

Physical Activity and Risk of Mortality from Heart Failure among Japanese Population

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Aim: Reports have shown that physical activity is inversely associated with heart failure risk, but evidence in Asian populations is lacking. We sought to examine the impacts of walking and sports participation on heart failure mortality among a Japanese population.

Methods: We involved 36,223 Japanese men and 50,615 women (aged 40–79 years) who completed a self-administered questionnaire between 1988 and 1990. We divided participants into four categories of walking (< 0.5, 0.5, 0.6–1.0, and ≥ 1 h/day) and sports participation (< 1, 1–2, 3–4, and ≥ 5 h/week) and examined associations with activity and heart failure mortality through 2009.

Results: We found inverse associations between physical activity and heart failure mortality. The multivariable hazard ratios (95% confidence intervals) for the highest category of walking time compared with the second-lowest category were 0.76 (0.59–0.99) in men and 0.78 (0.61–0.99) in women, while the ratios for the highest category of sports participation time compared with the second-lowest category were 0.62 (0.41–0.93) in men and 1.09 (0.73–1.65) in women. The lower hazard ratios in the highest categories of walking and sports participation time in men became no longer statistically significant after excluding heart failure deaths for the first 5, 10, and 15 years for walking time and 10 and 15 years for sports participation. However, in women, the low hazard ratios for the highest category ≥ 1.0 h/day of walking time did not change materially.

Conclusions: Physical activity was associated with a lower risk of mortality from heart failure in this Japanese community-based population. The attenuated and nonsignificant association of walking and sports participation with the risk in men after exclusion of first 5–15 years heart failure death was probably due to changes in physical activity and death certificate diagnosis during the follow-up and reverse causation. However, the persistent inverse association between walking and the risk in women suggests a beneficial preventive effect on heart failure.

Key words: Epidemiology, Risk factors, Exercise, Follow-up study, Cohort

Introduction

Physical activity is regarded as a beneficial lifestyle factor¹⁾ that leads to lowered blood pressure levels²⁾, increased insulin sensitivity³⁾, elevated high-

density lipoprotein cholesterol levels⁴⁾, and improved other lipid and lipoprotein levels⁵⁾ and endothelial function⁶⁾. Previous prospective studies have shown an inverse association between physical activity and risk of developing cardiovascular disease⁷⁾ and/or coronary

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heart disease among Japanese⁸). Exercise-based cardiac rehabilitation also contributes to improvements in cases of admission and all-cause or heart failure mortality among heart failure patients^{9, 10}). In addition, a meta-analysis involving prospective cohort studies from Western countries showed an inverse association between physical activity and risk of incident heart failure in a dose-responsive manner¹¹). In the NIPPON DATA90 study, a Japanese epidemiological study, the risk of mortality from heart failure was reported to be 68% higher in non-exercisers than in exercisers¹²). However, no epidemiological study has reported the relationship between physical activity levels and risk of heart failure in Asia. As there are differences in physical activity habits between East and West, the effects of exercise on heart failure prevention observed in Western studies may not be applicable to the Asian population. In this study, we examined the association between physical activity (walking and sports participation) and risk of heart failure mortality among Japanese men and women in a large cohort study.

Methods

Study Cohort

The Japan Collaborative Cohort Study for Evaluation for Cancer Risk (JACC Study) is comprised of 110,585 individuals (46,395 men and 64,190 women), aged 40 to 79 years, surveyed from 1988 to 1990 who lived in 45 communities across Japan and completed self-administered lifestyle questionnaires¹³). At baseline, the study participants completed self-administered questionnaires about their lifestyles such as physical activity and medical histories of hypertension, diabetes mellitus, stroke, coronary heart disease, and cancer. Details of the JACC study have been described elsewhere¹³). We excluded individuals with previous histories of stroke, coronary heart disease, or cancer ($n=6,234$), individuals in seven areas where the physical activity question was not administered ($n=14,561$), and individuals with missing information on both walking and sports participation times ($n=2,952$). Therefore, the data of 86,838 individuals (36,223 men and 50,615 women) in the 38 communities were used for the analysis. Compared to the 86,838 persons, the excluded 2,952 due to missing information were older, were more female, had lower body mass index, and had more hypertension (not shown). The Ethical Boards of Hokkaido University, Osaka University, and University of Tsukuba approved the protocol of this investigation, including the procedures used to obtain informed consent¹³). Individual informed consent

before participation in the study was obtained in 36 of the 45 communities (written consent in 35 communities and oral consent in one community); in the remaining nine communities, group consent from the area leader was obtained, which was accepted practice in Japan at that time.

