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Association between physical activity and stroke in a middle-aged and elderly Chinese population

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Abstract

Background: Accumulating evidence has reported that physical activity (PA) is effective in reducing stroke and mortality. However, whether PA levels are associated with stroke in middle-aged and elderly people in Jiangxi Province of China remains unclear. In the present study, we evaluated the association between PA and the risk of stroke in Jiangxi Province of China.

Methods: A cross-sectional survey was conducted in Jiangxi Province of China from November 2013 to August 2014, using standardized questionnaire forms and physical measurements. Self-reported PA was assessed using the international PA questionnaire. A history of stroke was self-reported by answering the questionnaire. Multivariate logistic regression analysis was performed to evaluate the association between PA levels and the risk of stroke after adjustment for sociodemographic characteristics, lifestyle factors, and disease-related risk factors.

Results: A total of 10,398 participants (4240 men and 6158 women, aged 45 to 97 years) completed the International Physical Activity Questionnaire (IPAQ). Compared with low-intensity PA, vigorous PA was associated with graded reduction in the risk of stroke (odds ratio [OR] of 0.763, 95% confidence interval [CI] 0.717–0.812, $P < .001$ for trend). However, there were no significant differences between individuals in the low-intensity PA and moderate-intensity PA group ($P > 0.05$).

Conclusions: Compared with low PA, vigorous PA, but not moderate PA, was associated with a lower risk of stroke in middle aged and elderly people in southern China, specifically among men. These findings suggested that increasing PA is beneficial.

Abbreviations: BMI = body mass index, BP = blood pressure, DBP = diastolic blood pressure, HR = heart rate, PA = physical activity, PP = pulse pressure, SBP = systolic blood pressure, WC = waist circumference.

Keywords: China, cross-sectional survey, physical activity, stroke

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1. Introduction

Since the availability of new devices has continued to increase, physical inactivity is rising in many regions, both at work and at home. This phenomenon has caused new problems for human health—a decrease in the frequency of infectious diseases and an increase in non-communicable diseases.[1,2] In 2009, physical inactivity was reported to be the fourth leading risk factor for non-communicable diseases.[3] Among these diseases, stroke has developed to be a leading health problem worldwide for it is the second most common cause of mortality and the most common cause of long-term disability.[4–10] Despite recent reductions in stroke mortality in developed countries, the global stroke burden is increasing for a majority of the cases are from developing countries where stroke is one of the most common causes of death.[5,6,8,11–13]

Physical activity (PA) is defined by the World Health Organization (WHO) as any bodily movement produced by skeletal muscles that results in energy expenditure, including activities performed while working, playing, carrying out household chores, traveling, and engaging in recreational pursuits.[14] Increasing PA is associated with a decreased mortality rate and improved quality of life. The results from observational and cohort studies all have demonstrated an inverse association between PA and the risk of stroke and all-cause mortality.[12,15] A prospective urban rural epidemiology (PURE) study, including >130,000 participants from 17 countries, confirmed that higher PA was associated with a lower risk of stroke and mortality.[12] Mcdonnell M and colleagues

observed that participation in regular moderate-to-vigorous PA (MVPA) reduced the risk of cardiovascular disease and stroke.[16]

To date, the information regarding the inverse associations of PA with people's health in China is increasing.[12,17,18] However, there were obvious differences between PA distributions and risks of diseases in different regions of China. The China Kadoorie Biobank Study whose participants were recruited from 10 diverse areas in China found that the percentage of stroke was 11.7% and each 4 MET-h/d higher PA (approximately 1 hour of brisk walking per day) associated with a 6% lower risk of stroke.[18,19] A large prospective cohort containing 359,067 Taiwanese adults reported a low proportion of moderate-high PA and prevalence rate of cardiovascular disease or stroke upped to 3.0%.[20] The Dongfeng-Tongji (DFTJ) cohort of 24,606 middle-aged and older people from Shiyan city observed that there were 82.2% of subjects performing equal to or more than the WHO recommended minimum (7.5 MET-h/wk) and the percentage of circulatory system diseases was 0.36%.[21]

China is the most populous nation in the world and there are great differences in local economic development and health care in different regions of China. All these affected PA distributions and the prevalent tendency of disease. In addition, China is experiencing a rapid aging transition and an increasing in the risk of stroke.[12] Therefore, it is necessary to analyze the relationship between PA and stroke in various domains of daily living. In this study, we examined whether PA is associated with a lower risk of stroke in Jiangxi Province, China.

