Physical Activity and Risk of Cerebrovascular Disease in the European Prospective Investigation Into Cancer and Nutrition-Spain Study

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Background—Large-scale prospective epidemiological data testing the association between physical activity (PA) and cerebrovascular diseases (CVDs) are scarce, particularly in Europe. The objective was to assess the risk of CVD according to PA levels in adults.

Methods—We included a total of 13 576 men and 19 416 women aged 29 to 69 years and participating in the European Prospective Investigation into Cancer and Nutrition cohort in Spain, recruited between 1992 and 1996 and followed-up until 2006 to ascertain incident CVD events. The validated European Prospective Investigation into Cancer and Nutrition PA questionnaire was used to assess metabolic equivalent × hours per week dedicated to different types of PA. Hazard ratios of CVD by PA levels were estimated using multivariate Cox regression. Extensive baseline data collected on diet, lifestyle habits, medical history, and anthropometry were available to adjust for.

Results—A total of 210 transient ischemic attacks and 442 stroke cases (80% ischemic, 10% hemorrhagic, 7% subarachnoid hemorrhage, and 3% mixed or unspecified) were registered after 12.3 years of mean follow-up. Recreational activity was inversely associated with risk of CVD in women but not in men. Women walking for ≥3.5 hours per week were at lower risk of stroke than those who did not engage in regular walking. No significant associations were found for other leisure time activities or vigorous PA with CVD in either sex.

Conclusions—Recreational PA of moderate intensity was inversely associated with stroke incidence in women, whereas PA showed no effect on CVD risk in men. Increasing time dedicated to activities such as walking would be expected to help to reduce the stroke burden in women.

Key Words: cerebrovascular accident ■ EPIC ■ epidemiology ■ physical activity ■ Spain ■ stroke

Cerebrovascular diseases (CVDs) are the second most frequent cause of death in the world after ischemic heart disease, accounting for ≈11% of all fatalities.1 World Health Organization projections for year 2025 foresee a significant increase in CVD prevalence in European countries as a direct consequence of the population ageing.2 In Spain, stroke and other CVDs remain as the leading cause of death in women and the third major cause among men.3

Low physical activity (PA) has been suggested to increase the risk of stroke. Previous meta-analyses showed that engaging in regular PA was consistently associated with lower risk of overall stroke,4 as well as hemorrhagic and ischemic events.6,7 Furthermore, PA guidelines have been developed to promote moderate-to-vigorous intensity PA on most days of the week as a means of improving overall cardiovascular health and reducing stroke risk.8,9 However, evidence thus far concerning the type and amount of PA that can be regarded as protective remains inconclusive. Results show heterogeneity according to type and intensity of activities performed,7,10,11 sex,12-14 and country.7 Previous data suggest that women might require higher levels of PA than men to achieve a comparable reduction in stroke risk.4 Furthermore, results from European
cohorts showed larger effect estimates than those of US studies, suggesting that direct extrapolation of results from different geographic settings to local populations might not be appropriate.\textsuperscript{2,11} Prospective epidemiological studies of a sufficient sample size to obtain precise risk estimates are still scarce, particularly in women, and country-level research is warranted to better account for specific environmental and lifestyle influences on the association between PA and CVD.

The aim of the present analysis was to determine whether PA was associated with CVD risk in adult men and women from the Spanish cohort of the European Prospective Investigation of Cancer and Nutrition (EPIC) study, diverse in age, diet, lifestyle habits, and clinical conditions.

Methods

Study Sample

The Spanish EPIC cohort is part of the larger EPIC study, an ongoing multicenter prospective investigation including >500,000 participants from 10 European countries.\textsuperscript{13,14} The EPIC-Spain sample was composed of 41438 participants (62.3\% women), 29 to 69 years old at recruitment, living in 5 different Spanish regions (Asturias, Gipuzkoa, Navarra, Granada, and Murcia).\textsuperscript{15} Questionnaire data on diet, PA, lifestyle habits, and morbidity were collected in face-to-face interviews between 1992 and 1996 among volunteers, including mainly blood donors, but also civil servants and general population. The study protocol was approved by the medical ethical committee of the Bellvitge Hospital (Barcelona), and all of the participants gave informed consent.

Assessment of PA

The specific PA questionnaire designed for the EPIC study (EPIC-PAQ) was used to record the type and time or intensity of physical activities carried out during a typical week of the previous year both in summer and winter. The EPIC-PAQ included 9 specific questions on 3 domains of PA, work, leisure time, and household activities.

For occupational PA, participants had to choose the category that better described the physical demand of their job, sedentary, standing occupation, manual work, or heavy manual work. For nonworking activities, participants were asked to specify the amount of time spent (in hours per week) in recreational (walking, cycling, and sports) and household activities (housework, gardening, and do-it-yourself activities), and the number of flights of stairs climbed per day. Participants were also asked to refer whether the practice of any such activities had caused them to experience palpitations or difficult breathing, and, if so, how many hours per week they dedicated to these vigorous activities. Recreational, household, and vigorous PA variables were then derived for the analyses. The estimated average time spent in each activity was weighted by a specific metabolic equivalent (MET) intensity value (1 MET representing a work metabolic rate of 1 kcal/kg per hour).\textsuperscript{15} Total MET-h/week spent in each activity were computed for every participant. A household PA variable (in MET-h/week) was defined as the sum of housework, do-it-yourself activities, gardening, and stair climbing. A recreational PA index was used to classify participants as inactive, moderately inactive, moderately active, and active, according to total MET-h/week spent in recreational activities. The EPIC-PAQ was validated for every EPIC center using accelerometer measures and heart rate monitoring, proving suitable for ranking participants across levels of PA.\textsuperscript{15}

Lifestyle, Diet, Anthropometry and Clinical Data

Diet of the previous year was assessed by means of a validated dietary history method\textsuperscript{15,20} using a specific questionnaire structured according to occasions of food intake. Participants were then asked to declare the foods consumed during a typical week of the previous year in each of these occasions. Total nutrient and energy intakes were estimated using specific food composition tables.\textsuperscript{21} Further questionnaire data were collected on educational level, habit of smoking, prevalence of ischemic heart disease, diabetes mellitus, hypertension, or hyperlipidemia, and, in women, menopausal status and ever use of oral contraceptives or hormonal replacement therapy. Height, weight, and waist circumference were measured in all of the participants using standard procedures. Body mass index was computed as weight (in kilograms) divided by height (in meters) squared.

