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Association between physical activity and risk of stroke subtypes: The Atherosclerosis Risk in Communities (ARIC) Study

Christine S. Autenrieth[1,2], **Kelly R. Evenson**[2], **Hiroshi Yatsuya**[3,4], **Eyal Shahar**[5], **Christopher Baggett**[2], and **Wayne D. Rosamond**[2]

[1]Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, GERMANY

[2]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA

[3]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA

[4]Department of Public Health, School of Medicine, Fujita Health University, Aichi, JAPAN

[5]Division of Epidemiology and Biostatistics, Mel and Enid Zuckerman College of Public Health, University of Arizona, USA

Abstract

Background—The relationship between stroke subtypes and physical activity is unclear.

Methods—Using data from 13,069 men and women aged 45-64 years who participated in the Atherosclerosis Risk in Communities (ARIC) Study, physical activity was assessed by self-report using the Baecke questionnaire at baseline (1987-1989). The American Heart Association's (AHA) ideal cardiovascular health guidelines served as basis for the calculation of three physical activity categories: poor, intermediate, and ideal. Stroke and its subtypes were ascertained from physician review of medical records. Multivariable adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox regression models.

Results—During a median follow-up of 18.8 years, a total of 648 incident ischemic strokes occurred. Significant inverse associations were found between physical activity categories and total, total ischemic, and nonlacunar stroke in adjusted models (age, sex, race-center, education, cigarette-years). Compared with poor physical activity, the adjusted HR (95% CI) for ideal physical activity were 0.78 (0.62, 0.97) for total, 0.76 (0.59, 0.96) for total ischemic, 0.85 (0.51, 1.40) for lacunar, 0.77 (0.47, 1.27) for cardioembolic, and 0.71 (0.51, 0.99) for nonlacunar stroke. Additional adjustments for waist-to-hip ratio, systolic blood pressure, antihypertensive medication, diabetes, left ventricular hypertrophy and laboratory parameters attenuated the HR. Further sex- and race-specific analysis revealed that the association was predominantly observed among males and among African-Americans.

Conclusion—These data suggest a tendency toward a reduced risk of total, total ischemic, and nonlacunar stroke with higher levels of physical activity.

Address for correspondence: Wayne D. Rosamond PhD, Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, 137 E. Franklin Street, Suite 306, Campus Box 7435, Chapel Hill, 27514, USA wayne_rosamond@unc.edu Phone: 919-962-3230 .

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INTRODUCTION

Although cardiovascular disease mortality rates have declined over the past several decades in the United States, the burden of stroke still remains high. Each year approximately 795,000 new or recurrent stroke events occur in the United States [1]. A number of modifiable risk factors have been linked to an increased risk of stroke, including high blood pressure, cigarette smoking, and physical inactivity [1,2]. To date, empirical data on whether physical activity helps in reducing stroke risk have yielded mixed results. Even though several meta-analyses [3-5] and other studies [6-9] generally have found evidence of some protective effect of physical activity in the prevention of stroke, other studies did not [10,11].

Studies examining the association of physical activity with stroke subtypes may refine our understanding of its potential in modifying stroke risk. Little information is available, however, on the association between ischemic stroke subtypes (lacunar, cardioembolic, nonlacunar thrombotic) and physical activity, as previous work on subtypes has mainly concentrated on hemorrhagic stroke subtypes (intracerebral, subarachnoid) and their relationship with physical activity [6,7]. In previous work from the Atherosclerosis Risk in Communities (ARIC) Study, some risk factors varied by ischemic stroke subtype [12], and physical activity was weakly associated with total ischemic stroke risk [10]. The role of physical activity on risk of stroke subtypes was not evaluated in that study, due to insufficient number of cases at that time.

In the present study, we sought to clarify in detail the relationship between physical activity with stroke subtypes in a large prospective cohort of men and women aged 45-64 years at baseline participating in the ARIC Study.

