ORIGINAL RESEARCH

Physical Activity Frequency and the Risk of Stroke: A Nationwide Cohort Study in Korea

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***Background*—**The current guideline recommends moderate- to vigorous-intensity physical activity (PA) at least 40 min/day for 3 to 4 days/week. Although recent evidence has demonstrated that low-dose PA could reduce cardiovascular mortality, the relationship between low-dose PA and the risk of stroke remains uncertain.

***Methods and Results*—**Using data from a nation-wide sample cohort in Korea, we examined 336 326 individuals who received a general health examination between 2009 and 2010. Level of PA was assessed using a questionnaire for weekly PA frequencies regarding 3 intensity categories: light, moderate, and vigorous. Moderate- to vigorous-intensity PA (MVPA) was classified into 4 frequency categories: none, 1 to 2, 3 to 4, or ≥5 times/week. Cox proportional hazard models were constructed to estimate the risk of stroke. During the average follow-up of 3.6 years, 2213 stroke cases occurred. MVPA was none in 50%, 1 to 2 times/week in 20%, 3 to 4 times/week in 13%, and ≥5 times/week in 18% of the cohort. Individuals with MVPA 1 to 2 times/week had a 16% reduced risk of stroke (adjusted hazard ratio, 0.84; 95% confidence interval, 0.73–0.96) compared with those with no MVPA. The population attributable fraction of no MVPA was 12%, which was the second most important risk factor for a stroke after hypertension.

***Conclusions*—**Even 1 to 2 times a week of MVPA might be beneficial to prevent a first-ever stroke in the general population, although a quantitative validation of the questionnaire is needed. From a public health perspective, we need to encourage inactive people to start exercising with more-achievable goals. **(*J Am Heart Assoc*. 2017;6:e005671. DOI: 10.1161/JAHA.117.005671.)**

Key Words: physical activity • primary prevention • risk factor • stroke

Physical activity (PA) is effective for preventing a stroke and reducing mortality.[1,2] However, approximately half of East Asians and 24% of US citizens still self-reported as being physically inactive, suggesting that PA may not sufficiently work as a preventive strategy for strokes.[3,4] The reason many people are still physically inactive could simply be attributed to being unaware of the substantial benefit of PA. However, it is also possible that the recommended standards are too high for people to initiate or continue PA. The current stroke guidelines from the American Stroke Association recommend at least 40 min/day of moderate- to vigorous-intensity aerobic PA 3 to 4 days/week.[5] The World Health Organization also recommends 150 min/week of moderate-intensity exercise or 75 min/week of vigorous-intensity exercise.[6] However, more than half the people in the United States and the United Kingdom and even up to 80% of all adults in Asian countries failed to comply with the guideline,[7–9] implying it is not a practical or easily achievable goal for Western societies' people. Recent studies showed a minimum of 90 min/week of moderate-intensity exercise or 30 to 59 min/week of vigorous-intensity exercise are markedly beneficial for all-cause and cardiovascular mortality.[3,10] We hypothesized that PAs, even below the current recommended level, are effective for preventing a first-ever stroke. To study this, we analyzed the database of general health examinations from a nation-wide sample cohort in Korea.

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Accompanying Figures S1, S2 and Tables S1 through S5 are available at http://jaha.ahajournals.org/content/6/9/e005671/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Even 1 to 2 times a week of moderate- to vigorous-intensity physical activity might be beneficial to prevent a first-ever stroke in the general population.

What Are the Clinical Implications?

- From a public health perspective, we need to encourage physically inactive people just to start any level of moderate- to vigorous-intensity physical activity, considering that 50% of individuals in this cohort were not participating in moderate- to vigorous-intensity physical activity.

Methods

National Health Insurance System-National Sample Cohort of Korea

In 1989, universal healthcare coverage was enacted in Korea, and the national health insurance system, a single-insurer system, began in 2000.[11] By maintaining healthcare utilization and prescription data, the national health insurance system has created a sample cohort of the population that provides useful health insurance and health examination data to public health researchers and policy makers. Of the total eligible population, 2.2%, or a cohort of 1 025 340 participants, was randomly sampled from the 2002 Korean health insurance database to obtain baseline data. These cohort participants were followed for 11 years. During the follow-up period, a representative sample of newborns (age 0) was added annually, and deceased or emigrated participants were excluded. After 11 years, in 2013, the database included 1 014 730 participants. Information regarding each participant's insurance eligibility, medical treatment history, healthcare provider's institution, and general health examination was included, because, in Korea, nation-wide general health examinations are conducted biennially for citizens aged ≥40 years. An insured employee and a household member of the insured self-employed can receive the examination regardless of his or her age.

Inclusion and Exclusion of Participants

From this cohort, we selected the participants who took the examination at least once between 2009 and 2010 because major changes were made in 2009 to the content of the examination and the questionnaire, especially related to PAs. Of the 352 896 individuals who received the general health examination between 2009 and 2010, we excluded participants who (1) had a previous stroke (N=5917), (2) had incomplete data on PA (N=5155), and (3) were disqualified because of death or emigration during the same year of the examination (N=5498). Finally, data for 336 326 participants (171 681 men and 164 645 women) were available for analyses. The present study was approved by the Institutional Review Board at the Seoul National University Hospital (Approval No. E-1610-092-799) and national health insurance system review committee of research support (NHIS-2017-2-337). Data were fully anonymized and de-identified for the analysis. Written informed consent was waived.

Assessment of PA and Potential Covariates at the Baseline

Level of PA was assessed using a questionnaire (Figure S1) for frequencies of weekly PA in each of the 3 intensity categories: vigorous (≥20 min/day; eg, running); moderate (≥30 min/day; eg, brisk walking); or light (≥30 min/day; eg, walking). Vigorous-intensity PA is defined as intense exercise that causes shortness of breath such as running, aerobic dancing, bicycling at high speeds, or uphill walking. Moderate-intensity PA is defined as exercises that cause mild shortness of breath such as brisk walking, tennis (doubles), or bicycling at a usual speed. Light-intensity PA is defined as walking at a usual pace. Frequencies of moderate- to vigorous-intensity PA (MVPA) were further classified into 4 categories: none, 1 to 2 times, 3 to 4 times, or ≥5 times/week. To reduce the possible confounding effect, the frequencies of light-intensity PA were adjusted in all multivariable regression models.

Age strata were defined by 19 age groups (Table S1; Figure S2). Income was categorized into 3 groups (lower 30%, middle 40%, and upper 30%) based on 10 strata. Cerebrovascular disease risk factors included the following: body mass index; smoking status (never versus past versus current use of cigarettes); alcohol use (heavy, >7 drinks/week for women, >14 per week for men; moderate, 1–7 for women, 1–14 for men; and none); diabetes mellitus (self-reported history of diabetes mellitus or fasting glucose ≥126 mL/dL); hypertension (self-reported history of hypertension, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg); and hyperlipidemia (self-reported history of hyperlipidemia or total cholesterol >240 mg/dL).

