been shown to be a protective factor against type 2 diabetes [4-6]. In Japan, few prospective epidemiological studies have investigated the relationship between cardiorespiratory fitness and type 2 diabetes. Sawada et al. showed that a low level of cardiorespiratory fitness in middle age is a strong risk factor for type 2 diabetes [7].

Few epidemiological studies have investigated the relationship between cardiorespiratory fitness and type 2

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diabetes in athletes. It has been reported that former top-level athletes, and particularly male former endurance athletes, have a lower prevalence of type 2 diabetes [8-11]. It has also been reported former that top-level athletes, such as weightlifters, boxers, and track and field throwers, have an equal or higher prevalence of type 2 diabetes compared with healthy men who are not athletes [8,9,11]. Although top athletes are a biologically selected group given particular training, maintaining high cardiorespiratory fitness levels may directly contribute to the prevention of type 2 diabetes. However, in these studies, former top athletes were grouped according to the type of sports they played rather than according to measured data of their cardiorespiratory fitness levels. As these studies [8,9,11] have been carried out only in Caucasian populations, it was not clear whether a high level of cardiorespiratory fitness at a young age can prevent the incidence of type 2 diabetes in Asian athletes, who are generally not overweight. Therefore, the present study examined the relationship between cardiorespiratory fitness at a young age and the development of type 2 diabetes in Japanese athletes using a cohort study.

Methods

Subjects

This study included male alumni of the Department of Physical Education of Juntendo University. Students were selected for admission to college by an entrance examination of motor skills and other tests. They came from all over Japan. Almost all students were members of a college sports club, such as track and field, gymnastics, soccer, or judo and they participated in training in these areas. In this college, an athletic test included an annual test of cardiorespiratory fitness, and these data were available for the years 1971 and thereafter. Between 2007 and 2009, 3,539 male alumni who graduated between 1956 and 1991 answered a follow-up questionnaire about their medical background. Those who had died or for whom no record of address could be found were excluded. Female alumni were not included in this study because this university has only admitted them since 1991. Along with the questionnaire, prospective participants were sent a letter of informed consent approving the collection and use of their athletic test data for research purposes. Responses with signed and answered questionnaires were regarded as giving consent. Privacy precautions were maintained through Juntendo University, and all data were anonymized before analysis. The study protocol was reviewed and approved by the Juntendo University ethics committee in 2007. In the present study, we selected subjects from alumni whose cardiorespiratory fitness data at the time of college was available, and who responded to the follow-up questionnaire (Figure 1). Therefore, the subjects of this study were male alumni who graduated between 1971 and 1991.

Cardiorespiratory fitness test

In this college, all alumni underwent an athletic test that included a test of cardiorespiratory fitness once a year. The test measured cardiorespiratory fitness using a 1,500-m endurance run. This study used the data from the subject's last fitness test. At the time of the test, the body height and weight of the subjects were measured. We calculated the subjects' body mass index (BMI: kg/m^2) from these data.

Investigation of diabetes prevalence

Between 2007 and 2009, a follow-up self-administered questionnaire was sent by mail to alumni. The questionnaire asked participants whether they had been diagnosed with type 2 diabetes by a physician after graduating from college. Those who had been diagnosed

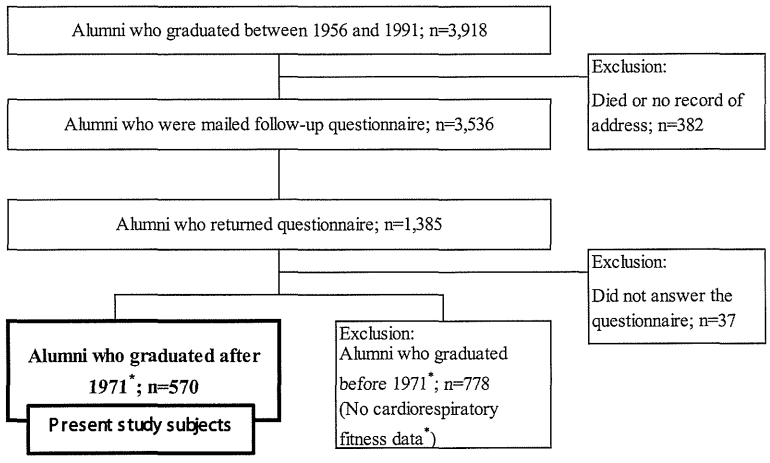

Figure 1 Flowchart of subjects in this study.