METHODS

Study population

The ARIC Study is a prospective population-based cohort study comprising 15,792 adults aged 45-64 years at recruitment in 1987-1989 [13]. Cohort participants were selected from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland. Participants completed the first exam in 1987-89. Baseline data served as a basis for the present study, and participants were followed-up through 2007 via annual telephone interviews. The study was approved by the institutional review board of the University of North Carolina as well as the other study centers and all participants provided informed consent.

Physical activity measurements

Physical activity was assessed at the baseline exam through an interviewer administered Baecke questionnaire [14]. Minor modifications to the original version of the Baecke questionnaire were made as detailed elsewhere [15] and are only briefly described here. On the baseline survey, participants were asked to report the amount of physical activity performed during leisure and sport. The participants' indications allowed the calculation of sport and leisure Baecke score ranging from 1 (low) to 5 (high). Leisure activities were assessed through four questions on walking, biking, television viewing and time spent commuting (walking/biking) to and from work or shopping. The sport score was based on three questions regarding the frequency of overall sport and exercise participation, and frequency of sweating. In addition, a fourth element on frequency, intensity and duration of up to four sport activities also contributed to the score. Furthermore, based on the guidelines of the compendium of physical activities [16], minutes per week (min/wk) of moderate or vigorous exercise were calculated from the Baecke sport questions, incorporating the number of months an individual engaged in the activity annually. The validity and reliability of the Baecke questionnaire has been reported elsewhere [17].

In order to determine the difference between participants who reached the necessary minimum of physical activity and those who did not, minutes per week of exercise were classified according to the American Heart Association's (AHA) ideal cardiovascular health guidelines for adults aged 20 years and above [18]. (1) Poor physical activity was defined as 0 min/wk of moderate or vigorous exercise. (2) Intermediate physical activity was defined as 1–149 min/wk of moderate intensity or 1–74 min/wk of vigorous intensity or 1–149 min/wk moderate + vigorous intensity. (3) Ideal physical activity was defined as ≥150 min/wk of moderate intensity or ≥75 min/wk of vigorous intensity or ≥150 min/wk of moderate + vigorous intensity.

Ascertainment of Stroke Events

Through annual phone interviews, follow-up examinations, surveillance of hospital discharges, and deaths in the ARIC communities, hospitalized stroke events and out-of-hospital fatal strokes among ARIC cohort participants were identified [13]. For the present analysis, hospitalized stroke events which occurred between baseline measurements (visit 1) and 31 December 2007 were included.

Evidence of stroke was ascertained via hospital reports if the discharge diagnosis contained a cerebrovascular disease code (International Classification of Diseases, 9th Revision code 430 to 438), if a cerebrovascular procedure was noted in the discharge summary, or if the computed tomography (CT) or magnetic resonance imaging (MRI) report showed evidence of cerebrovascular disease. Medical records for potential stroke events were then sent to a central ARIC office for abstraction by a single nurse. Each record was abstracted for number, type, and severity of neurological deficits and supporting angiographic, CT, MRI, spinal tap, or autopsy evidence. Each suspected stroke event was classified by National Survey of Stroke criteria using a computer algorithm as well as a physician reviewer [19]. When the algorithm and physician review disagreed, another physician-reviewer was consulted as an adjudicator. Quality assurance for ascertainment and classification of stroke are described in detail elsewhere [20]. In brief, a sub-classification of definite or probable hospitalized ischemic (cardioembolic or thrombotic), or hemorrhagic stroke was used based on the level of certainty assessed through neuroimaging studies and autopsy, when available.

If a CT or MRI revealed acute brain infarction or showed no evidence of hemorrhage, a stroke was categorized as ischemic. Using neuroimaging results, sub-categories of all definite ischemic strokes (lacunar, cardioembolic, nonlacunar thrombotic) were determined [12,20].

