# Exercise Habits Are Associated with Improved Long-Term Mortality Risks in the Nationwide General Japanese Population: A 20-Year Follow-Up of the NIPPON DATA90 Study

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Exercise habits are known as a protective factor for a variety of diseases and thus recommended worldwide; however, few studies have examined long-term effects of exercise habits on mortality. We continuously monitored death status in a nationwide population sample of 7,709 eligible persons from the National Integrated Project for Prospective Observation of Noncommunicable Disease and its Trends in the Aged in 1990 (NIPPON DATA90), for which baseline data were obtained in 1990. To investigate the long-term impact of baseline exercise habits, we calculated the relative risk of non-exercisers (participants without regular voluntary exercise habits) in reference to exercisers (those with these habits) for all-cause or cause-specific mortality using a Cox proportional hazard model, in which the following confounding factors were appropriately adjusted: sex, age, body mass index, total energy intake, smoking, drinking, and history of cardiovascular disease. During a median 20 years of follow-up, 1,747 participants died, 99 of heart failure. The risk for all-cause mortality was 12% higher in non-exercisers than in exercisers (95% confidence interval, 1%-24%), which was also observed for mortality from heart failure, as 68% higher in non-exercisers than in exercises (95% confidence interval, 3%-173%). These associations were similarly observed when the participants were divided to subgroups by sex, age, and the light, moderate, or vigorous intensity of physical activity, without any significant heterogeneities ($P > 0.1$). The present study has revealed significant impact of exercise habits on long-term mortality risks, supporting worldwide recommendations for improvement of exercise habits.

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## Introduction

Exercise habits are essential for human health. As a global health problem, physical inactivity is associated with a high burden of cardiovascular disease (CVD) and other non-communicable chronic diseases (NCDs). For the prevention and control of NCDs, the World Health Organization (WHO) currently recommends that adults do at least 150 minutes of moderate- to vigorous-intensity physical activity every week, or an equivalent combination of both (World Health Organization 2010). Recent research indicates that physical inactivity causes 9% of premature mortality, or more than 5.3 million of the 57 million deaths that occurred worldwide in 2008 (Lee et al. 2012). Therefore, engaging in exercise regularly helps not only to maintain health, but also to reduce the mortality risk.

Several studies reported a variety of health benefits of exercise habits, and it is known that exercise habits are associated with reduced risk of all-cause mortality (Wen et al. 2011; Lee et al. 2014; Kraschnewski et al. 2016; O'Donovan et al. 2017) and mortality from CVD (Lee et al. 2014; Eijsvogels et al. 2016; O'Donovan et al. 2017) and cancer(Wen et al. 2011; Bigley et al. 2013; O'Donovan et al. 2017). However, most findings were reported based on studies with follow-up periods of less than 10 years (Inoue et al. 2008; Wen et al. 2011). A few studies revealed that exercise habits at baseline predicted relatively long-term (around 15 years) risk of mortality (Hayashi et al. 2016; Kraschnewski et al. 2016). However, no studies have examined the long-term effects of exercise habits on mortality for 20 years or more.

We therefore investigated the long-term effects of exercise habits on mortality using 20-year follow-up of a representative Japanese population from a national survey, the National Integrated Project for Prospective Observation of Noncommunicable Disease and its Trends in the Aged in 1990 (NIPPON DATA90).

## Materials and Methods

### *Study participants*

The NIPPON DATA90 is a nationwide cohort of a random population sample based on the National Survey of Circulatory Disorder conducted in 1990 (Okuda et al. 2019; Kogure et al. 2020). In that year, we recruited a total of 8,383 community residents (4,880 women, 3,503 men) age 30 or older from 300 randomly selected districts across Japan. The baseline surveys were carried out at local public health centers. Of the 8,383 participants, 674 were excluded because of missing information on exercise habits ($n$ = 113), body mass index (BMI; $n$ = 5), or because the participant answered that "I am unable to do exercise due to a health-related reason" for the baseline questionnaire on exercise habit ($n$ = 556). The remaining 7,709 participants (4,447 women and 3,262 men; participation rate, 92.0%) were included in the analysis.

With permission from the Ministry of Health, Labour and Welfare, we used results from the National Survey of Circulatory Disorder and related databases. The study was approved by the Ethics Review Board of the Shiga University of Medical Science (12e18, 2000; 17e21-1, 2010; Shiga, Japan).

### *Baseline survey*

Public health nurses collected information on essential data in the baseline survey including regular voluntary exercise habits. BMI was calculated as the weight (kg) divided by the height squared ($m^2$), and categorized into three groups ($\leq$ 18.5, 18.5-25, $\geq$ 25 kg/$m^2$) according to the modified WHO criteria for the Japanese population (Anuurad et al. 2003). Baseline blood pressure was measured by public health nurses using a standard mercury sphygmomanometer and placing appropriately-sized cuffs on the right arm of the participants who were seated and remained at rest for more than 5 min. Blood samples were obtained at the baseline survey with data on postprandial time (hours). Serum was separated and centrifuged soon after blood coagulation. Plasma samples were collected in siliconized tubes containing sodium fluoride and shipped to one laboratory (SRL Inc., Tokyo, Japan) for blood measurements. Plasma glucose and total cholesterol were measured enzymatically. HbA1c as the National Glycohemoglobin Standardization Program (Kashiwagi et al. 2012) was measured using the high-performance liquid chromatography method.