Case Ascertainment and Follow-up

CVD cases occurring between recruitment and 2006 were identified from self-reported questionnaires at 3-year follow-up and by record linkage with 3 sources of information, death certificate data (codes I60–I68 of the 10th revision of the International Classification of Diseases), regional hospital discharge databases (International Classification of Diseases, Ninth Revision, codes 430–438), and computerized primary care registers (codes K89, K90, and K92 from the International Classification of Primary Care in Asturias, Navarra, and Murcia and International Classification of Diseases, Ninth Revision, codes 430–438 in Gipuzkoa). All of the EPIC-Spain cohorts took part in the study except Granada (n=7879).

A validation process was carried out to confirm and classify all of the identified stroke events. The validation was performed by a team of trained health professionals by carefully reviewing patient hospital medical charts or, if not available, primary care information and recording the date of diagnosis. Stroke cases were classified on the basis of symptoms, presence of cerebrovascular risk factors, and specific medical tests (computed tomography, magnetic resonance imaging, angiography, Doppler echography, and lumbar puncture) following the 2006 guidelines of the Spanish Society of Neurology.\textsuperscript{22} Two expert neurologists helped in the classification of the most difficult stroke cases.

After a mean follow-up (±SD) of 12.3 years (±1.6 years), 210 incident cases of transient ischemic attack and 442 incident stroke cases were identified. By type, most stroke cases were ischemic (n=352), followed by hemorrhagic strokes (n=46), subarachnoid hemorrhages (n=32), and mixed or unspecified events (n=12). After further excluding 177 participants with prevalent stroke at recruitment and 553 participants with baseline cancer or cardiovascular disease, a final cohort of 32992 subjects contributing 406441 person years was available for analyses.

Statistical Analyses

Descriptive statistics included means and SDs for continuous variables and numbers and percentages for categorical ones. Relative risks of cerebrovascular events by levels of PA variables were estimated as the hazard ratios (HRs) of multivariable Cox proportional hazards regression. Age was used as the time scale in Cox models, with entry time defined as the participant’s age at recruitment and exit time defined as age at diagnosis of a first incident transient ischemic attack or stroke, loss to follow-up, death, or December 31, 2006, whichever occurred first. The proportional hazards assumption of final models was checked on the basis of Schoenfeld residuals and graphical tests. All of the models were stratified by age (in 5-year categories) and study center and adjusted for educational level (no formal education, primary, technical/professional school, secondary, university, or unknown), prevalence of diabetes mellitus (yes, no, or unknown), self-reported hypertension or hyperlipidemia (yes, no, or unknown), habit of smoking (never smoker, former smoker who quit >10 years ago, former smoker who quit <10 years ago, current smoker of ≤10 cigarettes per day, current smoker of 11–20 cigarettes per day, current smoker of >20 cigarettes per day, or unknown), age at start of smoking, alcohol consumption (grams per day), total energy intake (kilocalories per day), total energy from proteins (percentage), total energy from fats, daily intake of vegetables (grams per day), daily intake of red meat (grams per day), daily intake of fish (grams per day), body mass index (kilograms per meter squared), waist circumference (centimeters), and, in women, menopausal status (premenopausal, perimenopausal, or postmenopausal). Other
covariates tested, such as intake of fruits, dairies, or fiber; ever use of oral contraceptives or hormonal therapy; or antithrombotic, antihemorrhagic, or cardiovascular drugs had no relevant influence on risk estimation or interpretation of data and were left out of the final analyses. Final models were mutually adjusted for PA at work, household, recreational, and vigorous PA.

Household PA (in MET·h/week) was classified into sex-specific tertiles to account for the large difference in time dedicated to household activities between men and women. A recreational PA index was used to rank participants into 4 categories of increasing PA level, using validated predefined cutoff values, including inactive (≤19.50 MET·h/week), moderately inactive (19.51–33.75 MET·h/week), moderately active (33.76–54.75 MET·h/week), and active (≥54.75 MET·h/week). Vigorous PA was analyzed by comparing subjects who never engaged in strenuous activities (the reference) with those performing ≤2 or >2 hours per week of demanding exercise.

A series of sensitivity analyses were carried out by stratifying the models according to presence of chronic disease at baseline, age group, or obesity status and by further excluding participants with <2 years of follow-up. Interactions were estimated by means of likelihood ratio tests.

Analyses were performed with STATA/SE version 10.1 (STATA Corp, College Station, TX). All of the P values were 2 sided, and the nominal significance level was set at 5%.

Results

Baseline sample characteristics are summarized in Table 1. Men with an active lifestyle had generally attained a higher educational level, were leaner, were less prone to smoke heavily, and consumed less alcohol. Active women had higher education and lower body mass index and waist circumference but showed little differences in smoking or alcohol consumption patterns. Prevalence of diabetes mellitus and hypertension were lower in active women, who also reported to a larger extent having ever used oral contraceptives. Active participants had lower energy intake on average than those considered inactive.

The estimated HRs of transient ischemic attack and stroke by levels of PA variables are shown separately for men (Table 2) and women (Table 3). No significant associations were found in men for any category of PA and transient ischemic attack risk, and there was only a borderline inverse association of household PA with stroke risk (P for trend=0.06). In women, recreational PA was inversely associated with risk of stroke (HR for active versus inactive, 0.45 [95% confidence interval, 0.22–0.90]; P for trend<0.01). On the other hand, there was borderline evidence of a direct association between standing occupation in women and stroke risk (P=0.05). Mutual adjustment by other types of PA did not substantially modify the risk estimates for the associations tested in either sex. Among recreational activities, walking for ≥3.5 hours per week was significantly associated with a reduced risk of stroke in women (HR, 0.57 [95% confidence interval, 0.35–0.92]; P for trend<0.01) but not in men (Table 4).