2. Methods

2.1. Study design and participants

This cross-sectional survey was supported by the National Key R&D Program in the Twelfth Five-year Plan (No. 2011BAI11B01) from the Chinese Ministry of Science. Using a stratified multistage random sampling method, Jiangxi Province was divided into urban areas and rural areas based on administrative data. The details of the overall study design are described below. Eight different areas were selected using the probability-proportional-to-size method, in which 2 districts or 2 townships were selected. Next, 3 communities or villages were chosen within each district and township, respectively, using the simple random sampling (SRS) method.[22] Finally, a given number of participants from each of the 14 strata were chosen using the SRS method according to the national demographic composition; participants who stay locally for >6 months in Jiangxi Province, aged ≥15 years old, living in the administrative divisions directly under control of the central government throughout China measurements were chosen from communities or villages using the lists compiled from the local government registers of households.[22] The design effect was also considered while estimating the sample size. Assuming a design effect of 2.5 and a prevalence of stroke of 1.48% among the residents, aged 15 years and older, it was estimated that 15,269 participants were required for the analysis to ensure that the average lengths of the 95% confidence intervals for prevalence in the entire population and in the subpopulations, defined by age and sex, were <0.4% and 1.8%, respectively.[22] As a result, 15,364 residents aged 15 years and older who were intending to stay locally for >6 months were approached for this survey from November 2013 to August 2014. After excluding participants with missing data, the final sample size included in the analysis based on the outcome of interest was middle-aged and elderly

people over 45 years. Only these populations were selected because the rate of stroke among people under 45 years of age was low. Therefore, 10,389 participants were included in the analysis.

2.2. Ethics statement

All participants who provided written informed consent were enrolled in the study. If the participants were unable to write, fingerprinting was used. This study was approved by the Medical Research Ethics Committee of the Second Affiliated Hospital of Nanchang University and the Fuwai Cardiovascular Hospital (Beijing, China).

2.3. Definitions

PA was assessed with the International Physical Activity Questionnaire (IPAQ) which was supported by the WHO and the Centers for Disease Control (CDC), suitable for assessing population levels of self-reported physical activity.[23–26] Participants in all groups were instructed to report the frequency and duration of walking or cycling and moderate-intensity and vigorous-intensity activity, including occupation or housework, transportation and leisure time, performed for at least 10 minutes per session. Both continuous and categoric indicators were obtained from the IPAQ. Weekly minutes of walking or cycling and moderate-intensity and vigorous-intensity activity were calculated separately by multiplying the number of d/wk by the duration on an average day. The reported minutes per week in each category were weighted by a metabolic equivalent of the task (MET; multiples of resting energy expenditure) resulting in a PA estimate independent of body weight, expressed in MET-min/wk and computed by multiplying METs by min/wk. The categoric analysis grouped each individual as performing low, moderate, or vigorous PA, according to the questionnaire scoring protocol previously described (standard scoring criteria http://www.ipaq. ki.se.). Participants were asked to report only episodes of activities of at least 10 minutes because it is the minimum time required to achieve health benefits. Values below 10 minutes were recorded as 0.

The detailed description of the categories is as follows:

(1) Low: Meets neither "moderate" nor "vigorous" criteria.
(2) Moderate: Meets any of the following 3 criteria: 3 days of vigorous activity of at least 20 min/d; 5 days of moderate-intensity activity or walking of >30 min/d for >10 minutes at a time; or 5 days of any combination of walking, moderate-intensity, or vigorous-intensity activities, achieving at least 600 MET-min/wk.
(3) Vigorous: Meets either of 2 criteria: vigorous-intensity activity for >3 d/wk and accumulating at least 1500 MET-min/wk, or (b) >5 days of any combination of walking, moderate-intensity, or vigorous-intensity activities, achieving at least 3000 MET min/wk.