Follow-up and Stroke Assessment

Participants were followed for incident stroke from the baseline examination through the date of hospitalization due to stroke or December 31, 2013, using claims data. The diagnosis of a stroke was coded by the physicians in charge during hospitalization upon discharge as indicated by the International Classification of Diseases, Tenth Revision codes I63.X for ischemic stroke and I61.X for intracerebral hemorrhage. Health Insurance Review & Assessment Service in

Korea has been conducting quality assessment program dedicated for acute stroke, which reported 92.6% accuracy of coding for acute stroke diagnosis in 2010.[12]

Statistical Analyses

We compared baseline characteristics of the patients within each categories of MVPA based on the chi-squared and 1-way ANOVAs for categorical and continuous variables, respectively. The values are presented as the means±SDs or as percentages, as appropriate. Multivariable Cox proportional hazards models were used to determine hazard ratios (HRs) and 95% confidence intervals (CIs) of incident stroke (total stroke, ischemic stroke, and intracerebral hemorrhage) across PA categories (any/no MVPA as well as the 4 MVPA categories). In the analyses for each stroke subtype, individuals were censored when the corresponding type of stroke occurred. The model was adjusted for age, sex, income, smoking, alcohol consumption, body mass index, hypertension, diabetes mellitus, hyperlipidemia, and frequencies of light-intensity PA. Population attributable fractions for physical inactivity and other stroke predictors (hypertension, diabetes mellitus, hypercholesterolemia, current smoker, and heavy drinker) determined by the baseline assessment were estimated by using adjusted HR and prevalence. We tested effect modification by each of the covariates on the associations between PA and incident stroke using interaction terms in the regression. Proportional hazard assumptions were examined and met by using scaled Schoenfeld residuals. Sensitivity analysis for residual confounding was performed using the R "obsSens" package, which evaluates the effect of hypothetical unmeasured confounding factor in the model.[13] Significance levels were set at a P value of <0.05 for 2-tailed tests. Statistical analyses were performed using R statistical software (R, version 3.3.0; R Project).

Results

Baseline characteristics according to MVPA are described in Table 1. More physically active participants tended to be men, younger, have higher incomes, more likely to smoke, use alcohol, and had a higher body mass index. Of the 1 198 033 person-years of follow-up (average, 3.6 years), 2213 incident stroke cases occurred (1866 ischemic strokes and 347 intracerebral hemorrhages).

Any MVPA was associated with a lower risk of total stroke (adjusted HR, 0.78; 95% CI, 0.71–0.86) and ischemic stroke (HR, 0.77; 95% CI, 0.70–0.85), but it was not significantly associated with the risk of an intracerebral hemorrhage (HR, 0.84; 95% CI, 0.67–1.04; Figure 1). Dose-response analysis showed even the individuals in the MVPA 1 to 2 times/week group had a 16% reduced risk of incident stroke (HR, 0.84; 95% CI, 0.73–0.96) compared with those in the no MVPA group. MVPAs 3 to 4 times/week and ≥5 times/week were also associated with a lower risk of stroke (HR, 0.79; 95% CI, 0.68–0.91 in 3–4 times/week; HR, 0.78; 95% CI, 0.70–0.89 in ≥5 times/week). Similar results were observed for ischemic stroke, but not for intracerebral hemorrhage (Figure 1; Table S2).

No significant interactions were observed between MVPA (any/no or the 4 categories) and each of the confounders (Figure 2; Table S3). Sensitivity analysis to examine the trend of estimates of hazard on model with add on of an unmeasured confounder with relative hazard of 0.7 to 0.9 (Table S4). In most situations, patients who did MVPA had lower risk of stroke even if a favorable unmeasured confounder exists. Comparison of the effect of different International Classification of Diseases, Tenth Revision codes for defining outcome was provided in Table S5.

We estimated population attributable fractions for physical inactivity and other stroke risk factors such as smoking, heavy drinking, hypertension, diabetes mellitus, and hypercholesterolemia. No MVPA was the second most important risk factor for a stroke after hypertension, which accounted for 12% of the total strokes and 13% of ischemic strokes found in the participants (Table 2).

Discussion

In this nation-wide and standardized Korean cohort, we found that MVPA is associated with an ≈20% lower risk of stroke compared with physical inactivity, which has a similar magnitude of effect compared with previous studies.[14] Interestingly, our study demonstrated, for the first time, that a level of MVPA below the recommendation (1–2 times/week) is also protective against a stroke, independent of other stroke risk factors.

The strengths of this study include the following: a very large sample size from a representative nation-wide cohort; the controlling of potential confounding factors, including dose of light-intensity PA; and the comparability with the current stroke guidelines in terms of PA dose. However, several limitations are also noted. Because our questionnaire is composed of a minimal duration of PA for each intensity and weekly frequencies (eg, How many times a week do you participate in ≥30 minutes of moderate-intensity PA?), we could not calculate the exact metabolic equivalent times for additional analysis. Thus, someone in the low-frequency group may actually have performed the recommended amount of PA. Validation of our questionnaire against a more-quantitative method is needed to confirm the protective effect of low-dose MVPA for stroke prevention. Changing

Table 1. Baseline Characteristics According to the Frequencies of Moderate to Vigorous PA Per Week

	Frequencies of Moderate-to-Vigorous PA (Per Week)				
	None	1 to 2	3 to 4	≥5	
	n=166 681	n=65 813	n=44 915	n=58 917	*P* Value
Sex					<0.001
Male	44.4%	57.9%	57.8%	57.1%	
Female	55.6%	42.1%	42.2%	42.9%	
Age, y					<0.001
<40	25.4%	38.0%	29.8%	20.3%	
40 to 49	24.8%	29.3%	29.1%	26.0%	
50 to 59	22.4%	19.6%	23.1%	26.9%	
60 to 69	16.1%	8.9%	12.6%	18.7%	
≥70	11.2%	4.1%	5.4%	8.1%	
Income					<0.001
Lower 30%	23.8%	18.8%	19.1%	20.4%	
Mid 40%	40.8%	40.8%	37.4%	35.5%	
Upper 30%	35.4%	40.4%	43.5%	44.1%	
Smoking status					<0.001
Never	68.2%	56.8%	57.9%	60.0%	
Former	9.9%	15.0%	17.0%	18.8%	
Current	21.9%	28.2%	25.1%	21.2%	
Alcohol drinking					<0.001
None	61.8%	43.5%	45.6%	50.5%	
Moderate	20.4%	33.1%	30.8%	27.4%	
Heavy	17.8%	23.4%	23.7%	22.2%	
Body mass index, kg/m^2	23.6±3.3	23.6±3.3	23.9±3.2	24.0±3.0	<0.001
<25.0	69.1%	68.7%	66.2%	65.6%	
25 to 29.9	27.4%	27.8%	30.1%	31.0%	
≥30.0	3.5%	3.5%	3.7%	3.4%	
Frequency of light-intensity PA, per week	2.0±2.5	2.5±2.1	3.1±2.1	4.3±2.2	<0.001
Systolic BP, mm Hg	122.6±15.6	121.3±14.5	122.2±14.6	123.6±14.9	<0.001
Diastolic BP, mm Hg	76.1±10.2	75.9±10.0	76.3±10.0	76.7±10.0	<0.001
Hypertension	26.2%	20.0%	23.6%	28.3%	<0.001
Fasting glucose, mg/dL	97.9±24.7	96.1±22.1	97.5±23.4	98.9±24.3	<0.001
Diabetes mellitus	9.2%	6.7%	8.4%	10.8%	<0.001
Total cholesterol, mg/dL	195.8±37.6	194.7±36.4	195.4±36.6	196.0±37.0	<0.001
Hypercholesterolemia	14.2%	12.6%	13.7%	14.5%	<0.001

Values are mean±SD or percentage of frequency. BP indicates blood pressure; PA, physical activity.

behavior during long-term periods could not be assessed in this study because of the relatively short-term study period. Diet, a possible important confounding factor, was not considered in the model because the questionnaire did not include it. Because the outcomes were defined with only hospitalized stroke with the administrative health data, nonhospitalized stroke, such as severe stroke with death at home, may be underestimated.

