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Physical Activity and Subclinical MRI Cerebral Infarcts: the ARIC Study

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Abstract

Background—We hypothesized that physical activity (PA), which is often associated with reduced risk of ischemic stroke, may also be associated with reduced risk of subclinical cerebral infarcts.

Objectives—We studied the cross-sectional association between PA and subclinical cerebral infarcts among African-Americans in the Atherosclerosis Risk in Communities (ARIC) Study.

Methods—PA self-reported at baseline and images from cerebral MRI examination obtained 6 years later were evaluated for presence and location of subclinical infarcts ≥3 mm in size. After exclusions, 944 participants were eligible for study.

Results—The results suggested an inverse relationship between odds of having a subclinical cerebral infarct and level of PA on several measures, although the multivariable adjusted odds ratios (OR) were statistically significant only for the sport score. A 1-unit increase in the sport score, indicating more leisure PA, was associated with an adjusted OR for having a subclinical cerebral infarct of 0.62 (0.44-0.87), with a statistically significant monotonic trend across quartiles of the score (P = 0.01). There was no association of work scores with subclinical infarcts.

Conclusions—In African-Americans, sport PA was inversely related to subclinical MRI-detected cerebral infarcts assessed six years later.

Keywords

physical activity; exercise; walking; cerebral infarct; stroke; African American

Introduction

Population-based studies have found that subclinical cerebral infarcts are commonly detected on magnetic resonance imaging (MRI) in middle-aged and elderly populations.(1) Although commonly seen in individuals without a clinical history of stroke, there is accumulating evidence that subclinical infarcts are associated with increased risk of clinical stroke and with

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negative outcomes such as cognitive decline and dementia.(2-4). However, most studies of subclinical infarcts have included few or no non-white minority participants, limiting understanding of prevalence, etiology, and impact in different populations (1).

Among the leading causes of death in the United States, the greatest disparity exists for stroke, with African Americans having twice the incidence compared with whites (5;6). This disparity may in part be explained by the greater prevalence of hypertension (7) and other risk factors including obesity and low levels of regular physical activity (PA) in African Americans (6). Regular PA has been found to reduce risk of hypertension and ischemic stroke (8-10). We hypothesized that regular PA may also be associated with reduced risk of subclinical cerebral infarcts. In the current study, we examined the cross-sectional association between various measures of PA and the presence of subclinical infarcts identified on MRI among African-Americans participating in the Atherosclerosis Risk in Communities (ARIC) Study.

Methods

Subjects and study design

The ARIC Study is a prospective study, designed to investigate the etiology and natural history of CVD in four U.S. communities. The study design and procedures have been reported previously.(11) Briefly, the ARIC baseline examination was conducted between 1986 and 1989 in a cohort of 15,792 men and women who comprised a probability sample of persons aged 45-64 years in four geographically dispersed communities: Forsyth County, NC; Jackson, MS; Washington County, MD, and suburbs of Minneapolis, MN. The baseline (ARIC visit 1) examination (1986-1989) included measures of PA. During the first two years of the visit 3 examination (1993-1994), participants aged 55 and older from ARIC field centers in Forsyth County, NC and Jackson, MS were invited to participate in a cerebral MRI exam. In the interests of safety, persons were excluded from the study for the following reasons: previous surgery for an aneurysm in the brain; metal fragments in the eyes, brain, or spinal cord; valvular implant, pacemaker, cochlear implant, spinal cord stimulator, or other internal electrical device; pregnancy; and occupations with exposure to metal fragments. Of 2,891 participants screened for MRI eligibility, 2% of women and 6% of men were ineligible. Of the participants meeting inclusion criteria, 21% of women and 25% of men declined the MRI procedure. A total of 887 persons were ineligible or declined, leaving 1,934 participants who underwent the cerebral MRI procedure, 960 of whom were African-American. For this study, persons were excluded who were missing data on PA (n=2) or on the presence of MRI infarcts (n=4), or used a cane (n=11) or a wheelchair, crutch, or walker (n=3), leaving N=944 for analysis (828 at the Jackson, MS center and 116 at the Forsyth County, NC center).