Table 1 Characteristic of all subjects

	All
Number of subjects	570
Age at follow up questionnaire	49 (45–52)
follow-up period	26 (23–29)
Person-years follow-up	14,576
Diagnosed type 2 diabetes#	22
1,500 meter endurance run time (seconds)*	325 (310–345)
Age (years)*	23 (23–23)
Year of graduation*	1982 (1979–1985)
BMI (kg/m^2)*	22.1 (21-23.0)
Smoker (n,%)*	275 (48.2)
College sports club participation (n,%)*	563 (98.8)

Estimates show as median (IQR: interquartile Range) or number (%).
The rate smoking and college sports club participation counted "yes".
*All items were the data at colleg age.
#Diabeters was diagnosed by physician.

with type 2 diabetes were asked to indicate their age at diagnosis. Participants were also asked about smoking habits. We estimated smoking habits at the time of college from the answer.

Statistical analysis

Thirty-nine percent of subjects, or 1,385 male alumni, returned the follow-up questionnaire. Cardiorespiratory fitness test data at the time of college were available for 41% of the respondents. In the present study, we analyzed 570 male alumni for whom cardiorespiratory fitness data were available, and who responded to the questionnaire (Figure 1). For each subject, the duration of follow-up was counted from the year of graduation (1971–1991) until the time of the follow-up questionnaire filled out between 2007 and 2009. Subjects' cardiorespiratory fitness levels were categorized into tertiles (low, medium, and high) based on their 1,500-m endurance run at the time of college. The association between cardiorespiratory fitness at the time of college and the incidence of type 2 diabetes was assessed by Cox proportional hazards models. Data were adjusted for age, year of graduation, BMI, smoking, and college sports club participation. Multivariable-adjusted hazards ratios for type 2 diabetes and 95 percent confidence interval (95% CI) were obtained using the low cardiorespiratory fitness group as the reference category. All statistical analyses were conducted using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL).

Results

This study covered a 26-year follow-up period (IQR: 23–29 years) that included 14,576 person-years of observation. The median age at the time of the follow-up questionnaire was 49 years (IQR: 45–52 years). At follow-up, 22 men had developed type 2 diabetes. The median age and BMI of subjects at time of college was 23 years and 22.1 kg/m^2. Ninety-nine percent of subjects had participated in a college sports club. The 1,500-m endurance run time was 325 seconds and the time taken ranged among subjects from 310 to 345 seconds (Table 1). Table 2 shows the physical characteristics of subjects at college stratified by cardiorespiratory fitness levels. Men in the highest cardiorespiratory fitness group had the lowest BMI levels and the lowest prevalence of smoking.

Table 3 shows the relationship between potential risk factors and type 2 diabetes risk estimated by the Cox proportional hazards model. Potential risk factors including age, year of graduation, BMI, smoking, and college sports club participation at the time of college showed no relationship with type 2 diabetes risk in this study.

The incidence of type 2 diabetes per 10,000 person-years was inversely correlated with cardiorespiratory fitness (Table 4). In addition, the low cardiorespiratory fitness level increased the cumulative incidence rate of type 2 diabetes during follow-up (Figure 2). There were progressively lower age-adjusted relative risks of type 2 diabetes across cardiorespiratory fitness levels (p =0.01 for trend). Age-adjusted hazards ratios from low to high

Table 2 Characteristics of male subjects by cardiorespiratory fitness level (tertile)

	Cardiorespiratory fitness level tertiles		
	Low	Medium	High
Number of subjects	189	186	195
1,500 meter endurance run time (seconds)	353 (345–365)	325 (320–330)	301 (290–310)
Age (years)	23 (23–23)	23 (23–23)	23 (23–23)
Year of graduation	1982 (1978–1985)	1981 (1978–1985)	1983 (1979–1986)
BMI (kg/m^2)	22.5 (21.4-23.7)	22.3 (21.3-23.4)	21.4 (20.5-22.3)
Smoker* (n,%)	111 (58.7)	106 (57.0)	58 (29.7)
College sports club participation* (n,%)	185 (97.9)	183 (98.4)	195 (100.0)

Estimates shown as median (IQR: interquartile Range) or number (%).
All items were the data at colleg age.
*The rate smoking and college sports club participation counted "yes".