Baseline Questionnaire about Physical Activity

Participants provided a valid response to the following question about the average daily time spent walking: "How long on average do you spend walking indoors or outside on a daily basis?" The possible answers were <0.5 h, 0.5 h, 0.6 to 0.9 h, or ≥ 1.0 h. Participants were also asked about the average weekly time spent in athletic and sporting events as follows: "What is the average amount of time you spend engaging in sports or physical exercise on weekly basis?" The possible answers were <1 h, 1 to 2 h, 3 to 4 h, or ≥ 5 h.

The validity of the estimation method for time spent participating in sports or physical activity was previously examined in a random sampling of 739 men and 991 women from the baseline participants¹⁴). The Spearman rank correlation coefficients between time spent participating in sports or physical activity derived from baseline questionnaire and leisure-time physical activity score derived from the interviewing method were 0.53 in men and 0.58 in women. The reliability for time spent walking and sports participation was estimated by comparing the response categories from two separate surveys conducted almost 1 year apart in a random sample of 416 men and 636 women¹⁴). The weighted kappa coefficients between the two surveys were modest: 0.32 in men and 0.31 in women for time spent walking and 0.45 in men and 0.40 in women for sports participation.

Mortality Surveillance

The investigators conducted a systematic review of death certificates, all of which were forwarded to the local public health center in each community. It is believed that all deaths in the cohort were ascertained, except for participants who died after they had moved from their original community, in which case the participant was treated as a censored case. The date of moving from the community was verified using population-registration documents. Mortality data were sent centrally to the Ministry of Health, Labour and Welfare, and the underlying causes of death were coded for National Vital Statistics according to the International Classification of Disease, 10th revision, with code I50 regarded as heart failure.

The mortality follow-up inquiry was conducted until the end of 2009 in most areas; however, it was

stopped at the end of 1999 in three areas, at the end of 2003 in two, and at the end of 2008 in two. Approximately 8% of participants were lost to follow-up due to moving out of their communities and treated as censored.

It should be noted that heart failure diagnoses based on death certificates were considered to be potentially inaccurate, especially before 1995 when Japanese physicians were likely to diagnose patients with diseases of unknown origin, and studies showed that approximately 50% of heart failure deaths were validated as coronary heart disease or sudden deaths¹⁵.

Statistical Analysis

Statistical analyses were conducted on the basis of cause-specific mortality rates. Person-years of follow-up were calculated from the date of the baseline questionnaire to the date of death, a move from the community, or the end of follow-up, whichever occurred first. The hazard ratios (HRs) and 95% confidence intervals (95% CIs) according to walking and sports participation time categories were calculated using the Cox proportional hazards model. Since the individuals in the lowest categories might have ill health and the goal of this study was to study physical activity in healthy participants, we chose the second-lowest categories of walking and sports participation as the reference.

Sex-specific age-adjusted means and proportions of selected cardiovascular risk factors were presented among the categories of walking and sports participation. Differences from the second-lowest category in sex-specific, age-adjusted mean values and proportions of baseline characteristics were examined based on the Dunnett-Hsu tests. Lifestyles, such as weight, height, and histories of hypertension and diabetes, were derived from the self-reported baseline questionnaire. Body mass index was calculated as body weight (kg) divided by the square of height (m²). The age-adjusted and multivariable HRs and the 95% CIs were calculated after adjustment for age and potential confounding factors using the Cox proportional hazards model. Confounding factors included body mass index (quartiles), smoking status (current and non-current smokers), alcohol intake category (never drinkers, ex-drinkers, and current drinkers), job style (manual worker, non-manual worker, and non-worker), and total fish intake (quartiles, defined elsewhere¹⁶). These factors are known cardiovascular risk factors and were associated with walking and/or sports participation at baseline inquiry in this cohort (**Table 1**). Histories of hypertension and diabetes were not included because these were considered as mediators. As a sensitivity analysis, we also included

these variables in the multivariable model. Study areas, hours of sleep, perceived mental stress, education, and perceived mental stress were not included because they did not strongly associate with outcomes in this model, and their inclusion did not change the results materially. To analyze walking time ($n=78,063$), we also adjusted for time spent in sports participation, and in the analysis of sports participation ($n=83,108$), we adjusted for time spent walking. To test for a potential modifying effect of sex on physical activity, we added cross-product terms of walking time or sports participation time and sex variables into the Cox proportional hazards model.

