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Association of physical activity with primary cardiac arrest risk in the general population: a nationwide cohort study of the dose-response relationship

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Association of physical activity with primary cardiac arrest risk in the general population: a nationwide cohort study of the dose-response relationship

A Dissertation Submitted
to the Department of Medicine
and the Graduate School of Yonsei University
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy in Medical Science

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June 2024

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Moonyun Jin

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ABSTRACT

Association of physical activity with primary cardiac arrest risk in the general population: a nationwide cohort study of the dose-response relationship

It is unclear how much physical activity is required to reduce the risk of cardiac arrest and whether high levels of physical activity are related to cardiac arrest risk increases in the general population. To quantify the dose-response relationship between moderate-to-vigorous physical activity and primary cardiac arrest (PCA). 506,805 participants aged over 18 years who underwent the Korean National Health Screening rogram, including self-administered questionnaire for physical activity from 2009 through 2014. Physical activity levels were converted into metabolic equivalent of task (MET) per week and categorised to correspond with multiples of public health recommendations. We evaluated the quantitative and categorical dose-response relationship between physical activity and PCA. A curvilinear dose-response relationship between physical activity and PCA was observed; the benefits started at two-thirds (5 MET-hour/week) of the United States and World Health Organization guidelines recommended minimum (7.5 MET-hour/week) and continued to five times (40 MET-hour/week) the recommended minimum (P non-linearity <.001). The largest benefit was noted at level of two to three times the recommended minimum (HR 0.58 [95% CI, 0.44-0.76]). In addition, there was no evidence of an increased PCA risk at level above five times the recommended minimum (HR 0.74 [95% CI, 0.50-1.09]). These associations were consistent regardless of age, sex, body mass index, comorbidities, and estimated 10-year risk of cardiovascular disease. The beneficial effect of physical activity on PCA started at two-thirds of the recommended minimum and continue to five times the recommended minimum. No excess risk of PCA was present among individuals with activity level above five times the recommended minimum, regardless of cardiovascular disease or lifestyle risk factor presence.

Key words : cardiac arrest, physical activity, sudden cardiac death

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1. INTRODUCTION

Physical activity is associated with a reduced risk of all-cause and cardiovascular mortality.(1, 2) On the basis of numerous findings, current public guidelines suggest that participation in at least 150 minutes/week of moderate physical activity or 75 minutes a week of vigorous-intensity activity or an equivalent combination can confer significant health benefits.(3, 4) However, as with any recommendation, physicians should consider both the risk and benefit of physical activity in different individuals. The ultimate concern among physicians in such settings is sudden cardiac arrest (SCA) onset. Although exertion-related SCA occurs relatively rarely, there is evidence to suggest that the risk of SCA increases transiently during physical exertion.(5, 6) SCA may result in death, and the associated fear likely reduces people's level of participation in physical activity. Previous studies demonstrated a paradox, wherein vigorous physical activity simultaneously increased the short-term risk of SCA while also offering protection against this overall risk.(5-7) The relative risk of SCA during or just after vigorous physical activity is higher than during periods of inactivity or lighter activity. Nevertheless, habitual vigorous activity significantly reduces the overall risk of SCA.(5-7)

What remains unknown is precisely how much exercise is required to produce these beneficial effects and, more controversially, if excessive exercise can cause harm. Recently, modest amount of predominately moderate-intensity physical activity were found to be associated with a decreased risk of SCA,(8, 9) whereas cardiac remodeling caused by prolonged endurance athletic training may result in mimic pathological conditions with the potential for SCA.(10) Whether high volumes of physical activity may lead to an increased risk of SCA remains unclear, and data on the dose-response relationship between physical activity and SCA is currently insufficient. To address the gap in knowledge regarding the dose-response relationship between physical activity and SCA, we aimed to quantify (1) the threshold for benefit from physical activity and (2) the SCA risk associated with high levels of physical activity. Specifically, we conducted analyses of the categorical and quantitative dose-response relationship between different volumes of moderate-to-vigorous intensity leisure-time physical activity and primary cardiac arrest (PCA)(11) using a community-based database in Korea, which includes

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>500,000 individuals who underwent health examinations.

2. MATERIALS AND METHODS

2.1. Data source and study population

The study was conducted based on the Korean National Health Insurance Service (NHIS) National Sample Cohort (NSC) database. This population-based cohort was extracted via systematic stratified random sampling from all beneficiaries of the NHIS depending on information on the entire national cohort and included 1,014,730 participants who were sampled from 2002 and followed-up for 12 years. The NHIS-NSC database comprises a dataset with data on beneficiaries' sociodemographic characteristics; a medical claims dataset, including information on diagnoses based on the 10th revision of the International Classification of Disease (ICD-10) codes, treatment, and admission; and the National Health Screening dataset.(12) The National Health Screening dataset comprises a health check-up database, data collection for which was conducted for the entire Korean population by the National Health Insurance Corporation. The National Health Screening Program included chest radiographic examinations, blood tests, physical examinations, anthropometric measurements, and the use of a questionnaire related to physical activity. In this study, we included people who participated in the screening program from 2009, as the standardised questionnaire for the ascertainment of physical activity status including intensity and frequency was established in that year. Data on a total of 506,805 participants aged over 18 years and who underwent the National Health Screening Program from 2009 to 2014 and completed surveys on physical activity were extracted from the cohort.

Several studies have used the NHIS-NSC database for epidemiologic studies, and its validity has been described in detail elsewhere.(13-16) Korean social security numbers link every individual in the cohort, and all social security numbers were deleted after the construction of the cohort by the assignment of serial numbers for the prevention of personal information leakage. The Institutional Review Board of the Yonsei University Health System (Seoul, Republic of Korea) approved this study (4-2019-1056) and

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the requirement for informed participant consent was waived because data in the NHIS-NSC database are anonymised in adherence with strict confidentiality guidelines.

2.2. Assessment of physical activity

The National Health Screening Program health interview included a self-administered standardised questionnaire for the ascertainment of participants' leisure-time physical activity status.(17, 18) The survey included questions that addressed the frequency per week of participation in physical activity of a vigorous intensity for at least 20-minute increments and moderate intensity for at least 30-minute increments. Vigorous-intensity physical activity was defined as intense exercise that caused severe shortness of breath, such as running. Moderate-intensity physical activity was defined as exercise that caused mild shortness of breath, such as brisk walking and bicycling at each participant's usual speed. Based on the responses, we used data on leisure-time physical activity of a moderate or vigorous intensity, which is the intensity level recommended by current the United States and World Health Organization (WHO) guidelines.(3, 4, 19) Each type of activity was assigned a metabolic equivalent task (MET) score based on the energy cost (4 for moderate, and 8 for vigorous exercise).(20, 21) We computed the energy expended in each activity by multiplying the associated MET score by the number of minutes spent on that activity and summed the energy expended across the moderate- to vigorous-intensity activity levels for the estimation of the total energy expenditure per week.