History of stroke was included if the subjects self-answered "yes" to the question, "Have you ever been told by a doctor or other health professional that you had a stroke?" These patients were also asked for symptoms, initial dates, and diagnostic units to make a reasonable assessment of the original diagnosis. Stroke included subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral ischemic necrosis but did not include secondary stroke caused by transient cerebral ischemia, brain tumor, brain metastasis tumor, or trauma.

Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg, and if the individual was at least on one of antihypertensive drugs for 2 weeks.[27]

Body mass index (BMI) was calculated as the weight (kg)/height (m²). BMI ≥24 kg/m² was defined as an elevated BMI. Abnormal WC was defined as above 0.85 for women and girls and above 0.9 for men and boys.

Smoking habit was defined as never, current (daily smoking, >6 months), and former (cessation of smoking, >6 months). Alcohol drinking was defined as drinking alcohol at least one time per week during the previous year.[28–31]

Educational level was divided into 3 domains according to the number of years of education, including 0 to 6, 7 to 9, and ≥10 years.

The inclusion criteria referred to the reference norm of BP, BMI, and WC for the screening of hypertension, overweight, and abnormal WC in Chinese people from Chinese guidelines.[27,32,33]

2.4. Data collection procedures

Participants were required to complete a questionnaire developed by the coordinating center, Fuwai Hospital which was administered through face-to-face interviews by trained staff to obtain information on demographic characteristics and socioeconomic factors.[22] There are 11 questions included in the questionnaire in this study, including demographic data (such as age, sex, marital status, residence, education, and employment status), behavioral characteristics (such as smoking habits, drinking, and physical activity), and medical history (hypertension and stroke, which was collected and verified with medical or hospital records). The details of anthropometric data and clinical variables will be detailed below.

Physical measurements, including body height, weight, waist circumference (WC), heart rate (HR), and blood pressure (BP), were collected by standardized methods for anthropometrics. All investigators were medical professionals who were systematically trained, and standard protocols and instruments were used. Body weight without heavy clothing and shoes to the nearest 0.1 kg was measured indoors using an Omron body fat and weight measurement device (V-BODY HBF-371, Omron, Kyoto, Japan). Height was measured without shoes and hats using a standard right-angle device and a fixed measurement tape to the nearest 0.5 cm. In addition, participants whose hair fluffy should be compacted and the hair knot should be unraveled. When measuring waist circumference, participants were asked to take off their coat and waist circumference was obtained to the nearest 0.5 cm by putting the measuring tape at the midpoint between the lower margin of the last rib and the top of the hip bone (at the level of umbilicus directly on the skin) at the end of the expiration. All measurements were taken twice, and the average of the 2 values was used. Blood pressure and heart rate were measured with the OMRON HBP-1300 professional portable blood pressure monitor (OMRON) 3 times on the right arm positioned at heart level after the participant was sitting at rest for 5 minutes without talking, with 30 seconds between each measurement with an observer present, the average of the 3 readings was used for analysis.[22,34] Participants were asked to avoid vigorous exercise, smoking, drinking, and consumption of coffee and tea for at least 30 minutes before the measurements.

To ensure standardization and data quality, comprehensive operations manuals, reinforced by periodic training workshops and regular communication, were used at all sites. Data were entered locally at each site into a customized database programmed with range and consistency checks and transmitted electronically to the coordinating center, where further quality control measures were implemented.

2.5. Statistical analysis

All data were established using the EpiData version 3.02 software (Odense, Denmark). After alignment correction, both Empower (R) (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA) and Microsoft Excel 2007 were used for statistical analysis. Multiple imputation, based on 5 replications and a chained equation approach method in the R MI procedure was used to account for missing data. Continuous variables are presented as the mean ± standard deviation and are compared using the t test. Categorical variables are expressed as percentages and analyzed using the chi-square test or Fisher exact test, as appropriate. Because of significant differences in various baseline characteristics between stroke and non-stroke patients, a propensity score weighting method was applied. Inverse probability of treatment weight (IPTW) was then calculated as the inverse of the propensity score for stroke patients and as the inverse of (1 − propensity score) for the non-stroke patients. Therefore, IPTW multivariate logistic regression analysis was used to assess the association between PA and stroke.[35] Statistical significance was based on $P < .05$.