In the previous reports which investigated the dose-response relationship between MVPA frequency and risk of stroke, the multivariable analysis adjusted with risk factors was inconclusive, and a different cutoff from the current

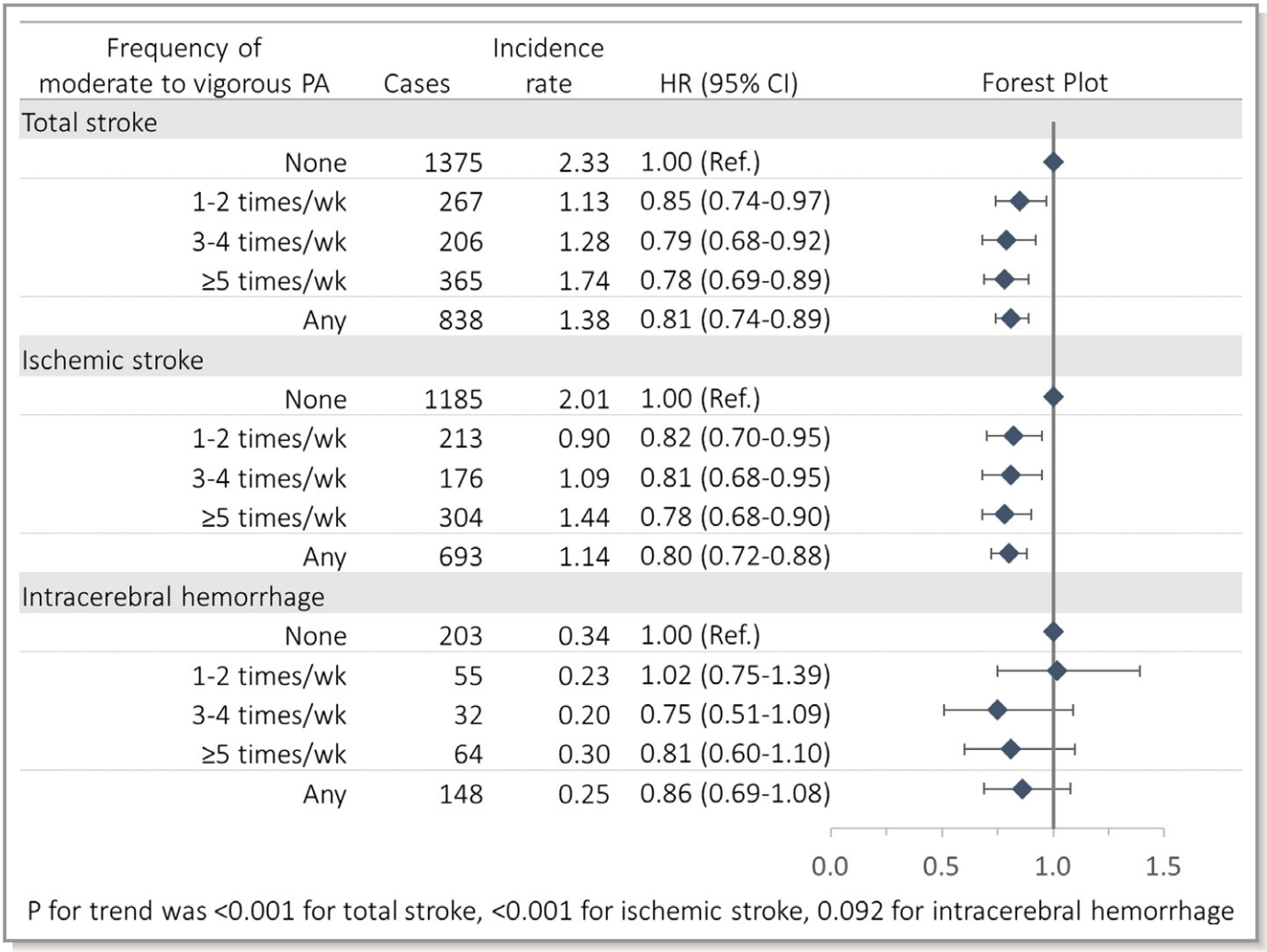

Figure 1. Frequency of moderate to vigorous PA and risk of incident stroke. CI indicates confidence interval; HR, hazard ratio; PA, physical activity.

stroke guidelines made it difficult to compare with. The current stroke guidelines recommend MVPA at least 40 min/day for 3 to 4 days/week for primary stroke prevention.[5] We found that 31% of our cohort met the recommended level of PA and had approximately a 20% lower risk of stroke. The World Health Organization recommends ≥150 min/week of moderate-intensity or 75 min/week of vigorous-intensity aerobic physical activity or an equivalent combination.[6] In our cohort, only ≈18% of participants met this guideline and had a 21% reduction of risk. Similarly, ≈80% of the adult population of East Asian countries, such as Taiwan, China, or Japan, did not meet this recommendation.[3] The far more serious problem is that currently over half of our cohort did not participate in any level of MVPA and were in a physically inactive state. In this study, we found reduction of stroke risk with even 1 to 2 times/week of MVPA, which is slightly less than the recommendation but significant. Although there was a statistically significant trend for dose-response relationship, the difference of point estimates was modest between each group. This finding has importance from a clinical and public health perspective, because time is one of the larger hurdles when physically inactive modern people begin to exercise.[15,16] There is an opinion that the current recommendation may not be perceived as a practical, achievable, and sustainable goal for physically inactive people.[17] If all physically inactive people start to perform any level of MVPA, in this population, 12% of total strokes and 13% of ischemic strokes would be prevented based on the estimation of population attributable fractions.

Although the efficacy of PA for preventing a stroke is supported by many studies, there were still some discrepancies found in previous evidence. It may be necessary to confirm intensity and volume of PA, the different effects by sex and ethnic groups, and the different effects on ischemic stroke and intracerebral hemorrhage. Overall, our study showed that MVPA is effective for preventing a stroke even