Measures of PA

For the first aim of our study, the primary measures of PA were the ARIC baseline (visit 1) Baecke PA scores. The modified Baecke instrument used in the ARIC Study (12;13) produces 3 ordinal index scores for PA during the past year (sport, leisure, and occupational indices, ranging from 1 (least active) to 5 (most active), and has well established reliability and validity (14). The sport score was computed from items including frequency, intensity, and duration of up to 4 specific activities, frequency of overall sport and exercise participation, sweating during leisure activities, and comparison of PA to others of one's age. Hypothetically, the Baecke sport index score could increase by one unit if a person moved from the lowest (1) to the highest (5) response category for any of the questions, holding all other responses to component questions constant. For example, if an individual reported never sweating during leisure and another individual reported sweating very often, the sport score would be one point higher for the latter individual given that all other responses to the sport component questions remained identical. Similarly, responses indicating frequent vigorous sports participation as compared to no vigorous sports participation could increase the sport score by one point, holding all other responses the same. The leisure score was computed from 4 items including frequency of leisure walking and biking, time spent biking and walking (ascertained separately) for transportation and shopping, and (reverse scored) frequency of television watching. The score for work PA included responses to 8 items including how often the participant sits, stands, walks, sweats, lifts heavy loads, and leaves work physically tired. Participants were also asked to compare their work activity to others their own age. The last component of the work score consisted of ranking (low, medium, high) of activity based on occupational job title. Other measures derived from the sport and leisure score questions included "regular physical activity" (participation in sports and exercise activities for at least 1 hour per week for ≥ 10 months in the past year); "vigorous activity" (participation in at least one sport of vigorous intensity);(8) and frequency of walking during leisure time (never/seldom versus often/very often).

MRI neuroimaging

The MRI screening protocol and image analysis in the ARIC Study were identical to those employed in the Cardiovascular Health Study and have been previously described.(15) Briefly, 1.5T magnetic resonance scanners (GE and Picker) were used. Axial images were angled to be parallel to the anterior commissure-posterior commissure line. The digital scan data, including SD/T2 weighted (3000, 30-100, TR, and TE) and T1 weighted images, were evaluated at the MRI Reading Center on a Vortech Personal Display System (PDS-4) workstation. The PDS-4 monitors measure 16 inches diagonally with 1024 × 1024 pixel elements and 256 gray scale intensities. The image evaluation was conducted by trained and certified MRI readers. Subclinical cerebral infarcts were defined as focal, non-mass lesions ≥3 mm in diameter having arterial vascular distribution and being hyperintense to gray matter on both spin-density and T2-weighted images. To be considered an infarct in cerebral white matter and the brain stem, lesions were required to be hypointense on T1-weighted images, similar to CSF; in basal ganglia or cortical gray matter, lesions were considered infarcts regardless of intensity on T1-weighted images. For anatomic localization, lesions were assigned to one or more of 23 anatomic regions defined by gross anatomic and vascular characteristics; the primary anatomic region occupied by the lesion was used for analysis.

Clinical measurements and definitions

All clinical measures were assessed at baseline (ARIC visit 1) using standardized instruments and a strict protocol. Diabetes was defined based on the American Diabetes Association guidelines(16) as fasting serum glucose of ≥126 mg/dL (7 mmol/L) or non-fasting glucose of ≥200 mg/dL (11.1 mmol/L), or self-reported use of diabetic medications within two weeks of the clinic visit, or a history of physician-diagnosed diabetes. Hypertension was defined based on Joint National Committee VII guidelines(17) as systolic blood pressure (BP) ≥140 mmHg or diastolic BP ≥90 mmHg or self-reported use of anti-hypertensive medication, or a history of physician diagnosis. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Self-reported smoking and drinking status were categorized into 3 levels (current, former, never). Serum fibrinogen was measured by the thrombin-time titration method(18) with reagents and calibration materials (Fibriquik) obtained from General Diagnostics (Organon-Technika Co). Fasting serum total and high density lipoprotein (HDL) cholesterol concentrations were assessed with Roche enzymatic methods using a Cobras centrifuge analyzer (Hoffman-La Roche), with the laboratory certified by the CDC-NHLBI Lipid Standardization Program. Self-reported highest level of education was categorized into 2 levels (less than high school graduate, high school graduate or higher).