3. Results

As shown in Fig. 1, a total of 15,296 participants from 15,364 eligible participants were included in the statistical analysis and 10,389 participants were finally included in this study. Sixty-eight participants were excluded because of missing data including sex, age, and so on. The majority of non-responders were young people because of their busy work. Then 200 participants were excluded because of missing data for PA (n = 72) and stoke (n = 128). Based on the outcome of our interest that middle-aged and elderly people over 45 years had higher risk of stroke, the next 4698 individuals who were <45 years old were excluded.

3.1. Characteristics of the subjects

A total of 10,398 participants out of 15,364 eligible participants (4240 men and 6158 women, aged 45–97 years) were included in this analysis and the average age was 62.8 ± 11.1 years in Table 1. Of these participants, 5462 (52.5%) came from urban areas, and 4936 (47.5%) came from rural areas. The prevalence of stroke was 215.0 per 10,000 people (224 cases). Of the 10,398 participants, the percentage of PA levels from low-intensity, moderate-intensity, and vigorous-intensity were 15.5%, 26.7%, and 57.8%, respectively. Compared with the control group, those who had stroke were more likely to have men, a higher mean age, BMI, WC, and HR, history of hypertension, drinkers, and those retired or unemployed. In addition, there was significant difference in the distribution of PA being observed between disease group and the control group.

3.2. Distribution of PA

Table 2 presents the distribution of physical activity by sex and age. People were younger with PA changes from low to high (P < .001). Compared with men, women had lower rate of low-intensity PA and higher rate of moderate- and vigorous-intensity PA. The same trend was occurred in urban and rural.
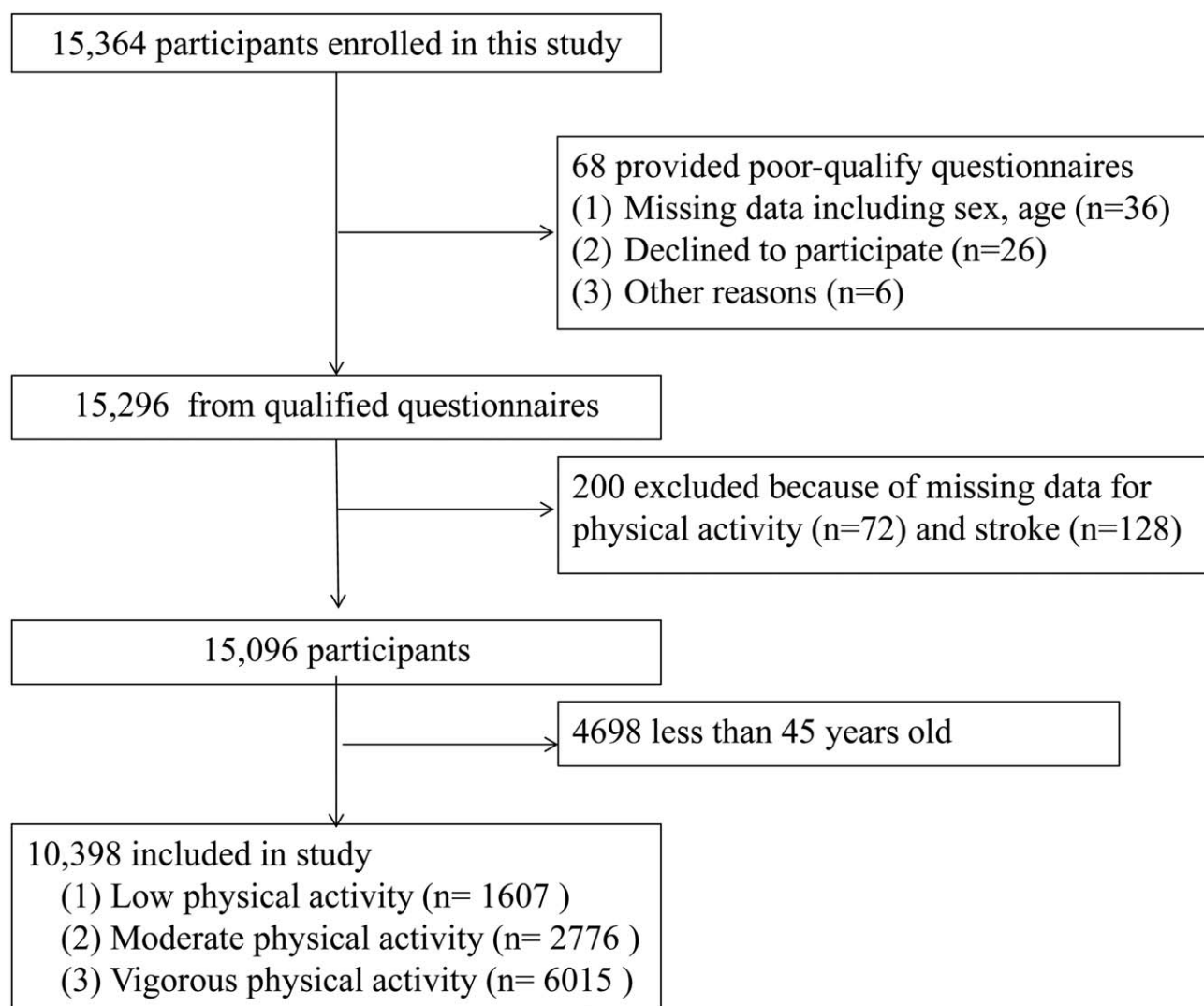
Figure 1. Participant selection for the study.

