Daily Total Physical Activity and Incident Stroke

The Japan Public Health Center–Based Prospective Study

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***Background and Purpose*—**There is limited evidence on the association between total physical activity and stroke in Asian populations experiencing a greater burden of hemorrhagic stroke than Western populations. We aimed to understand their optimal level of physical activity for stroke prevention.

***Methods*—**A total of 74 913 Japanese people 50 to 79 years of age without histories of cardiovascular disease or cancer were followed from 2000 to 2012.

***Results*—**During the 698 946 person-years of follow-up, we documented a total of 2738 incident cases of stroke, including 1007 hemorrhagic strokes (747 intraparenchymal and 260 subarachnoid hemorrhages) and 1721 ischemic strokes (1206 nonembolic and 515 embolic infarctions). Individuals in the second or third metabolic equivalents of task–hours per day quartile had the lowest risks of total stroke (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.75–0.93), intraparenchymal hemorrhage (HR, 0.79; 95% CI, 0.64–0.97), subarachnoid hemorrhage (HR, 0.78; CI, 0.55–1.11), and nonembolic infarction (HR, 0.78; CI, 0.67–0.92), whereas those in the fourth quartile had the lowest risk of embolic infarction (HR, 0.76; CI, 0.59–0.97). Cubic spline graphs revealed a steep decrease in stroke risk (30% risk reduction) from the lowest level to a plateau at 5 to 10 metabolic equivalents of task–hours per day (50th percentile). The associations of total physical activity level with hemorrhage stroke showed U or J shape, which were because of vigorous-intensity activities, whereas the association with ischemic stroke showed L shape.

***Conclusions*—**For Japanese people, moderate levels of total physical activity, particularly achieved by moderate-intensity activities, may be optimal for stroke prevention because excessive vigorous-intensity activities might not be beneficial or even disadvantageous for prevention of hemorrhagic stroke. **(*Stroke*. 2017;48:1730-1736. DOI: 10.1161/STROKEAHA.117.017560.)**

Key Words: Asia ■ exercise ■ humans ■ infarction ■ stroke

Physical inactivity is considered as one of the most important modifiable risk factors for stroke.[1] Physical activity may reduce the risk of stroke by preventing some risk factors for stroke, such as obesity, hypertension, dyslipidemia, and diabetes mellitus.[2] In addition, several previous studies suggested direct effects of physical activity, such as improved endothelial function and reduced systemic inflammation or platelet aggregation, which attenuates the progression of atherosclerosis.[3–5] Population-based studies have demonstrated a beneficial effect of physical activity on stroke incidence.[6]

However, the evidence has been mainly developed from research in Western countries.[6] Asian populations, such as Japanese and Chinese, have different lifestyles and genetic variants from Western populations, and Asian populations experience a greater burden of stroke, particularly hemorrhagic stroke, than Western populations.[7–9] Although physical activity has protective effects on stroke risk, a high-intensity physical activity may be a trigger factor for hemorrhagic stroke probably because of an increase in blood pressure during activity.[10–15] Thus, it is important to accumulate evidence on Asian populations with a high risk of hemorrhagic stroke.

Therefore, the objective of this study was to investigate the dose–response relation of daily total physical activity with stroke and its subtypes in a Japanese population-based prospective study to understand their optimal level of physical activity for stroke prevention.

Materials and Methods

Study Design, Setting, and Population

The Japan Public Health Center–Based Prospective (JPHC) study is an ongoing prospective study comprising a population-based sample of 140 420 Japanese adults (68 722 men and 71 698 women).

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Details of the JPHC study have been reported previously.[16] Briefly, the JPHC Study comprises 2 cohorts: cohort I and cohort II were initiated, respectively, in 5 public health center (PHC) areas (Iwate, Akita, Tokyo, Nagano, and Okinawa-Chubu), with 61 595 subjects 40 to 59 years of age in 1990 and in 6 PHC areas (Ibaraki, Niigata, Osaka, Kochi, Nagasaki, and Okinawa-Miyako), with 78 825 subjects 40 to 69 years of age in 1993 (the first survey; 81% response of 140 420 participants). The participants were followed in 1995 to 1998 (the second survey; 74% response) and in 2000 to 2003 (the third survey; 71% response). Subjects were asked to complete self-administered questionnaires concerning their lifestyles and medical histories. Questionnaires concerning detailed daily physical activities were added to the third survey (2000 and 2003 for cohorts I and II, respectively), and the third survey was considered the baseline for this study.