Public health nurses further confirmed smoking habit (never, past, and current smoker categories), alcohol habit (never, past, and current drinker categories) and medical history, including histories of diseases (CVD, hypertension, diabetes, and hypercholesterolemia). Treatment for diseases was self-reported. CVD history included stroke, myocardial infarction, and angina. Hypertension was defined as having systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, and/or use of antihypertensive drugs. Diabetes was defined as HbA1c $\geq$ 6.5%, non-fasting (post prandial time < 8 hours) blood glucose level $\geq$ 11.1 mmol/L ($\geq$ 200 mg/dL), fasting blood glucose level $\geq$ 7.0 mmol/L ($\geq$ 126 mg/dL), or a history of diabetes. Hypercholesterolemia was defined as serum total cholesterol $\geq$ 12.2 mmol/L ($\geq$ 220 mg/dL) (Kurabayashi et al. 2000; Hata et al. 2002) or use of medication for hypercholesterolemia. Total energy intake estimated from the food frequency questionnaire on total intake of household members (Okuda et al. 2019; Kogure et al. 2020) was categorized into four groups using sex-specific cut-off points of the 25th, 50th, 75th, and 100th percentiles.

### *Definition of exerciser*

According to the Recommended Exercise Allowances for Health Promotion (The Office for Lifestyle-Related Diseases Control, General Affairs Division, Health Service Bureau, Ministry of Health, Labour and Welfare of Japan 2006) and the National Health and Nutrition Survey

(Ishikawa-Takata and Tabata 2007), which was adopted in the Basic Direction for Comprehensive Implementation of National Health Promotion (Health Japan 21 second edition) (Ministry of Health, Labour and Welfare 2012), we defined "exercisers," participants with regular voluntary exercise habits, as having the following three criteria: (1) the frequency of exercise is ≥ 2 times/week, (2) the time of duration is ≥ 30 min, and (3) the term of duration is ≥ 1 year. Those who did not fulfill all three criteria were defined as "non-exercisers." Considering the possibility that even those without exercise habits would be moving in daily physical activity, we categorized participants by the self-reported intensity of physical activity based on their daily life as light (e.g., under 2 hours walking and 2 hours standing per day), moderate (2-4 hours walking and 2-6 hours standing per day), and vigorous (2-4 hours walking, 6-9 hours standing and 1-hour muscular movement and more per day) activity levels. The activity levels were indicated as those corresponding to the following examples of daily life: office worker, administrative worker, or a housewife not caring for an infant as light level; manufacturing worker, sales worker, service worker, or a housewife caring for an infant as moderate level; and farmer, fisherman, construction worker, or professional sports player as vigorous level.

*Follow-up survey*

After the baseline survey, we utilized the National Vital Statistics of the Ministry of Health, Labour and Welfare, Japan, to ascertain the cause of death. The 9th International Classification for Disease (ICD-9) was used for deaths by the end of 1994, and the 10th International Classification for Disease (ICD-10) for deaths from the beginning of 1995 to the end of follow-up, November 15, 2010. The cause of death used in the current study was defined as follows: CVD (290-459 by ICD-9; I00-I99 by ICD-10), stroke (430-438; I60-I69), coronary heart disease (CHD) (410-414; I20-I25), heart failure (428; I50) and cancer (140-208; C00-D48).

*Statistical analysis*

For database management and statistical analysis, we used SAS software, version 9.4 (SAS Institute Inc., Cary, NC). Descriptive statistics are presented as means with SDs and proportions as appropriate unless otherwise stated. All confidence intervals were estimated at the 95% level. A $P$ value of less than 0.05 was considered significant.

For comparison of baseline characteristics between exercisers and non-exercisers, Student's $t$-test and chi-square test were used appropriately. After verification of the proportionality assumption, the Cox proportional hazard model was used to investigate the risk of non-exercisers for all-cause and cause-specific mortalities, i.e., total CVD, heart failure, CHD, stroke, and cancer mortalities, in reference to exercisers. In addition to sex and age, BMI (≤ 18.5, 18.5–25, ≥ 25 kg/m$^2$), total energy intake, smoking habits (never, past, current), drinking habits (never, past, current), and histories of CVD, hypertension, diabetes, and hypercholesterolemia were used in the multivariable-adjusted model. As supplementary analysis, we further adjusted for the intensity of physical activity.

We performed sensitivity analysis based on the first 10 years of follow-up from the baseline to investigate the influence of the follow-up period. Another sensitivity analysis among participants with complete follow-up information, excluding death within the first 6 years, was conducted because heart failure as the cause of death was revised in line with the introduction of ICD-10 for the National Demographic Statistics of Japan on January 1995; thereafter, doctors should not use heart failure or respiratory failure at most as the direct cause of death in a death certificate. Additional sensitivity analysis was conducted after excluding participants with CVD history. We also conducted subgroup analysis by sex (women or men), by age (30-64 or ≥ 65 years old), and by the intensity of physical activity (light, moderate, or vigorous activity level). Interactions were assessed by adding an interaction term to the model.

Finally, as supplementary analysis, we assessed mortality risk associated with the intensity of physical activity.

## Results

The baseline characteristics of the participants, a total of 1,683 exercisers and 6,026 non-exercisers, are shown in Table 1. The proportions of women were higher in non-exercisers (58.9%) than in exercisers (53.3%; $P < 0.0001$). Mean age among exercisers (55.9 years) was 4.5 years older than non-exercisers (51.4 years; $P < 0.0001$) while no differences in BMI ($P = 0.08$) and total energy intake ($P = 0.08$) were observed between the two groups. Compared with non-exercises, exercisers had a higher proportion of history of CVD, hypertension, diabetes, and hypercholesterolemia ($P \leq 0.0001$).