Excluding participants with chronic disease at baseline or those with <2 years of follow-up did not appreciably affect the results (see the online-only Data Supplement). However, effect modification was suggested, with associations reported as being significant in older (≥55 years) and obese women, as well as those with baseline chronic disease. By type of CVD, the inverse association of walking with stroke risk in women was observed for ischemic but not for hemorrhagic events, for which low numbers limited the power to make meaningful statistical comparisons.

Discussion

Moderate-intensity recreational activity, such as walking, was significantly inversely associated with risk of stroke in women from the EPIC-Spain study, whereas no such association was found in men. On the other hand, sports and other types of PA of higher intensity were not associated with CVD in this cohort.

Our results show that recreational PA was inversely associated with stroke risk in women. Previous case-control and prospective studies suggested that PA would be protective against stroke risk, both in men and women, with an estimated stroke risk reduction of >20% to 25% for high versus low levels. However, literature in the field is still scarce, methodologically diverse, and fragmentary by domain of PA, sex, and type of CVD end point. Most prospective studies have focused on recreational activities only, some showing no association with overall activity, others showing a protective inverse association of PA with CVD risk, and some others revealing higher stroke incidence at increasing levels of recreational activities suggesting a U-shaped relationship. Heterogeneity limits direct comparability across studies.

Our result of a reduced stroke incidence in women regularly engaging in recreational activities is in agreement with most previous large-scale prospective studies. Our data showed that time spent walking largely accounted for this effect. Interestingly, most previous studies examining the role of walking on CVD risk have revealed the existence of such an inverse association with stroke, which was consistent when considering either intensity (walking pace) or amount (total time or distance walked). Our results add strong evidence to the existing literature supporting a beneficial role for walking with regard to CVD in women. The effect was observed for older and obese participants, suggesting that people with a poorer cardiorespiratory fitness may be those who benefit the most from increased exercise. Although there is support in the literature for a cerebrovascular enhancing effect of increased PA in the elderly, prospective evidence of an effect modification by obesity has not been extensively documented. Our results are in line with a previous report by Hooker et al, who showed that the reduction in stroke risk per 1-MET increase in a maximal treadmill exercise performance test was much larger among overweight (HR, 0.64 [95% confidence interval, 0.45–0.90]) than among normal weight women (HR, 0.90 [95% confidence interval, 0.82–0.98]), whereas no such interaction was observed in men. In our study, adjustment by body mass index or waist circumference did not attenuate stroke risk estimates (unadjusted data not shown), which supports further health benefits of PA in addition to that of reducing adiposity.

The lack of association between recreational PA and CVD in men was an unexpected finding. Neither exclusion of participants with prevalent ischemic disease or diabetes mellitus nor further excluding those with a short follow-up time revealed any significant association between type or intensity of PA and overall or specific stroke types in men. Only a borderline inverse trend for stroke risk was found at levels roughly equivalent to 1 daily hour of household activities of moderate intensity (Table 3) and an increased...
Overall CVD risk for the intermediate walking category (Table 4), but the meaning of such findings is uncertain. Lack of statistical power is unlikely to explain our results, and there is no suggestive evidence of publication bias in the literature that may give support to these null effects.4,6,7 Unfortunately, information on the functional capacity of the participants was not available. A future re-evaluation study is warranted to confirm the null effect of PA on CVD risk in men from this cohort.