Covariates

Information on risk factors was obtained through standardized questionnaires, clinical examination, and laboratory measurements. Cigarette years of smoking was defined as the average number of cigarettes per day times the number of years smoked. Educational level was dichotomized into high (>high school) and low education (≤ high school). Body mass index (BMI) was calculated as measured weight in kilograms divided by height in meters squared. The ratio of waist and hip circumferences was also calculated as a measure of fat distribution. Three successive measurements of systolic and diastolic blood pressure were taken using a random-zero sphygmomanometer after a five-minute rest. For the present analysis, the average of the two last measurements was used. Antihypertensive medication use was defined as having taken hypertension lowering medication in the past two weeks. Prevalent diabetes was defined as nonfasting glucose level ≥200mg/dl, fasting glucose level ≥126 mg/dl, medication treatment for or history of diabetes. Left ventricular hypertrophy was determined by Cornell voltage criteria, after a 12-lead electrocardiography (ECG) tracing was obtained [21]. Blood levels of high-density (HDL) cholesterol, low-density (LDL) cholesterol, lipoprotein (a), fibrinogen, von Willebrand factor and white blood cell count were measured centrally by standard methods [22]. Prevalent coronary heart disease (CHD) and stroke, for exclusion, was defined as one of the following: self-report of physician-diagnosed myocardial infarction (MI) or stroke, prior MI by ECG, or having had coronary revascularization surgery.

Statistical analyses

Due to small numbers, we excluded participants who were not African-American or white (n=48) and African-Americans from Minneapolis (n=22) or Washington County (n=33). Participants with missing data physical activity, any of the covariates, as well as participants with a positive history of stroke or coronary heart disease were sequentially removed from the dataset (n=2,620). The final analysis cohort consisted of 13,069 ARIC participants.

General linear and logistic regression models were used to assess trends across physical activity quartiles of baseline risk factors for continuous and categorical variables, respectively. Multivariate Cox proportional hazards models were used to compute hazard ratios (HR) and 95 % confidence intervals (CI) for the association between incident stroke types with physical activity categories. Three Cox regression models with the following covariates were evaluated: (1) basic-adjusted model (adjusted for age, sex, and race-center), (2) partially-adjusted model (additional adjustment for educational level and cigarette-years), (3) fully-adjusted model (additionally adjusted for waist-to-hip ratio, systolic blood pressure, antihypertensive medication use, diabetes, left ventricular hypertrophy, HDL cholesterol, LDL cholesterol, lipoprotein (a), fibrinogen, von Willebrand factor, and white blood cell count. In addition, sex- and race-specific analyses were performed. P for trend was calculated by including the physical activity variable in the model as a continuous variable. SAS version 9.2 (SAS Institute, Inc., Cary, NC) was used to perform all analyses.

RESULTS

Over a median-follow-up of 18.8 years, 648 incident ischemic strokes occurred. Of those, 144 were lacunar, 150 were cardioembolic, and 354 were nonlacunar. Generally, participants in the higher sport quartiles had higher education, lower BMI, as well as less prone to chronic conditions such as diabetes or left ventricular hypertrophy compared to those in the lower quartiles of sport scores (Table 1). Laboratory measures consistently declined with increasing sport quartiles except for HDL and LDL cholesterol. Compared to participants not having suffered from a stroke event, mean sport scores were lower in any stroke type (data not shown). The lowest mean baseline score was found in participants who subsequently suffered a hemorrhagic stroke (2.32).

As shown in Table 2, the incidence rate per 1,000 person-years was lowest in the ideal physical activity category for total and total ischemic stroke.

Significant risk reductions in total and total ischemic stroke were observed with increasing physical activity level in both the basic-adjusted model and the partially-adjusted model (p

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for trend<0.05). In the partially-adjusted model, HR (95%CI) for the highest vs. the lowest physical activity category for total and total ischemic stroke were 0.78 (0.62, 0.97) and 0.76 (0.59, 0.96), respectively. Sex-specific analyses revealed that this association was much stronger in men, and that no significant relation between physical activity and neither total nor total ischemic stroke could be observed for women. In the fully-adjusted model, additional adjustments were performed for variables that were likely biological intermediates, such as systolic blood pressure or lipids. We observed an attenuation towards the null for the total analytical sample; however, among men, the association between physical activity and total stroke remained significant, even in the fully-adjusted model.