During a median 20.0 years of follow-up (interquartile range, 19.0-20.0; person-years, 135,666), 1,747 participants (12.8 participants per 1,000 person-years) died. Of those, we observed 511 CVD deaths, of which 99 were heart failure, 111 CHD, and 197 stroke, and 621 cancer deaths.

Based on the multivariable-adjusted Cox model (Table 2), non-exercisers had a significantly higher risk of mortality from all-cause (hazard ratios [HR], 1.12; 95% confidence intervals [CI], 1.01-1.24) and from heart failure (HR, 1.68; 95% CI, 1.03-2.73) compared with exercisers. The risk in non-exercisers for all-cause mortality was evident when we limited the follow-up period to the first 10 years (HR, 1.35; 95% CI, 1.13-1.61; Table 3); this was also the case with heart failure death, though not significant (HR, 2.23; 95% CI, 0.92-5.37; Table 3). Risks of other subtypes of mortality were not significantly different between the two groups regardless of the follow-up period (Tables 2, 3; $P \geq 0.057$). Similar results were observed when subtypes of cancer death, i.e. lung cancer ($n$ = 113), stomach ($n$ = 109), and others ($P \geq 0.054$), were considered. The results

Table 1. Characteristics of the study participants.

| Variables | All ($n$ = 7,709) | Exercisers ($n$ = 1,683) | Non-Exercisers ($n$ = 6,026) |
|---|---|---|---|
| Women (%) | 4,447 (57.7) | 897 (53.3) | 3,550 (58.9)† |
| Age, years (SD) | 52.4 (13.7) | 55.9 (14.3) | 51.4 (13.4)† |
| ≥ 65 (%) | 1,628 (21.1) | 550 (32.7) | 1,078 (17.9)† |
| Energy intake, kcal (SD) | 2,062 (465) | 2,051 (477) | 2,065 (462) |
| Body mass index, kg/m$^2$ (%) | | | |
| ≤ 18.5 | 482 (6.3) | 91 (5.4) | 391 (6.5) |
| 18.5-25 | 5,413 (70.2) | 1,216 (72.3) | 4,197 (69.7) |
| ≥ 25 | 1,814 (23.5) | 376 (22.3) | 1,438 (23.9) |
| Smoking status (%) | | | |
| Never | 4,596 (59.6) | 952 (56.6) | 3,644 (60.5)† |
| Past | 877 (11.4) | 266 (15.8) | 611 (10.1) |
| Current | 2,237 (29.0) | 465 (27.6) | 1,771 (29.4) |
| Alcohol drinking (%) | | | |
| Never | 5,226 (67.8) | 1,070 (63.6) | 4,156 (69.0)† |
| Past | 248 (3.2) | 77 (4.6) | 171 (2.8) |
| Current | 2,235 (29.0) | 536 (31.9) | 1,699 (28.2) |
| Intensity of physical activity (%) | | | |
| Light | 3,930 (51.0) | 994 (59.1) | 2,936 (48.7)† |
| Moderate | 3,038 (39.4) | 605 (36.0) | 2,433 (40.4) |
| Vigorous | 741 (9.6) | 84 (5.0) | 657 (10.9) |
| Disease history (%) | | | |
| Cardiovascular disease | 284 (3.7) | 90 (5.3) | 194 (3.2)† |
| Hypertension | 3,598 (46.7) | 875 (52.0) | 2,723 (45.2)† |
| Diabetes | 488 (6.3) | 143 (8.5) | 345 (5.7)† |
| Hypercholesterolemia | 2,426 (31.5) | 585 (34.8) | 1,841 (30.6)* |

Values are numbers of participants (%) or arithmetic means (SD). Definitions of exerciser and non-exerciser are provided in Methods. Disease history of cardiovascular disease includes stroke, myocardial infarction, and angina. Hypertension was defined as systolic/diastolic blood pressure ≥ 140/ ≥ 90 mmHg or taking antihypertensive medication. Diabetes was a self-reported diagnosis, a fasting or random blood glucose level of ≥ 7.0 mmol/L (126 mg/dL) or ≥ 11.1 mmol/L (200 mg/dL), respectively, or HbA1c of ≥ 6.5%. Hypercholesterolemia was a self-reported diagnosis or serum total cholesterol ≥ 12.2 mmol/L (200 mg/dL).
*$P < 0.01$, and †$P < 0.0001$ for significance of the difference between exercisers and non-exercisers.

Table 2. Hazard ratios associated with all cause and specific mortality in non-exercisers compared with exercisers.

| Mortality Subtypes | Nº of Deaths | | Sex-and Age-Adjusted Model | Multivariable-Adjusted Model |
|---|---|---|---|---|
| | Exercisers ($n$ = 1,683) | Non-Exercisers ($n$ = 6,026) | | |
| All cause | 496 | 1,251 | 1.10 (0.99-1.22) | 1.12 (1.01-1.24)* |
| Cardiovascular | 160 | 351 | 0.99 (0.82-1.19) | 1.00 (0.83-1.21) |
| Heart failure | 21 | 78 | 1.68 (1.03-2.72)* | 1.68 (1.03-2.73)* |
| Coronary heart disease | 40 | 71 | 0.76 (0.51-1.12) | 0.81 (0.55-1.21) |
| Stroke | 69 | 128 | 0.85 (0.63-1.14) | 0.86 (0.64-1.15) |
| Cancer | 163 | 458 | 1.12 (0.94-1.35) | 1.14 (0.95-1.37) |

Definitions of exerciser and non-exerciser are provided in Methods. Hazard ratios and 95% confidence intervals (within parentheses) based on the Cox models express the risk in non-exercisers compared with exercisers. Multivariable model was adjusted for sex, age, energy intake, body mass index, smoking, drinking, and disease histories of cardiovascular complications, hypertension, diabetes, and hypercholesterolemia.
*$P < 0.05$ for significance of the hazard ratios.