For sensitivity analyses, we also excluded heart failure deaths within the first 5, 10, and 15 years from the baseline to examine the potential effect of any existing preclinical disorders that might have interfered with participation in walking and sports.

We used SAS version 9.4 (SAS Institute Inc., Cary, NC) for the analyses. All probability values for statistical tests were two-tailed, and values of $p < 0.05$ were regarded as statistically significant.

Results

Table 1 shows sex-specific, age-adjusted selected cardiovascular risk factors according to the four categories of walking time and sports participation time. Compared with men and women who reported 0.5 h/day of walking (second-lowest category), those who reported ≥ 1.0 h/day of walking (highest category) were more likely to possess a lower mean body mass index, were less likely to have a history of hypertension and diabetes, and were less educated, were more likely to be manual workers, have perceived mental stress, and have higher fish intake. Men who reported ≥ 1.0 h/day of walking were likely to be older, drink more, sleep more, and smoke more, compared with those who reported 0.5 h/day of walking. Similar associations were observed according to sports participation categories.

A total of 86,838 individuals (36,223 men and 50,615 women) were followed up for a median of 19.1 years, and 994 enrollees (458 men and 536 women) died from heart failure over the study period. As shown in **Table 2**, compared with persons who reported 0.5 h/day of walking, the multivariable HRs (95% CIs) of mortality from heart failure for persons who reported a walking time of 0.6 to 0.9 h/day and ≥ 1.0 h/day compared with 0.5 h/day were 0.78 (0.57 to 1.07) and 0.76 (0.59 to 0.99) in men and 0.87 (0.66 to 1.15) and 0.78 (0.61 to 0.99) in women. There was no sex interaction for the association

Table 1. Sex-specific age-adjusted mean values or prevalence of cardiovascular risk factors at baseline according to walking time and sports participation time

	Walking time (h/Day)							
	Men				Women			
	<0.5	0.5	0.6-0.9	≥ 1.0	<0.5	0.5	0.6-0.9	≥ 1.0
No. at risk	4,116	6,119	6,397	16,550	4,901	7,957	9,373	23,531
Age, yrs	55.5***	56.6	57.3**	57.2***	56.1***	57.7	57.6	57.4*
Body mass index, kg/m ²	22.9	22.8	22.7	22.5***	23.1*	22.9	22.9	22.8**
History of hypertension, %	20.9	21.7	21.6	18.3***	22.6	23.4	23.0	21.0***
History of diabetes, %	7.8	8.3	6.5***	5.5***	4.5*	5.4	4.6*	3.3***
Ethanol intake, g/day	28.6	28.0	28.6	29.9***	31.7	33.7	32.3	32.9
Hours of sleep, h/day	7.5*	7.4	7.4	7.5***	7.1*	7.1	7.1	7.1
Current smoker, %	53.5	52.1	52.5	55.6***	6.5*	5.1	5.1	5.0
College or higher education, %	16.5***	23.9	22.2	14.4***	8.7***	12.0	10.9	9.9***
Office worker, %	47.0	49.7	47.7*	41.8***	27.1	26.2	25.0	20.8***
High perceived mental stress, %	27.3	27.1	23.5***	20.7***	22.3	20.8	19.5	19.4*
Amount of total fish intake, g/day	47.1**	45.1	47.4***	50.7***	47	47.7	48.3	50.6***
Sports 5h/week and more, %	1.6***	3.6	6.0***	11.1***	1.2	1.6	3.2***	7.4***