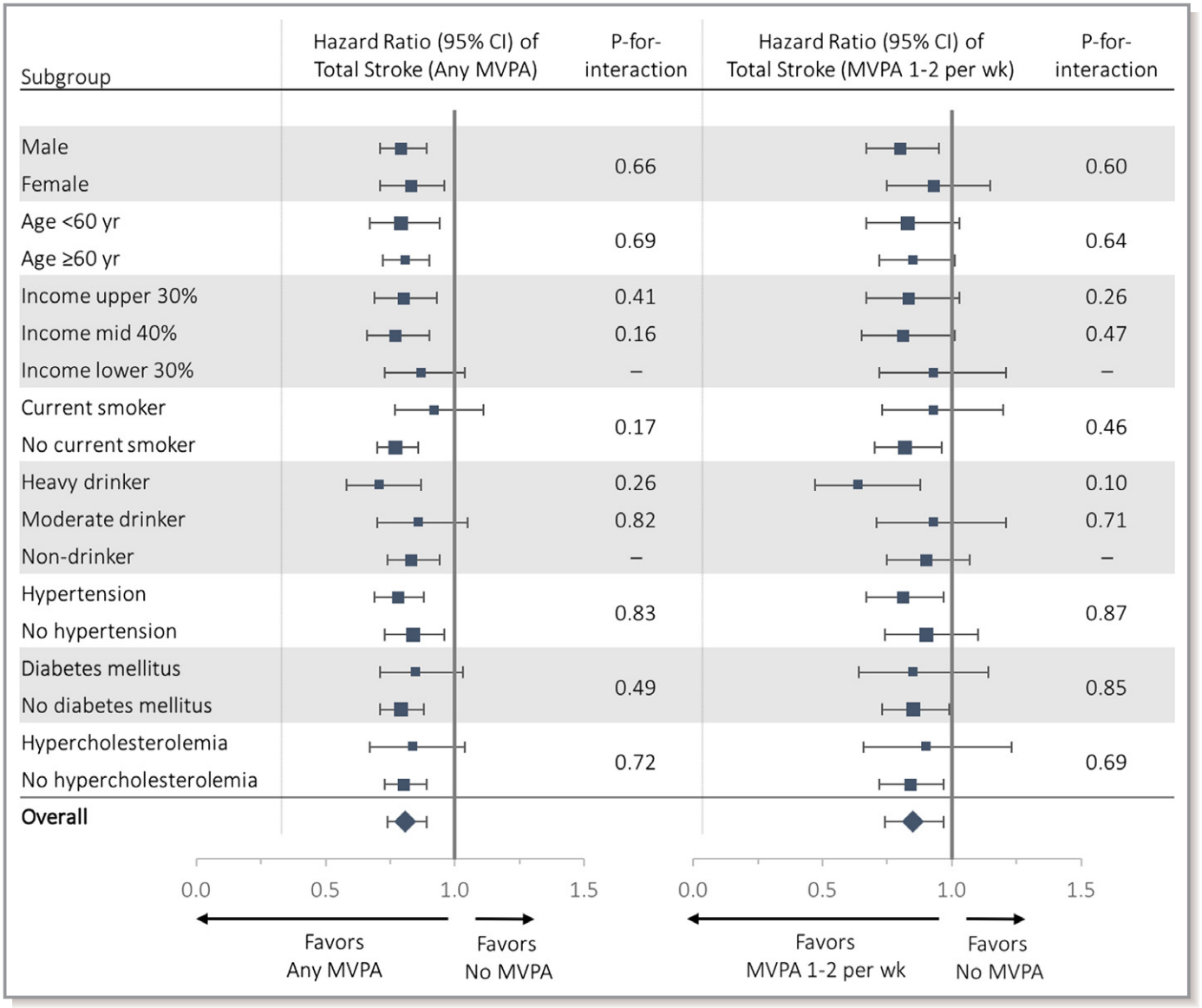

Figure 2. Forest plot of the effect of interaction between confounders and moderate-to-vigorous physical activity on risk of stroke. The reference group for all analyses is the group of not having moderate-to-vigorous physical activity. Please refer to full detail of the analysis in Table S3. CI indicates confidence interval; MVPA, moderate-to-physical activity.

after adjusting traditional risk factors, and MVPA is effective in most subgroups except for the current smoker and low-income-status groups. This finding supports the results of previous studies that it is suitable to recommend moderate- to vigorous-intensity PA rather than light-intensity PA in the guideline for preventing a stroke.[18] There were disparities of effects according to sex with some studies, suggesting that PA is only effective in men and others only in women.[1] However, our study from representative population-based cohort data showed no significant effect modification by sex, which is consistent with the recent meta-analysis.[19] Another interesting point was that participants with older age or more vascular risk factors performed the highest frequency of MVPA, which is different from the previous results of Western countries.[20,21] Although MVPA had a similar degree of effect on the risk of an ischemic stroke and an intracerebral hemorrhage (20% versus 15% lower risk, respectively), the association was significant in an ischemic stroke, but not in an intracerebral hemorrhage. Hypertension and heavy drinking was significantly associated with an increased risk of an intracerebral hemorrhage with population attributable fractions of 33% and 12%, respectively. Whether the benefit of MVPA extends to intracerebral hemorrhage is less certain, possibly attributed to true biological difference compared to ischemic stroke or attributed to insufficient power to detect a significant difference. A study from China showed a similar magnitude of effect in intracerebral hemorrhages, but no statistical significance. Thus, for the association of PA and

Table 2. Population Attributable Fraction and Adjusted HRs of Physical Inactivity and Other Stroke Predictors

	Total Stroke		Ischemic Stroke		Intracerebral Hemorrhage	
Stroke Predictor	Adjusted HR (95% CI)	PAF*	Adjusted HR (95% CI)	PAF	Adjusted HR (95% CI)	PAF
Moderate-to-vigorous PA: none (vs any moderate-to-vigorous PA)	1.24 (1.14–1.36)	12%	1.26 (1.14–1.39)	13%	1.18 (0.94–1.47)	9%
Current smoker (vs nonsmoker)	1.53 (1.36–1.73)	9%	1.61 (1.41–1.83)	9%	1.13 (0.83–1.55)	3%
Heavy drinker (vs nondrinker)	1.11 (0.98–1.26)	2%	1.02 (0.89–1.18)	0%	1.76 (1.32–2.36)	12%
Hypertension	1.63 (1.49–1.78)	22%	1.53 (1.39–1.69)	20%	2.29 (1.82–2.90)	33%
Diabetes mellitus	1.52 (1.38–1.68)	8%	1.68 (1.52–1.87)	11%	0.85 (0.62–1.14)	−3%
Hypercholesterolemia	1.05 (0.94–1.17)	1%	1.04 (0.93–1.18)	1%	1.04 (0.78–1.37)	1%

Each model was adjusted for baseline age group, sex, income, body mass index, frequency of light-intensity PA, and all other stroke predictors in the table. CI indicates confidence interval; HR, hazard ratio; PA, physical activity; PAF, population attributable fraction.

*PAF was calculated as Pc (1−1/HRadj). Pc (ordered as listed in the table), the prevalence of the stroke predictor among stroke cases, was 62.1, 24.9, 18.8, 57.7, 24.2, and 17.8 for total stroke; 63.1, 25.1, 17.4, 57.4, 26.2, and 17.7 for ischemic stroke; and 57.3, 24.0, 27.4, 59.0, 14.4, and 17.5 for intracerebral hemorrhage.

risk of intracerebral hemorrhage, data are needed from a longer follow-up period or a pooled analysis of recent studies.

The minimal goals such as 1 to 2 times/week or 10 minutes daily of MVPA may be perceived easier to start and sustain exercise, because lack of time or low self-efficacy are important barriers to PA.[22] Furthermore, once an individual regularly completes the minimum exercise goals, they may be more likely to increase their amount of exercise to achieve more benefits. Recent data showed that a minimal amount of MVPA might be effective to reduce all-cause and cardiovascular mortality. Based on these results, the Japanese government is encouraging people to conduct "+10 min/day of moderate to vigorous PA" as a minimal starting dose of PA to encourage both sedentary and active individuals to become progressively more active.[23] We agree that "Let's start with +10 min/day of activity" is an appropriate and more-attainable public health message, although the effectiveness of which needs to be validated.