Table 3. Hazard ratios associated with all cause and specific mortality in non-exercisers compared with exercisers during the first 10 years of follow-up.

| Mortality Subtypes | Nº of Deaths | | Sex-and Age-Adjusted Model | Multivariable-Adjusted Model |
|---|---|---|---|---|
| | Exercisers ($n$ = 1,683) | Non-Exercisers ($n$ = 6,026) | | |
| All cause | 174 | 502 | 1.32 (1.11-1.57)† | 1.35 (1.13-1.61)‡ |
| Cardiovascular | 55 | 135 | 1.16 (0.85-1.59) | 1.19 (0.86-1.64) |
| Heart Failure | 6 | 32 | 2.45 (1.02-5.88)* | 2.23 (0.92-5.37) |
| Coronary heart disease | 15 | 29 | 0.91 (0.49-1.71) | 1.05 (0.55-2.01) |
| Stroke | 24 | 52 | 1.04 (0.64-1.69) | 1.04 (0.64-1.71) |
| Cancer | 65 | 197 | 1.31 (0.99-1.74) | 1.32 (0.99-1.76) |

Definitions of exerciser and non-exerciser are provided in Methods. Hazard ratios and 95% confidence intervals (within parentheses) based on the Cox models express the risk in non-exercisers compared with exercisers during the first 10 years of follow-up. Multivariable model was adjusted for sex, age, energy intake, body mass index, smoking, drinking, and disease histories of cardiovascular complications, hypertension, diabetes, and hypercholesterolemia.

*$P < 0.05$, †$P < 0.01$, and ‡$P < 0.001$ for significance of the hazard ratios.

Table 4. Sensitivity analyses when adjusted the intensity of physical activity in daily life (left) or when participants were limited to those without cardiovascular disease history at baseline (right) during the total follow-up (above) or the first 10 years of follow-up (below).

| Mortality Subtypes | Intensity of physical activity-adjusted | | | Without cardiovascular disease history at baseline | | |
|---|---|---|---|---|---|---|
| | Nº of Deaths | | Hazard Ratio (95% CI) | Nº of Deaths | | Hazard Ratio (95% CI) |
| | Exercisers ($n$ = 1,683) | Non-Exercisers ($n$ = 6,026) | | Exercisers ($n$ = 1,593) | Non-Exercisers ($n$ = 5,832) | |
| Total follow-up | | | | | | |
| All cause | 496 | 1,251 | 1.12 (1.01-1.20)* | 436 | 1,152 | 1.13 (1.01-1.27)* |
| Cardiovascular | 160 | 351 | 1.00 (0.83-1.21) | 138 | 315 | 1.00 (0.82-1.22) |
| Heart failure | 21 | 78 | 1.69 (1.03-2.75)* | 21 | 75 | 1.60 (0.98-2.61) |
| Coronary heart disease | 40 | 71 | 0.83 (0.56-1.24) | 33 | 60 | 0.77 (0.50-1.18) |
| Stroke | 69 | 128 | 0.84 (0.62-1.13) | 59 | 113 | 0.84 (0.61-1.16) |
| Cancer | 163 | 458 | 1.14 (0.95-1.37) | 144 | 437 | 1.20 (0.99-1.45) |
| First 10 years of follow-up | | | | | | |
| All cause | 174 | 502 | 1.35 (1.13-1.61)‡ | 151 | 456 | 1.35 (1.12-1.63)† |
| Cardiovascular | 55 | 135 | 1.19 (0.87-1.65) | 48 | 115 | 1.06 (0.76-1.50) |
| Heart failure | 6 | 32 | 2.30 (0.95-5.53) | 6 | 31 | 2.12 (0.88-5.12) |
| Coronary heart disease | 15 | 29 | 1.02 (0.53-1.94) | 13 | 20 | 0.70 (0.34-1.42) |
| Stroke | 24 | 52 | 1.05 (0.64-1.71) | 21 | 45 | 0.97 (0.57-1.63) |
| Cancer | 65 | 197 | 1.33 (1.00-1.77) | 57 | 188 | 1.39 (1.03-1.88)* |

Definitions of exerciser, non-exerciser and the intensity of physical activity in daily life (light, moderate, vigorous) are provided in Methods. Hazard ratios (95% confidence intervals [CIs]) express the risk in non-exercisers compared with exercisers adjusted for sex, age, energy intake, body mass index, smoking, drinking, intensity of physical activity, and disease histories of cardiovascular complications, hypertension, diabetes, and hypercholesterolemia. The intensity of physical activity in daily life was further adjusted in the left columns.

*$P < 0.05$, †$P < 0.01$, and ‡$P < 0.001$ for significance of the hazard ratios.

were confirmatory when the intensity of physical activity was further adjusted in the model and when 284 participants with a history of CVD at baseline were excluded (Table 4).