A slightly different pattern is shown in Table 3 for the ischemic stroke subtypes. In the basic-adjusted model, and the partially-adjusted model, only nonlacunar stroke was significantly associated with physical activity in the total sample and among men. Compared to the reference group poor activity in the partially-adjusted model, a HR of 0.71 (0.51, 0.99) was observed for ideal activity in the total sample. However, in the fully-adjusted model, no inverse relationship between physical activity with any of the ischemic stroke subtypes could be observed.

In an additional sub-analysis, we performed race-specific analysis. The beneficial effects of higher physical activity levels in model 2 are predominantly observed among African-Americans for total, total ischemic, and nonlacunar stroke, whereas no significant relations were observed for Caucasians (Table S1 and S2).

Examining the effect of quartiles of sport and leisure scores on stroke and its subtypes in the total sample revealed a weaker association, but a trend in risk reductions across sport quartiles for total, total ischemic stroke, and nonlacunar stroke were generally still observed (Table S3 and S4).

DISCUSSION

In this prospective cohort study, we found that physical activity was inversely associated with ischemic stroke and some subtypes among middle-aged men and women. The observed inverse associations between physical activity and total, total ischemic, and nonlacunar stroke in both the basic-adjusted and the partially-adjusted model were no longer statistically significant in the fully-adjusted models, that accounted for potential intermediates. The observed associations were stronger in men and in African-Americans. In addition, we found that the overall effect of physical activity is consistent across stroke subtypes.

Evidence in the literature as to the role of physical activity in stroke risk is mixed. Three meta-analyses have shown relatively clear inverse associations between physical activity and stroke risk [3-5], while others studies have not [10,11]. Our results are generally in accordance with previous work supporting a beneficial effect from physical activity by revealing a significant trend towards lower stroke risk with higher levels of physical activity. In particular, our results are very similar to recent data from the Northern Manhattan Study, in which moderate to heavy physical activity was found to be associated with ischemic stroke risk in men among 238 ischemic stroke cases during 9.1 years of follow-up [9]. In the Women's Health Study, a relationship of borderline significance was found between leisure physical activity and total as well as total ischemic stroke in women [23]. Likewise, in the Nurses' Health Study, quintiles of leisure physical activity were significantly associated with lower risks of total and ischemic stroke, but not hemorrhagic stroke, after multivariable adjustments and during 8 years of follow up [6]. However, we did not find an inverse association between physical activity and stroke among women.

With almost a decade of longer follow-up time and more stroke cases, we were able to evaluate the role of physical activity on risk of ischemic stroke subtypes to better specify the relationship to physical activity. Indeed, previous work has examined hemorrhagic stroke subtypes and reported significant associations between leisure activities and both subarachnoid and intracerebral stroke [7]. But, to our knowledge, no study has specifically examined the impact of physical activity on ischemic stroke subtypes. In other ARIC studies on ischemic stroke subtypes, it has been shown that the impact of traditional and novel risk factors of stroke as well as carotid artery wall thickness [24] may vary between lacunar, cardioembolic and nonlacunar thrombotic stroke [12]. Obesity measures such as BMI and waist-to-hip ratio were positively related with all three investigated ischemic stroke subtypes [25]. As to the results of our study, the impact of physical activity did not vary according to ischemic stroke subtypes. Our data suggest that the somewhat inconsistent findings on the association between physical activity and stroke risk in the literature may not be due to differences in varying proportion of stroke subtypes across studies.

A possible explanation for a similar association across ischemic stroke subtypes is that factors such as vascular risk factors play the key role in explaining the reduced risk of all investigated stroke types, as physical activity is commonly known to lower risk of atherosclerosis and thrombosis [26]. It is therefore challenging to isolate the single effect of physical activity and the possibility that physical activity acts through those risk factors is plausible. Indeed, the results of our baseline characteristics depict that physical activity was significantly associated with many risk factors for stroke. These results along with the continuous attenuation of the inverse association of physical activity and stroke subtypes between the basic-adjusted, partially-adjusted as well as fully- adjusted model support this assumption.