In conclusion, even 1 to 2 times a week of MVPA might be beneficial to prevent a first-ever stroke in the general population compared with physical inactivity. From a public health perspective, we need to encourage physically inactive people just to start any level of MVPA, considering that 50% of individuals in this cohort were not participating in MVPA. Future research is needed to validate how effectively such a policy would work to compel more people to start increasing their PA and thus prevent stroke.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Figure S1. Questionnaire used in general health examination in Korea (English version)

[Annex No. 1] <Front>

National Screening Program

☐ **Regular checkup** ☐ **Life cycle-based checkup**

※ Answers must be provided for all questions so the information will be reported correctly.

First Name		Residential ID No.		Telephone	Home	
Given Name					Mobile phone	
Current address					Zip code	-
					E-mail	

※ These are questions about your medical history.

※ Please answer the following questions about your present condition by ticking the appropriate box.

1. Have you ever been diagnosed by a doctor with any of the following diseases (Box a) or are you currently taking any medication (Box b)?

Disease	Brain stroke / paralysis	Heart disease (cardiac infarction / angina)	High blood pressure	Diabetes	Dyslipidemia	Tuberculosis	Others (including cancer)
a							
b							

2. Has anyone in your family died from or gotten any of the following diseases?

Disease	Brain stroke / paralysis	Heart disease (cardiac infarction / angina)	High blood pressure	Diabetes	Others (including cancer)
Yes					

3. Are you a Hepatitis B virus antigen carrier? ① Yes ② No ③ No idea

※ These are questions about smoking.

4. Please answer the following questions about your present condition by ticking the appropriate box.

4-1. Have you ever smoked over 5 packs of tobacco (100 cigarettes) in your life?

① No, I never smoked. (☞ Go to Question 5) ② Yes, I used to smoke but I stopped. (☞ Go to Question 4-2)

③ Yes, I'm still smoking (☞ Go to Question 4-3)

4-2. If you used to smoke but stopped, please answer the following.

For how many years had you smoked?	Total_____years
How many cigarettes in a typical day did you smoke before you stopped?	_____cigarettes

4-3. If you are still smoking, please answer the following.

How long have you been smoking?	Total_____years
How many cigarettes on average do you smoke on a regular day?	_____cigarettes

※ These are questions about drinking.

5. Please answer the following questions about your current drinking habit by ticking the appropriate box.

5-1. How many times a week do you drink alcohol?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

5-2. When you drink, how much do you usually drink on a regular day? (glass(es))

(※ No matter what kind of liquor it may be, each glass will be considered as 1 glass. However, 1 can of beer (355 cc) is equal to 1.6 glasses of beer.)

[Annex No. 1] <Back>

※ These are questions about exercising.

6. These are questions about your physical activity for the last week. Please answer the following questions by ticking the appropriate box.

6-1. During the last week, how many days did you exercise vigorously for over 20 minutes until you were almost out of breath? (example: running, aerobics, high-speed cycling, mountain hiking, etc.)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

6-2. During the last week, how many days did you exercise in a moderate level for more than 30 minutes until you had to breathe a little faster than usual? (example: fast walking, tennis, bicycle riding, cleaning, etc.) ※ Except the relevant answer from 6-1

☐ 0 ☐ 1 ☐ 2 ☐3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

6-3. During the last week, how many days did you walk for a total of 30 minutes or more in a day, including separate 10-minute walks? (example: light exercise, walk for work or for leisure, etc.)

※ Please exclude exercises you answered in 6-1 and 6-2

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

※ **These are questions about cognitive functions. (Only answer if you are 66, 70, or 74 years old.)** (If a family member accompanied you, please let him/her answer the questions. If not, answer the following questions by yourself.)

7. Please answer the following questions about your current cognitive condition compared to last year by ticking the appropriate box.

7-1. Compared to friends or other people, your memory is worse than others.

① No ② Occasionally ③ Yes

7-2. Your memory is worse compared to last year.

① No ② Occasionally ③ Yes

7-3. You experience problems related to your memory when handling important matters.

① No ② Occasionally ③ Yes

7-4. Has anyone noticed that you have a short memory?

① No ② Occasionally ③ Yes

7-5. Do you experience difficulties in performing daily chores that you used to do well before?

① No ② Occasionally ③ Yes

※ Emotional status (Only answer if you are 40 years old.)

8. Please identify how many times you experienced the following during the last week by ticking the appropriate box.

During the last week, I	Hardly ever (less than 1 day)	Not too often (couple of days)	Sometimes (more than 3 days)	Always (over 5 days)
8-1. Was annoyed and bothered by things that were not there before.				
8-2. Did not want to eat and even lost appetite.				
8-3. Felt sad even when someone tried to help me out.				
8-4. Felt depressed.				

※ Please complete this form with Annex No. 2 only 66 years old.

210 ㎜ × 297 ㎜ [백상지 80 g/㎡]

Figure S2. Histogram of the number of study participants within age strata

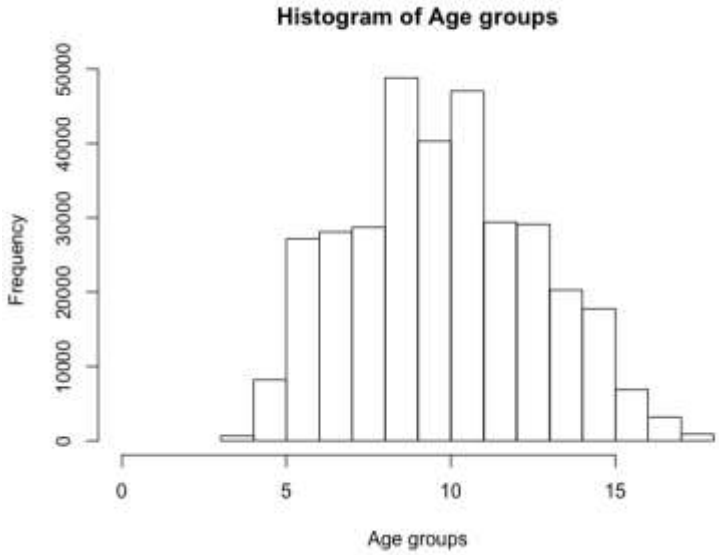

Table S1. Age strata and frequencies of the participants in the analyzed dataset.

Age groups	Range (yrs old)	Number	Percentage
0	0	0	0.00%
1	1 to 4	0	0.00%
2	5 to 9	0	0.00%
3	10 to 14	3	0.00%
4	15 to 19	622	0.18%
5	20 to 24	8160	2.43%
6	25 to 29	27140	8.07%
7	30 to 34	28084	8.35%
8	35 to 39	28716	8.54%
9	40 to 44	48830	14.52%
10	45 to 49	40292	11.98%
11	50 to 54	47043	13.99%
12	55 to 59	29397	8.74%
13	60 to 64	29129	8.66%
14	65 to 69	20276	6.03%
15	70 to 74	17758	5.28%
16	75 to 79	6841	2.03%
17	80 to 84	3143	0.93%
18	85 or more	892	0.27%
Total		336326	100.00%