Of responders to the third survey, 90 886 participants were eligible for follow-up because individuals in 2 PHC areas (Tokyo and Osaka) were excluded from the current study because of the incomplete follow-up data.[17] Of the 90 886 subjects, 87 169 residents completed the questionnaire about daily physical activity. We excluded 11 035 persons with a history of stroke, myocardial infarction, angina pectoris, or cancer at the third survey. In addition, participants with missing data on potential confounding factors (n=1221; 1.6%) were excluded. Thus, a total of 74 913 participants (34 874 men and 40 038 women) remained for the present analyses.

The Institutional Human Ethics Review Boards of Osaka University and the National Cancer Center approved the study.

Risk Factor Measurements

Stroke risk factors were measured via self-reports. The main exposure of interest was daily total physical activity. Participants were asked to provide the information concerning the average daily amount of time and frequency spent in work-related (including commuting and housework) physical activity and leisure-time physical activity.[18,19] Daily total physical activity level (metabolic equivalents of task [MET]-hours per day) was calculated as the sum of physical activity levels spent during work-related walking and strenuous work and leisure-time physical activities, such as brisk walking and jogging.[18,19] The correlation between daily activities reported in 24-hour records and that reported on the questionnaire was 0.69. The test–retest correlation for daily activities was 0.68.[18]

Potential confounding factors included age (continuous), sex (male or female), smoking status (never, ex-smoker, or current smoker), ethanol intake (gram per week; continuous), parental history of cardiovascular disease (yes or no), daily sedentary time,[19] living alone (yes or no), and PHC areas.

Because obesity, hypertension, hypercholesterolemia, and diabetes mellitus may mediate the association between physical activity and stroke risk,[2] baseline body mass index (weight [kg]/height [m^2]; measured value], systolic and diastolic blood pressure (measured value; data available on 51 721 participants), use of medication for hypertension, hypercholesterolemia, diabetes mellitus, and history of diabetes mellitus (data available on 74 913 participants) were not considered as potential confounding factors but potential mediators in the present study and were, therefore, not included in the final model.

Confirmation of Stroke

Stroke events were registered at a total of 81 hospitals in the 9 PHC areas. At each hospital, physicians blinded to the patients' lifestyle data reviewed the patients' medical records. Strokes were confirmed according to the criteria of the National Survey of Stroke.[20] According to these criteria, the presence of sudden or rapid-onset focal neurologic deficits lasting at least 24 hours, or until death, was required. Strokes were classified according to subtypes, that is, intraparenchymal hemorrhage, subarachnoid hemorrhage, or cerebral infarction (nonembolic or embolic).[21] Almost all registered hospitals were equipped with computed tomography or magnetic resonance imaging scanners. Only first-ever stroke events during follow-up were included.

Statistical Analysis

SAS software, version 9.4 (SAS Institute, Inc, Cary, NC) was used for the statistical analyses. All statistical tests were 2-tailed, and P values <0.05 were regarded as significant.

Using PROC-GLM (least squares means), age- and sex-adjusted means, and prevalences of selected participant characteristics at baseline were calculated according to MET-hours per day quartiles. A linear trend was tested using linear or logistic regression. Person-years of follow-up were calculated from the baseline to the first end point: stroke event, death, emigration, or end of the follow-up (2012), whichever came first. For individuals who were lost to follow-up (<1%), we used the last confirmed date of their participation in the study area as the censoring date. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated for each outcome using Cox proportional hazard models after adjusting for potential confounding factors. The proportional hazards assumption in the Cox regression analysis was checked using risk factor-by-time interactions and was not violated. Because we found no statistical interactions between sex and main exposure in relation to stroke risk, analyses pooled across sex were conducted. We constructed cubic spline graphs to evaluate in detail the dose–response relationship between the daily total physical activity level and stroke risk. We chose 5 knots with 5th, 25th, 50th, 75th, and 95th percentiles.