Physical activity level was divided into seven categories (0, 0.1 to <7.5, 7.5 to <15.0, 15.0 to <22.5, 22.5 to <30, 30.0 to <37.5, and ≥ 37.5 MET hours per week) to correspond with multiples of the United States and WHO physical activity guideline recommendations, and ranged from one to two times the recommended minimum (7.5 to <15.0 MET-hour/week; comparable to 150 minute/week of moderate-intensity activity or 75 minute/week of vigorous-intensity activity or an equivalent combinations)(3, 4, 22) to five or more times the recommended level (≥ 37.5 MET-hour/week). We also created separate moderate- and vigorous-intensity categories ranging from 0 to more than 22.5 MET-hour/week, and performed models mutually adjusted for both exercise intensities.

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2.3. Covariates

Baseline comorbidities were defined using medical claims data and prescription medication information before the index date. To ensure diagnostic accuracy, the patients were considered to have a comorbidity when the condition had a discharge diagnosis or had been confirmed at least twice in an outpatient setting, in line with previous studies using NHIS data (Table 1).(13-16)

<Table 1> Definitions and ICD-10 (International Classification of Diseases-10th Revision) codes used for defining the comorbidities and clinical outcomes

	Definitions	ICD-10 codes or conditions
Primary cardiac arrest	Defined from hospitalization diagnosis code, diagnosis code at the emergency room, and diagnosis code written on the death certificate	I46.x, I49.0 *To avoid erroneous inclusion of the patients with non-cardiac arrest, we excluded the patient with sudden arrest diagnosis accompanied by respiratory arrest* (R09.0, R09.2), *gastrointestinal bleeding* (I85.0, K25.0, K25.4, K26.0, K26.4, K27.0, K27.4, K92.0-K92.2), *brain hemorrhage* (I60.x-I62.x, S06.4-S06.6), *septic shock* (A41.9, R57.2), *pregnancy and delivery* (O00-O99), *diabetic ketoacidosis* (E14.1), *anaphylaxis* (T78.2), *and accidents including suicide* (T71, T75.1, T36-T65, V80-V89, W76.x, X60-X84).
Atrial fibrillation	Defined from diagnosis†	I48
Heart failure	Defined from diagnosis†	ICD-10: I11.0, I50, I97.1
Diabetes	Defined from diagnosis† plus treatment	ICD-10: E10, E11, E12, E13, E14 *Treatment: all kinds of oral antidiabetics and insulin.*
Myocardial infarction	Defined from diagnosis†	ICD-10: I21, I22, I25.2

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Peripheral arterial disease	Defined from diagnosis[†]	ICD-10: I70.0, I70.1, I70.2, I70.8, I70.9
Chronic kidney disease	Defined from eGFR or diagnosis[†] (if laboratory value was not available, diagnosis code was used)	estimated glomerular filtration rate <60mL/min per 1.73 m^2 ICD-10: N18, N19
Dyslipidemia	Defined from diagnosis[†]	ICD-10: E78
Hypertension	Defined from diagnosis[†]	I10, I11, I12, I13, I15 *and antihypertensive medication*
TIA	Defined from diagnosis[†]	G45
Arterial embolism	Defined from diagnosis[†]	I74, N280
Chronic obstructive pulmonary disease	Defined from diagnosis[†] plus treatment	J42, J43(except J43.0), J44 *Treatment: SABA, SAMA, LABA, LAMA, ICS, ICS+LABA, or methylxanthine (>1 months).*
Chronic Liver disease	Defined from diagnosis of chronic liver disease, cirrhosis, and hepatitis[†]	B18, K70, K71, K72, K73, K74, K76.1
Malignancy	Defined from diagnoses of cancer (non-benign)[†]	C00-C97
ESRD	Defined from national registry for severe illness.[†]	*Patients with ESRD undergoing chronic dialysis or received a kidney transplant.*
Ischemic stroke	Defined from any discharge diagnoses with concomitant imaging studies[†]	ICD-10: I63, I64 *with concomitant brain-imaging studies, including computed tomography or magnetic resonance imaging.*
Intracranial hemorrhage	Defined from any discharge diagnoses with concomitant imaging studies[†]	ICD-10: I60, I61, I62 *with concomitant brain-imaging studies, including computed tomography or magnetic resonance imaging.*
Gastrointestinal bleeding	Defined from admission diagnosis or related death[†]	K25-28 (subcodes 0-2 and 4-6 only), K92.0, K92.1, K92.2, K62.5, I85.0, I98.3

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Respiratory or urinary tract bleeding, etc.	Defined from admission diagnosis or related death†	N02, R31, R04, J942, K661, D62

†To ensure accuracy, comorbidities were established based on one inpatient or two outpatient records of ICD-10 codes in the database.

2.4. Study outcome

PCA was defined as a sudden pulseless condition in the absence of evidence of a non-cardiac cause. This definition has been used in prior publications and is similar to those initially proposed by the Joint International Society and Federation of Cardiology-WHO Task Force on Standardization of Clinical Nomenclature.(5, 8, 11, 23) In the NHIS-NSC database, we identified patients with PCA using the ICD-10 code I46.x (cardiac arrest) and I49.0 (ventricular fibrillation). Patients who were hospitalized from an inpatient clinic or emergency department with the diagnosis code I46.x or I49.0 were included. To avoid the erroneous inclusion of patients with non-cardiac, and in-hospital arrest, we excluded those with a sudden arrest diagnosis accompanied by respiratory arrest, gastrointestinal bleeding, brain haemorrhage, septic shock, pregnancy and delivery, diabetic ketoacidosis, anaphylaxis, accidents including asphyxiation, drowning, poisoning, traffic accident, trauma, and suicide. To evaluate the accuracy of our definition of PCA, we conducted a validation study using medical records from independent hospitals from 2009 to 2014. We could identify 731 patients with the code I46.x or I49.0 after the exclusion of patients with diagnostic codes for non-cardiac causes as mentioned above (Detailed the ICD-10 codes criteria for PCA in Table 1). Their medical records were then reviewed by five physicians, and true PCA patients were then ascertained. The positive predictive value was 80.2% (586 of 731), as determined using our PCA criteria, suggesting the definition's good diagnostic accuracy. All participants were followed-up for mortality until the end of 2014. The mortality registration database of the Korea National Statistical Office, which includes information on the date and cause of the mortality, was linked with the NHIS cohort database.