Table S2. Full multivariable models for dose-response analysis

Total Stroke

Variables	Adjusted HR [95% CI]	P-value
MVPA frequency		
None	Referent	Referent
1-2 per wk	0.85 [0.74 – 0.97]	0.016
3-4 per wk	0.79 [0.68 – 0.92]	0.002
≥5 per wk	0.78 [0.69 – 0.89]	<0.001
Sex: Female	0.66 [0.60 – 0.73]	<0.001
Age group, per 5 years old increase	1.52 [1.49 – 1.55]	<0.001
Socioeconomic status		
Lower 30%	Referent	Referent
Mid 40%	1.01 [0.91 – 1.13]	0.810
Upper 30%	0.77 [0.69 – 0.86]	<0.001
Current smoking, per 1-pack year increase	1.011 [1.008 – 1.014]	<0.001
Drinking		
None	Referent	Referent
Moderate	1.01 [0.90 – 1.14]	0.875
Heavy	1.09 [0.96 – 1.24]	0.172
Body mass index, per 1kg/m^2 increase	1.009 [0.995 – 1.023]	0.193
Light PA frequency, per 1 per wk increase	0.999 [0.982 – 1.016]	0.899
Hypertension	1.31 [1.18 – 1.46]	<0.001
Systolic BP, per 1 mmHg increase	1.013 [1.010 – 1.016]	<0.001
Diabetes	1.42 [1.25 – 1.61]	<0.001
Fasting blood glucose, per 1mg/dL increase	1.002 [1.000 – 1.003]	0.016
Hyperlipidemia	0.93 [0.82 – 1.07]	0.315
Total cholesterol, per 1mg/dL increase	1.002 [1.001 – 1.003]	0.008

Ischemic Stroke

Variables	Adjusted HR [95% CI]	P-value
MVPA frequency		
None	Referent	Referent
1-2 per wk	0.82 [0.70 – 0.95]	0.007
3-4 per wk	0.81 [0.68 – 0.95]	0.009
≥5 per wk	0.78 [0.68 – 0.90]	<0.001
Sex: Female	0.63 [0.57 – 0.70]	<0.001
Age group, per 5 years old increase	1.57 [1.54 – 1.60]	<0.001
Socioeconomic status		

Lower 30%	Referent	Referent
Mid 40%	1.01 [0.89 – 1.13]	0.915
Upper 30%	0.79 [0.70 – 0.88]	<0.001
Current smoking, per 1-pack year increase	1.012 [1.008 – 1.015]	<0.001
Drinking		
None	Referent	Referent
Moderate	1.03 [0.90 – 1.17]	0.674
Heavy	1.00 [0.87 – 1.15]	0.987
Body mass index, per 1kg/m^2 increase	1.013 [0.998 – 1.028]	0.095
Light PA frequency, per 1 per wk increase	0.990 [0.972 – 1.008]	0.264
Hypertension	1.30 [1.16 – 1.46]	<0.001
Systolic BP, per 1 mmHg increase	1.010 [1.006 – 1.013]	<0.001
Diabetes	1.56 [1.36 – 1.78]	<0.001
Fasting blood glucose, per 1mg/dL increase	1.002 [1.000 – 1.004]	0.017
Hyperlipidemia	0.89 [0.77 – 1.03]	0.111
Total cholesterol, per 1mg/dL increase	1.003 [1.001 – 1.004]	<0.001

Intracerebral Hemorrhage

Variables	Adjusted HR [95% CI]	P-value
MVPA frequency		
None	Referent	Referent
1-2 per wk	1.02 [0.75 – 1.39]	0.882
3-4 per wk	0.75 [0.51 – 1.09]	0.131
≥5 per wk	0.81 [0.60 – 1.10]	0.170
Sex: Female	0.86 [0.66 – 1.11]	0.248
Age group, per 5 years old increase	1.32 [1.26 – 1.38]	<0.001
Socioeconomic status		
Lower 30%	Referent	Referent
Mid 40%	1.04 [0.80 – 1.36]	0.773
Upper 30%	0.69 [0.52 – 0.91]	0.008
Current smoking, per 1-pack year increase	1.005 [0.997 – 1.014]	0.222
Drinking		
None	Referent	Referent
Moderate	0.92 [0.67 – 1.27]	0.618
Heavy	1.63 [1.22 – 2.19]	0.001
Body mass index, per 1kg/m^2 increase	0.994 [0.960 – 1.028]	0.708
Light PA frequency, per 1 per wk increase	1.050 [1.007 – 1.095]	0.021
Hypertension	1.38 [1.05 – 1.82]	0.020
Systolic BP, per 1 mmHg increase	1.029 [1.022 – 1.036]	<0.001

Diabetes	0.76 [0.51 – 1.13]	0.172
Fasting blood glucose, per 1mg/dL increase	1.002 [0.997 – 1.006]	0.535
Hyperlipidemia	1.24 [0.89 – 1.73]	0.209
Total cholesterol, per 1mg/dL increase	0.997 [0.993 – 1.000]	0.041

Table S3. Analysis of the effect of interaction between confounders and moderate-to-vigorous physical activity on risks of stroke (total stroke, ischemic stroke and intracerebral hemorrhage)

Outcome: Total stroke			Any MVPA		Dose-response analysis					
					MVPA 1-2 per wk		MVPA 3-4 per wk		MVPA >=5 per wk	
Subgroups	N	Events	Adjusted HR (95% CI)	P-for-interaction	Adjusted HR (95% CI)	P-for-interaction	Adjusted HR	P-for-interaction	Adjusted HR (95% CI)	P-for-interaction
Male	171681	1291	0.79 (0.71-0.89)	0.66	0.80 (0.67-0.95)	0.60	0.82 (0.68-0.98)	0.25	0.78 (0.67-0.91)	0.69
Female	164645	922	0.83 (0.71-0.96)		0.93 (0.75-1.15)		0.74 (0.57-0.96)		0.81 (0.65-1.00)	
Age <60	258287	624	0.79 (0.67-0.94)	0.69	0.83 (0.67-1.03)	0.64	0.81 (0.63-1.04)	0.32	0.74 (0.58-0.94)	0.72
Age >=60	78039	1589	0.81 (0.72-0.90)		0.85 (0.72-1.01)		0.77 (0.63-0.92)		0.80 (0.69-0.92)	
SES high	131047	837	0.8 (0.69-0.93)	0.41	0.83 (0.67-1.03)	0.26	0.8 (0.63-1.01)	0.15	0.79 (0.65-0.96)	0.66
SES mid	132641	813	0.77 (0.66-0.90)	0.16	0.81 (0.65-1.01)	0.47	0.71 (0.55-0.92)	0.45	0.77 (0.62-0.94)	0.8
SES low	72638	563	0.87 (0.73-1.04)		0.93 (0.72-1.21)		0.9 (0.68-1.21)		0.8 (0.62-1.03)	
Current smoker	78776	552	0.92 (0.77-1.11)	0.17	0.93 (0.73-1.2)	0.46	1.00 (0.76-1.31)	0.08	0.87 (0.67-1.12)	0.68
No current smoker	257550	1661	0.77 (0.7-0.86)		0.82 (0.7-0.96)		0.73 (0.61-0.87)		0.77 (0.67-0.89)	
Heavy drinker	68767	416	0.71 (0.58-0.87)	0.26	0.64 (0.47-0.88)	0.1	0.82 (0.61-1.12)	0.58	0.69 (0.52-0.9)	0.31
Moderate drinker	85691	415	0.86 (0.70-1.05)	0.82	0.93 (0.71-1.21)	0.71	0.82 (0.60-1.11)	0.67	0.82 (0.62-1.07)	0.8
No drinker	181868	1382	0.83 (0.74-0.94)		0.90 (0.75-1.07)		0.76 (0.62-0.94)		0.82 (0.7-0.97)	
Hypertension	84113	1276	0.78 (0.69-0.88)	0.83	0.81 (0.67-0.97)	0.87	0.78 (0.64-0.95)	0.69	0.76 (0.65-0.9)	0.98
No hypertension	252213	937	0.84 (0.73-0.96)		0.90 (0.74-1.10)		0.81 (0.65-1.01)		0.8 (0.66-0.97)	
Diabetes	29915	535	0.85 (0.71-1.03)	0.49	0.85 (0.64-1.14)	0.85	0.76 (0.55-1.04)	0.79	0.91 (0.72-1.15)	0.23
No diabetes	306411	1678	0.79 (0.71-0.88)		0.85 (0.73-0.99)		0.80 (0.68-0.95)		0.74 (0.64-0.86)	
Hypercholesterolemia	46723	1820	0.84 (0.67-1.04)	0.72	0.90 (0.66-1.23)	0.69	0.70 (0.48-1.02)	0.46	0.87 (0.65-1.17)	0.42
No hypercholesterolemia	289603	393	0.80 (0.73-0.89)		0.84 (0.72-0.97)		0.81 (0.69-0.96)		0.77 (0.67-0.88)	
Overall	336326	2213	0.81 (0.74-0.89)		0.85 (0.74-0.97)		0.79 (0.68-0.92)		0.78 (0.69-0.89)	