As an additional sensitivity analysis, when death within the first 6 years ($n$ = 325) was excluded, simultaneously taking into account that heart failure as the cause of death was revised by the introduction of ICD-10 in January 1995, the risks of all-cause mortality and heart failure were less remarkable (HR for all-cause mortality, 1.09; 95% CI, 0.97-1.23; HR for heart failure, 1.52, 95% CI, 0.90-2.57) as shown in Table 5. In subgroup analyses, there was no evidence of significant heterogeneity by sex, age group, or the intensity of physical activity in daily life (Tables 6, 7 and 8;

Table 5. Sensitivity analyses when participants who died within the first 6 years were excluded.

| Mortality Subtypes | Nº of Deaths | | Hazard Ratio (95% CI) |
|---|---|---|---|
| | Exercisers ($n$ = 1,594) | Non-Exercisers ($n$ = 5,790) | |
| All cause | 407 | 1,015 | 1.09 (0.97-1.23) |
| Cardiovascular | 134 | 291 | 0.99 (0.80-1.22) |
| Heart failure | 19 | 61 | 1.52 (0.90-2.57) |
| Coronary heart disease | 32 | 58 | 0.79 (0.51-1.23) |
| Stroke | 58 | 103 | 0.82 (0.59-1.14) |
| Cancer | 126 | 365 | 1.15 (0.93-1.41) |

Definitions of exerciser and non-exerciser are provided in Methods. Hazard ratios (95% confidence intervals [CI]) express the risk in non-exercisers compared with exercisers. Multivariable model was adjusted for sex, age, energy intake, body mass index, smoking, drinking, and disease histories of cardiovascular complications, hypertension, diabetes, and hypercholesterolemia.
$^{*}P < 0.05$, and $^{\dagger}P < 0.01$ for significance of the hazard ratios.

Table 6. Subgroup analyses stratified by sex.

| Mortality Subtypes | Women ($n$ = 4,447) | | | Men ($n$ = 3,262) | | | Interaction $P$ |
|---|---|---|---|---|---|---|---|
| | Nº of Deaths | | Hazard Ratio (95% CI) | Nº of Deaths | | Hazard Ratio (95% CI) | |
| | Exercisers ($n$ = 897) | Non-Exercisers ($n$ = 3,550) | | Exercisers ($n$ = 786) | Non-Exercisers ($n$ = 2,476) | | |
| Total follow-up | | | | | | | |
| All cause | 221 | 587 | 1.10 (0.94-1.29) | 275 | 664 | 1.16 (1.01-1.34)* | 0.56 |
| Cardiovascular | 81 | 169 | 0.91 (0.70-1.20) | 79 | 182 | 1.14 (0.87-1.50) | 0.21 |
| Heart failure | 13 | 51 | 1.82 (0.98-3.36) | 8 | 27 | 1.58 (0.70-3.55) | 0.82 |
| Coronary heart disease | 16 | 29 | 0.79 (0.43-1.46) | 24 | 42 | 0.83 (0.49-1.40) | 0.69 |
| Stroke | 35 | 54 | 0.66 (0.43-1.02) | 34 | 74 | 1.11 (0.73-1.69) | 0.11 |
| Cancer | 66 | 203 | 1.11 (0.84-1.47) | 97 | 255 | 1.20 (0.94-1.52) | 0.95 |
| First 10 years of follow-up | | | | | | | |
| All cause | 67 | 228 | 1.42 (1.08-1.87)* | 107 | 274 | 1.33 (1.06-1.68)* | 0.72 |
| Cardiovascular | 23 | 61 | 1.21 (0.74-1.96) | 32 | 74 | 1.30 (0.84-2.01) | 0.77 |
| Heart failure | 3 | 16 | 2.58 (0.75-8.94) | 3 | 16 | 2.22 (0.63-7.81) | 0.90 |
| Coronary heart disease | 3 | 12 | 1.78 (0.50-6.38) | 12 | 17 | 0.84 (0.39-1.84) | 0.41 |
| Stroke | 13 | 22 | 0.76 (0.38-1.53) | 11 | 30 | 1.60 (0.77-3.30) | 0.18 |
| Cancer | 22 | 91 | 1.58 (0.99-2.53) | 43 | 106 | 1.20 (0.83-1.72) | 0.24 |

Definitions of exerciser and non-exerciser are provided in Methods. Hazard ratios (95% confidence intervals [CI]) express the risk in non-exercisers compared with exercisers stratified by sex during the entire follow-up (20 years) and the first 10 years of follow-up. Multivariable model was adjusted for age, energy intake, body mass index, smoking, drinking, and disease histories of cardiovascular complications, hypertension, diabetes, and hypercholesterolemia.
$^{*}P < 0.05$ for significance of the hazard ratios.

all $P$ for interaction > 0.1) although point estimates of the HR in the vigorous physical activity group were consistently < 1.0 (Table 8). Meanwhile, mortality risk in participants in the light and moderate physical activity groups was not significantly different from that in the vigorous group (Table 9; $P \geq 0.09$).

## Discussion

Based on the nationwide cohort, we assessed the protective effect of exercise habits for long-term mortality. The risk among participants without exercise habits was estimated to be 12% higher for all-cause mortality compared with those with exercise habits. We emphasize that this study had a prospective design with longitudinal ascertainment of deaths, length of follow-up for 20 years, and enrollment of both sexes with a broad age range based on the National Survey on randomly sampled areas nationwide, which made our cohort representative of the Japanese population.