The strengths of our study include a long follow-up time and the separate analysis of ischemic stroke subtypes. Only very few studies have looked at ischemic stroke subtypes as outcome [12,24,25], but have not reported on physical activity as an exposure variable so far. In addition, ARIC is a well-characterized cohort with good comprehensive through annual phone contact and surveillance of community hospitals. However, several limitations need to be considered. First, physical activity measures were based on self-report, which may have led to reporting bias and misclassification. Second, although stroke subtypes were carefully evaluated through neuroimaging studies and clinical features [20], misclassification in some cases may have occurred and an over- or underestimation of the association between physical activity and stroke subtypes cannot be fully ruled out. Third, the number of cases for each ischemic stroke subtype was relatively small. Fourth, although physical activity information was collected before the occurrence of stroke events, there may be individuals who had modified their exercise habit because of their health status, which might have distorted the true association.

In conclusion, our work supports the body of evidence concerning a tendency towards a decreased risk of stroke associated with higher physical activity levels. The present study also provides novel information on the role of physical activity and risk of ischemic stroke subtypes. With nonlacunar stroke being the major ischemic stroke subtype, increasing the number of people meeting AHA goal for ideal and intermediate physical activity criteria may help reduce the stroke burden in the American population through improvement in the known mediators. However, further large cohort studies are needed to verify these results before they can be incorporated into specific practical advice for the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Means (SD) and percentages of baseline risk factors by quartiles* of the Baecke sport score.

	Q1 (n=3,692)	Q2 (n=3,076)	Q3 (n=3,677)	Q4 (n=2,624)	p-value
Age (years)	53.7 (5.7)	54.1 (5.7)	54.2 (5.8)	54.0 (5.8)	0.003
Men (%)	35.5	39.0	44.9	55.8	<0.001
Blacks (%)	36.6	30.6	18.9	13.0	<0.001
High education (%)	36.7	38.8	48.8	57.6	<0.001
Cigarette-years	306.6 (437.0)	315.2 (439.7)	284.3 (399.8)	298.6 (388.8)	0.018
Body mass index (kg/m^2)	28.4 (6.0)	28.0 (5.6)	27.3 (4.9)	26.5 (4.2)	<0.001
Waist to hip-ratio	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	<0.001
Systolic blood pressure (mmHg)	122.9 (19.8)	121.7 (18.5)	120.1 (17.8)	118.3 (17.2)	<0.001
Antihypertensive mediation use (%)	32.8	30.1	25.7	20.0	<0.001
Diabetes (%)	13.0	11.1	9.4	6.9	<0.001
Left ventricular hypertrophy (%)	2.7	2.2	1.5	1.3	<0.001
HDL cholesterol (mg/dl)	52.6 (17.1)	52.3 (16.5)	51.9 (16.8)	53.0 (17.3)	0.073
LDL cholesterol (mg/dl)	137.1 (40.0)	137.8 (41.1)	137.8 (38.0)	135.4 (37.2)	0.061
Lipoprotein A (μg/mL)†	62.5 (3.2)	56.7 (3.2)	54.6 (3.2)	49.4 (3.2)	<0.001
Fibrinogen (mg/dl)	311.8 (69.6)	305.9 (65.4)	298.6 (60.0)	288.8 (59.0)	<0.001
von Willebrand Factor	121.6 (51.2)	116.6 (46.6)	115.1 (46.2)	113.1 (44.6)	<0.001
White blood cell count (cells/mm^3)	6 ,162.6 (2,000.0)	6,115.4 (1,893.8)	6,056.2 (1,984.2)	5,963.7 (1,759.5)	<0.001

*Cut-points for the approximated quartiles were 1.75/2.25/3.0 of the Baecke sport score.

†Geometric mean (antilog of SD).

Table 2

Multivariable adjusted hazard ratios and 95% confidence intervals for physical activity and stroke.