For sensitivity analyses, we also ran models by (1) excluding those with early cardiovascular events (1 to 3 years from baseline) to assess the possibility of reverse causation, (2) using early follow-up data only (within 3, 6, and 9 years of baseline), (3) including participants with a baseline history of coronary heart disease or cancer but not stroke, and (4) excluding participants who developed subarachnoid hemorrhage during follow-up because the cause of subarachnoid hemorrhage is usually the rupture of intracerebral aneurysms.

Results

Baseline Characteristics According to Daily Total Physical Activity Level

Table 1 lists the baseline characteristics according to MET-hours per day quartiles in men and women. The median values in successive quartiles were 1, 5.4, 13, and 28 MET-hours per day. Individuals in higher MET-hours per day quartiles were more likely to be younger and male and have a higher mean value for ethanol intake and lower mean values for sedentary time, body mass index, and systolic and diastolic blood pressure, and were less likely to live alone, and have a history of diabetes mellitus and use medication for hypertension, hypercholesterolemia, and diabetes mellitus.

Daily Total Physical Activity and Incident Stroke

During the 698 946 person-years of follow-up for the 74 913 participants, we documented a total of 2738 incident cases of stroke, including 1007 hemorrhagic strokes (747 intraparenchymal hemorrhages and 260 subarachnoid hemorrhages) and 1721 ischemic strokes (1206 nonembolic and 515 embolic infarctions; Table 2). Age- and sex-adjusted analyses revealed that, compared with the lowest quartile of daily total physical activity, higher daily physical activity levels were associated with reduced risks of total and ischemic stroke, whereas the highest physical activity level was not statistically significantly associated with reduced risks of hemorrhagic strokes. Further adjustment for potential confounding factors did little to alter those associations. Men and women in the second or third MET-hours per day quartile had the lowest risk of total stroke (HR, 0.83; 95% confidence interval [CI], 0.75–0.93 in the second quartile), hemorrhagic stroke (HR, 0.79; CI, 0.66–0.94 in the second quartile),

Table 1. Age- and Sex-Adjusted Baseline Characteristics According to Daily Total Physical Activity Level Quartiles, Japan Public Health Center Study, 2000 to 2003 (74 913 Men and Women)

	Quartiles of MET-h/d in Men and Women				
	Lowest	Second	Third	Highest	*P* Trend
Median (Range)	1 (0–3.2)	5.4 (3.3–8.3)	13 (8.4–18.7)	28 (18.8–68.4)	
No. at risk	16 955	20 386	18 779	18 793	
Potential confounding factors					
Age, y	62.8±8.1	60.5±7.6	60.8±7.2	60.2±6.9	<0.001
Male, %	44.6	41.2	44.6	56.1	<0.001
Current smoker, %	22.8	20.3	20.5	21.8	0.571
Ethanol intake, g/wk	95.2±196.8	97.5±182.5	102.4±200	115.8±247.6	<0.001
Parental history of cardiovascular disease, %	10.2	11.4	11.6	9.8	0.404
Sedentary time, h/d	9.6±3.4	10.1±3	9.6±2.6	8.3±2.4	<0.001
Living alone, %	8.5	7.1	6.2	5.6	<0.001
Potential mediators					
Body mass index, kg/m^2	23.8±3.4	23.8±3.2	23.7±3.1	23.6±3	<0.001
Systolic blood pressure, mm Hg*	131.9±16.6	131.6±16.7	131.5±18.6	131.3±19.3	0.005
Diastolic blood pressure, mm Hg*	78.9±17.8	78.9±16.4	78.7±13.6	78.3±18.9	0.004
Medication use for hypertension, %	25.8	25.7	24	22.1	<0.001
Medication use for hypercholesterolemia, %	8.1	8.6	8.2	7.1	0.001
History of diabetes mellitus, %	6.5	6.3	5.7	5.3	<0.001
Medication use for diabetes mellitus, %	5.1	4.4	3.9	3.6	<0.001

Values are presented as age- and sex-adjusted mean±SD for continuous variables and age- and sex-adjusted percentages for categorical variables.