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Statistical analysis

Although PA was measured 6 years prior to the MRI exams, this was a cross-sectional study because incident cerebral infarcts could not be distinguished from prevalent infarcts. Data are presented as mean ± SD for continuous variables and percentages for categorical variables. To test for trend in means across quartiles of ARIC/Baecke sport scores, quartiles were coded as an ordinal variable (1-4) and the p value for the parameter estimate for the ordinal variable examined in a linear model; trend in proportions across quartiles was tested by the Mantel-Haenszel chi-square trend test. Because of convergence problems encountered when using log-binomial regression, the association between subclinical cerebral infarcts and PA was modeled using logistic regression with cerebral infarct as the dependent variable and PA as the independent variable. Multivariable-adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated using SAS PROC LOGISTIC (SAS Institute, Cary, NC).

The interaction terms for PA with age, sex, systolic BP, and BMI were examined; none were statistically significant and thus not included in the final models. In the basic regression model (model 1) adjustment was made, a priori, for age (continuous) and sex. Then in the multivariable model (model 2) further adjustment was made for the potential confounding effects of ARIC study center (NC or MS), education (less than high school vs high school graduate), and smoking (never, quit, current). Finally, in step three, covariates that can be considered to be, at least partly, intermediate risk factors in the relationship between PA and subclinical cerebral infarct were added individually to the multivariable model: hypertension (yes or no), diabetes (yes or no), and fibrinogen level (continuous) (models 3A, 3B, and 3C, respectively). Additional analyses used age at MRI instead of age at baseline and adjusted for time elapsed between PA assessment with the Baecke scores and the MRI. These analyses did not change any of the estimates, probably because the MRIs were scheduled close to the third ARIC visit, which was almost exactly 6 years after the baseline visit; therefore we reported only the analyses using baseline age. We did not adjust for BMI or drinking as these covariates did not show a statistically significant association with PA and MRI infarcts in univariate analyses. A two-sided alpha value of 0.05 was used as the cut point to assess statistical significance.

Results

Study Population Characteristics

The study population of 944 African-American men and women had a mean age of 55.8 years (standard deviation or SD, 4.6); 64.0% were female; 23.8% were current smokers, 29.7% were current drinkers, 15.4% had diabetes, and 57.2% had hypertension. The mean BMI was 29.1 kg/m^2 (SD, 5.1). About one quarter (23.2%) reported regular activity (at least 1 hour/week for >= 10 months in the past year), but only 4.7% reported vigorous activity (participation in at least one sport of vigorous intensity in the past year). The average ARIC/Baecke scores of 2.1 (SD, 0.6) for sport, 2.2 (SD, 0.6) for leisure, and 2.3 (SD, 1.0) for work PA were somewhat lower than the larger ARIC cohort.(8;19) Walking frequently during leisure time was reported by 17.7% of participants. Subclinical cerebral infarcts were identified in 145 persons: 94 had one infarct, 35 had two infarcts, and 16 had three or more.

The clinical characteristics of participants are shown by quartile of ARIC/Baecke sport score in Table 1. The most active quartile (quartile 1) had fewer women, a higher level of education, fewer participants with hypertension, and lower mean systolic and diastolic BPs. Because African Americans, on average, were less active than whites in ARIC (19), the number of participants with scores in the lowest quartile of overall ARIC PA was greater than the number in the highest activity quartile.