	Poor Physical Activity	Intermediate Physical Activity	Ideal Physical Activity	P for trend
Total sample				
Total stroke				
No. of cases	496	147	97	
Person-years	12,7263.5	57,604.0	40,703.3	
Incidence rate *	3.90 (3.57,4.26)	2.55 (2.17,3.00)	2.38 (1.95,2.91)	
Model 1 †	1	0.78 (0.65,0.95)	0.72 (0.57,0.90)	<0.001
Model 2 ‡	1	0.83 (0.68,1.00)	0.78 (0.62,0.97)	0.010
Model 3 §	1	0.89 (0.73,1.07)	0.85 (0.68,1.07)	0.104
Total ischemic stroke				
No. of cases	430	135	83	
Person-years	12,7563.6	57,653.9	40,773.3	
Incidence rate *	3.37 (3.07,3.71)	2.34 (1.98,2.77)	2.04 (1.64,2.52)	
Model 1 †	1	0.82 (0.67,1.00)	0.70 (0.55,0.89)	0.002
Model 2 ‡	1	0.87 (0.71,1.06)	0.76 (0.59,0.96)	0.016
Model 3 §	1	0.93 (0.76,1.14)	0.84 (0.65,1.07)	0.142
Men				
Total stroke				
No. of cases	213	77	58	
Person-years	45,980.5	26,126.6	22,739.3	
Incidence rate *	4.63 (4.05,5.30)	2.95 (2.36,3.68)	2.55 (1.97,3.30)	
Model 1 † #	1	0.73 (0.56,0.96)	0.64 (0.48,0.87)	0.001
Model 2 ‡ #	1	0.76 (0.58,0.99)	0.68 (0.50,0.91)	0.005
Model 3 § #	1	0.80 (0.61,1.05)	0.76 (0.56,1.02)	0.042
Total ischemic stroke				
No. of cases	190	72	53	
Person-years	46,084.1	26,141.5	22,785.7	
Incidence rate *	4.12 (3.58,4.75)	2.75 (2.19,3.47)	2.33 (1.78,3.04)	
Model 1 † #	1	0.76 (0.58,1.00)	0.66 (0.48,0.89)	0.004
Model 2 ‡ #	1	0.79 (0.60,1.05)	0.69 (0.51,0.95)	0.014
Model 3 § #	1	0.84 (0.63,1.11)	0.78 (0.57,1.07)	0.090
Women				
Total stroke				
No. of cases	283	70	39	
Person-years	81,283.0	31,477.4	17,964.0	
Incidence rate *	3.48 (3.10,3.91)	2.22 (1.76,2.81)	2.17 (1.59,2.97)	

	Poor Physical Activity	Intermediate Physical Activity	Ideal Physical Activity	P for trend
Model 1 †#	1	0.83 (0.64,1.09)	0.80 (0.57,1.13)	0.109
Model 2 ‡#	1	0.90 (0.69,1.19)	0.88 (0.63,1.24)	0.364
Model 3 §#	1	0.98 (0.75,1.29)	0.94 (0.67,1.33)	0.735
Total ischemic stroke				
No. of cases	240	63	30	
Person-years	81,479.5	31,512.3	17,987.6	
Incidence rate *	2.95 (2.60,3.34)	2.00 (1.56,2.56)	1.67 (1.17,2.39)	
Model 1 †#	1	0.89 (0.67,1.19)	0.74 (0.50,1.08)	0.102
Model 2 ‡#	1	0.97 (0.72,1.29)	0.81 (0.55,1.19)	0.323
Model 3 §#	1	1.05 (0.79,1.41)	0.87 (0.59,1.28)	0.654

*Incidence rate per 1,000 person-years.

†Adjusted for age, sex and race-center.

‡Adjusted for age, sex, race-center, cigarette-years and education.

§Adjusted for age, sex, race-field center, cigarette-years, educational level, waist-to-hip ratio, systolic blood pressure, antihypertensive medication use, diabetes, left ventricular hypertrophy, HDL cholesterol, LDL cholesterol, lipoprotein(a),fibrinogen, van Willebrand Factor and white blood cell count.

#Not adjusted for sex.