Outcome: Ischemic stroke			Any MVPA		Dose-response analysis					
					MVPA 1-2 per wk		MVPA 3-4 per wk		MVPA >=5 per wk	
Subgroups	N	Events	Adjusted HR (95% CI)	P-for-interaction	Adjusted HR (95% CI)	P-for-interaction	Adjusted HR (95% CI)	P-for-interaction	Adjusted HR (95% CI)	P-for-interaction
Male	171681	1099	0.79 (0.70-0.90)	0.51	0.77 (0.63-0.93)	0.67	0.84 (0.69-1.02)	0.22	0.78 (0.66-0.92)	0.56
Female	164645	779	0.82 (0.69-0.96)		0.89 (0.70-1.13)		0.74 (0.55-0.98)		0.80 (0.63-1.02)	
Age <60	258287	480	0.78 (0.65-0.95)	0.57	0.77 (0.6-0.99)	0.55	0.82 (0.61-1.08)	0.24	0.77 (0.59-1.01)	0.69
Age >=60	78039	1398	0.80 (0.71-0.90)		0.84 (0.70-1.01)		0.78 (0.64-0.96)		0.78 (0.66-0.91)	
SES high	131047	725	0.78 (0.66-0.91)	0.24	0.76 (0.59-0.97)	0.3	0.80 (0.62-1.03)	0.44	0.78 (0.63-0.96)	0.53
SES mid	132641	676	0.76 (0.64-0.9)	0.11	0.81 (0.63-1.03)	0.31	0.72 (0.54-0.97)	0.18	0.73 (0.58-0.93)	0.34
SES low	72638	477	0.90 (0.74-1.10)		0.93 (0.69-1.24)		0.93 (0.68-1.27)		0.86 (0.66-1.12)	
Current smoker	78776	1407	0.94 (0.77-1.14)	0.17	0.89 (0.68-1.18)	0.46	1.03 (0.77-1.39)	0.08	0.92 (0.70-1.21)	0.68
No current smoker	257550	471	0.76 (0.67-0.85)		0.79 (0.66-0.94)		0.73 (0.60-0.89)		0.75 (0.65-0.88)	
Heavy drinker	68767	326	0.72 (0.57-0.90)	0.45	0.65 (0.45-0.93)	0.17	0.79 (0.55-1.13)	0.85	0.72 (0.53-0.98)	0.74
Moderate drinker	85691	357	0.87 (0.70-1.08)	0.78	0.83 (0.62-1.13)	0.8	0.89 (0.64-1.23)	0.56	0.9 (0.67-1.20)	0.77
No drinker	181868	1195	0.81 (0.71-0.92)		0.87 (0.72-1.06)		0.77 (0.62-0.97)		0.77 (0.65-0.92)	
Hypertension	84113	1078	0.77 (0.68-0.88)	0.9	0.79 (0.64-0.97)	0.88	0.77 (0.62-0.96)	0.98	0.76 (0.64-0.91)	0.89
No hypertension	252213	800	0.83 (0.71-0.97)		0.85 (0.69-1.06)		0.85 (0.67-1.08)		0.8 (0.65-0.99)	
Diabetes	29915	492	0.83 (0.68-1.01)	0.65	0.8 (0.59-1.09)	0.95	0.76 (0.54-1.06)	0.76	0.89 (0.69-1.14)	0.35
No diabetes	306411	1386	0.79 (0.70-0.89)		0.82 (0.69-0.97)		0.82 (0.68-0.99)		0.74 (0.63-0.87)	
Hypercholesterolemia	46723	332	0.84 (0.66-1.07)	0.54	0.83 (0.58-1.18)	0.96	0.79 (0.53-1.17)	0.94	0.88 (0.65-1.21)	0.29
No hypercholsterolemia	289603	1546	0.79 (0.71-0.89)		0.82 (0.69-0.96)		0.81 (0.68-0.97)		0.77 (0.66-0.89)	
Overall	336326	1878	0.80 (0.72-0.88)		0.82 (0.70-0.95)		0.81 (0.68-0.95)		0.78 (0.68-0.9)	