3.3. Association between PA and stroke

Table 3 shows the weighted association between PA and stroke. There were 224 individuals with incident of stroke. When stratified by PA, there was a downward trend in the risk of stroke from low to moderate-vigorous PA. Participants in the vigorous-intensity PA group were significantly associated with lower rates of stroke compared with the low group ($P<.001$). After adjustment for sex, age, area, smoking, drinking, employment, BMI, WC, HR, and hypertension, the trend still existed and participants with vigorous-intensity PA had an OR of 0.763 (95% confidence interval [CI] 0.717–0.812) for stroke ($P<.001$). However, there was no difference between individuals in the low-intensity PA and the moderate group ($P>.05$).

4. Discussion

Increased PA in daily life may contribute to various health benefits and decreased risk of diseases, such as stroke. In our study, we observed that participants with vigorous PA, but not moderate PA, had a lower risk of stroke in Jiangxi Province, China. The assessment of PA levels referenced the International Physical Activity Questionnaire (IPAQ) whose activities come

from different sources activities, including occupation or housework, transportation, and leisure time. It is different from previous research which analyzed the benefits of leisure related physical activity. Furthermore, the benefit of vigorous PA was independent of a range of socioeconomic and stroke risk factors.

Although it is accepted that PA reduces the risk for stroke events, agreement about the levels of different types of PA, including frequency, intensity, and duration, has not been established because study results for the effects of PA on stroke have been inconsistent. For example, the study conducted by the Reasons for Geographic and Racial Differences in Stroke (REGARDS) reported that participation in regular moderate-to-vigorous physical activity (MVPA) reduces the risk of cardiovascular disease and stroke, which was in agreement with the results reported by Lear et al.[12] A prospective study from the Japan Public Health Center, which contained 74,913 people, confirmed that moderate-intensity PA may prevent stroke, but vigorous-intensity activity may not be beneficial or even disadvantageous for the prevention of hemorrhagic stroke.[36] However, in our study, we observed a graded effect, such that participants with vigorous-intensity PA had a lower stroke risk than participants engaging in low PA after adjusting for

Table 1

Characteristics of participants[*].