2.5. Statistical analysis

Descriptive statistics were used to characterise the participants' baseline characteristics and

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comorbidities. We used Cox proportional hazards regression stratified by cohort to generate hazard ratios (HRs) and their 95% confidence intervals (CIs) for physical activity and study outcome. Models for clinical variable adjustments were used to assess the association. Multivariable models were adjusted for age, sex, body mass index (BMI), heart failure, hypertension, diabetes, previous myocardial infarction (MI), prior stroke or transient ischemic attack, atrial fibrillation, chronic kidney disease, malignancy, dyslipidaemia, smoking, and alcohol intake. These covariates were selected on the basis of their previously established roles as predictive factors in SCA and coronary heart disease-related death.(24) To assess the dose-response relationship between physical activity and mortality, we used a restricted cubic spline model. We further examined the physical activity levels by separating moderate-intensity and vigorous-intensity activity levels and creating mutually adjusted models. We entered interaction terms into the Cox model to assess the consistency of the physical activity effect across subgroups. We stratified them by the potential effect modifiers of age, sex, BMI, heart failure, hypertension, diabetes, previous MI, dyslipidaemia, malignancy, smoking, alcohol intake, and the Framingham risk score. A *p-value <.05* was considered statistically significant. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) and the R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

3. RESULTS

In total, 506,805 individuals (mean age 48±14) were included in the analyses. The baseline characteristics of the study participants stratified according to their physical activity levels are presented in Table 2. With regard to physical activity level, 49.4 % of the participants met the public health recommended minimum. During the median follow-up of 4 (Interquartile Range: Q1=3, Q3=5) years, 799 PCAs, 6,411 all-cause deaths, and 1,195 cardiovascular deaths were observed. The incidences of PCA, all-cause death, and cardiovascular death were 41.1, 329.9, and 61.5 events per 100,000 person-years, respectively.

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<Table 2> Baseline characteristics stratified by moderate- to vigorous-intensity leisure-time physical activity level

Multiples of recommended minimum physical activity		0	<1	1-2×	2-3×	3-4×	4-5×	≥5×
Physical activity (MET-hour/week)	All	None	0.1 to <7.5	7.5 to <15.0	15.0 to <22.5	22.5 to <30.0	30.0 to <37.5	≥37.5
Characteristic								
Participants	504,840 (100%)	124,931 (25%)	130,715 (26%)	147,753 (29%)	57,113 (11%)	17,777 (4%)	14,896 (3%)	11,655 (2%)
Age	48±14	51±15	46±14	47±14	47±14	49±14	49±14	53±14
Male	252687 (50%)	55,595 (45%)	62,436 (48%)	77,009 (52%)	32,068 (56%)	9,966 (56%)	8,682 (58%)	6,931 (60%)
BMI (kg/m^2)	23.7±3.3	23.7±3.4	23.6±3.4	23.7±3.3	23.9±3.2	23.9±3.1	24.0±3.0	24.1±3.0
BMI <25	339,799 (67%)	83,623 (67%)	89,501 (68%)	100,163 (68%)	37,768 (66%)	11,689 (66%)	9,612 (64%)	7,443 (64%)
BMI 25 to <30	145,111 (29%)	36,066 (29%)	36,083 (28%)	41,928 (28%)	17,128 (30.0%)	5,432 (30%)	4,725 (32%)	3,749 (32%)
BMI ≥30	19,668 (4%)	5,109 (4%)	5,079 (4%)	5,616 (4%)	2,198 (4%)	647 (4%)	557 (4%)	462 (4%)
Heart failure	12,559 (2%)	4,400 (3%)	2,727 (2%)	3,156 (2%)	1,109 (2%)	405 (2%)	329 (2%)	433 (4%)
Hypertension	111,452 (22%)	32,009 (26%)	24,762 (19%)	30,458 (21%)	12,085 (21%)	4,450 (25%)	3,894 (26%)	3,794 (32%)
Diabetes	66,118 (13%)	18,523 (15%)	14,638 (11%)	18,125 (12%)	7,348 (13%)	2,664 (15%)	2,390 (16%)	2,430 (21%)
Previous MI	5,133 (1%)	1,597 (1%)	1,125 (1%)	1,350 (1%)	525 (1%)	201 (1%)	162 (1%)	173 (1%)
Vascular disease	40,714 (8%)	12,498 (10%)	9,048 (7%)	10,878 (7%)	4,149 (7%)	1,533 (9%)	1,266 (8%)	1,342 (11%)

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History of stroke/TIA	19,545 (4%)	6,351 (5%)	4,282 (3%)	5,082 (3%)	1,839 (3%)	700 (4%)	631 (4%)	660 (6%)
Atrial fibrillation	4,826 (1%)	1,476 (1%)	1,065 (1%)	1,298 (1%)	491 (1%)	184 (1%)	149 (1%)	163 (1%)
Chronic kidney disease	30,270 (6%)	8,824 (7%)	6,910 (5%)	8,390 (6%)	3,155 (5%)	1102 (6%)	955 (6%)	934 (8%)
Dyslipidemia	99,202 (20%)	26,854 (21%)	22,985 (18%)	27,534 (19%)	11,136 (19%)	3,966 (22%)	3,466 (23%)	3,261 (28%)
Malignancy	34,356 (7%)	9,296 (7%)	7,952 (6%)	9,457 (6%)	3,886 (7%)	1,376 (8%)	1,204 (8%)	1,185 (10%)
Smoking								
Current	123,757 (25%)	28,984 (23%)	32,156 (25%)	38,120 (26%)	14,392 (25%)	4,124 (23%)	3,381 (23%)	2,599 (22%)
Former	66,526 (13%)	11,244 (9%)	16,078 (12%)	21,276 (14%)	9,652 (17%)	3,111 (18%)	3,009 (20%)	2,156 (19%)
Never	314,556 (62%)	84,703 (68%)	82,481 (63%)	88,356 (60%)	33,068 (58%)	10,542 (59%)	8,506 (57%)	6,900 (59%)
Alcohol (≥1time/week)								
Yes	237,828 (47%)	45,225 (36%)	63,789 (49%)	75,797 (51%)	31,012 (54%)	8,882 (50%)	7,761 (52%)	5,361 (46%)
No	267,012 (53%)	79,706 (64%)	66,926 (51%)	71,956 (49%)	26,101 (46%)	8,895 (50%)	7,135 (48%)	6,294 (54%)
Economy level								
Low	109,688 (22%)	30,358 (24%)	27,973 (21%)	31,176 (21%)	11,194 (20%)	3,591 (20%)	2,890 (19%)	2,506 (21%)
Mid	199,407 (39%)	51,597 (41%)	51,894 (40%)	57,919 (39%)	21,646 (38%)	6,631 (37%)	5,467 (37%)	4,254 (37%)
Upper	195,745 (39%)	42,976 (34%)	50,848 (39%)	58,658 (40%)	24,273 (42%)	7,555 (43%)	6,539 (44%)	4,895 (42%)
Framingham risk score								
Low	320,327 (63%)	74,209 (59%)	85,880 (66%)	98,108 (66%)	37,181 (65%)	10,862 (61%)	8,610 (58%)	5,478 (47%)