Table 2 shows the characteristics of participants according to presence or absence of subclinical cerebral infarct. Compared to those without infarcts, participants with one or more infarcts on MRI were older, had more current smokers, diabetics, and hypertensives, and had higher mean values for systolic and diastolic BP.

Association between PA and subclinical cerebral infarcts

Table 2 also shows the distribution of activity categories and the mean ARIC/Baecke scores for participants with and without subclinical cerebral infarcts prior to covariate adjustment. The group with subclinical cerebral infarcts had slightly lower mean ARIC/Baecke sport and leisure scores.

In Table 3, the age-adjusted and multivariable-adjusted ORs for having a subclinical cerebral infarct are provided for each of the measures of PA. The adjusted ORs were significant only for the ARIC/Baecke sports score, but the results with some of the other PA measures also suggested an inverse relationship. A 1-unit increase in the ARIC/Baecke sports score was associated with a multivariable-adjusted OR for having a subclinical cerebral infarct, 0.62 (0.44-0.87). Further, there was a significant monotonic trend across quartiles of ARIC/Baecke sports score (Figure 1; P = 0.01). In models adjusting only for age and sex, a 1-unit increase in leisure PA and frequent leisure walking (compared with infrequent walking) were associated with lower ORs for having a subclinical infarct, but adjustment for hypertension (model 3a), diabetes (model 3b), and fibrinogen (model 3c), which are likely intermediate risk factors in the relationship between PA and subclinical cerebral infarct, attenuated the adjusted OR values.

Discussion

The results of this cross-sectional study suggested an inverse relationship in African-Americans between sport and leisure PA and prevalent subclinical cerebral infarct on MRI. Higher sport scores and frequent walking (compared with infrequent) were associated with reduced odds of having a subclinical infarct. Work scores were not associated with the odds of having a subclinical infarct. These findings are consistent with those of previous studies that have found higher levels of sports and leisure physical activity associated with lower stroke incidence (8;20).

A recent meta-analysis of PA and cardiovascular disease in women found higher PA was associated with a lower risk of stroke in a dose-response relationship (9). In ARIC, both white and African American participants in the lowest quartiles of sport, leisure, and work PA scores had the highest incidence of ischemic stroke during 7 years of follow-up (8). Frequent walking, but not vigorous activity, was associated with a non-significant trend for decreased ischemic stroke risk in the ARIC analyses. Both overall PA and walking, specifically, were inversely associated with stroke in women of the Nurses Health Study,(22) and, in this study, the associations remained after adjusting for other cardiovascular disease risk factor covariates. In an 11-year follow-up of male physicians, exercise vigorous enough to work up a sweat was inversely related to stroke.(10) Overall PA energy expenditure and walking, specifically, were associated with decreased stroke risk in a U-shaped relationship in male Harvard alumni,(20) but the association was attenuated when adjusted for covariate risk factors.

In contrast to stroke, the risk factors for subclinical or “silent” cerebral infarction or asymptomatic white matter lesions are not well understood,(23). The possible protective role of PA has received little attention. One recent study reported that progression of white matter lesions was not significantly associated with PA energy expenditure in cognitively impaired older adults of the Cardiovascular Health Study Cognition Cohort(24).

These results are consistent with previous studies characterizing individuals with subclinical or silent cerebral infarcts, who are likely to be older, less well educated, smokers, and with diabetes and hypertension.(25-28) Alcohol consumption was previously shown to not be related to silent cerebral infarction in the ARIC MRI cohort.(29)

Our results extend the literature on subclinical cerebral infarcts in African Americans and add to accumulating evidence indicating that PA is associated with lower risk of cerebrovascular disease. Similar to the findings for studies of stroke, we found leisure PA was inversely associated with prevalence of subclinical infarcts (8;22). In our sample, work PA failed to show any association with subclinical infarcts, and this may possibly be due to confounding adverse cardiovascular risk factors in those with heavy labor occupations. There could also be a differential effect of PA involving upper body activity such as heavy lifting and long periods of standing, which contribute to the ARIC/Baecke work score. Some, but not all, other studies that have examined different domains of PA have also failed to find an association between occupational PA and cardiovascular disease outcomes (19;21).