Characteristics	Total (n = 10,398)	Stroke No (n = 10,174)	Stroke Yes (n = 224)	P value
Sex, n (%)				.001
Male	4240 (40.8%)	4125 (40.5%)	115 (51.3%)	
Female	6158 (59.2%)	6049 (59.5%)	109 (48.7%)	
Age, y	62.8 ± 11.1	62.7 ± 11.2	68.1 ± 9.2	<.001
Residence, n (%)				.652
Urban	5462 (52.5%)	5341 (52.5%)	121 (54.0%)	
Rural	4936 (47.5%)	4833 (47.5%)	103 (46.0%)	
Education, y, n (%)				.754
0–6	6488 (63.2%)	6347 (63.2%)	141 (63.2%)	
7–9	2335 (22.8%)	2281 (22.7%)	54 (24.2%)	
≥10	1439 (14.0%)	1411 (14.1%)	28 (12.6%)	
Marital status, n (%)				.855
Unmarried	116 (1.1%)	114 (1.1%)	2 (0.9%)	
Married	8606 (84.0%)	8422 (84.0%)	184 (82.9%)	
Divorced or widowed	1525 (14.9%)	1489 (14.9%)	36 (16.2%)	
Employment status, n (%)				<.001
Employed	2927 (28.6%)	2905 (29.0%)	22 (10.1%)	
Retired	1905 (18.6%)	1818 (18.2%)	87 (39.9%)	
Students	15 (0.1%)	15 (0.1%)	0 (0.0%)	
Unemployed	5374 (52.6%)	5265 (52.6%)	109 (50.0%)	
Drink status, n (%)				.02
No	7802 (75.2%)	7649 (75.4%)	153 (68.6%)	
Yes	2567 (24.8%)	2497 (24.6%)	70 (31.4%)	
Smoke status, n (%)				.916
Never	8348 (80.4%)	8167 (80.4%)	181 (81.2%)	
Current	1853 (17.8%)	1815 (17.9%)	38 (17.0%)	
Former	181 (1.7%)	177 (1.7%)	4 (1.8%)	
BMI, kg/m^2	23.1 ± 3.7	23.1 ± 3.7	23.9 ± 4.3	.012
WC, cm	80.2 ± 9.4	80.2 ± 9.4	82.5 ± 9.5	<.001
HR, bpm	77.5 ± 11.2	77.5 ± 11.2	79.5 ± 11.1	.004
SBP, mmHg	126.4 ± 19.3	126.4 ± 19.3	126.2 ± 18.2	.931
DBP, mmHg	74.2 ± 10.6	74.3 ± 10.6	73.4 ± 9.6	.51
PP, mmHg	52.38 ± 15.73	52.36 ± 15.73	53.16 ± 15.86	.488
Hypertension, n (%)		<0.001		
No	6321 (60.8%)	6274 (61.7%)	47 (21.0%)	
Yes	4077 (39.2%)	3900 (38.3%)	177 (79.0%)	
Physical activity, n (%)				.01
Low	1607 (15.5%)	1561 (15.3%)	46 (20.5%)	
Moderate	2776 (26.7%)	2706 (26.6%)	70 (31.2%)	
Vigorous	6015 (57.8%)	5907 (58.1%)	108 (48.2%)	

BMI = body mass index; DBP = diastolic blood pressure; HR = heart rate; PP = pulse pressure; SBP = systolic blood pressure; WC = waist circumference. P value was calculated by comparing data from control group and disease group.

[*] Data are expressed as n (%) or the mean (SD).

Table 2

Distribution of physical activity levels.

Variables[*]	Low (n = 1607)	Moderate (n = 2776)	Vigorous (n = 6015)	P value
Age, y	65.9 ± 12.4	64.2 ± 11.7	61.3 ± 10.3	<.001[a]
Sex, n (%)				<.001[b]
Male	871 (54.2%)	1126 (40.6%)	2243 (37.3%)	
Female	736 (45.8%)	1650 (59.4%)	3772 (62.7%)	
Residence, n (%)				<.001[b]
Urban	951 (59.18%)	1489 (53.64%)	3022 (50.24%)	
Rural	656 (40.82%)	1287 (46.36%)	2993 (49.76%)	

[*] n (%) or mean (SD).
[a] One-way ANOVA.
[b] Chi-square tests.

Table 3

Association between physical activity and lower risk of stroke.

Category	N	Events	Non-adjusted OR		Multivariable-adjusted OR*	
			OR (95%CI)	P value	OR (95%CI)	P value
Low	1607	46	1		1	
Moderate	2776	70	1.023 (0.966, 1.083)	.437	0.959 (0.896, 1.027)	.231
Vigorous	6015	108	0.792 (0.752, 0.834)	<.001	0.763 (0.717, 0.812)	<.001

CI = confidence interval; OR = odds ratio. Low physical activity was designated an OR of 1.