	Sports participation time (h/Week)							
	Men				Women			
	<1	1-2	3-4	≥ 5	<1	1-2	3-4	≥ 5
No. at risk	24,083	5,862	2,550	2,512	36,606	6,625	2,640	2,230
Age, yrs	56.4***	55.8	58.9***	61.7***	56.7	56.8	59.6***	62.1***
Body mass index, kg/m ²	22.6	22.7	22.8	22.7	22.9	22.9	22.9	22.8
History of hypertension, %	19.6	20.1	22	19.4	22.0	22.9	22.0	19.9*
History of diabetes, %	6.1	7	7.2	6.8	3.7*	4.5	4.5	4.4
Ethanol intake, g/day	29.4	29.2	29.4	30.2	3.0***	3.9	3.8	4.7*
Hours of sleep, h/day	7.5**	7.4	7.4	7.5**	7.1	7.1	7.1	7.1
Current smoker, %	55.4***	51.5	51.7	52.4	5.5***	4.3	5.4	5.0
College or higher education, %	15.7***	23.6	24.0	19.8***	9.4***	13.5	13.9	11.3*
Office worker, %	46.6**	49.7	47.7	41.8***	24.3**	26.8	25	23.1*
High perceived mental stress, %	23.4*	23.1	22.0*	22.7*	20.9**	18.9	18.8	17.9
Amount of total fish intake, g/day	48.7*	47.6	47.9	51.3***	49.2	49.8	49.7	52.3**
Walking 1h/day and more, %	48.3***	44.0	47.9	73.4***	49.3	48.8	56.5***	78.4***

Test for difference from the second lowest category based on the Dunnett-Hsu tests; *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

between any walking time category and risk of mortality from heart failure.

The multivariable HRs (95% CIs) of heart failure mortality for persons who reported participation in sports for 3 to 4 h/week and ≥ 5 h/week compared with 1 to 2 h/week were 0.67 (0.44 to 1.02) and 0.62 (0.41 to 0.93) in men and 0.95 (0.63 to 1.45) and 1.09 (0.73 to 1.65) in women (Table 3). The sex interaction was of borderline significance for the association between the highest sports participation time category and risk of heart failure mortality ($p = 0.048$). When histories of hypertension

and diabetes were added as adjustment variables in the multivariable model, the results were generally the same. The multivariable HRs (95% CIs) of mortality from heart failure for persons who reported a walking time of ≥ 1.0 h/day compared with 0.5 h/day were 0.78 (0.60 to 1.01) in men and 0.79 (0.62 to 1.00) in women. The multivariable HRs (95% CIs) for persons who reported participation in sports of ≥ 5 h/week compared with 1 to 2 h/week were 0.63 (0.41 to 0.94) in men and 1.09 (0.72 to 1.64) in women (not shown in Table).

The lower HRs of heart failure mortality for men

Table 2. Sex-specific hazard ratios (HRs) and 95% confidence intervals (95% CIs) of mortality from heart failure according to walking time

	Walking time (h/Day)							
	Men				Women			
	<0.5	0.5	0.6-0.9	≥ 1.0	<0.5	0.5	0.6-0.9	≥ 1.0
Person-years	63,614	94,709	100,192	267,489	79,282	125,325	151,032	393,319
No. of heart failure deaths	47	84	75	199	55	98	100	223
Age-adjusted HR (95% CI)	1.00 (0.70-1.42)	1.0	0.76 (0.55-1.03)	0.77 (0.60-0.99)	1.19 (0.85-1.65)	1.0	0.88 (0.66-1.16)	0.77 (0.60-0.97)
Multivariable HR (95% CI)*	0.93 (0.65-1.34)	1.0	0.78 (0.57-1.07)	0.76 (0.59-0.99)	1.15 (0.83-1.61)	1.0	0.87 (0.66-1.15)	0.78 (0.61-0.99)
Exclusion for the first 5-year deaths from heart failure								
Person-years	63,561	94,632	100,117	267,352	79,221	125,267	150,982	393,229
No. of heart failure deaths	26	49	50	150	34	78	80	194
Age-adjusted HR (95% CI)	0.96 (0.59-1.54)	1.0	0.86 (0.58-1.27)	0.95 (0.69-1.31)	0.93 (0.62-1.40)	1.0	0.88 (0.64-1.20)	0.81 (0.62-1.06)
Multivariable HR (95% CI)*	0.90 (0.56-1.46)	1.0	0.88 (0.59-1.31)	0.93 (0.67-1.29)	0.90 (0.60-1.35)	1.0	0.86 (0.63-1.17)	0.81 (0.62-1.06)
Exclusion for the first 10-year deaths from heart failure								
Person-years	63,514	94,539	99,961	267,128	79,154	125,194	150,831	392,924
No. of heart failure deaths	19	35	31	120	24	69	61	153
Age-adjusted HR (95% CI)	0.96 (0.55-1.69)	1.0	0.75 (0.46-1.21)	1.03 (0.71-1.51)	0.74 (0.46-1.18)	1.0	0.75 (0.53-1.05)	0.70 (0.53-0.93)
Multivariable HR (95% CI)*	0.91 (0.51-1.60)	1.0	0.75 (0.46-1.22)	0.99 (0.68-1.46)	0.73 (0.46-1.18)	1.0	0.74 (0.52-1.04)	0.71 (0.53-0.95)
Exclusion for the first 15-year deaths from heart failure								
Person-years	63,408	94,409	99,866	266,527	79,042	124,900	150,609	392,305
No. of heart failure deaths	11	25	24	72	15	46	43	105
Age-adjusted HR (95% CI)	0.77 (0.38-1.57)	1.0	0.81 (0.46-1.42)	0.87 (0.55-1.37)	0.73 (0.41-1.31)	1.0	0.80 (0.53-1.21)	0.72 (0.51-1.01)
Multivariable HR (95% CI)*	0.72 (0.35-1.47)	1.0	0.81 (0.46-1.42)	0.81 (0.51-1.29)	0.72 (0.40-1.30)	1.0	0.80 (0.53-1.22)	0.71 (0.50-1.02)