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Intermediate	153,955 (31%)	41,977 (34%)	38,038 (29%)	41,371 (28%)	16,677 (29%)	5,689 (32%)	5,169 (35%)	5,035 (43%)
High	30,558 (6%)	8,745 (7%)	6,797 (5%)	8,274 (6%)	3,255 (6%)	1,227 (7%)	1,117 (7%)	1,142 (10%)
Systolic BP (mmHg)	122±15	123±16	121±15	122±15	123±15	123±15	124±15	125±15
Diastolic BP (mmHg)	76±10	76±10	76±10	76±10	76±10	76±10	77±10	77±10
Fasting glucose (mg/dl)	98±25	99±27	97±24	97±24	98±24	99±25	99±25	101±28
Total cholesterol (mg/dl)	195±37	196±38	195±37	194±37	194±36	195±37	195±37	194±37
Triglyceride (mg/dl)	132±94	136±95	132±94	131±94	130±94	128±89	127±91	129±91
LDL (mg/dl)	114±37	115±39	114±37	113±37	113±38	114±37	114±36	113±37
HDL (mg/dl)	56±28	56±34	56±26	56±25	57±25	57±27	57±25	57±27

Values are expressed as number (%) or means ± standard deviations.

BMI: body mass index, BP: blood pressure, HDL: high-density lipoprotein, LDL: low-density lipoprotein, MET: metabolic equivalent task, MI: myocardial infarction, TIA: transient ischemic attack

As shown in Figure 1A and Table 3, compared to inactivity (0 MET-hour/week), the beneficial effect of physical activity on PCA started at a level lower than the recommended minimum (0.1 to <7.5 MET-hour/week; HR 0.80, 95% CI 0.66 to 0.96). The beneficial effect of physical activity on PCA grew stronger among those with levels one to two times (7.5 to <15.0 MET-hour/week; HR 0.64, 95% CI 0.53 to 0.77) and two to three times (15.0 to <22.5 MET-hour/week; HR 0.58, 95% CI 0.44 to 0.76) the recommended minimum. Similar benefits were observed at levels three to four times (22.5 to <30.0 MET-hour/week; HR 0.62, 95% CI 0.41 to 0.93) and four to five times (30.0 to <37.5 MET-hour/week; HR 0.63, 95% CI 0.41 to 0.98) the recommended minimum.

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<Table 3> Risk of primary cardiac arrest, all-cause mortality, and cardiovascular mortality in relation to the moderate- to vigorous-intensity leisure-time physical activity level

Multiples of recommended minimum physical activity	0	<1	1-2×	2-3×	3-4×	4-5×	≥5×
Physical activity (MET-hour/week)	None	0.1 to <7.5	7.5 to <15.0	15.0 to <22.5	22.5 to <30.0	30.0 to <37.5	≥37.5
Primary cardiac arrest							
Cases, No. (%)	309 (0.25%)	179 (0.14%)	176 (0.12%)	61 (0.11%)	24 (0.14%)	22 (0.15%)	28 (0.24%)
Incidence (100,000 person-years)	65	35	31	28	35	38	62
Hazard ratio† (95% CI)	1.0 (ref.)	0.8 (0.7-0.96)	0.6 (0.5-0.8)	0.6 (0.4-0.8)	0.6 (0.4-0.9)	0.6 (0.4-0.98)	0.7 (0.5-1.1)
All-cause mortality							
Cases, No. (%)	2,689 (2.2%)	1,267 (1.0%)	1,470 (1.0%)	480 (0.8%)	162 (0.9%)	149 (1.0%)	194 (1.7%)
Incidence (100,000 person-years)	564	251	259	217	235	256	429
Hazard ratio† (95% CI)	1.0 (ref.)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.5 (0.4-0.6)	0.6 (0.5-0.6)	0.6 (0.5-0.7)
Cardiovascular death							
Cases, No. (%)	567	251	233	79	19	17	29

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	(0.5%)	(0.2%)	(0.2%)	(0.1%)	(0.1%)	(0.1%)	(0.3%)
Incidence (100,000 person-years)	119	50	41	36	28	29	64
Hazard ratio† (95% CI)	1.0 (ref.)	0.7 (0.6-0.8)	0.6 (0.5-0.7)	0.5 (0.4-0.7)	0.4 (0.2-0.6)	0.4 (0.2-0.6)	0.5 (0.3-0.7)

†The model was adjusted for age, sex, body mass index, heart failure, hypertension, diabetes, previous myocardial infarction, prior stroke or transient ischemic attack, atrial fibrillation, chronic kidney disease, malignancy, dyslipidemia, smoking and alcohol.

CI: confidence interval, MET: metabolic equivalent task

In addition, there was no significant increased risk of PCA at more than five times the recommended level (≥37.5 MET-hour/week; HR 0.74, 95% CI 0.50 to 1.09). Using the same multivariable adjusted model, it was observed that all-cause and cardiovascular mortality were inversely associated with greater levels of physical activity. Compared to inactivity, any level of physical activity was associated with a significantly lower risk of all-cause and cardiovascular mortality, even at five or more times the recommended level (all-cause mortality; HR 0.62, 95% CI 0.54 to 0.72, and cardiovascular mortality; HR 0.50, 95% CI 0.34 to 0.73) (Figure 1B and 1C, and Table 3). Cox models with restricted cubic splines showed a curvilinear relationship between physical activity and PCA risk (*P non-linearity <0.001*), all-cause mortality (*P non-linearity <0.001*), and cardiovascular mortality (*P non-linearity <0.001*) (Figure 1D, 1E, and 1F).