Table 1. Baseline Characteristics of the European Prospective Investigation Into Cancer and Nutrition-Spain Participants (N=32,992) According to Categories of Recreational Physical Activity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men n=4635</th>
<th>Moderately Inactive n=3537</th>
<th>Moderately Active n=2911</th>
<th>Active n=2493</th>
<th>Women n=7206</th>
<th>Moderately Inactive n=6496</th>
<th>Moderately Active n=3903</th>
<th>Active n=1811</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at recruitment, mean (SD), y</td>
<td>50.1 (6.7)</td>
<td>50.7 (7.0)</td>
<td>51.1 (7.4)</td>
<td>50.8 (7.5)</td>
<td>48 (8.1)</td>
<td>48.3 (8.2)</td>
<td>48.0 (8.3)</td>
<td>47.4 (8.5)</td>
</tr>
<tr>
<td>Educational level, n (%)*</td>
<td>Primary or none 3101 (66.9)</td>
<td>2208 (62.4)</td>
<td>1761 (60.5)</td>
<td>1366 (54.8)</td>
<td>5505 (76.4)</td>
<td>4908 (75.6)</td>
<td>2836 (72.7)</td>
<td>1242 (68.6)</td>
</tr>
<tr>
<td>Technical/professional school</td>
<td>578 (12.5)</td>
<td>469 (13.3)</td>
<td>396 (13.6)</td>
<td>426 (17.1)</td>
<td>377 (5.2)</td>
<td>347 (5.3)</td>
<td>273 (7.0)</td>
<td>150 (8.3)</td>
</tr>
<tr>
<td>Secondary</td>
<td>324 (7.0)</td>
<td>259 (7.3)</td>
<td>263 (9.0)</td>
<td>210 (8.4)</td>
<td>350 (4.9)</td>
<td>354 (5.5)</td>
<td>294 (7.5)</td>
<td>153 (8.5)</td>
</tr>
<tr>
<td>University</td>
<td>487 (10.5)</td>
<td>522 (14.8)</td>
<td>437 (15)</td>
<td>437 (17.5)</td>
<td>617 (8.6)</td>
<td>625 (9.6)</td>
<td>390 (10.0)</td>
<td>224 (12.4)</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>28.9 (3.5)</td>
<td>28.3 (3.3)</td>
<td>28.2 (3.3)</td>
<td>27.8 (3.2)</td>
<td>28.3 (4.8)</td>
<td>27.8 (4.5)</td>
<td>27.4 (4.4)</td>
<td>26.9 (4.2)</td>
</tr>
<tr>
<td>Waist circumference, mean (SD), cm</td>
<td>101.1 (9.1)</td>
<td>99.2 (8.8)</td>
<td>98.5 (8.5)</td>
<td>97.1 (8.9)</td>
<td>88.8 (11.5)</td>
<td>86.8 (10.9)</td>
<td>85.4 (10.4)</td>
<td>83.8 (10.3)</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)*</td>
<td>Never smoker 1374 (29.6)</td>
<td>1033 (29.2)</td>
<td>871 (29.9)</td>
<td>728 (29.2)</td>
<td>4986 (69.2)</td>
<td>4659 (71.7)</td>
<td>2674 (68.5)</td>
<td>1161 (64.1)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1343 (29.0)</td>
<td>1218 (34.4)</td>
<td>988 (33.9)</td>
<td>992 (39.8)</td>
<td>669 (9.3)</td>
<td>651 (10.0)</td>
<td>482 (12.4)</td>
<td>255 (14.1)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1579 (34.1)</td>
<td>1097 (31.0)</td>
<td>868 (29.8)</td>
<td>642 (25.8)</td>
<td>1536 (21.3)</td>
<td>1175 (18.1)</td>
<td>735 (18.8)</td>
<td>391 (21.6)</td>
</tr>
<tr>
<td>Started cigarette smoking before age 20 y, n (%)*†</td>
<td>2060 (63.2)</td>
<td>1568 (62.6)</td>
<td>1212 (59.4)</td>
<td>1086 (61.7)</td>
<td>1268 (57.2)</td>
<td>1060 (57.8)</td>
<td>712 (58.1)</td>
<td>403 (62.2)</td>
</tr>
<tr>
<td>Alcohol consumption, mean (SD), g/d</td>
<td>32.7 (31.7)</td>
<td>29.1 (29.2)</td>
<td>29.5 (30.3)</td>
<td>28.0 (28.8)</td>
<td>5.3 (9.3)</td>
<td>4.8 (9.0)</td>
<td>4.7 (8.8)</td>
<td>5.6 (10.1)</td>
</tr>
<tr>
<td>Total energy intake, mean (SD), kcal/d</td>
<td>2681.2 (691.7)</td>
<td>2575.8 (677.3)</td>
<td>2571.1 (667)</td>
<td>2591.9 (697.9)</td>
<td>1994.8 (573.7)</td>
<td>1913.3 (552.5)</td>
<td>1887.4 (558.9)</td>
<td>1876.4 (550.7)</td>
</tr>
<tr>
<td>Percentage of energy from protein, mean (SD)</td>
<td>18.8 (2.6)</td>
<td>19.1 (2.7)</td>
<td>19.0 (2.7)</td>
<td>19.0 (2.7)</td>
<td>19.6 (3.2)</td>
<td>20.0 (3.3)</td>
<td>20.0 (3.4)</td>
<td>20.0 (3.6)</td>
</tr>
<tr>
<td>Percentage of energy from carbohydrates, mean (SD)</td>
<td>38.4 (6.9)</td>
<td>39.1 (7.0)</td>
<td>39.0 (7.1)</td>
<td>39.4 (7.1)</td>
<td>42.0 (6.6)</td>
<td>42.2 (6.7)</td>
<td>42.5 (7.0)</td>
<td>42.4 (7.1)</td>
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<tr>
<td>Percentage of energy from lipids, mean (SD)</td>
<td>34.6 (5.9)</td>
<td>34.2 (5.8)</td>
<td>34.2 (5.9)</td>
<td>34.3 (5.7)</td>
<td>36.6 (5.9)</td>
<td>36.1 (6.1)</td>
<td>35.8 (6.1)</td>
<td>35.7 (6.1)</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>193 (4.2)</td>
<td>140 (4.0)</td>
<td>83 (2.9)</td>
<td>85 (3.4)</td>
<td>271 (3.8)</td>
<td>222 (3.4)</td>
<td>86 (2.2)</td>
<td>19 (1.1)</td>
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<tr>
<td>Hypertension, n (%)/‡</td>
<td>1010 (21.8)</td>
<td>749 (21.3)</td>
<td>603 (20.7)</td>
<td>462 (18.5)</td>
<td>1447 (20.1)</td>
<td>1254 (19.3)</td>
<td>639 (16.4)</td>
<td>265 (14.6)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)‡</td>
<td>1195 (25.8)</td>
<td>983 (27.8)</td>
<td>813 (27.9)</td>
<td>593 (23.8)</td>
<td>1212 (16.8)</td>
<td>1077 (16.6)</td>
<td>608 (15.6)</td>
<td>289 (16.0)</td>
</tr>
<tr>
<td>Postmenopausal, n (%)‡</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2530 (35.1)</td>
<td>2335 (36.0)</td>
<td>1411 (36.2)</td>
<td>613 (33.9)</td>
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<tr>
<td>Oral contraceptive use (ever), n (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2989 (41.5)</td>
<td>2638 (40.6)</td>
<td>1695 (43.4)</td>
<td>833 (46.0)</td>
</tr>
<tr>
<td>Hormonal replacement therapy use (ever), n (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>666 (9.2)</td>
<td>656 (10.1)</td>
<td>424 (10.9)</td>
<td>171 (9.4)</td>
</tr>
</tbody>
</table>

Range values for recreational physical activity categories (metabolic equivalent × h/wk): ≤19.50 (inactive), 19.51–33.75 (moderately inactive), 33.76–54.75 (moderately active), or >54.75 (active).

*Numbers in categories do not add up because of missing data.
†Data show the percentage estimated among ever smokers.
‡Data were self-reported.