	Walking time (h/Day)			
	Men and Women**			
	<0.5	0.5	0.6-0.9	≥ 1.0
Person-years	142,895	220,034	251,223	660,807
No. of heart failure deaths	102	182	175	422
Age-adjusted HR (95% CI)	1.09 (0.86-1.39)	1.0	0.81 (0.66-1.00)	0.76 (0.64-0.91)
Multivariable HR (95% CI)*	1.05 (0.82-1.35)	1.0	0.83 (0.67-1.02)	0.77 (0.64-0.92)
Exclusion for the first 5-year deaths from heart failure				
Person-years	142,782	219,899	251,100	660,582
No. of heart failure deaths	60	127	130	344
Age-adjusted HR (95% CI)	0.94 (0.69-1.28)	1.0	0.86 (0.67-1.10)	0.86 (0.70-1.05)
Multivariable HR (95% CI)*	0.90 (0.66-1.23)	1.0	0.87 (0.68-1.11)	0.86 (0.70-1.05)
Exclusion for the first 10-year deaths from heart failure				
Person-years	142,668	219,734	250,792	660,051
No. of heart failure deaths	43	104	92	273
Age-adjusted HR (95% CI)	0.81 (0.57-1.16)	1.0	0.74 (0.56-0.98)	0.81 (0.64-1.01)
Multivariable HR (95% CI)*	0.79 (0.55-1.13)	1.0	0.74 (0.56-0.98)	0.80 (0.64-1.01)
Exclusion for the first 15-year deaths from heart failure				
Person-years	142,449	219,309	250,475	658,832
No. of heart failure deaths	26	71	67	177
Age-adjusted HR (95% CI)	0.74 (0.47-1.16)	1.0	0.80 (0.57-1.11)	0.76 (0.58-1.00)
Multivariable HR (95% CI)*	0.71 (0.45-1.13)	1.0	0.80 (0.57-1.11)	0.74 (0.56-0.98)

* Adjusted for age, sports participation time, body mass index, drinking status, smoking status, job, and total fish intake.

** Further adjusted for sex.

Table 3. Sex-specific hazard ratios (HRs) and 95% confidence intervals (95% CIs) of mortality from heart failure according to sports participation time