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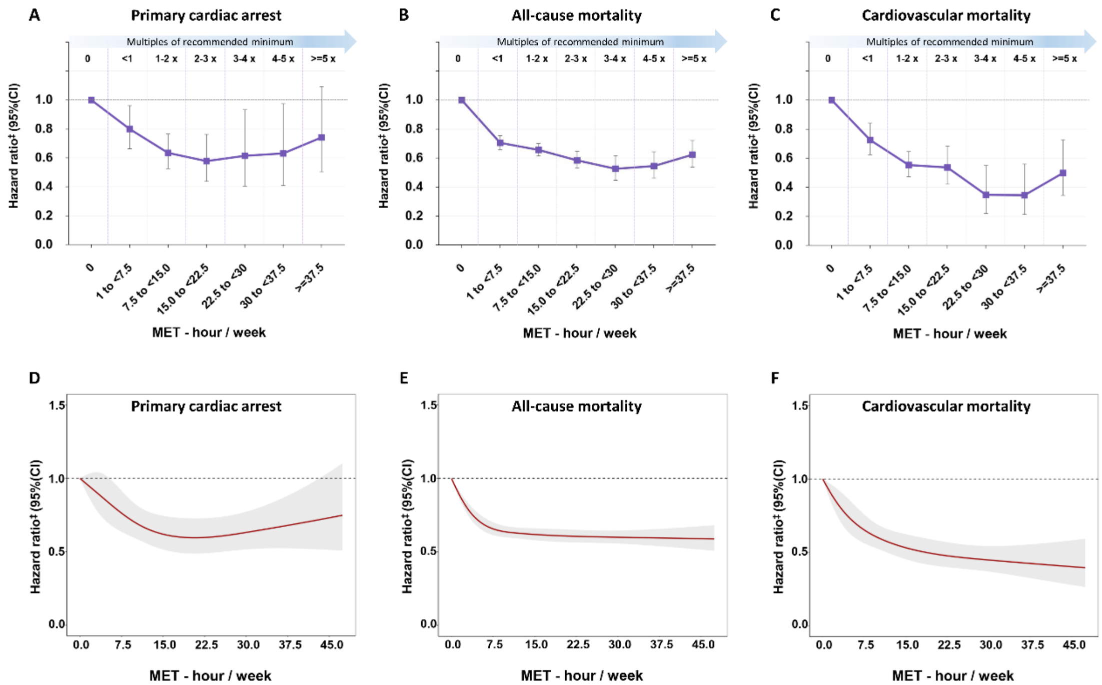

<Figure 1> Dose-response association between moderate-to-vigorous intensity physical activity and risk of primary cardiac arrest, all-cause mortality, and cardiovascular mortality. **A, B, C,** the points shown represent the adjusted hazard ratios (HRs) for each of the physical activity categories and the vertical bars represent the 95% confidence intervals (CIs). **D, E, F,** restricted cubic spline curves were constructed using physical activity as a continuous variable. The redlines and gray shades indicate the adjusted HRs and 95% CIs, respectively.

In the stratified analyses, the same direction of associations was observed regardless of the presence of several risk factors and lifestyle variables, although some variations were noted in the point estimates when the number of events was low (Table 4). We only found statistically significant differences between different diabetes status groups, the benefit in the diabetes group was shown to be greater than that in the non-diabetes group: A 7.5 MET-hour/week increase in physical activity was associated with a 16% and 7% risk reduction in PCA in the diabetes and non-diabetes group, respectively (P for

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interaction=0.024). In addition, there was no evidence of harm at the highest level of physical activity across the subgroups of heart failure, prior myocardial infarction, and high estimated 10-year cardiovascular disease risk score. Similarly, stratified analyses showed the same direction of the benefits of physical activity in terms of the risk of all-cause and cardiovascular mortality by prespecified subgroups and reduction risk in all-cause and cardiovascular mortality even at the highest level of physical activity across the subgroups.

<Table 4> Risk of primary cardiac arrest, all-cause mortality, and cardiovascular mortality in relation to the moderate- to vigorous-intensity leisure-time physical activity level

Multiples of recommended minimum physical activity	0	<1	1-2×	2-3×	3-4×	4-5 ×	≥5×	
Physical activity (MET-hour/week)	None	0.1 to <7.5	7.5 to <15.0	15.0 to <22.5	22.5 to <30.0	30.0 to <37.5	≥37.5	
Characteristics	Fully adjusted hazard ratio[†] (95% CI)							*P for interaction*
Age								
<65	1.0 (ref.)	0.8 (0.6-1.1)	0.7 (0.5-0.9)	0.5 (0.3-0.8)	0.6 (0.4-1.1)	0.5 (0.3-1.0)	1.0 (0.5-1.7)	*.55*
≥65	1.0 (ref.)	0.8 (0.6-1.0)	0.6 (0.5-0.8)	0.6 (0.4-0.9)	0.6 (0.3-1.1)	0.7 (0.4-1.3)	0.6 (0.3 -1.0)	
Sex								
Men	1.0 (ref.)	0.9 (0.7-1.1)	0.6 (0.5-0.8)	0.5 (0.4-0.8)	0.7 (0.5-1.2)	0.7 (0.4-1.1)	0.6 (0.4-1.0)	*.88*
Women	1.0 (ref.)	0.7 (0.5-0.9)	0.7 (0.5-0.9)	0.8 (0.5-1.2)	0.3 (0.1-0.99)	0.4 (0.1-1.4)	1.3 (0.7-2.4)	
BMI								
<25	1.0 (ref.)	0.8 (0.6-0.99)	0.7 (0.5-0.8)	0.6 (0.4-0.8)	0.5 (0.3-0.9)	0.7 (0.4-1.2)	0.7 (0.4-1.1)	*.70*
≥25	1.0 (ref.)	0.8 (0.6-1.1)	0.6 (0.4-0.8)	0.7 (0.4-1.1)	0.8 (0.4-1.5)	0.5 (0.2-1.1)	0.9 (0.5-1.7)	