PA at work showed no significant associations with stroke in men or in women. This finding is in agreement with previous studies that found no relationship between occupational activity and stroke risk after accounting for relevant confounders.25 However, women with standing occupations were at higher risk of stroke than those with sedentary jobs (an association that strengthened when combining all of the cerebrovascular cases together; P for trend <0.01; data not shown). Further research is needed to corroborate these results.
Table 2. HRs of Incident Cerebrovascular Disease by Levels of Physical Activity Variables in Men From the European Prospective Investigation Into Cancer and Nutrition-Spain Cohort (N=13576)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Transient Ischemic Attack</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person-y Cases HR 95% CI</td>
<td>Person-y Cases HR 95% CI</td>
</tr>
<tr>
<td>Physical activity at work</td>
<td></td>
<td></td>
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<tr>
<td>Sedentary occupation</td>
<td>56775</td>
<td>56927</td>
</tr>
<tr>
<td>Standing occupation</td>
<td>55449</td>
<td>55619</td>
</tr>
<tr>
<td>Manual/heavy manual occupation</td>
<td>46428</td>
<td>46543</td>
</tr>
<tr>
<td>Not working*</td>
<td>7415</td>
<td>7499</td>
</tr>
<tr>
<td>Household physical activity†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (≤2.6 MET-h/wk)</td>
<td>55353</td>
<td>55527</td>
</tr>
<tr>
<td>Medium (2.7–21 MET-h/wk)</td>
<td>55831</td>
<td>55969</td>
</tr>
<tr>
<td>High (&gt;21 MET-h/wk)</td>
<td>54883</td>
<td>55091</td>
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<tr>
<td>Recreational physical activity</td>
<td></td>
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<tr>
<td>Inactive (≤19.50 MET-h/wk)</td>
<td>56216</td>
<td>56396</td>
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<tr>
<td>Moderately inactive (19.51–33.75 MET-h/wk)</td>
<td>43259</td>
<td>43368</td>
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<tr>
<td>Moderately active (33.76–54.75 MET-h/wk)</td>
<td>35858</td>
<td>35966</td>
</tr>
<tr>
<td>Active (&gt;54.75 MET-h/wk)</td>
<td>30734</td>
<td>30858</td>
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<tr>
<td>Vigorous physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>151851</td>
<td>152343</td>
</tr>
<tr>
<td>≤2 h/wk</td>
<td>4684</td>
<td>4706</td>
</tr>
<tr>
<td>&gt;2 h/wk</td>
<td>8234</td>
<td>8241</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; and MET, metabolic equivalent.

Model 1 was stratified by age and center and adjusted by baseline educational level, self-reported hypertension or hyperlipidemia, diabetes mellitus, habit of smoking, age at start smoking, alcohol consumption, total energy intake, body mass index, waist circumference, and consumption of protein, lipids, vegetables, red meat, and fish. Model 2 was as model 1 plus mutual adjustment by all physical activity variables in the table.

*Data were excluded from trend analysis.
†Data show sex-specific tertile cutoffs.

Actual PA guidelines recommend a minimum of 500 MET-min/week to promote health and well being or, similarly, 150 min/week of moderate-intensity activities. According to these guidelines, greater health benefits would be expected for larger amounts of PA, which would be achievable either by increasing time or intensity. Our results would partly support these recommendations. On the one hand, the equivalent to daily walking for ≥30 minutes (>210 minutes per week) was estimated to significantly reduce stroke risk in women. However, equivalent amounts of cycling or sporting activities did not have a measurable effect on CVD outcomes in either sex, nor was vigorous PA associated with CVD risk. According to our results, PA of moderate rather than high or vigorous intensity would be advisable for helping to reduce the stroke burden in women.

PA exerts favorable effects over a large number of CVD risk factors, such as hypertension, hemostatic and inflammatory processes, hypercholesterolemia, diabetes mellitus, and obesity. Furthermore, as part of a healthy lifestyle, increased PA frequently combines with better adherence to dietary recommendations that would benefit cardiovascular health. In this regard, in the present study, active participants averaged lower total energy and red meat consumption, but significantly higher vegetable intake, than inactive participants (data not shown). However, nevertheless, PA would still have an independent effect on stroke risk once these factors have been accounted for. PA improves cardiorespiratory fitness and muscular tone and prevents the decline in functional capacity that is characteristic of advancing age. Moreover, regular training would modulate the tissular antioxidant profile by decreasing basal oxidative damage and increasing resistance to oxidative stress. Our result of an independent association between moderate-intensity PA and stroke risk is in agreement with previous evidence in giving support to a beneficial role of PA on cerebrovascular health by independent mechanisms.
Table 3. HRs of Incident Cerebrovascular Disease by Levels of Physical Activity Variables in Women From the European Prospective Investigation Into Cancer and Nutrition-Spain Cohort (N=19,416)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Transient Ischemic Attack</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person-y Cases</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Physical activity at work</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary occupation</td>
<td>31,963 3 1</td>
<td>1</td>
</tr>
<tr>
<td>Standing occupation</td>
<td>80,675 38</td>
<td>3.33 1.00–11.15</td>
</tr>
<tr>
<td>Manual/heavy manual occupation</td>
<td>5591 3</td>
<td>4.52 0.87–23.3</td>
</tr>
<tr>
<td>Not working*</td>
<td>122,145 54</td>
<td>2.73 0.82–9.13</td>
</tr>
<tr>
<td>Household physical activity†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (≤84.0 MET-h/wk)</td>
<td>84,946 34</td>
<td>1</td>
</tr>
<tr>
<td>Medium (84.1–116.6 MET-h/wk)</td>
<td>75,517 35</td>
<td>0.96 0.59–1.56</td>
</tr>
<tr>
<td>High (≥116.6 MET-h/wk)</td>
<td>79,911 29</td>
<td>0.68 0.41–1.14</td>
</tr>
<tr>
<td>Recreational physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive (≤19.50 MET-h/wk)</td>
<td>88,348 44</td>
<td>1</td>
</tr>
<tr>
<td>Moderately inactive (19.51–33.75 MET-h/wk)</td>
<td>80,202 25</td>
<td>0.62 0.37–1.03</td>
</tr>
<tr>
<td>Moderately active (33.76–54.75 MET-h/wk)</td>
<td>48,889 21</td>
<td>0.96 0.55–1.65</td>
</tr>
<tr>
<td>Active (≥54.75 MET-h/wk)</td>
<td>22,335 8</td>
<td>0.73 0.32–1.67</td>
</tr>
<tr>
<td>Vigorous physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>223,956 89</td>
<td>1</td>
</tr>
<tr>
<td>≤2 h/wk</td>
<td>4,296 3</td>
<td>1.42 0.44–4.57</td>
</tr>
<tr>
<td>&gt;2 h/wk</td>
<td>10,224 6</td>
<td>1.08 0.46–2.51</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; and MET, metabolic equivalent.