To the best of our knowledge, this is the first study that directly examines the long-term association over 20 years between exercise habits and total mortality in individuals with a broad age range and with adequate adjustment for major confounding factors. The 1997-2001 National Health

Table 7. Subgroup analyses stratified by age group.

| Mortality Subtypes | 30-64 years old ($n$ = 6,081) | | | ≥ 65 years old ($n$ = 1,628) | | | Interaction $P$ |
|---|---|---|---|---|---|---|---|
| | Nº of Deaths | | Hazard Ratio (95% CI) | Nº of Deaths | | Hazard Ratio (95% CI) | |
| | Exercisers ($n$ = 1,133) | Non-Exercisers ($n$ = 4,948) | | Exercisers ($n$ = 550) | Non-Exercisers ($n$ = 1,078) | | |
| Total follow-up | | | | | | | |
| All cause | 137 | 552 | 1.04 (0.89-1.26) | 359 | 699 | 1.14 (1.004-1.30)* | 0.93 |
| Cardiovascular | 40 | 133 | 0.87 (0.61-1.24) | 120 | 218 | 1.04 (0.83-1.31) | 0.73 |
| Heart failure | 5 | 27 | 1.34 (0.51-3.50) | 16 | 51 | 1.83 (1.04-3.23)* | 0.72 |
| Coronary heart disease | 12 | 35 | 0.82 (0.42-1.60) | 28 | 36 | 0.78 (0.47-1.29) | 0.77 |
| Stroke | 16 | 11 | 0.72 (0.40-1.28) | 53 | 84 | 0.90 (0.64-1.28) | 0.49 |
| Cancer | 61 | 246 | 1.01 (0.76-1.34) | 102 | 212 | 1.23 (0.97-1.56) | 0.83 |
| First 10 year of follow-up | | | | | | | |
| All cause | 32 | 187 | 1.51 (1.04-2.21)* | 142 | 315 | 1.29 (1.05-1.57)* | 0.16 |
| Cardiovascular | 8 | 43 | 1.35 (0.63-2.91) | 47 | 92 | 1.11 (0.78-1.59) | 0.41 |
| Heart failure | 2 | 10 | 1.11 (0.24-5.17) | 4 | 22 | 2.73 (0.93-8.02) | 0.68 |
| Coronary heart disease | 2 | 11 | 1.68 (0.36-7.90) | 13 | 18 | 0.91 (0.44-1.88) | 0.52 |
| Stroke | 4 | 15 | 0.94 (0.31-2.87) | 20 | 37 | 1.03 (0.59-1.79) | 0.73 |
| Cancer | 15 | 85 | 1.40 (0.81-2.44) | 50 | 112 | 1.29 (0.92-1.81) | 0.91 |

Definitions of exerciser and non-exerciser are provided in Methods. Hazard ratios (95% confidence intervals [CI]) express the risk in non-exercisers compared with exercisers stratified by age group (30-64 vs. ≥ 65 years old) during the entire follow-up (20 years) and the first 10 years of follow-up. Multivariable model was adjusted for sex, age, energy intake, body mass index, smoking, drinking, and disease histories of cardiovascular complications, hypertension, diabetes, and hypercholesterolemia.

*$P < 0.05$ for significance of the hazard ratios.

Table 8. Subgroup analyses stratified by the intensity of physical activity in daily life.

| Mortality Subtypes | Light ($n$ = 3,930) | | | Moderate ($n$ = 3,038) | | | Vigorous ($n$ = 741) | | | Interaction $P$ |
|---|---|---|---|---|---|---|---|---|---|---|
| | Nº of Deaths | | Hazard Ratio (95% CI) | Nº of Deaths | | Hazard Ratio (95% CI) | Nº of Deaths | | Hazard Ratio (95% CI) | |
| | Exercisers ($n$ = 994) | Non-Exercisers ($n$ = 2,936) | | Exercisers ($n$ = 605) | Non-Exercisers ($n$ = 2,433) | | Exercisers ($n$ = 84) | Non-Exercisers ($n$ = 657) | | |
| Total follow-up | | | | | | | | | | |
| All cause | 340 | 766 | 1.19 (1.05-1.36)‡ | 133 | 374 | 1.01 (0.82-1.24) | 23 | 111 | 0.70 (0.44-1.13) | 0.11 |
| Cardiovascular | 117 | 211 | 0.96 (0.76-1.20) | 36 | 113 | 1.23 (0.83-1.81) | 7 | 27 | 0.55 (0.23-1.35) | 0.83 |
| Heart failure | 16 | 53 | 1.67 (0.95-2.94) | 4 | 21 | 1.88 (0.63-5.61) | 1 | 4 | 0.48 (0.04-6.23) | 0.37 |
| Coronary heart disease | 29 | 40 | 0.74 (0.45-1.20) | 10 | 28 | 1.12 (0.53-2.37) | 1 | 3 | 0.06 (0.001-2.94) | 0.51 |
| Stroke | 50 | 75 | 0.82 (0.57-1.18) | 14 | 38 | 1.02 (0.54-1.93) | 5 | 15 | 0.55 (0.18-1.70) | 0.35 |
| Cancer | 102 | 261 | 1.25 (0.99-1.58) | 53 | 153 | 0.98 (0.71-1.35) | 8 | 44 | 0.82 (0.37-1.84) | 0.53 |
| First 10 year of follow-up | | | | | | | | | | |
| All cause | 126 | 325 | 1.38 (1.12-1.70)† | 40 | 137 | 1.33 (0.93-1.92) | 8 | 40 | 0.70 (0.31-1.55) | 0.60 |
| Cardiovascular | 41 | 87 | 1.12 (0.77-1.64) | 11 | 42 | 1.57 (0.79-3.13) | 3 | 6 | 0.34 (0.07-1.61) | 0.79 |
| Heart failure | 4 | 27 | 3.15 (1.10-9.06)* | 1 | 4 | 1.28 (0.14-11.9) | 1 | 1 | NA | NA |
| Coronary heart disease | 9 | 15 | 1.00 (0.43-2.35) | 5 | 13 | 1.09 (0.37-3.24) | 1 | 1 | 0.17 (0.004-7.64) | 0.22 |
| Stroke | 20 | 33 | 0.87 (0.49-1.52) | 3 | 16 | 2.23 (0.62-8.03) | 1 | 3 | 0.82 (0.06-10.7) | 0.97 |
| Cancer | 45 | 123 | 1.35 (0.96-1.91) | 16 | 60 | 1.43 (0.81-2.52) | 4 | 14 | 0.53 (0.16-1.73) | 0.44 |