Increasing evidence from both animal models and humans offers neurobiological bases for the benefits of exercise on brain health.(30) Cardiovascular fitness has been inversely associated with reduced age-related tissue loss in the frontal, parietal, and temporal cortices (31) and positively associated with whole brain and white matter volume in early Alzheimer's Disease patients after controlling for age (32). Aerobic fitness training increased brain volume in both gray and white matter regions in a recent randomized clinical trial. Participation in PA, including walking at an easy pace, has been also been found to predict preserved cognitive function in a longitudinal study of women over age 70.(33)

Limitations

Although the baseline measurements of PA preceded the MRI exams by 6 years, we acknowledge that the study design cannot rule out reverse causality, and we cannot be certain whether the MRI findings detected at visit 3 predated the PA assessment at visit 1. The duration of the MRI lesions is unknown, and incident cerebral infarcts can not be distinguished from prevalent infarcts. Also, the measures of PA used in ARIC do not allow estimation of energy expenditure and cannot be used to determine if participants met current public health guidelines for PA.(34)

Conclusions

In this population based sample of African-American men and women 44 to 66 years of age, measures of non-occupational sport and leisure walking frequency were inversely related to the prevalence of subclinical MRI-detected cerebral infarcts. The results are generally similar to those reported previously for studies of PA and ischemic stroke. Our results add to the evidence that regular PA may protect brain health, and further support current public health guidelines encouraging frequent participation in leisure PA.(34)

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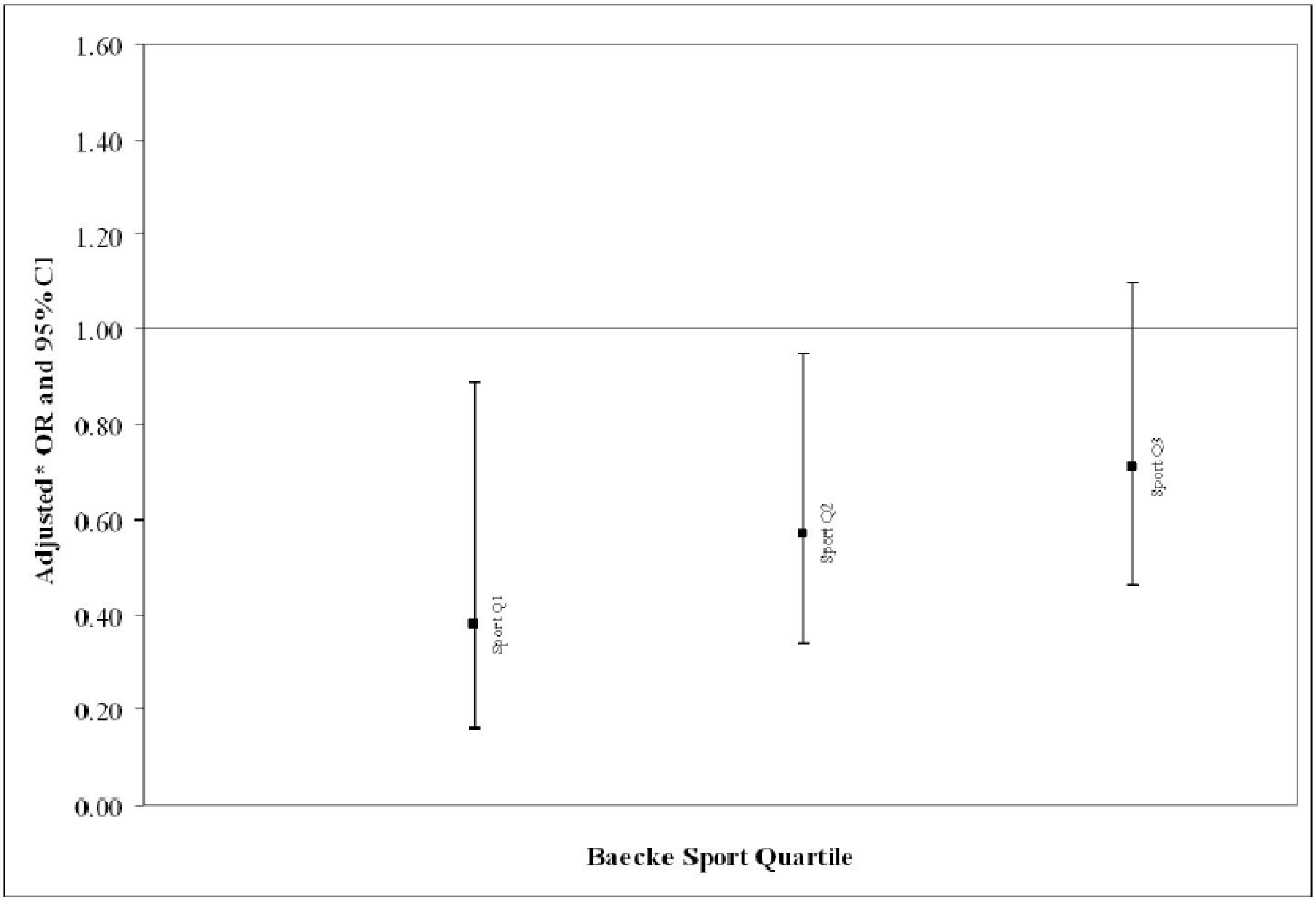