Model 1 was stratified by age and center and adjusted by baseline educational level, self-reported hypertension or hyperlipidemia, diabetes mellitus, habit of smoking, age at start smoking, alcohol consumption, total energy intake, body mass index, waist circumference, menopausal status, and consumption of protein, lipids, vegetables, red meat, and fish. Model 2 was as model 1 plus mutual adjustment by all physical activity variables in the table.

Data were excluded from trend analysis.

Data show sex-specific tertile cutoffs.

other than the modulation of cardiovascular disease risk factors.

This study has important strengths, such as the large sample size; the use of a validated PA questionnaire, which includes several domains and types of activity; a large number of validated CVD cases; and an extensive set of confounding variables available for adjustment. There are, however, some limitations. The questionnaire on PA registered activities practiced during a typical week of the previous year, and this exposition might not be representative of the participants’ fitness of the participants, which could have provided valuable information for assessing the effectiveness of PA in participants with distinct functional capacity. Subgroup analyses by stroke types were limited by the small number of cases in some categories, such as hemorrhagic stroke, and likely underpowered. As an additional limitation, the EPIC-Spain study is not representative of the general population, and this should be taken into account when considering the generalizability of these results. Finally, as in all observational studies, the possibility of confounding by unmeasured factors or residual confounding cannot be completely discarded. Data on hypertension, an important risk factor for stroke, were self-reported. A previous validation study within the cohort showed that self-reported hypertension was in moderate agreement with clinically diagnosed high blood pressure, and, therefore, some residual confounding might persist.

have no direct information available on the cardiorespiratory fitness of the participants, which could have provided valuable information for assessing the effectiveness of PA in participants with distinct functional capacity. Subgroup analyses by stroke types were limited by the small number of cases in some categories, such as hemorrhagic stroke, and likely underpowered. As an additional limitation, the EPIC-Spain study is not representative of the general population, and this should be taken into account when considering the generalizability of these results. Finally, as in all observational studies, the possibility of confounding by unmeasured factors or residual confounding cannot be completely discarded. Data on hypertension, an important risk factor for stroke, were self-reported. A previous validation study within the cohort showed that self-reported hypertension was in moderate agreement with clinically diagnosed high blood pressure, and, therefore, some residual confounding might persist.
Table 4. HRs of Incident Cerebrovascular Disease by Levels of Recreational Physical Activity Variables in the European Prospective Investigation Into Cancer and Nutrition–Spain Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Transient Ischemic Attack</th>
<th>Stroke</th>
<th>All Cerebrovascular Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person-y/Cases HR 95% CI</td>
<td>Person-y/Cases HR 95% CI</td>
<td>Person-y/Cases HR 95% CI</td>
</tr>
<tr>
<td>Men (N=13,576)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>19,443/8 1.00 0.59–1.71</td>
<td>19,492/25 1.56 0.95–2.53</td>
<td>19,443/33 1.59 1.04–2.42</td>
</tr>
<tr>
<td>&lt;3.5 h/wk</td>
<td>29,695/19 1.66 0.72–3.82</td>
<td>29,759/50 1.23 0.80–1.90</td>
<td>29,695/69 1.23 0.80–1.90</td>
</tr>
<tr>
<td>≥3.5 h/wk</td>
<td>116,929/15 1.54 0.73–3.25</td>
<td>117,337/196 0.80–1.90</td>
<td>116,929/281 1.33 0.91–1.94</td>
</tr>
<tr>
<td></td>
<td>40 0.57 0.35–0.92</td>
<td>49 0.57 0.35–0.92</td>
<td>49 0.57 0.35–0.92</td>
</tr>
<tr>
<td>Sum of cycling and sports</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>96,458/69 1.00 0.59–1.71</td>
<td>96,807/177 0.86 0.53–1.37</td>
<td>96,458/246 1.00 0.59–1.71</td>
</tr>
<tr>
<td>&lt;1.75 h/wk</td>
<td>17,704/11 1.11 0.58–2.14</td>
<td>17,735/20 0.86 0.53–1.37</td>
<td>17,704/31 0.93 0.64–1.36</td>
</tr>
<tr>
<td>≥1.75 h/wk</td>
<td>51,906/32 1.28 0.82–2.01</td>
<td>52,046/74 1.26 0.94–1.69</td>
<td>51,906/106 1.26 0.99–1.61</td>
</tr>
<tr>
<td></td>
<td>49 0.68 0.40–1.08</td>
<td>96 0.68 0.40–1.08</td>
<td>96 0.68 0.40–1.08</td>
</tr>
<tr>
<td>Women (N=19,416)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>22,832/13 1.00 0.59–1.71</td>
<td>22,878/22 1.00 0.59–1.71</td>
<td>22,832/25 1.00 0.59–1.71</td>
</tr>
<tr>
<td>&lt;3.5 h/wk</td>
<td>40,945/16 0.69 0.33–1.46</td>
<td>41,023/40 1.00 0.59–1.71</td>
<td>40,945/56 0.90 0.59–1.39</td>
</tr>
<tr>
<td>≥3.5 h/wk</td>
<td>176,597/69 0.68 0.37–1.26</td>
<td>176,888/109 0.57 0.35–0.92</td>
<td>176,597/178 0.62 0.42–0.91</td>
</tr>
<tr>
<td></td>
<td>177 0.68 0.37–1.26</td>
<td>177 0.68 0.37–1.26</td>
<td>177 0.68 0.37–1.26</td>
</tr>
<tr>
<td>Sum of cycling and sports</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>165,897/79 1.00 0.59–1.71</td>
<td>166,211/137 1.00 0.58–1.72</td>
<td>165,897/216 1.00 0.58–1.72</td>
</tr>
<tr>
<td>&lt;1.75 h/wk</td>
<td>25,323/3 0.34 0.11–1.08</td>
<td>25,334/15 1.00 0.58–1.72</td>
<td>25,323/18 0.73 0.44–1.19</td>
</tr>
<tr>
<td>≥1.75 h/wk</td>
<td>49,153/16 1.08 0.62–1.88</td>
<td>49,244/19 0.66 0.40–1.08</td>
<td>49,153/35 0.79 0.55–1.14</td>
</tr>
<tr>
<td></td>
<td>49 0.66 0.40–1.08</td>
<td>49 0.66 0.40–1.08</td>
<td>49 0.66 0.40–1.08</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and HR, hazard ratio.