Table 3

Multivariable adjusted hazard ratios and 95% confidence intervals for physical activity and ischemic stroke subtypes

	Poor Physical Activity	Intermediate Physical Activity	Ideal Physical Activity	P for trend
Total sample				
Lacunar stroke				
No. of cases	101	24	19	
Model 1 *	1	0.71 (0.45,1.13)	0.74 (0.45,1.22)	0.132
Model 2 †	1	0.79 (0.50,1.25)	0.85 (0.51,1.40)	0.371
Model 3 ‡	1	0.85 (0.54,1.36)	0.95 (0.57,1.59)	0.695
Cardioembolic stroke				
No. of cases	100	30	20	
Model 1 *	1	0.78 (0.51,1.18)	0.72 (0.44,1.18)	0.130
Model 2 †	1	0.82 (0.54,1.25)	0.77 (0.47,1.27)	0.237
Model 3 ‡	1	0.87 (0.57,1.34)	0.83 (0.50,1.37)	0.402
Nonlacunar stroke				
No. of cases	229	81	44	
Model 1 *	1	0.87 (0.67,1.13)	0.66 (0.48,0.92)	0.014
Model 2 †	1	0.91 (0.70,1.19)	0.71 (0.51,0.99)	0.046
Model 3 ‡	1	0.99 (0.76,1.28)	0.78 (0.56,1.08)	0.187
Men				
Lacunar stroke				
No. of cases	44	13	12	
Model 1 *§	1	0.65 (0.35,1.23)	0.66 (0.35,1.28)	0.152
Model 2 †§	1	0.71 (0.37,1.34)	0.74 (0.38,1.43)	0.286
Model 3 ‡§	1	0.74 (0.39,1.40)	0.80 (0.41,1.55)	0.403
Cardioembolic stroke				
No. of cases	39	14	15	
Model 1 *§	1	0.68 (0.37,1.27)	0.87 (0.47,1.60)	0.504
Model 2 †§	1	0.70 (0.37,1.30)	0.89 (0.48,1.65)	0.570
Model 3 ‡§	1	0.71 (0.38,1.34)	0.96 (0.51,1.79)	0.729
Nonlacunar stroke				
No. of cases	107	45	26	
Model 1 *§	1	0.82 (0.57,1.16)	0.56 (0.36,0.87)	0.009
Model 2 †§	1	0.84 (0.59,1.21)	0.59 (0.38,0.92)	0.019
Model 3 ‡§	1	0.91 (0.63,1.31)	0.67 (0.43,1.04)	0.084
Women				
Lacunar stroke				
No. of cases	57	11	7	

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	Poor Physical Activity	Intermediate Physical Activity	Ideal Physical Activity	P for trend
Model 1 *§	1	0.78 (0.40,1.52)	0.83 (0.37,1.83)	0.486
Model 2 †§	1	0.90 (0.46,1.76)	0.96 (0.43,2.14)	0.838
Model 3 ‡§	1	0.97 (0.50,1.91)	1.14 (0.51,2.56)	0.814
Cardioembolic stroke				
No. of cases	61	16	5	
Model 1 *§	1	0.90 (0.51,1.59)	0.47 (0.19,1.18)	0.126
Model 2 †§	1	0.98 (0.55,1.73)	0.52 (0.21,1.31)	0.225
Model 3 ‡§	1	1.06 (0.59,1.88)	0.54 (0.21,1.37)	0.307
Nonlacunar stroke				
No. of cases	122	36	18	
Model 1 *§	1	0.93 (0.64,1.37)	0.82 (0.50,1.35)	0.428
Model 2 †§	1	0.99 (0.68,1.46)	0.88 (0.53,1.45)	0.665
Model 3 ‡§	1	1.08 (0.73,1.60)	0.94 (0.56,1.56)	0.959

*Adjusted for age, sex and race-center.

†Adjusted for age, sex, race-center, cigarette-years and education.

‡Adjusted for age, sex, race-center, cigarette-years, educational level, waist-to-hip ratio, systolic blood pressure, antihypertensive medication use, diabetes, left ventricular hypertrophy, HDL cholesterol, LDL cholesterol, lipoprotein(a), fibrinogen, van Willebrand Factor and white blood cell count.

§Not adjusted for sex.