	Sports Participation Time (h/Week)							
	Men				Women			
	<1	1-2	3-4	≥ 5	<1	1-2	3-4	≥ 5
Person-years	385,273	94,383	38,998	38,133	605,281	109,414	42,736	35,627
No. of heart failure deaths	283	75	30	34	356	65	33	37
Age-adjusted HR (95% CI)	1.00 (0.77-1.29)	1.0	0.67 (0.44-1.03)	0.61 (0.41-0.92)	1.12 (0.86-1.46)	1.0	0.93 (0.61-1.42)	1.00 (0.67-1.50)
Multivariable HR (95% CI)*	0.93 (0.72-1.21)	1.0	0.67 (0.44-1.02)	0.62 (0.41-0.93)	1.06 (0.81-1.38)	1.0	0.95 (0.63-1.45)	1.09 (0.73-1.65)
Exclusion for the first 5-year deaths from heart failure								
Person-years	385,046	94,317	38,979	38,103	605,096	109,378	42,719	35,614
No. of heart failure deaths	194	52	22	24	290	54	27	33
Age-adjusted HR (95% CI)	0.98 (0.72-1.33)	1.0	0.72 (0.44-1.19)	0.61 (0.37-0.99)	1.12 (0.84-1.50)	1.0	0.92 (0.58-1.47)	1.08 (0.70-1.67)
Multivariable HR (95% CI)*	0.92 (0.68-1.26)	1.0	0.70 (0.42-1.15)	0.59 (0.36-0.96)	1.08 (0.80-1.44)	1.0	0.94 (0.59-1.49)	1.17 (0.75-1.81)
Exclusion for the first 10-year deaths from heart failure								
Person-years	384,694	94,159	38,943	38,083	604,640	109,358	42,662	35,536
No. of heart failure deaths	146	31	17	22	229	51	20	23
Age-adjusted HR (95% CI)	1.21 (0.82-1.79)	1.0	0.96 (0.53-1.74)	0.94 (0.54-1.63)	0.95 (0.70-1.28)	1.0	0.74 (0.44-1.24)	0.82 (0.50-1.34)
Multivariable HR (95% CI)*	1.15 (0.77-1.71)	1.0	0.94 (0.52-1.70)	0.89 (0.51-1.54)	0.92 (0.68-1.25)	1.0	0.75 (0.45-1.26)	0.90 (0.54-1.48)
Exclusion for the first 15-year deaths from heart failure								
Person-years	383,963	94,031	38,847	38,004	603,634	109,152	42,538	35,473
No. of heart failure deaths	88	21	10	16	150	35	10	18
Age-adjusted HR (95% CI)	1.09 (0.68-1.76)	1.0	0.85 (0.40-1.82)	1.05 (0.55-2.02)	0.93 (0.64-1.34)	1.0	0.55 (0.27-1.11)	0.96 (0.54-1.69)
Multivariable HR (95% CI)*	1.09 (0.67-1.77)	1.0	0.85 (0.40-1.81)	1.04 (0.54-2.02)	0.92 (0.63-1.33)	1.0	0.56 (0.28-1.13)	1.05 (0.59-1.87)

	Sports Participation Time (h/Week)			
	Men and Women**			
	<1	1-2	3-4	≥ 5
Person-years	990,554	203,797	81,734	73,760
No. of heart failure deaths	639	140	63	71
Age-adjusted HR (95% CI)	1.06 (0.88-1.27)	1.0	0.79 (0.58-1.06)	0.76 (0.57-1.01)
Multivariable HR (95% CI)*	1.00 (0.83-1.21)	1.0	0.79 (0.58-1.06)	0.80 (0.60-1.07)
Exclusion for the first 5-year deaths from heart failure				
Person-years	990,143	203,695	81,699	73,717
No. of heart failure deaths	484	106	49	57
Age-adjusted HR (95% CI)	1.05 (0.85-1.30)	1.0	0.82 (0.58-1.15)	0.81 (0.59-1.12)
Multivariable HR (95% CI)*	1.02 (0.82-1.26)	1.0	0.81 (0.58-1.14)	0.83 (0.60-1.15)
Exclusion for the first 10-year deaths from heart failure				
Person-years	989,334	203,517	81,605	73,619
No. of heart failure deaths	375	82	37	45
Age-adjusted HR (95% CI)	1.05 (0.83-1.33)	1.0	0.82 (0.56-1.21)	0.85 (0.59-1.23)
Multivariable HR (95% CI)*	1.02 (0.80-1.30)	1.0	0.82 (0.55-1.21)	0.87 (0.60-1.26)
Exclusion for the first 15-year deaths from heart failure				
Person-years	987,596	203,183	81,385	73,477
No. of heart failure deaths	238	56	20	34
Age-adjusted HR (95% CI)	0.99 (0.74-1.33)	1.0	0.66 (0.40-1.11)	0.97 (0.64-1.49)
Multivariable HR (95% CI)*	0.99 (0.74-1.33)	1.0	0.67 (0.40-1.12)	1.02 (0.66-1.57)

* Adjusted for age, walking time, body mass index, drinking status, smoking status, job, and total fish intake.