Mutually adjusted models were stratified by age and center and adjusted by physical activity at work, household physical activity, vigorous physical activity, educational level, self-reported hypertension or hyperlipidemia, diabetes mellitus, habit of smoking, age at start smoking, alcohol consumption, total energy intake, body mass index, waist circumference, consumption of protein, lipids, vegetables, red meat, and fish, and further adjusted by menopausal status in women.

In conclusion, this study shows that moderate-intensity recreational activity, such as walking, was independently associated with a reduced risk of stroke in women. This effect was evident among the obese and older participants. Sports and other types of PA of higher intensity were unrelated to CVD incidence. No significant associations were found between PA levels and CVD risk in men, but the relationship between type of work and CVD risk deserves further investigation in women. The promotion of moderate-intensity activities is recommended to aid in the prevention of stroke risk, at least in women.

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We thank Dr Maite Martínez Zabaleta and Dr Fermín Moreno Izco from Donostia University Hospital (Gipuzkoa) for helping in the classification of the most difficult cerebrovascular cases.

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Disclosures

None.

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Physical Activity and Risk of Cerebrovascular Disease in the European Prospective Investigation Into Cancer and Nutrition-Spain Study
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### Table S1. Hazard ratios (HR) of incident cerebrovascular disease by levels of recreational physical activity variables in the EPIC-Spain cohort.

<table>
<thead>
<tr>
<th></th>
<th>Person-years</th>
<th>Ischemic stroke</th>
<th>Hemorrhagic stroke</th>
<th>Subarachnoid hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cases</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Men (N = 13576)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>19492</td>
<td>20</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&lt;3.5 h/week</td>
<td>29759</td>
<td>39</td>
<td>1.46</td>
<td>0.85 - 2.53</td>
</tr>
<tr>
<td>≥3.5 h/week</td>
<td>117337</td>
<td>164</td>
<td>1.25</td>
<td>0.77 - 2.03</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Sum of cycling and sports</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>96807</td>
<td>146</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&lt;1.75 h/week</td>
<td>17735</td>
<td>15</td>
<td>0.79</td>
<td>0.46 - 1.35</td>
</tr>
<tr>
<td>≥1.75 h/week</td>
<td>52046</td>
<td>62</td>
<td>1.33</td>
<td>0.97 - 1.83</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td><strong>Women (N = 19416)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>22878</td>
<td>16</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&lt;3.5 h/week</td>
<td>41023</td>
<td>30</td>
<td>0.95</td>
<td>0.51 - 1.77</td>
</tr>
<tr>
<td>≥3.5 h/week</td>
<td>176888</td>
<td>83</td>
<td>0.54</td>
<td>0.31 - 0.94</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td></td>
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<tr>
<td>Sum of cycling and sports</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>166211</td>
<td>100</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&lt;1.75 h/week</td>
<td>25334</td>
<td>13</td>
<td>1.31</td>
<td>0.72 - 2.39</td>
</tr>
<tr>
<td>≥1.75 h/week</td>
<td>49244</td>
<td>16</td>
<td>0.85</td>
<td>0.49 - 1.47</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>0.74</td>
<td></td>
</tr>
</tbody>
</table>

Mutually adjusted models stratified by age and centre, and adjusted by physical activity at work, household physical activity, vigorous physical activity, educational level, self-reported hypertension or hyperlipidemia, diabetes, habit of smoking, age at start smoking, alcohol consumption, total energy intake, consumption of protein, lipids, vegetables, red meat, and fish, body mass index, and waist circumference, and further adjusted by menopausal status in women.
<table>
<thead>
<tr>
<th></th>
<th>Recreational physical activity</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inactive</td>
<td>Moderately inactive</td>
<td>Moderately active</td>
<td>Active</td>
<td>P for trend</td>
<td>Inactive</td>
<td>Moderately inactive</td>
</tr>
<tr>
<td>All participants</td>
<td>1</td>
<td>0.81 (0.62-1.07)</td>
<td>0.82 (0.61-1.10)</td>
<td>0.99 (0.73-1.34)</td>
<td>0.73</td>
<td>1</td>
<td>0.66 (0.49-0.88)</td>
</tr>
<tr>
<td>Age groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55 years at baseline</td>
<td>1</td>
<td>0.78 (0.51-1.21)</td>
<td>1.16 (0.75-1.58)</td>
<td>0.98 (0.60-1.62)</td>
<td>0.73</td>
<td>1</td>
<td>0.67 (0.42-1.07)</td>
</tr>
<tr>
<td>≥55 years at baseline</td>
<td>1</td>
<td>0.88 (0.61-1.27)</td>
<td>0.74 (0.50-1.10)</td>
<td>1.04 (0.70-1.54)</td>
<td>0.83</td>
<td>1</td>
<td>0.62 (0.43-0.91)</td>
</tr>
<tr>
<td>Chronic disease at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0.73 (0.48-1.10)</td>
<td>0.67 (0.43-1.06)</td>
<td>0.85 (0.54-1.35)</td>
<td>0.30</td>
<td>1</td>
<td>0.67 (0.43-1.06)</td>
</tr>
<tr>
<td>Yes*</td>
<td>1</td>
<td>0.90 (0.62-1.31)</td>
<td>0.97 (0.66-1.43)</td>
<td>1.14 (0.75-1.73)</td>
<td>0.58</td>
<td>1</td>
<td>0.65 (0.44-0.95)</td>
</tr>
<tr>
<td>Obesity status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without general or central obesity</td>
<td>1</td>
<td>1.01 (0.66-1.53)</td>
<td>1.09 (0.71-1.68)</td>
<td>0.89 (0.56-1.43)</td>
<td>0.78</td>
<td>1</td>
<td>1.20 (0.71-2.04)</td>
</tr>
<tr>
<td>With general or central obesity</td>
<td>1</td>
<td>0.64 (0.44-0.94)</td>
<td>0.65 (0.43-0.98)</td>
<td>1.04 (0.69-1.56)</td>
<td>0.62</td>
<td>1</td>
<td>0.47 (0.32-0.69)</td>
</tr>
</tbody>
</table>