*Only available for subsample (23 243 men and 28 478 women).

intraparenchymal hemorrhage (HR, 0.79; CI, 0.64–0.97 in the second quartile), subarachnoid hemorrhage (HR, 0.78; CI, 0.55–1.10 in the second quartile), ischemic stroke (HR, 0.79; CI, 0.69–0.90 in the third quartile), and nonembolic infarction (HR, 0.78; CI, 0.67–0.92 in the third quartile), whereas those in the fourth quartile had the lowest risk of embolic infarction (HR, 0.75; CI, 0.59–0.96).

We also assessed the dose–response relations between daily total physical activity level and stroke risks by drawing cubic spline graphs. Cubic spline graphs showed a steep decrease in stroke risk (≈30% risk reduction) from the lowest MET-hours per day individuals to around 5 to 10 MET-hours per day (around the 50th percentile) regardless of stroke subtypes and then a plateau (Figure 1). Although ischemic stroke and nonembolic infarction risks kept a plateau and embolic infarction risk was likely to further decrease, hemorrhagic stroke risk was likely to increase after a plateau. Particularly, individuals with >30 to 35 MET-hours per day (around the 90th percentile) were likely to have increased risk of subarachnoid hemorrhage although the association was not statistically significant.

We further investigated associations of moderate- (eg, walking) and vigorous-intensity (eg, jogging) activities with hemorrhagic stroke risk (Figure 2). In contrast to the inverse association between moderate-intensity activities and hemorrhagic stroke risk, vigorous-intensity activities were associated with increased risk of hemorrhagic stroke from around the 80th percentile of physical activity level.

Sensitivity Analyses

All of the sensitivity analyses described in the methods produced similar results to main results (data not shown).

Discussion

In this prospective population-based cohort study of an Asian population experiencing a greater burden of hemorrhagic stroke than Western populations, we observed nonlinear dose–response relations between daily total physical activity and stroke risk. Being active in the middle of the MET-hours per day distributions (in this study; 5 to 10 MET-hours per day) seemed to be sufficient to achieve the maximum risk reduction of stroke, although the risk of embolic infarction was significantly decreased in a higher physical activity level. The associations between physical activity level and hemorrhagic stroke risk showed U or even J shape, which were because of vigorous-intensity activities, whereas the association with ischemic stroke showed L shape.

A previous meta-analysis mostly from Western countries reported that compared with inactivity, moderately intense physical activity was sufficient to achieve the maximum risk reduction for both ischemic and hemorrhagic strokes,[6] with which our

Table 2. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Incident Stroke According to Daily Total Physical Activity Level Quartiles, Japan Public Health Center Study, 2000 to 2012 (74 913 Men and Women)