Outcome: Intracerebral hemorrhage			Any MVPA		Dose-response analysis					
					MVPA 1-2 per wk		MVPA 3-4 per wk		MVPA >=5 per wk	
Subgroups	N	Events	Adjusted HR (95% CI)	P-for-interaction	Adjusted HR	P-for-interaction	Adjusted HR	P-for-interaction	Adjusted HR (95% CI)	P-for-interaction
Male	171681	203	0.83 (0.62-1.12)	0.76	0.95 (0.64-1.41)	0.79	0.73 (0.45-1.18)	0.98	0.80 (0.54-1.18)	0.76
Female	164645	151	0.92 (0.64-1.30)		1.12 (0.69-1.83)		0.76 (0.40-1.42)		0.85 (0.52-1.38)	
Age <60	258287	148	0.85 (0.60-1.19)	0.72	1.05 (0.69-1.61)	0.57	0.81 (0.48-1.35)	0.99	0.65 (0.39-1.07)	0.73
Age >=60	78039	206	0.87 (0.64-1.17)		0.96 (0.60-1.53)		0.64 (0.36-1.14)		0.93 (0.63-1.37)	
SES high	131047	116	0.99 (0.67-1.46)	0.45	1.3 (0.78-2.17)	0.52	0.81 (0.43-1.53)	0.93	0.87 (0.52-1.46)	0.38
SES mid	132641	146	0.84 (0.59-1.21)	0.91	0.85 (0.51-1.42)	0.61	0.67 (0.35-1.26)	0.57	0.95 (0.60-1.51)	0.31
SES low	72638	92	0.75 (0.48-1.17)		0.98 (0.53-1.80)		0.80 (0.39-1.63)		0.56 (0.29-1.08)	
Current smoker	78776	85	0.87 (0.56-1.36)		1.14 (0.65-2.00)		0.86 (0.43-1.72)		0.64 (0.33-1.24)	
No current smoker	257550	269	0.87 (0.67-1.13)		0.98 (0.68-1.42)		0.71 (0.45-1.12)		0.87 (0.62-1.23)	
Heavy drinker	68767	97	0.70 (0.46-1.07)	0.18	0.64 (0.34-1.21)	0.24	0.94 (0.52-1.72)	0.47	0.59 (0.32-1.08)	0.07
Moderate drinker	85691	60	0.83 (0.48-1.41)	0.96	1.50 (0.81-2.76)	0.2	0.49 (0.19-1.29)	0.73	0.51 (0.23-1.11)	0.21
No drinker	181868	197	1.00 (0.74-1.36)		1.05 (0.67-1.65)		0.71 (0.4-1.27)		1.14 (0.77-1.69)	
Hypertension	84113	209	0.83 (0.62-1.12)	0.86	0.90 (0.59-1.38)	>0.99	0.81 (0.51-1.30)	0.29	0.79 (0.53-1.18)	0.77
No hypertension	252213	145	0.89 (0.62-1.26)		1.19 (0.75-1.88)		0.63 (0.33-1.20)		0.81 (0.51-1.30)	
Diabetes	29915	51	1.13 (0.63-2.05)	0.16	1.48 (0.65-3.34)	0.28	0.78 (0.27-2.28)	0.81	1.12 (0.55-2.31)	0.14
No diabetes	306411	303	0.82 (0.65-1.05)		0.97 (0.70-1.36)		0.74 (0.49-1.11)		0.76 (0.54-1.06)	
Hypercholesterolemia	46723	62	0.83 (0.48-1.45)	0.64	1.26 (0.64-2.47)	0.44	0.26 (0.06-1.11)	0.11	0.84 (0.40-1.79)	0.69
No hypercholesterolemia	289603	292	0.87 (0.68-1.12)		0.97 (0.69-1.38)		0.85 (0.58-1.27)		0.81 (0.58-1.12)	
Overall	336326	354	0.86 (0.69-1.08)		1.02 (0.75-1.39)		0.75 (0.51-1.09)		0.81 (0.60-1.10)	

Table S4. Simple bias analysis for unmeasured residual confounders

Prevalence of unmeasured confounder (%)		HR adjusted for unmeasured confounder [95% CI]		
No MVPA group	MVPA 1-2 per wk group	Unmeasured confounder HR 0.70	Unmeasured confounder HR 0.80	Unmeasured confounder HR 0.90
5	10	0.86 [0.75 – 0.98]	0.86 [0.75 – 0.98]	0.85 [0.75 – 0.97]
	15	0.88 [0.77 – 1.001]	0.87 [0.76 – 0.99]	0.86 [0.75 – 0.98]
	20	0.89 [0.78 – 1.02]	0.88 [0.77 – 1.001]	0.86 [0.75 – 0.99]
10	15	0.86 [0.75 – 0.99]	0.86 [0.85 – 0.98]	0.85 [0.75 – 0.98]
	20	0.88 [0.77 – 1.001]	0.87 [0.76 – 0.99]	0.86 [0.75 – 0.98]
	25	0.89 [0.78 – 1.02]	0.88 [0.77 – 1.001]	0.86 [0.75 – 0.99]
15	20	0.86 [0.75 – 0.99]	0.86 [0.75 – 0.98]	0.85 [0.75 – 0.98]
	25	0.88 [0.77 – 1.002]	0.87 [0.76 – 0.99]	0.86 [0.75 – 0.98]
	30	0.89 [0.78 – 1.02]	0.88 [0.77 – 1.001]	0.86 [0.75 – 0.99]
No MVPA group	MVPA 3-4 per wk group	Unmeasured confounder HR 0.70	Unmeasured confounder HR 0.80	Unmeasured confounder HR 0.90
5	10	0.81 [0.69 – 0.93]	0.80 [0.69 – 0.93]	0.80 [0.69 – 0.93]
	15	0.82 [0.70 – 0.95]	0.81 [0.70 – 0.94]	0.80 [0.69 – 0.93]
	20	0.83 [0.72 – 0.96]	0.82 [0.70 – 0.95]	0.81 [0.69 – 0.93]
10	15	0.81 [0.69 – 0.93]	0.80 [0.69 – 0.93]	0.80 [0.69 – 0.93]
	20	0.82 [0.70 – 0.95]	0.81 [0.70 – 0.94]	0.80 [0.69 – 0.93]
	25	0.83 [0.72 – 0.97]	0.82 [0.70 – 0.95]	0.81 [0.69 – 0.93]
15	20	0.81 [0.69 – 0.94]	0.80 [0.69 – 0.93]	0.80 [0.69 – 0.93]
	25	0.82 [0.71 – 0.95]	0.81 [0.70 – 0.94]	0.80 [0.69 – 0.93]
	30	0.83 [0.72 – 0.97]	0.82 [0.70 – 0.95]	0.81 [0.69 – 0.93]
No MVPA group	MVPA ≥5 per wk group	Unmeasured confounder HR 0.70	Unmeasured confounder HR 0.80	Unmeasured confounder HR 0.90
5	10	0.80 [0.72 – 0.90]	0.79 [0.70 – 0.90]	0.79 [0.70 – 0.89]
	15	0.81 [0.72 – 0.92]	0.80 [0.71 – 0.91]	0.79 [0.70 – 0.90]
	20	0.82 [0.73 – 0.93]	0.81 [0.72 – 0.92]	0.80 [0.70 – 0.90]
10	15	0.80 [0.70 – 0.90]	0.79 [0.70 – 0.90]	0.79 [0.70 – 0.89]
	20	0.81 [0.72 – 0.92]	0.80 [0.71 – 0.91]	0.79 [0.70 – 0.90]
	25	0.82 [0.73 – 0.93]	0.81 [0.72 – 0.92]	0.80 [0.70 – 0.90]
15	20	0.80 [0.70 – 0.90]	0.79 [0.70 – 0.90]	0.79 [0.70 – 0.89]
	25	0.81 [0.72 – 0.92]	0.80 [0.71 – 0.91]	0.79 [0.70 – 0.90]
	30	0.82 [0.73 – 0.93]	0.81 [0.72 – 0.92]	0.80 [0.70 – 0.90]

Table S5. Comparison of effects of different ICD-10 codes for defining acute stroke

	Adjusted HR (95% CI)			
Variable	I61 or I63 (n = 2,213)	I60 – I63 (n = 2,499)	I60 – I66 (n = 2,749)	I60 – I68 (n = 3,402)
MVPA frequency				
None	[referent]	[referent]	[referent]	[referent]
1 – 2 per wk	0.85 (0.74 – 0.97)	0.85 (0.75 – 0.96)	0.88 (0.78 – 0.99)	0.91 (0.82 – 1.01)
3 – 4 per wk	0.79 (0.68 – 0.92)	0.79 (0.69 – 0.91)	0.81 (0.71 – 0.93)	0.81 (0.72 – 0.91)
>=5 per wk	0.78 (0.69 – 0.89)	0.82 (0.73 – 0.92)	0.80 (0.72 – 0.90)	0.86 (0.78 – 0.95)

All models were adjusted for sex, age group, socioeconomic status (lower, middle, upper), current smoking (pack-years), drinking (none, moderate, heavy), body mass index, frequency of light intensity PA, hypertension, diabetes, hypercholesterolemia, systolic blood pressure, fasting serum glucose, and total cholesterol level.