*P for heterogeneity = 0.22, P for heterogeneity = 0.11, P for heterogeneity = 0.04, P for heterogeneity = 0.64, P for heterogeneity = 0.66, P for heterogeneity = 0.04, P for heterogeneity < 0.01.
Excluding the first two years of follow-up (n = 121 participants; 44 cases)

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.79 (0.59-1.05)</td>
<td>0.79 (0.58-1.06)</td>
<td>0.98 (0.71-1.34)</td>
</tr>
<tr>
<td>Participants without chronic disease at baseline</td>
<td>0.72 (0.47-1.10)</td>
<td>0.64 (0.40-1.01)</td>
<td>0.79 (0.49-1.27)</td>
</tr>
</tbody>
</table>

Values are hazard ratios (HR) and 95% confidence intervals (CI).
Adjusted models stratified by age and centre, and adjusted (when applicable) by physical activity at work, household physical activity, vigorous physical activity, educational level, self-reported hypertension or hyperlipidemia, diabetes, habit of smoking, age at start smoking, alcohol consumption, total energy intake, consumption of protein, lipids, vegetables, red meat, and fish, body mass index, and waist circumference, and further adjusted by menopausal status in women.

* Diabetes, self-reported hypertension or self-reported hyperlipidemia at baseline.
Table S3. Baseline characteristics of the EPIC-Spain participants (N = 32992) according to cerebrovascular disease (CVD) status.

<table>
<thead>
<tr>
<th></th>
<th>Cerebrovascular disease</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-cases (n = 13193)</td>
<td>Non-cases (n = 19147)</td>
<td>Cases (n = 383)</td>
<td>Cases (n = 269)</td>
<td></td>
</tr>
<tr>
<td>Age at recruitment (y), mean (s.d.)</td>
<td>50.5 (7.0)</td>
<td>47.9 (8.2)</td>
<td>55.6 (6.7)</td>
<td>55.0 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Educational level, n (%)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary or none</td>
<td>8172 (61.9)</td>
<td>14279 (74.6)</td>
<td>264 (68.9)</td>
<td>212 (78.8)</td>
<td></td>
</tr>
<tr>
<td>Technical / professional school</td>
<td>1833 (13.9)</td>
<td>1139 (6)</td>
<td>36 (9.3)</td>
<td>8 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>1027 (7.8)</td>
<td>1139 (6)</td>
<td>29 (7.5)</td>
<td>12 (4.4)</td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>1846 (14)</td>
<td>1845 (9.6)</td>
<td>37 (9.5)</td>
<td>11 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (s.d.)</td>
<td>28.4 (3.3)</td>
<td>27.8 (4.6)</td>
<td>29.2 (3.3)</td>
<td>29.4 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm), mean (s.d.)</td>
<td>99.2 (9)</td>
<td>86.9 (11.1)</td>
<td>102.6 (8.8)</td>
<td>91.6 (10.8)</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking, n (%)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>3909 (29.6)</td>
<td>3423 (58.3)</td>
<td>97 (25.3)</td>
<td>20 (35.7)</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>4411 (33.4)</td>
<td>2044 (10.7)</td>
<td>130 (33.9)</td>
<td>13 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>4054 (30.7)</td>
<td>3796 (19.8)</td>
<td>132 (34.5)</td>
<td>41 (15.2)</td>
<td></td>
</tr>
<tr>
<td>Started cigarette smoking before age 20 y, n (%)†</td>
<td>5752 (62.0)</td>
<td>3423 (58.3)</td>
<td>174 (60.8)</td>
<td>20 (35.7)</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption (g/day), mean (s.d.)</td>
<td>30.1 (30.2)</td>
<td>32.2 (32.5)</td>
<td>5.0 (9.2)</td>
<td>4.3 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Total energy intake (kcal/day), mean (s.d.)</td>
<td>2617.8 (686.4)</td>
<td>1936.2 (563.5)</td>
<td>2474.8 (641.5)</td>
<td>1840.7 (568.1)</td>
<td></td>
</tr>
<tr>
<td>Energy from protein (%), mean (s.d.)</td>
<td>19 (2.7)</td>
<td>19.8 (3.3)</td>
<td>19.2 (2.9)</td>
<td>19.9 (3.5)</td>
<td></td>
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<tr>
<td>Energy from carbohydrates (%), mean (s.d.)</td>
<td>38.9 (7)</td>
<td>42.2 (6.8)</td>
<td>38.3 (7.6)</td>
<td>43.9 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Energy from lipids (%), mean (s.d.)</td>
<td>34.4 (5.8)</td>
<td>36.2 (6.0)</td>
<td>33.8 (6)</td>
<td>34.6 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>471 (3.6)</td>
<td>565 (3.0)</td>
<td>30 (7.7)</td>
<td>33 (12.3)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)‡</td>
<td>2696 (20.4)</td>
<td>3489 (18.2)</td>
<td>128 (32.9)</td>
<td>116 (42.3)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)‡</td>
<td>3467 (26.3)</td>
<td>3104 (16.2)</td>
<td>117 (30.1)</td>
<td>82 (29.9)</td>
<td></td>
</tr>
<tr>
<td>Post-menopausal, n (%)</td>
<td>-</td>
<td>-</td>
<td>6694 (35.0)</td>
<td>195 (71.2)</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive use (ever), n (%)</td>
<td>-</td>
<td>8083 (42.2)</td>
<td>-</td>
<td>72 (26.3)</td>
<td></td>
</tr>
<tr>
<td>Hormonal replacement therapy use (ever), n (%)</td>
<td>-</td>
<td>-</td>
<td>1880 (9.8)</td>
<td>37 (13.5)</td>
<td></td>
</tr>
</tbody>
</table>
S.d.: standard deviation.
Range values for recreational physical activity categories (MET·h/week): ≤19.50 (inactive), 19.51-33.75 (moderately inactive), 33.76-54.75 (moderately active), >54.75 (active).
* Numbers in categories do not add up due to missing data.
† Percentage estimated among ever smokers.
‡ Self reported.