	Quartiles of MET-h/d in Men and Women			
	Lowest	Second	Third	Highest
Median (Range)	1 (0–3.2)	5.4 (3.3–8.3)	13 (8.4–18.7)	28 (18.8–68.4)
No. at risk	16 955	20 386	18 779	18 793
Person-years	153 091	191 052	177 027	177 776
Total stroke, n (%)	756 (4.5)	663 (3.3)	638 (3.4)	681 (3.6)
Age- and sex-adjusted HR (95% CI)	1	0.83 (0.75–0.92)	0.82 (0.74–0.92)	0.86 (0.78–0.96)
Multivariable* HR (95% CI)	1	0.83 (0.75–0.93)	0.83 (0.75–0.92)	0.87 (0.78–0.96)
Hemorrhagic stroke, n (%)	260 (1.5)	230 (1.1)	248 (1.3)	269 (1.4)
Age- and sex-adjusted HR (95% CI)	1	0.79 (0.66–0.94)	0.90 (0.75–1.01)	0.96 (0.81–1.15)
Multivariable* HR (95% CI)	1	0.79 (0.66–0.94)	0.90 (0.76–1.07)	0.98 (0.82–1.17)
Intraparenchymal hemorrhage, n (%)	195 (1.2)	169 (0.8)	180 (1)	203 (1.1)
Age- and sex-adjusted HR (95% CI)	1	0.80 (0.65–0.98)	0.88 (0.72–1.08)	0.96 (0.79–1.17)
Multivariable* HR (95% CI)	1	0.79 (0.64–0.97)	0.88 (0.72–1.08)	0.98 (0.80–1.20)
Subarachnoid hemorrhage, n (%)	65 (0.4)	61 (0.3)	68 (0.4)	66 (0.4)
Age- and sex-adjusted HR (95% CI)	1	0.77 (0.54–1.09)	0.94 (0.67–1.32)	0.97 (0.68–1.37)
Multivariable* HR (95% CI)	1	0.78 (0.55–1.10)	0.95 (0.68–1.34)	0.98 (0.69–1.39)
Ischemic stroke, n (%)	494 (2.9)	429 (2.1)	388 (2.1)	410 (2.2)
Age- and sex-adjusted HR (95% CI)	1	0.85 (0.75–0.97)	0.79 (0.69–0.90)	0.81 (0.71–0.92)
Multivariable* HR (95% CI)	1	0.86 (0.75–0.98)	0.79 (0.69–0.90)	0.81 (0.71–0.92)
Nonembolic infarction, n (%)	340 (2)	306 (1.5)	268 (1.4)	292 (1.6)
Age- and sex-adjusted HR (95% CI)	1	0.87 (0.74–1.01)	0.78 (0.66–0.91)	0.82 (0.70–0.96)
Multivariable* HR (95% CI)	1	0.87 (0.75–1.02)	0.78 (0.67–0.92)	0.83 (0.71–0.98)
Embolic infarction, n (%)	153 (0.9)	120 (0.6)	121 (0.6)	118 (0.6)
Age- and sex-adjusted HR (95% CI)	1	0.80 (0.63–1.02)	0.82 (0.64–1.04)	0.78 (0.61–0.99)
Multivariable* HR (95% CI)	1	0.82 (0.64–1.04)	0.82 (0.65–1.04)	0.75 (0.59–0.96)

*Adjusted for age, sex, smoking status, ethanol intake, parental history of cardiovascular disease, daily sedentary time, living alone, and public health area. HR indicates hazard ratios; and CI, 95% confidence intervals.

results are consistent. In addition, a recent systematic review and meta-analysis mostly from Western countries also showed that being active in the middle of total physical activity level distributions (3000 to 4000 MET-minutes per week [ie, 7 to 10 MET-hours per day]) seemed to be sufficient for most health gains.[22] These results, including ours, suggest that there might be a limit to protective effects of physical activity on stroke risk and, thus, other healthy behaviors, such as not smoking and eating healthy diets might be necessary to further reduce stroke risk.

In contrast to ischemic stroke, the associations between physical activity level and hemorrhagic stroke risk showed U or J shape, which were because of vigorous-intensity activities but not because of moderate-intensity activities, suggesting that some individuals engaging in a high level of vigorous-intensity activities might have even disadvantages, as well as no advantage. A high-intensity physical activity is known to cause a short-lasting and sudden increase in blood pressure.[13,14] In addition, several previous reports suggested that a high-intensity physical activity might trigger the occurrence of hemorrhagic stroke through increased blood pressure.[10–12,15] In particular, patients with an intracerebral aneurysm, which is a major risk factor for subarachnoid hemorrhage, may have disadvantages from a high physical activity level. In fact, individuals with a high physical activity level had increased risk of subarachnoid hemorrhage (J shape), compared with intraparenchymal hemorrhage (U shape). Thus, there may be an optimal level (in this study; 5 to 10 MET-hours per day) of total physical activity for prevention of hemorrhagic stroke.

Interestingly, a high level of physical activity was associated with decreased risk of embolic infarction. A previous study suggested a tendency toward a reduced risk of embolic stroke with higher levels of physical activity, but the association was not statistically significant ([HR, 0.77; 95% CI, 0.47–1.27] in ideal physical activity level compared with poor level) probably because of a small power.[23] Because embolic infarction is mainly caused by heart diseases, particularly AF,[24–26] this inverse association might be in part through prevention of AF by physical activity. Thus, the difference between associations of physical activity with nonembolic and embolic stroke risk may reflect the difference between effects of physical activity on intracranial