Definitions of exerciser, non-exerciser, and the intensity of physical activity in daily life (light, moderate, vigorous) are provided in Methods. Hazard ratios (95% confidence intervals [CI]) express the risk in non-exercisers compared with exercisers. Multivariable model was adjusted for sex, age, energy intake, body mass index, smoking, drinking, and disease histories of cardiovascular complications, hypertension, diabetes, and hypercholesterolemia.

NA, not available because hazard ratio was not calculated due to small number of events.

*$P < 0.05$, †$P < 0.01$, and ‡$P < 0.001$ for significance of the hazard ratios.

Table 9. Risks for all cause and specific mortalities according to the intensity of physical activity in daily life.

| Mortality Subtypes | Nº of Deaths | | | Hazard Ratio (95% CI) | |
|---|---|---|---|---|---|
| | Light (*n* = 3,930) | Moderate (*n* = 3,038) | Vigorous (*n* = 741) | Light (*n* = 3,930) | Moderate (*n* = 3,038) |
| Total follow-up | | | | | |
| All cause | 1,106 | 507 | 134 | 1.07 (0.89-1.29) | 0.99 (0.82-1.20) |
| Cardiovascular | 328 | 149 | 34 | 1.08 (0.75-1.55) | 1.08 (0.74-1.57) |
| Heart failure | 69 | 25 | 5 | 1.31 (0.51-3.32) | 1.10 (0.42-2.89) |
| Coronary heart disease | 69 | 38 | 4 | 2.20 (0.79-6.15) | 2.43 (0.86-6.83) |
| Stroke | 125 | 52 | 20 | 0.69 (0.42-1.14) | 0.66 (0.39-1.11) |
| Cancer | 363 | 206 | 52 | 1.06 (0.78-1.43) | 1.07 (0.79-1.45) |
| First 10 years of follow-up | | | | | |
| All cause | 451 | 177 | 48 | 0.96 (0.71-1.31) | 0.91 (0.66-1.26) |
| Cardiovascular | 128 | 53 | 9 | 1.25 (0.62-2.52) | 1.39 (0.68-2.82) |
| Heart failure | 31 | 5 | 2 | 1.70 (0.39-7.43) | 0.59 (0.11-3.09) |
| Coronary heart disease | 24 | 18 | 2 | 0.89 (0.20-3.96) | 1.92 (0.44-8.38) |
| Stroke | 53 | 19 | 4 | 1.15 (0.40-3.30) | 1.12 (0.38-3.32) |
| Cancer | 168 | 76 | 18 | 1.13 (0.69-1.88) | 1.10 (0.65-1.84) |

Definition of the intensity of physical activity in daily life (light, moderate, vigorous) are provided in Methods. Hazard ratios (95% confidence intervals [CI]) express the risk in participants in the light or the moderate physical activity group compared with those in the vigorous physical activity group. Multivariable model was adjusted for sex, age, energy intake, body mass index, smoking, drinking, and disease histories of cardiovascular complications, hypertension, diabetes, and hypercholesterolemia.

Interview Survey (NHIS) linked to death certificate data in the National Death Index study in the United States reported that exercise habits (strength training twice each week) at baseline was associated with 46% lower risk of all-cause mortality during 15 years than those without an exercise habit (Kraschnewski et al. 2016). However, their study consisted of the elderly aged ≥ 65 years. Regarding non-Western populations, a 19.2-year follow-up from the Japan collaborative cohort (JACC) study showed a significant 16% lower risk of CVD mortality associated with exercise habits (30 min or more walking per day, and/or those who participated in sports "5 h or more" per week) at baseline in Japanese men and women aged 40-79 years (Hayashi et al. 2016). However, in their analysis, information on major confounding factor such as history of hypertension and diabetes was based on self-reports alone. Furthermore, hypercholesterolemia, an important confounding factor, was not adjusted in the multivariate analysis.