Figure 1.
Adjusted* ORs and 95% CIs for having a subclinical cerebral infarct by quartile of Baecke sport score.
Q1, most active; Q4, least active (reference group).
*adjusted for age, sex, center, education, and smoking.

Table 1

Clinical Characteristics of Participants by ARIC/Baecke Sport Score Quartile (Q1=most active, Q4=least active)

	Q1 (N=87)	Q2 (N=209)	Q3 (N=289)	Q4 (N=359)	
Quartile cut-points	**>3.00**	**2.26 - 3.00**	**1.76 - 2.25**	**0 - 1.75**	
Baecke sports score [min., max.]	**3.5 (0.3) [3.3, 4.8]**	**2.7 (0.2) [2.5, 3.0]**	**2.1 (0.1) [2.0, 2.3]**	**1.6 (0.2) [1.0, 1.8]**	**P for linear trend***
Age, yrs	55.2 (4.9)	56.1 (4.8)	56.0 (4.7)	55.6 (4.3)	0.84
Women, %	50.6	60.3	67.1	66.9	0.004
High school graduate or higher, %	74.7	63.5	54.3	58.9	0.01
Current cigarette smoking, %	22.1	18.7	26.6	24.8	0.18
Current drinking, %	38.8	29.6	28.9	28.3	0.14
Diabetes, %	13.1	15.1	15.5	16.2	0.51
Hypertension, %	47.1	52.6	56.1	63.1	0.001
BMI, kg/m^2	28.1 (4.5)	29.1 (5.1)	29.3 (5.2)	29.1 (5.3)	0.26
Systolic BP, mmHg	126 (17)	128 (21)	128 (17)	130 (20)	0.08
Diastolic BP, mmHg	77 (10)	79 (12)	79 (12)	81 (11)	0.005
Total cholesterol, mmol/L	5.6 (1.1)	5.7 (1.2)	5.6 (1.2)	5.6 (1.2)	0.91
HDL cholesterol, mmol/L	1.3 (0.4)	1.5 (0.4)	1.5 (0.4)	1.4 (0.4)	0.35
Fibrinogen, mg/dL	308.8 (69.2)	309.3 (56.5)	313.5 (69.0)	317.9 (70.3)	0.11

Values are means (SD) or percentages. SD, standard deviation; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein.

*Mantel-Haenzel χ^2 for proportions, ANOVA (with quartiles coded as an ordinal variable) for means.