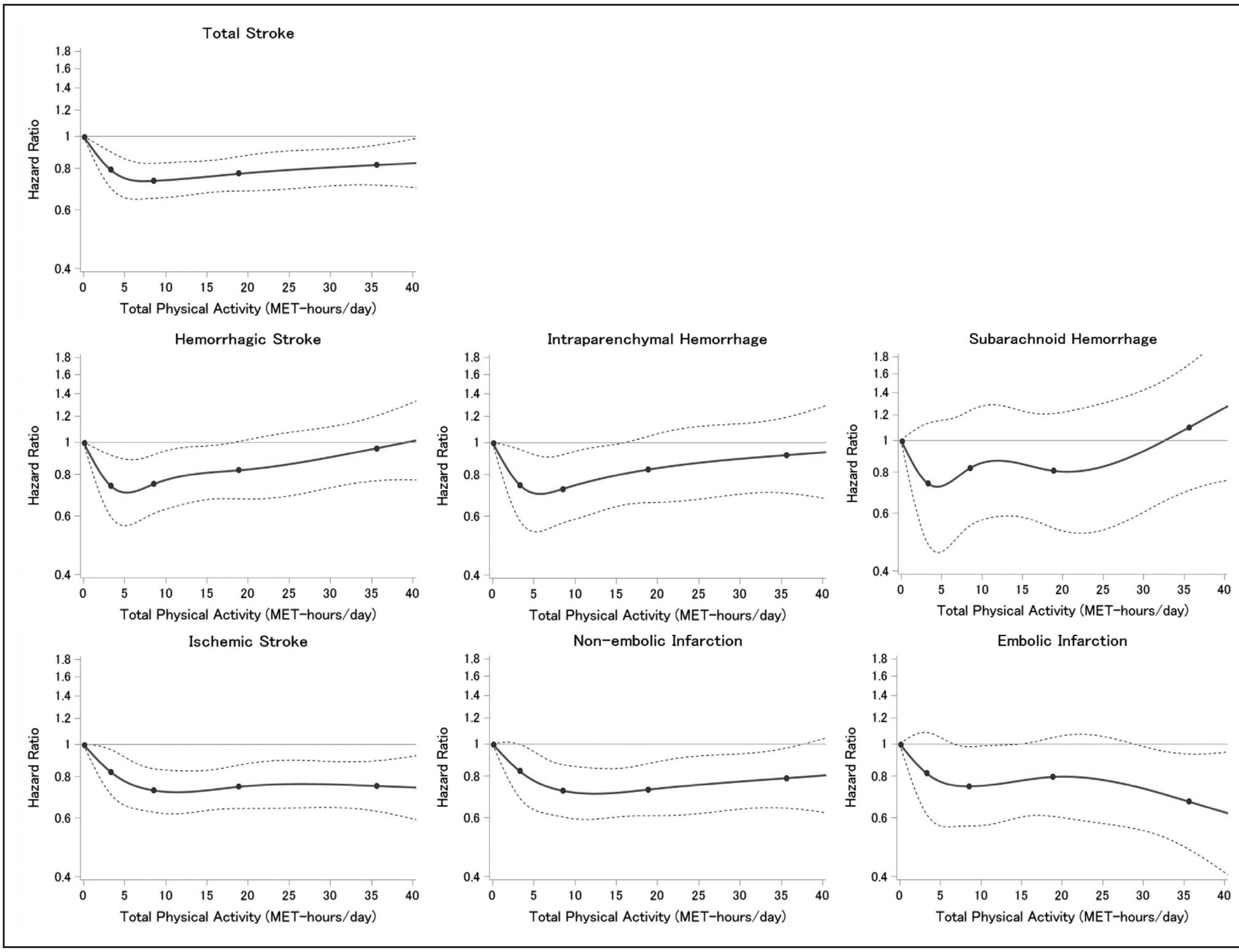

Figure 1. Multivariable-adjusted (age, smoking status, ethanol intake, parental history of cardiovascular disease, daily sedentary time, living alone, and public health area) associations of total physical activity level (METs/d) with stroke outcomes in men and women. Solid, dashed lines, and dots represent hazard ratios, 95% confidence intervals, and 5th, 25th, 50th, 75th, and 95th percentiles, respectively. The reference value was the zero percentile for all graphs.

arteries and heart, including coronary arteries. Because of the larger size of infarction, embolic infarction is more severe (increased risk of in-hospital death, greater disability, longer hospital stays, reduced likelihood of patients returning to their own home, and increased risk of recurrent stroke) than nonembolic infarction.[27–29] With an increasingly aging population, the