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Heart failure								
Yes	1.0 (ref.)	0.7 (0.5-1.2)	0.4 (0.2-0.8)	0.6 (0.2-1.4)	0.5 (0.1-2.1)	0.3 (0.04-2.1)	0.6 (0.2-1.8)	*.25*
No	1.0 (ref.)	0.8 (0.7-0.99)	0.7 (0.6-0.8)	0.6 (0.4-0.8)	0.6 (0.4-0.98)	0.7 (0.4-1.1)	0.8 (0.5-1.2)	
Hypertension								
Yes	1.0 (ref.)	0.8 (0.6-0.99)	0.5 (0.4-0.7)	0.5 (0.3-0.7)	0.7 (0.4-1.2)	0.6 (0.3-1.1)	0.7 (0.4-1.1)	*.38*
No	1.0 (ref.)	0.9 (0.6-1.2)	0.8 (0.6-1.1)	0.7 (0.5-1.1)	0.5 (0.2-0.98)	0.7 (0.3-1.3)	0.8 (0.4-1.5)	
Diabetes								
Yes	1.0 (ref.)	0.7 (0.5-0.97)	0.6 (0.5-0.8)	0.4 (0.2-0.7)	0.6 (0.3-1.1)	0.6 (0.3-1.1)	0.4 (0.2-0.9)	*.02*
No	1.0 (ref.)	0.9 (0.7-1.1)	0.7 (0.5-0.8)	0.7 (0.5-0.96)	0.6 (0.4-1.1)	0.7 (0.4-1.2)	1.0 0.6-1.6)	
Previous MI								
Yes	1.0 (ref.)	0.6 (0.3-1.3)	0.3 (0.1-0.8)	0.6 (0.2-1.7)	*	0.8 (0.1-3.3)	0.6 (0.1-2.3)	*.49*
No	1.0 (ref.)	0.8 (0.7-0.99)	0.7 (0.6-0.8)	0.6 (0.4-0.8)	0.7 (0.4-1.0)	0.6 (0.4-0.98)	0.8 (0.5-1.1)	
Dyslipidemia								
Yes	1.0 (ref.)	0.8 (0.6-1.1)	0.7 (0.5-0.9)	0.6 (0.4-0.9)	0.6 (0.3-1.2)	0.4 (0.2-0.9)	0.7 (0.4-1.4)	*.46*
No	1.0 (ref.)	0.8 (0.6-0.98)	0.6 (0.5-0.8)	0.6 (0.4-0.8)	0.6 (0.4-1.1)	0.8 (0.5-1.3)	0.8 (0.5-1.2)	
Malignancy								
Yes	1.0 (ref.)	0.7 (0.4-1.1)	0.5 (0.3-0.8)	0.6 (0.3-1.1)	0.5 (0.2-1.4)	0.6 (0.2-1.8)	0.6 (0.2-1.5)	*.74*
No	1.0 (ref.)	0.8 (0.7-1.0)	0.7 (0.5-0.8)	0.6 (0.4-0.8)	0.6 (0.4-1.0)	0.6 (0.4-1.0)	0.8 (0.5-1.2)	
Alcohol (≥1time/week)								*.69*
Drinker	1.0 (ref.)	0.9 (0.7-1.3)	0.7 (0.5-1.0)	0.6 (0.4-0.9)	0.6 (0.3-1.2)	0.9 (0.5-1.6)	0.6 (0.3-1.3)	

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Non-drinker	1.0 (ref.)	0.8 (0.6-0.96)	0.6 (0.5-0.8)	0.6 (0.4-0.9)	0.6 (0.3-1.0)	0.5 (0.3-0.96)	0.8 (0.5-1.3)	
Smoking								
Current	1.0 (ref.)	0.8 (0.6-1.2)	0.6 (0.4-0.8)	0.6 (0.4-0.99)	0.7 (0.3-1.5)	0.3 (0.1-1.0)	0.5 (0.2-1.3)	
Former	1.0 (ref.)	0.8 (0.5-1.3)	0.8 (0.5-1.2)	0.3 (0.1-0.6)	0.5 (0.2-1.4)	1.1 (0.5-2.2)	0.7 (0.3-1.7)	*.09*
Never	1.0 (ref.)	0.8 (0.6-0.99)	0.7 (0.5-0.9)	0.8 (0.6-1.1)	0.7 (0.4-1.2)	0.6 (0.3-1.3)	1.0 (0.6-1.6)	
Framingham risk score								
Low	1.0 (ref.)	0.9 (0.7-1.2)	0.8 (0.6-0.97)	0.6 (0.4-0.9)	0.5 (0.3-1.0)	0.6 (0.3-1.2)	0.8 (0.4-1.5)	
Intermediate	1.0 (ref.)	0.8 (0.6-1.1)	0.6 (0.4-0.8)	0.6 (0.4-0.9)	0.8 (0.4-1.4)	0.7 (0.4-1.2)	0.9 (0.5-1.4)	*.53*
High	1.0 (ref.)	0.6 (0.4-1.1)	0.5 (0.3-0.9)	0.4 (0.2-0.9)	0.4 (0.1-1.4)	0.6 (0.2-2.0)	0.2 (0.1-1.1)	

†The model was adjusted for age, sex, body mass index, heart failure, hypertension, diabetes, previous myocardial infarction, prior stroke or transient ischemic attack, atrial fibrillation, chronic kidney disease, malignancy, dyslipidemia, smoking and alcohol.

BMI: body mass index, CI: confidence interval, MET: metabolic equivalent task, MI: myocardial infarction

*There were no events in this category.

We employed separate moderate-intensity and vigorous-intensity categories with levels ranging from 0 to >22.5 MET-hour/week, and the analytical models were mutually adjusted for both moderate- and vigorous-intensity physical activity (Table 5). We observed PCA risk reductions at levels below (0.1 to <7.5 MET-hour/week; HR 0.80, 95% CI 0.67 to 0.95), meeting (7.5 to <15.0 MET-hour/week; HR 0.69, 95% CI 0.57 to 0.82), and two to three times (15.0 to <22.5 MET-hour/week; HR 0.61, 95% CI 0.43 to 0.87) the recommended level of moderate-intensity physical activity. There was no statistically significant association between vigorous-intensity physical activity and PCA risk. In this subset mutually adjusted analyses, any level of moderate-intensity activity was associated with lower all-cause and

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cardiovascular mortality risk values.