In the present study, we defined exercisers according to the national health promotion measures in Japan (The Office for Lifestyle-Related Diseases Control, General Affairs Division, Health Service Bureau, Ministry of Health, Labour and Welfare of Japan 2006; Ishikawa-Takata and Tabata 2007; Ministry of Health, Labour and Welfare 2012), since the level of proper exercise habits varies from the country to the country. The results of the median 20 years of follow-up could support significance of these targets recommended by Health Japan 21. The Japanese government recommended that 33% of women and 36% of men aged 20-64 years and 48% of women and 58% of men aged 65 years or over should fulfill these targets by 2022 (Ministry of Health, Labour and Welfare 2012). Although the criteria are less strict than the WHO recommendation, i.e., (1) ≥ 150 min per week of moderate-intensity aerobic activity or (2) ≥ 75 min per week of vigorous intensity aerobic activity, the WHO recommendation is reported to be impractical in the daily life because "barriers exist to meet this 30 min a day, 5 day a week recommendation (e.g., time constraints or an individual's uncertainty about the amount of exercise needed to benefit health)" (Wen et al. 2011). Lee and colleagues (2017) noted that it is important, in particular for older people, to set achievable activity goals and to provide specific recommendations on the type, frequency, and intensity of activities in the prescription of exercise. We are confident that the exercise habits used in the present study are feasible and should be recommended particularly for East Asians who are reported to be less physically active than those in western countries, and also tend to exercise at lower intensity (Wai et al. 2008).

Mortality risk was not significantly different among participants in the light, moderate, and vigorous physical activity group. Previous studies demonstrated that moderate to vigorous physical activity was associated with lower mortality risk (Samitz et al. 2011; Murtagh et al. 2015). In these studies, physical activity was accessed quantitatively using metabolic equivalents (MET) (Samitz et al. 2011) or an accelerometer (Murtagh et al. 2015). However, the intensity of physical activity in the present study consisted of the three grades based on self-reports, and only 84 exercisers classified in the vigorous group could be assessed.

We cannot say for certain whether the current results are more valid than the previous findings.

Because it is difficult for unhealthy people to engage in exercise, they may tend to be non-exercisers. However, healthy people may be more conscious of living a healthy lifestyle, and engage in health seeking behavior more than other leisure time activities. To eliminate the effect of reverse causality, we excluded 556 participants who were unable to do exercise due to a health-related reason at baseline. Furthermore, 284 participants with a history of CVD at baseline and 325 who died within the first 6 years were excluded, as shown in Tables 4 and 5, respectively. Although the influence of reverse causality is inevitable for this kind of observational study, it would not largely affect the conclusion of the present study according to the consistent findings by these sensitivity analyses.

We compared the risk of mortality of the first 10 years of follow-up and the total 20 years of follow up, and the former risk tended to be higher than the latter in all analysis. It would be a reasonable assumption that the shorter the follow-up term, the more likely reverse causality remains, in particular among young people who died in because they could not exercise due to a health condition. When we stratified participants by age (young, 30-64; elderly, $\geq$ 65 years old), the point estimate of the hazard ratio of all-cause mortality in the young, 1.51 (95% CI, 1.04-2.21), was higher than that in the elderly, 1.29 (95% CI, 1.05-1.57) during the first 10 years of follow-up. In contrast, exercise habit did not affect the mortality risk during the total 20 years follow-up in the young, but it did in the elderly (HR, 1.14; 95% CI, 1.004-1.30). The impact of habitual exercise might be remarkable for the first 10 years of follow-up but be attenuated after the total 20 years follow up. It is therefore important to take careful consideration when the follow-up period is insufficient. Nevertheless, we emphasize that the protective effect of habitual exercise remained 20 years later in the present study, which enhances motivation of habitual exercise in individuals.

We investigated the risk of non-exercisers for cause-specific mortality (i.e., total CVD, heart failure, CHD, stroke and cancer mortality), and in some analyses the risks were significantly higher for heart failure death (Tables 2, 4 and 7). Moderate exercise would be effective for the prevention of heart failure as reported by the Swedish study conducted during 1997-2010 (Andersen et al. 2014); in that study of 39,805 participants aged 20-90 years without heart failure, the HR for the development of heart failure by any cause in the light (e.g., casual walking) and moderate (e.g., walking at a brisk speed, jogging, or swimming) physical activity during a leisure time group (MET hours per day, > 4.7) was 0.54 (95% CI, 0.44-0.66) when compared with a non-active group (MET hours per day, < 1.2) (Andersen et al. 2014). However, there may remain a certain effect of reverse causality because a person prone to heart failure might refrain from exercise, even before the diagnosis.

Our findings must be interpreted within the context of the potential limitations. First, we captured information on exercise habits at baseline once by self-reported questionnaire. Although trained medical staff inspected the results, a response bias might occur, and data might not accurately reflect the status of exercise habits during the follow-up period. It should be further noted that a change of exercise habits throughout the study period might damage the assumption of the proportionality of the hazards in the Cox models, though it was verified before its application. Second, we did not collect data on the sedentary time, which has been known as a strong confounder that might at least partly attenuate the mortality benefits of habitual exercise, although results were confirmatory when the intensity of physical activity, an alternate index for daily activity in individuals, was further adjusted in the multivariate model. Third, there were no data regarding a cancer history in individuals, which may affect the characteristics and results, in particular exercise habits at baseline. Furthermore, the comparably small number of each subtype of cancer death made it impossible to assess the various impacts of exercise habits on these outcomes. Finally, we did not collect non-fatal cardiovascular outcomes as an endpoint. The introduction of stroke units and the increasing availability of invasive coronary care and thrombolysis has reduced the case-fatality rates of most cardiovascular complications. Further studies are needed to validate the present findings to non-fatal cardiovascular outcomes.

In conclusion, exercise habits had a protective effect on mortality risks over 20 years. These results support worldwide recommendations for improvement of exercise habits.

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## Conflict of Interest

The authors declare no conflict of interest.

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