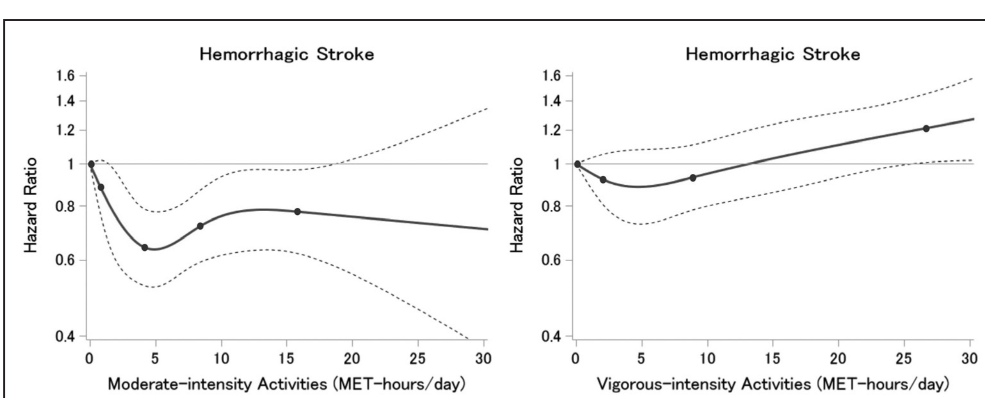

Figure 2. Multivariable-adjusted (age, smoking status, ethanol intake, parental history of cardiovascular disease, daily sedentary time, living alone, public health area, and moderate-intensity [for vigorous activities] or vigorous-intensity [for moderate activities] activities) associations of moderate- and vigorous-intensity activities (METs/d) with hemorrhagic stroke in men and women. Solid, dashed lines, and dots represent hazard ratios, 95% confidence intervals, and 5th, 25th, 50th, 75th, and 95th percentiles, respectively (for vigorous-intensity activities, 5th and 25th percentiles were the same value). The reference value was the zero percentile for all graphs.

prevalence of AF is expected to rise substantially in Asian and Western populations.[30,31] Thus, it is noteworthy that physical activity may also prevent embolic infarction.

We used total physical activity but not just leisure-time physical activity, which has been used in most epidemiologic studies,[32–34] and, thus, the distribution of physical activity levels in the present study should be carefully compared with those in previous studies.

The strengths of our study include its prospective design, inclusion of a large sample from the general population, the large number of stroke cases, and wide availability of computed tomography/magnetic resonance imaging for stroke diagnosis. In addition, sufficient hemorrhagic and ischemic stroke events in the present study enabled us to investigate the association between physical activity and stroke subtypes.

Nonetheless, some limitations must be addressed. First, information about daily physical activities was obtained via self-report only at baseline. Thus, we cannot negate the possibility of misclassifications of physical activity level at baseline and over time. However, as data were collected before stroke events, such misclassification should be generally nondifferential with respect to the stroke outcomes, and associations would have thus been biased toward the null. In addition, the results from both long- (12 years) and short-interval (3, 6, and 9 years) follow-ups showed similar trends, and, thus, we assume that such misclassification, if present, was not sufficiently influential to change our conclusions. Second, physical activities were measured via self-report, as often used in previous epidemiologic studies, but not objective measurement methods, such as accelerometer.[35] Third, our participants were 50 to 79 years of age. Although stroke is common among the elderly, it is unclear whether our results are also applicable to younger populations. Finally, as in most observational studies, the possibility of residual confounding of the observed associations cannot be negated.

Conclusions

For Asian populations experiencing a greater burden of stroke, particularly hemorrhagic stroke, than Western populations, moderate levels of total physical activity, particularly achieved by moderate-intensity activities, such as walking, may be optimal for stroke prevention, although a higher level of physical activity was associated with decreased risk of embolic infarction because excessive vigorous-intensity activities might not be beneficial or even disadvantageous for prevention of hemorrhagic stroke. This may be feasible for middle-aged or elderly people because they can relatively easily start and continue those activities.

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Disclosures

None.

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