<Table 5> Risk of primary cardiac arrest according to the intensity of physical activity

MET-hour/week / Intensity of activity	None	0.1 to <7.5	7.5 to <15.0	15.0 to <22.5	≥22.5
Moderate intensity activity					
Participants, No. (%)	138878 (28%)	166633 (33%)	149235 (30%)	38237 (8%)	11857 (2%)
Cases, No. (%)	326 (41%)	213 (27%)	190 (24%)	41 (5%)	29 (4%)
Separate model					
Model 1 HR	1.0(ref.)	0.8(0.7-0.9)	0.7(0.6-0.8)	0.5(0.4-0.8)	0.7(0.5-1.1)
Model 2 HR	1.0(ref.)	0.8(0.7-0.9)	0.7(0.6-0.8)	0.6(0.4-0.8)	0.7(0.5-1.1)
Mutual adjustment model					
Model 3 HR	1.0(ref.)	0.8(0.7-0.9)	0.7(0.6-0.8)	0.6(0.4-0.9)	0.9(0.6-1.4)
Model 4 HR	1.0(ref.)	0.8(0.7-0.9)	0.7(0.6-0.8)	0.6(0.4-0.9)	0.9(0.6-1.4)
Vigorous intensity activity					
Participants, No. (%)	138913 (28%)	292376 (58%)	47816 (10%)	17752 (3%)	7983 (2%)
Cases, No. (%)	349 (44%)	346 (43%)	62 (8%)	24 (3%)	18 (2%)
Separate model					
Model 1 HR	1.0(ref.)	0.8(0.7-1.0)	0.8(0.6-0.99)	0.6(0.4-0.96)	0.7(0.4-1.1)
Model 2 HR	1.0(ref.)	0.8(0.7-1.1)	0.8(0.6-1.0)	0.7(0.4-0.99)	0.7(0.4-1.1)
Mutual adjustment model					
Model 3 HR	1.0(ref.)	0.9(0.7-1.1)	0.9(0.6-1.2)	0.8(0.5-1.2)	1.0(0.6-1.7)
Model 4 HR	1.0(ref.)	0.9(0.7-1.1)	0.9(0.7-1.2)	0.8(0.5-1.3)	1.0(0.6-1.7)

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Values are expressed as number (%) or hazard ratio (95% confidence interval)

Model 1: adjusted for age, sex and each intensity activity.

Model 2: adjusted for age, sex, body mass index, heart failure, hypertension, diabetes, previous myocardial infarction, prior stroke or transient ischemic attack, atrial fibrillation, chronic kidney disease, malignancy, dyslipidemia, smoking and alcohol and each intensity activity.

Model 3: adjusted for age, sex and moderate- and vigorous- intensity activities were mutually adjusted for each other.

Model 4: adjusted for age, sex, body mass index, heart failure, hypertension, diabetes, previous myocardial infarction, prior stroke or transient ischemic attack, atrial fibrillation, chronic kidney disease, malignancy, dyslipidemia, smoking, alcohol and moderate- and vigorous- intensity activities were mutually adjusted for each other.

4. DISCUSSION

In the present study, which investigated the dose-response association between physical activity and PCA risk in a nationwide general population, the beneficial effect of physical activity started at two-thirds of the recommended minimum and continued to five times the recommended minimum level. Individuals who met the current public health guideline-recommended physical activity level had a 36% lower risk of PCA than those who were inactive. The largest benefit was noted at levels two to three times the minimum recommended level, and the guideline-recommended minimum was associated with nearly the maximum benefit. There was no evidence of increased risk at levels of physical activity above five times the recommended minimum (the highest level recorded in this cohort) regardless of cardiovascular disease or lifestyle risk factors.

In restricted cubic spline model for using physical activity as a continuous variable, the beneficial effect of physical activity on PCA started at two-thirds of the recommended minimum (5 MET-hour/week; equivalent to approximately 75 minutes/week of moderate physical activity), the greatest benefit occurred at two to three times the recommended minimum (20 MET-hour/week; equivalent to

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approximately 300 minutes/week of moderate physical activity), and the benefit continued to five times the recommended minimum (40 MET-hour/week; equivalent to approximately 600 minutes/week of moderate physical activity) (Figure 1D). We observed monotonic decreases in the risks of all-cause and cardiovascular mortality with increasing exercise volumes up to levels greater than 40 MET hour/week (Figure 1E and IF). These results were consistent with those observed when physical activity was treated as a categorical variable, reflecting multiples of the public health recommendations.

Previous studies have shown that although the risk of SCA transiently increases during vigorous exercise, regular participation in vigorous physical activity is associated with an overall reduction in the risk of SCA.(5, 6) More recently, habitual moderate exertion also showed minimisations in the small transient risk and lowered the overall risk of cardiac arrest.(8, 9) The risk of cardiac arrest in the presence of physical activity is expected to be low, but quantitative estimates on the same are rare. The present study confirms and extends the findings of previous research through the quantification of the lower and upper thresholds of benefit, demonstrating that adults whose physical activity levels are at the recommended range also experience PCA risk-related benefits.

Findings on the association between high physical activity levels and mortality risk are contradictory. Some studies reported that participation in very high levels of physical activity for prolonged periods could be harmful to the heart. In the Copenhagen City Heart Study, the mortality risk was insignificantly higher among vigorous joggers than sedentary non-joggers.(25) Chronic sustained endurance exercise training has been shown to be associated with an increased risk of SCA even in the absence of coronary heart disease and hypertrophic cardiomyopathy.(26) Most studies on this topic focused on athletes rather than members of the general population. The present study’s findings suggest that the benefit of participation in high levels of physical activity to a level of five times the recommended minimum outweighs the potential risk of cardiac arrest in the general population. This finding may encourage people to increase their activity levels to a range that exceeds the recommended minimum level. Notably, no increases in the risk of PCA were observed among participants with even five or more times the recommended activity level regardless of the presence of risk factors. At five or more times the minimum recommended level, still reduced all-cause mortality and cardiovascular mortality values were observed. This result may provide relief to highly active individuals in terms of any concern they may have about

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exercise-associated cardiac arrest, and can also motivate inactive individuals, especially those with cardiovascular disease who are at a higher risk for cardiac arrest and tend to have sedentary lifestyles(27) to exercise, as the ultimate risk that concerns physicians providing care to such patients is the onset of SCA.