** Further adjusted for sex.

who reported a walking time of ≥ 1.0 h/day became no longer statistically significant after excluding heart failure deaths for the first 5, 10, and 15 years, and those for men who reported participation in sports of ≥ 5 h/week did so after excluding deaths for 10 and 15 years. On the other hand, in women, the exclusion did not change the HRs materially; the HRs in women who reported a walking time of ≥ 1.0 h/day were 0.81 (0.62–1.06) after the first 5 years of exclusion, 0.71 (0.53–0.95) after 10 years of exclusion, and 0.71 (0.50–1.02) after 15 years of exclusion.

Discussion

We observed inverse associations of walking time (in men and women) and sports participation time (in men only) with mortality due to heart failure. These findings were not substantially altered after adjustment for known risk factors. The inverse associations were consistent with the results of the meta-analysis of data from Europe and US cohort, which showed that the light, moderate, and highest levels of physical activities were associated with 15%, 22%, and 30% lower risks of heart failure, respectively, compared with participants at the lowest levels of physical activity¹¹).

The inverse association between physical activity and heart failure was largely attenuated in the analysis restricted to participants with more than 5 years of follow-up. The association may be affected by reverse causation that arises from changes in physical activity in the preclinical phase of heart failure. In addition, misclassification in physical activity habits during follow-up may also have attenuated the association. In the group of women with long walking time, the inverse association with heart failure remained even after excluding early heart failure death during follow-up period. The reasons for this are unknown, but may be that walking for a long time is easy to continue and that women have more opportunities to go out such as for shopping or for meeting with friends than men.

Several mechanisms have been proposed for the observed reduction in heart failure mortality due to physical activity. Exercise decreases sympathetic nervous activity¹⁷), lowers blood pressures²), and contributes to the improvement of insulin sensitivity³) and blood lipid profiles^{4, 5}), leading to lower risk of heart failure via or independent of coronary heart disease.

We did not find any inverse associations between sports participation and mortality from heart failure in women; the sex interaction was only of borderline significance. The mechanism for this observed sex difference is unknown, but women who ranked in the

highest sports participation category may have actually spent less time engaging in their sport than men. In the validation study for our sports participation questionnaire, the median time spent in sports in women in that category (≥ 5 h/week) was 244 min compared to 295 min in men¹⁴).

This study has several limitations. First, as discussed, was a lack of history of heart failure at the baseline. Participants in the lowest categories of walking or sports participation may have included some participants who already had heart failure or other preclinical diseases. Therefore, to avoid this cause-effect reversal, we used the second-lowest physical activity category as a reference. We also conducted an additional analysis after excluding deaths from heart failure occurring within 5, 10, and 15 years from baseline to determine the impact of this limitation on our results. The results for the group with the lowest category of sports participation time did not change, suggesting that the possibility of reverse causality for sports participation may be small. For walking time, the hazard ratio of heart failure for the lowest group decreased with the exclusion, suggesting that the lowest category of walking time may have included participants who already had heart failure or other preclinical diseases. Second, as mentioned in the methods, heart failure diagnoses based on death certificates may not be accurate, especially before 1995. Vital statistics showed a steep decline in mortality from heart failure by 70% and an increase in mortality from coronary heart disease by 36% from 1993 to 1995¹⁵). When we excluded deaths from heart failure occurring within the first 5 years (which means all deaths from heart failure occurring after 1995), the inverse associations between walking time and risk of mortality from heart failure were attenuated in men. The significant inverse association before the exclusion could be due to the contamination of coronary heart disease. Third, the physical activity was evaluated by self-report. Ideally, objectively measured physical activity (i.e., accelerometer-derived metrics) should be more precise at estimating the exposure levels than self-reported one, which may change the strength of the association with outcome. However, these devices were not available at that time, and if so, it was not practical to have these devices implemented on more than 80,000 people.

In conclusion, physical activity through walking in men and women and sports participation in men was associated with a lower risk of mortality from heart failure in this Japanese community-based population. The association was weakened after excluding earlier deaths from heart failure, which may

be due to changes in physical activity and death certificate diagnoses during the follow-up and reverse causation. Nonetheless, the persistent inverse association between walking and the risk of heart failure in women suggests that a long-term habit of walking is expected to prevent heart failure.

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Conflict of Interest

The authors declare no conflict of interests.

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