* Adjusted for sex, age, area, employment status, smoking, drinking, hypertension, HR, BMI, and WC. P value was calculated by weighted regression model.

confounding factors. Although there was a tendency toward a lower risk of stroke in participants with moderate PA compared with that in participants with low activity, the benefit was not significantly different. This inconsistent association of stroke with PA from previous studies may be due to racial differences and differences in population and sample sizes, measurement methods, classifications of physical activity, and diagnosis of stroke. In our study, physical activity was self-reported and its assessment was based on the IPAQ which included information not only leisure time but also occupation, housework, and transportation. All these may overestimate the levels of PA compared with other research.[37] Therefore, to some extent, it might explain why there was no statistical difference in low PA group and moderate PA group. Moreover, the population distribution among the 3 different strengths of PA was uneven, wherein 15.5% participants showed low-intensity PA, 26.7% showed moderate-intensity PA, and 57.8% showed vigorous-intensity PA. Differences in population distribution in different groups might have certain of limitation for analysis of results in our study. Future studies with respect to the relationship between PA and stroke need larger sample sizes and should consider the consistency in measurement and classification methods for PA, in greater detail, to increase the reliability and accuracy of the conclusions.

To our knowledge, there were different lifestyles in different regions, these may also makes a difference in the prevalence of stroke and the distribution of PA.[38,39] PA may increase physical fitness and retain strength and muscle mass, which may reduce disease risk and benefit people.[40,41] But, differences in race, sex, age, habits, and personal health status all affect the benefit of PA in decreasing risk of stroke. Moreover, population characteristics, such as sex ratio, age, personal health status, and the percentage of smoking and drinking, were different in almost all studies. These may explain the disparities of the effects of PA on the risk of stroke observed in our study and others. There was a negative relationship between vigorous PA and the risk of stroke in our analysis, but it is weak. It might because the prevalence of stroke in Jiangxi, China was lower compared with other regions.[42,43] This is, people in south of China may need relatively high levels of physical activity to achieve the goal of reduced risk of stroke. Altogether, increased PA has benefit in reduced risk of stroke but with differing effects.[44,45]

This study has several limitations. First, it is a cross-sectional study that cannot provide causal relationships. Prospective longitudinal data are needed for future research. Second, the study participants were from Jiangxi Province, China, and hence, the generalizability of the results to other populations remains to be verified. Furthermore, only individuals aged over 45 years were selected, and although stroke is common among the elderly, it is unclear whether our results are also applicable to younger populations. Third, PA was assessed from the self-reported IPAQ responses. Imprecise reporting of the variables, at least in part,

may have occurred, and an overall tendency to overestimate PA, compared with objective measurements, was inevitable, which may have masked the potential benefits occurring at lower physical activity levels than those reported here.[37] However, the reliability and validity of the IPAQ has been demonstrated by several studies from different countries.[37,46] In addition, objective measurement methods, such as accelerometers, are not cost-effective in such large sample sizes. The use of self-reported measures for assessing PA using the IPAQ is considered acceptable in large studies. Fourth, stroke was also assessed according to the self-reported questionnaire responses. The type and extent of stroke was not evaluated accurately; hence, our results are more prone to bias. Finally, although we considered demography, smoking and drinking habits, and several risk factors, such as BMI, WC, and hypertension, the influence of the potential confounding effects cannot be excluded entirely.

Despite these limitations, our study has several strengths. An important merit is the cross-sectional study design and inclusion of a large sample from the south of China, based on city-sex-age distribution, whereby the validity is better than that of studies based on hospital data; moreover, the data in our study were obtained from face-to-face interviews, which are more reliable than telephone interviews. Another strength of this study is the method used to assess PA levels. Since there are various methods to evaluate PA data, to date, there is no consensus on a criterion standard for defining levels of PA. Herein, we used a questionnaire (IPAQ version) that has been validated in several studies and for several populations and requires responses for the intensity, frequency, and duration of activity to investigate the association between PA and stroke, thus reducing the risk of misclassification or over- and under-estimation.

5. Conclusion

In conclusion, our findings demonstrated that vigorous PA, but not moderate PA, was associated with a lower risk of stroke in south of China, and this association was independent of demography and other risk factors. These findings suggest that people may get benefit from increased PA in daily life. Still, further longitudinal epidemiologic studies are needed to assess the effects between PA and stroke.

Author contributions

Huihui Bao and Xiaoshu Cheng conceived the study and revised the manuscript. Xiaoshu Cheng participated in its design and

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