Approximately one-third to half of all adults in the United States do not meet the recommendation for aerobic physical activity.(4) East Asians tend to be less physically active than people from Western countries, and also tend to participate in lower-intensity exercise.(28, 29) Barriers are present in the adherence to the 30 minutes a day, 5 days or more a week recommendation. The identification of a minimum physical activity level sufficient to confer beneficial effects is desirable as participation in a small amount of physical activity may be easier to achieve. No studies till date have determined the precise minimum level of physical activity that is beneficial in terms of SCA prevention. Our findings suggest that a physical activity level of 5 MET-hour/week, corresponding to 10 minutes of brisk walking daily, may be easy to achieve by most adults and have a beneficial effect on PCA as well as all-cause and cardiovascular mortality.

Earlier studies reported that vigorous physical activity is required for reductions in the risk of cardiac arrest.(5, 6) Limited data with MET expenditure-related information are available for the evaluation of the risk of cardiac arrest in relation to non-vigorous physical activity. We found that the total volume of physical activity is associated with a lower risk of PCA, and the relative contributions of moderate- and vigorous-intensity activity are different. In the separate intensity model, moderate-intensity activity was associated with a reduced risk of PCA and conferred a larger number of benefits than vigorous-intensity activity. Our findings are in agreement with the results of the Multiple Risk Factor Intervention Trial, in which participation in a modest amount of predominantly moderate-intensity physical activity was associated with lower rates of sudden cardiac death.(30) Heavy strenuous exercise is associated with a potential risk of SCA,(31) especially among people with coronary risk factors.(32) From the public health standpoint, it is encouraging that predominantly moderate-intensity physical activity levels may be sufficient in reducing the risk of cardiac arrest; however, it should be pointed out that habitual vigorous-intensity activity was not associated with an excess risk of cardiac arrest both in the present population and that of the Multiple Risk Factor Intervention Trial.

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To the best our knowledge, this study is the first to quantify the dose-response association between physical activity and cardiac arrest. The upper and lower benefit thresholds associated with physical activity were distinctively estimated as were the potential PCA-related harms, which have not been previously evaluated. The stratified analyses further strengthened our findings, indicating the same direction of the association between physical activity and PCA, regardless of age, sex, BMI, heart failure, prior myocardial infarction, various lifestyle variables, and 10-year cardiovascular disease score group. As the performance of randomised controlled trials is difficult owing to the relatively low incidence rate of cardiac arrest, the use of nationwide cohort data seems the most suitable for the investigation of the association between physical activity and PCA risk.

This study also has several limitations. First, it relied on self-reported data on physical activity, as collected at a single time-point. The conditions at the time of questionnaire completion may not represent the actual physical activity conditions throughout life. Further, behavioural changes occurring during the follow-up period could not be assessed in our study. However, the large sample size of this study reduces the level of potential uncertainty, and the use of a self-report questionnaire provided a reliable approximation of the level of physical activity at a population level. Second, this study is potentially susceptible to errors arising from coding inaccuracies owing to the use of claims data. To minimise the strength of this problem, we applied the definition that was validated in two independent tertiary hospitals, and the diagnostic reliability of the cohort data was deemed high. The validity of the identification of cardiac arrest using ICD codes has been established in several studies, showing reliability and high positive predictive value.(33-35) Third, we were unable to examine the levels of occupational physical activity or sedentary time in the current study. Fourth, although we rigorously adjusted for many confounding factors, several unmeasured confounders such as dietary habits were not captured.

5. CONCLUSION

The beneficial effect of physical activity on PCA started at two-thirds of the recommended minimum

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and, continued to five times the recommended minimum level. There was no evidence of increased risk of PCA at level of physical activity above five times the recommended minimum regardless of cardiovascular diseases or lifestyle risk factors. These findings are informative for people at both ends of the physical activity spectrum. For inactive individuals they show that even small amounts of activity are good for health, while reassuring very active individuals that exercise is not associated with an increased risk of SCA. Health professionals should encourage inactive adults to participate in exercise and may refrain from discouraging adults who already participate in high levels of physical activity.

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Abstract in Korean

일반 인구 집단에서 신체 활동과 급성 심정지 발생 위험 관계에 대한 용량 반응 분석

급성 심정지 위험 감소에 필요한 신체 활동량이 어느 정도인지 밝혀지지 않았으며, 높은 활동량의 운동이 심정지 위험을 증가시키는지 여부도 불분명하다. 본 연구는 중등도 강도 이상의 신체 활동과 주요 심정지 (PCA, primary cardiac arrest) 사이의 용량-반응 관계를 정량화 하고자 했다. 본 연구는 2009년부터 2014년까지 대한민국 국민건강검진을 통해 신체 활동 평가를 위한 자가 진단 설문을 완료한 18세 이상의 506,805명 참가자를 대상으로 하였다. 신체 활동 수준은 공중보건 권장 지침의 배수에 해당하는 신진대사 해당치 (MET, metabolic equivalent) 로 변환하여 분류하여, 신체 활동과 주요 심정지 간의 정량적 및 범주적 용량-반응 관계를 평가하였다. 신체 활동과 주요 심정지 간의 비례 곡선형 용량-반응 관계가 관찰되었다. 신체활동에 따른 주요 심정지 위험 감소의 효과는 세계보건기구 신체 활동 최소 권장량의 3분의 2 (7.5MET-시간/주) 지점에서 시작되어, 최소 권장량의 5배 (40 MET-시간/주) 까지 지속되었다 (*P non-linearity <.001*). 가장 큰 주요 심정지 감소 효과를 보인 구간은 최소 권장량의 2배에서 3배사이에서 확인되었다 (위험 비 0.58 [95% 신뢰구간, 0.44-0.76]). 또한, 최소 권장량의 5배 이상 수준에서도 주요 심정지 위험 증가를 보이지 않았다 (위험 비 0.74 [95% 신뢰구간, 0.50-1.09]). 이러한 관련성은 연령, 성별, 체질량지수, 동반 질환 및 심혈관 질환 10년 추정 위험지수와 관계없이 일관되었다. 신체 활동의 주요 심정지에 대한 유익한 효과는 신체 활동 최소 권장량의 3분의 2 지점에서 시작하여 5배 구간까지 이어졌다. 심혈관 질환이나 생활양식 위험 요인 유무와 관계없이 최소 권장량의 5배 이상의 높은 신체 활동 범위에서도 주요 심정지의 위험 증가를 보이지 않았다.

핵심되는 말 : 심정지, 신체활동, 심장돌연사

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Publication List

1. Jin MN, et al. Association of Physical Activity with Primary Cardiac Arrest Risk in the General Population: A Nationwide Cohort Study of the Dose-Response Relationship. Mayo Clin Proc. 2022 Apr;97(4):716-29.