Table 2
Sociodemographic, Clinical, and Physical Activity Characteristics of Participants by Infarct Status

	Any infarct (N=145)	No infarct (N=799)	P value
Age, years	57.6 (4.5)	55.5 (4.5)	<0.0001
Women, %	63.5	64.1	0.88
High school graduate or higher, %	53.5	61.2	0.08
Current cigarette smoking, %	31.7	22.3	0.01
Current drinking, %	30.8	29.5	0.77
Diabetes, %	23.4	14.0	0.005
Hypertension, %	72.4	54.4	<0.0001
BMI, kg/m^2	29.0 (5.2)	29.1 (5.1)	0.82
Systolic BP, mmHg	134 (23)	127 (18)	0.001
Diastolic BP, mmHg	82 (13)	79 (11)	0.02
Total cholesterol, mmol/L	5.7 (1.2)	5.6 (1.2)	0.47
HDL cholesterol, mmol/L	1.4 (0.4)	1.4 (0.4)	0.07
Fibrinogen, mg/dL	321.3 (71.8)	312.5 (66.1)	0.16
ARIC/Baecke Sport Score	2.0 (0.5)	2.2 (0.7)	0.001
ARIC/Baecke Leisure Score	2.1 (0.6)	2.2 (0.6)	0.05
ARIC/Baecke Work Score	2.2 (1.1)	2.3 (1.0)	0.14
Regular activity, %	17.2	24.3	0.06
Vigorous activity, %	2.8	5.0	0.24
Walking, frequent, %	13.1	18.5	0.13[*]
Walking, infrequent, %	46.2	41.7	

Values are means (SD) or percentages. SD, standard deviation; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein.

[*] for a test of association in a 3×2 table using all 3 categories of walking (frequent, sometimes, infrequent).

Table 3

Adjusted Odds Ratios (95% CI) for Having a Subclinical Cerebral Infarct by Measures of PA

	Odds Ratio (95% CI) & P value				
	Model 1:	**Model 2:**	**Model 3A:**	**Model 3B:**	**Model 3C:**
	adjusted for age & sex	**adjusted for age, sex, center, education, smoking**	**adjusted for age, sex, center, education, smoking & hypertension**	**adjusted for age, sex, center, education, smoking & diabetes**	**adjusted for age, sex, center, education, smoking, & fibrinogen**
Sport (per 1-unit increase in score)	0.61 (0.45, 0.84) 0.003	0.62 (0.44, 0.86) 0.004	0.64 (0.46, 0.89) 0.01	0.60 (0.43, 0.84) 0.003	0.62 (0.44, 0.87) 0.01
Leisure (per 1-unit increase in score)	0.73 (0.53, 0.99) 0.04	0.77 (0.56, 1.05) 0.09	0.76 (0.56, 1.04) 0.09	0.79 (0.57, 1.08) 0.13	0.77 (0.56, 1.06) 0.11
Work (per 1-unit increase in score)	0.98 (0.81-1.19) 0.86	0.97 (0.80, 1.17) 0.76	0.99 (0.82, 1.20) 0.93	1.01 (0.84, 1.23) 0.90	0.99 (0.82, 1.20) 0.93
Regular activity (yes vs. no)	0.63 (0.40, 1.01) 0.05	0.69 (0.43, 1.11) 0.12	0.73 (0.45, 1.17) 0.19	0.68 (0.42, 1.10) 0.12	0.69 (0.42, 1.13) 0.14
Vigorous activity (yes vs. no)	0.64 (0.22, 1.84) 0.40	0.72 (0.25, 2.09) 0.55	0.84 (0.29, 2.45) 0.75	0.75 (0.26, 2.21) 0.61	0.77 (0.26, 2.23) 0.62
Walking (frequent vs. infrequent)	0.56 (0.32, 0.97) 0.04	0.59 (0.33, 1.03) 0.07	0.56 (0.31, 0.99) 0.05	0.62 (0.35, 1.09) 0.10	0.56 (0.31, 1.02) 0.06